HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

≥ 12 Month Follow-Up of Patients with Spinal Muscular Atrophy (SMA) treated with Spinraza®, Zolgensma® or Combination Therapies

Endbericht

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≥ 12 Month Follow-Up of Patients with Spinal Muscular Atrophy (SMA) treated with Spinraza®, Zolgensma® or Combination Therapies

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Content

Figures

Tables

Abbreviations

6 MWT ..... 6-minute walk test
10MWT ..... 10 minute walk test
AE ..... adverse event
AHI ..... apnoea-hypopnoea index
AIHTA ..... Austrian Institute for Health Technology Assessment
CFS ..... cerebrospinal fluid
CGI-I ..... Clinical Global Impression – Improvement scale
CHOP INTEND ..... Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP ..... compound muscle action potential
CoI ..... conflict of interest
CRD ..... Centre for Reviews and Dissemination
DARE ..... Database of Abstracts of Reviews of Effects
ECG ..... electrocardiogram
FSS ..... fatigue severity scale
FSTA ..... fast skeletal muscle troponin activator
FU ..... follow-up
FVC ..... forced vital capacity
HFMSE ..... Hammersmith Functional Motor Scale Expanded for SMA
HINE-2 ..... Hammersmith Infant Neurological Examination
HRQoL ..... health-related quality of life
HTA ..... health technology assessment
IHE ..... Institute of Health Economics
INAHTA ..... International Network of Agencies for Health Technology Assessment
IQWiG ..... Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV ..... invasive ventilation
LSMUP ..... largest single motor unit potential
n ..... number
NINDS ..... National Institute of Neurological Disorders and Stroke
NIV ..... non-invasive ventilation
n.r. ..... not reported
m ..... month
MCID ..... minimal clinically important difference
MFI ..... multidimensional fatigue inventory
MIE ..... mechanical insufflation-exsufflation
MFM ..... motor function measure
MRC ..... Medical Research Council
MUNE ..... motor unit number estimation
NICE ..... National Institute for Health and Care Excellence
OS ..... overall survival
PedsQL ..... pediatric quality of life
RULM ..... revised upper limb module for SMA
SAE ..... serious adverse event

SF-36 ..... 36-Item Short Form Survey,
SMA ..... spinal muscular atrophy
SMAFRS ..... spinal muscular atrophy functional rating scale
SMC ..... Scottish Medicines Agency
SMN ..... survival motor neuron
WHO ..... World Health Organisation
WHO-MGRS ..... WHO Multicentre Growth Reference Study

Zusammenfassung

Hintergrund: Spinale Muskelatrophie (SMA) ist eine genetisch-bedingte Erkrankung, die autosomal rezessiv vererbt wird. SMA-Patient*innen werden je nach Erkrankungsalter, erreichten motorischen Fähigkeiten und Lebenserwartung in Typ 1 (die schwerwiegendste Form) bis Typ 4 eingeteilt. Bis vor kurzem war die einzige verfügbare Behandlung „Best Supportive Care". Seit 2017 sind drei Medikamente von der FDA und EMA zur Behandlung von SMA-Patient*innen zugelassen: Nusinersen/ Spinraza®, Onasemnogen-Abeparvovec/ Zolgensma®, und Risdiplam/ Evrysdi®. Nusinersen und Risdiplam wurden jeweils auf der Grundlage von zwei Zulassungsstudien zugelassen; Onasemnogen-Abeparvovec hat eine Marktzulassung basierend auf drei Zulassungsstudien erhalten.

SMA: genetische Erkrankung

SMA Typ 1-4
3 Medikamente zugelassen (Spinraza®, Zolgensma®,Evrysdi®)

Die Ergebnisse der Zulassungsstudien zeigten klinisch relevante Verbesserungen der motorischen Fähigkeiten bei SMA Typ 1 Patient*innen, insbesondere bei Patient*innen mit frühem Behandlungsbeginn, sowie eine Stabilisierung des Gesundheitszustands bei SMA Typ 2 bis 4 Patient*innen. Während sich die motorischen Fähigkeiten bei SMA Typ 1 Patient*innen verbesserten, wurden keine Veränderungen (manchmal sogar einige Verschlechterungen) beim Bedarf an Atem- und Ernährungsunterstützung beobachtet.

SMA1: Ergebnisse der Zulassungsstudien:

Verbesserung bei motorischen Fähigkeiten, keine Veränderung bei Beatmung und Ernährung

Ziel des vorliegenden Berichts ist es, die Evidenz zur mittel- und langfristigen (≥ 12 Monate) Follow-Up der zugelassenen Medikamente als Monotherapien oder als Kombinationstherapien zusammenzufassen. Das Ziel war es, einerseits die Endpunkte und die zu ihrer Messung verwendeten Instrumente, andererseits die berichteten Ergebnisse zu den gemessenen Endpunkten zusammenzufassen.

Forschungsfragen:
Endpunkte und deren Messung,
Ergebnisse zu Endpunkten ≥ 12 Monaten

Methoden: Im Juni 2021 wurde eine systematische Literatursuche durchgeführt. Es folgte eine Bewertung der ausgewählten Publikationen in Bezug auf interne Validität und Verzerrungsrisiko und die entsprechenden Daten wurden in standardisierte Datenextraktionstabellen überführt. Aufgrund der Heterogenität der Studien wurde keine quantitative Synthese durchgeführt.

systematische Literatursuche

qualitative Synthese

Ergebnisse: In den meisten Studien wurden die Ergebnisse der SMA Typ 1 Patient*innen mit HINE-2 und CHOP INTEND, und bei SMA Typ 2 bis 4 Patient*innen mit HFSME, RULM und 6MWT gemessen. Für jedes dieser Instrumente wurde eine validierte MCID definiert. Nur wenige Studien verwendeten andere Instrumente wie MFM oder MRC ohne MCID.

Endpunkte und deren Messung

Zur Analyse der mittel- und langfristigen Ergebnisse wurden 22 Beobachtungsstudien eingeschlossen. Diese berichteten über 840 SMA Patient*innen, von denen 289 SMA Typ 1 und 521 SMA Typ 2 Patient*innen mit Nusinersen behandelt wurden, nur 12 SMA Typ 1 Patient*innen erhielten Onasemnogen-Abeparvovec, und 18 SMA Typ 1 Patient*innen wurde eine Kombinationstherapie verabreicht.

mittel-langfristige Ergebnisse: 22 Beobachtungsstudien mit insg. 840 Pts. eingeschlossen

Ergebnisse der **SMA Typ 1** Patient*innen, die mit *Nusinersen* behandelt wurden (n=225): es starben neun Patient*innen, sechs brachen wegen fehlender Verbesserung ab und 35 Patient*innen konnten nicht nachbeobachtet werden. Für die Kinder, die nachbeobachtet werden konnten, fehlten viele Daten. Alle Patient*innen, bei denen CHOP INTEND gemessen

SMA1: Ergebnisse der Nusinersen Studien

wurde, erreichten den MCID. Bei HINE-2 erreichten weniger Patient*innen (67-100 %) den MCID.

SMA1: Ergebnisse der Onasemnogen-Abeparvovec Studien und Kombinationstherapie-Studien

Bei **SMA Typ 1** Patient*innen, die mit *Onasemnogen-Abeparvovec* behandelt wurden (n=12): 75% erreichten eine Sitzdauer ≥30 Sekunden und 17 % konnten ohne Unterstützung stehen. Alle 18 Patient*innen (100%), die mit einer *Kombinationstherapie* (Onasemnogen-Abeparvovec und Nusinersen) behandelt wurden, erreichten den MCID bei CHOP INTEND, aber nur 40 % erreichten den MCID bei HINE-2. 40% erreichten die Fähigkeit ohne Unterstützung zu sitzen und 20% konnten den Kopf halten oder konnten stehen.

SMA2-4: Ergebnisse der Nusinersen Studien

Ergebnisse der **SMA Typ 2 bis 4** Patient*innen, die mit *Nusinersen* behandelt wurden (n=341): ein/e Patient*in verstarb, und neun brachen die Therapie ab wegen fehlender Verbesserung. Die Patient*innen mit späterem Krankheitsbeginn erreichten eine Stabilisierung oder eventuell kleine Verbesserungen (meist unter des MICD bei HFSME und bei RULM), aber auch einige Verschlechterungen wurden beobachtet.

alle SMA Typen, alle Medikamente: keine Verbesserungen bei Beatmung und Ernährung

In **allen Patient*innengruppen**, unabhängig vom SMA Typ und dem verwendeten Medikament, wurden keine signifikanten Verbesserungen (aber in einigen Fällen jedoch eine Verschlechterung) beim Bedarf an Atem- oder Ernährungsunterstützung berichtet.

unerwünschte Ereignisse: sehr häufig

Unerwünschte Ereignisse traten in allen Studien (in fast 100 % der Patient*innen), die darüber berichteten, häufig auf, sei es mit Nusinersen oder mit Onasemnogen-Abeparvovec.

mittel-fristige Ergebnisse unterstützen die Ergebnisse der Zulassungsstudien, keine Langzeit-Daten, kaum unabhängige Studien

Schlussfolgerungen: Die mittelfristigen Ergebnisse unterstützen die Ergebnisse der Zulassungsstudien Es liegen noch keine von unabhängigen Klinikern veröffentlichten Langzeitdaten vor, und es bleiben noch viele offene Fragen. Dennoch zeigen die vorliegenden klinischen Daten, dass eine frühzeitige Behandlung bei (prä-)symptomatischen Kindern mit mindestens zwei SMN2-Kopien und ohne Notwendigkeit einer Atemunterstützung zu den besten Ergebnissen zu führen scheint.

Summary

Background: Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease. According to age of onset, achieved motor abilities, and life span, SMA patients are classified into type 1 (most severe) to type 4. Until recently, the only treatment was best supportive care. Since 2017, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved three drugs for the treatment of SMA: nusinersen/ Spinraza®, onasemnogene abeparvovec/ Zolgensma®, and risdiplam/ Evrysdi®. The approval was based on two pivotal trials each for nusinersen and risdiplam and on three pivotal trials for onasemnogene abeparvovec.

SMA: genetic disease SMA type 1 – 4

3 approved therapies: Spinraza®, Zolgensma®,Evrysdi®

Results of the pivotal trials showed clinically meaningful improvements (MCID) in motor skills in SMA type 1 (especially those with early treatment initiation and ≥2 SMN2 copies), as well as a stabilisation of health status in SMA type 2 to 4 patients. In SMA type 1 patients, while motor skills improved, no changes (sometimes even a deterioration) in the need for ventilation and nutritional support could be observed.

pivotal trials: improvement in motor skills, no change in the need for ventilation and nutrition support

The present report aims to synthesize the evidence on mid- and long-term (≥ 12 months) follow-up of the approved drugs as monotherapies or as combination therapies. We aimed to present, on the one hand, which endpoints and with which instruments were measured in studies, on the other hand, the reported results on the measured endpoints.

research questions: endpoints and instruments, results on the measured endpoints

Methods: A systematic literature search was conducted in June 2021. The selected publications were assessed for internal validity and risk of bias and respective data were extracted into standardised data extraction tables. No quantitative analysis of outcomes was performed due to the heterogeneity of the studies.

systematic literature search, qualitative synthesis

Results: Most studies measured the outcomes of SMA type 1 patients with HINE-2 and CHOP INTEND, while SMA type 2 to 4 patients were measured with HFSME, RULM and 6MWT. For each of these instruments a validated MCID is defined. Only a few studies used different instruments such as MFM or MRC without MCID.

measured endpoints and instruments

Twenty-two observational studies were included for analysing mid- and long-term outcomes. The included studies reported on 840 SMA patients, of which 289 SMA type 1 patients and 521 SMA type 2 to 4 patients were treated with nusinersen, only 12 SMA type 1 patients with onasemnogene abeparvovec and 18 SMA type 1 patients received a combination therapy.

for mid-and long-term outcomes: 22 observational studies with 840 pts included

SMA type 1 patients treated with *nusinersen* (n=225): nine patients died despite therapy, six withdrew due to lack of improvement and 35 patients were lost to follow-up. For those children that could be followed-up many data were lacking. All patients in whom CHOP INTEND was measured reached the MCID. On HINE-2 fewer patients (67-100 %) reached the MCID.

SMA type 1 pts treated with nusinersen

SMA type 1 patients treated with *onasemnogene abeparvovec* (n=12): 75% achieved sitting (≥30 s) and 17% standing without support. All patients (n=18) treated with a *combination* of onasemnogene abeparvovec and nusinersen reached the MCID on CHOP INTEND, but only 40 % reached the MCID on HINE-2. 40% learned to sit without support and 20% could control the head or stand.

SMA type 1 pts treated with onasemnogene abeparvovec or combination therapy

SMA type 2-4 pts treated with nusinersen

SMA type 2 to 4 patients (n=341) treated with *nusinersen*: one patient died and nine withdrew due to lack of improvement. Patients achieved a stabilisation or eventually small improvements (mostly below the MCID on HFSME and on RULM), but also some deterioration occurred.

all SMA types, all treatments

In all patient groups, independent of the type of SMA and the drug used, no significant improvements (but in some cases worsening) were reported for the need of respiratory or nutritional support.

adverse events: very frequent

Adverse events were common in all studies (nearly 100 % of patients) that reported on it, be it with nusinersen or with onasemnogene abeparvovec.

findings of the pivotal trials supported by the mid-term outcomes long-term data and independent studies lacking

Conclusions: The mid-term outcomes support the findings of the pivotal trials. Long-term data published by independent clinicians are not available yet and many open questions remain. Nevertheless, evidence suggests that early treatment in (pre-) symptomatic children, with at least two SMN2 copies and no need for pulmonary support seems to lead to the best outcomes.

1 Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive genetic disease. Patients suffering from SMA have an altered SMN1 gene (SMN = survival motor neuron) or it is missing completely. According to age of onset, achieved motor abilities, and life span, SMA patients are classified into type 1 (never sit), 2 (never walk unaided), 3 (walk assisted) or 4 (walk unaided) (see Table 1-1). This gene is responsible for the production of the SMN protein, which is responsible for the function or maintenance of the motor neurons. If the defect is present, the motor neurons (nerve cells responsible for motor function) die off, resulting in a lack of muscle control and progressive muscle atrophy. The death of the nerve cells means that impulses are not transmitted to the muscles. If cranial nerves are affected, swallowing, chewing and speaking functions are also restricted. SMA is a rare disease (1/10,000 births) [1].

SMA: autosomal rezessive genetische Erkrankung verursacht durch Mutation am SMN1 Gen

Absterben der Motorneuronen

SMA Typ 1-4

Patients with SMA lack the SMN1 gene, while the SMN2 (a homologous copy of SMN1) gene exists, resulting in most cases in a short SMN protein that does not function as well as a full-length protein. SMN2 is considered to be the most important phenotypic modifier of the disease. Determination of SMN2 copy number is essential to establish careful genotype–phenotype correlations, predict disease evolution, and to stratify patients for clinical trials [2].

SMN2 (= Kopie von SMN1): Modifier für Phänotyp

Table 1-1: Clinical classification of spinal muscular atrophy (SMA) [3] schwerste Form SMA1

Type	Age of onset	Requires respiratory support at birth	Able to sit	Able to stand	Able to walk	Life expectancy	Predicted *SMN2* copy number
0	Prenatal	Yes	No	No	No	<6 months	1
1	<6 months	No	No	No	No	<2 years	2
2	6–18 months	No	Yes	No	No	10–40 years	3
3	>18 months	No	Yes	Yes	Assisted	Adult	3–4
4	>5 years	No	Yes	Yes	Yes	Adult	>4

An analysis of genetically confirmed SMA patients classified by clinical criteria (age of disease onset, highest achieved motor milestones, and evolution of the disease) and the correlation between with the determined SMN2 copy number allows quantitative estimates of the probability of developing a particular SMA type as a function of SMN2 copy number (see Table 1-2).

bislang nur „Best Supportive Care“ zur Symptomlinderung und Verbesserung der Lebensqualität

Table 1-2: Correlation between SMN2 copy number and SMA Type 1 to 3 [2]

SMN2 copy number	Type I (n = 1256)	Type II (n = 1160)	Type III (n = 1043)
1	88 (7%)	4 (<1%)	0 (0%)
2	919 (73%)	192 (16%)	54 (5%)
3	245 (20%)	902 (78%)	515 (49%)
4	3 (<1%)	59 (5%)	455 (44%)
5	1 (<1%)	3 (<1%)	16 (2%)
6	0 (0%)	0 (0%)	3 (<1%)

Lebenserwartung von SMA 1 Patient*innen: 12-24 Monate

bislang nur unterstützende Betreuung

The life expectancy of the most severely affected patients (infantile SMA, type 1) is 18-24 months. Patients with SMA are treated with "best supportive care" (the best possible, patient-specific, optimised, supportive treatment to alleviate symptoms and improve quality of life). This includes respiratory care, nutrition and gastrointestinal support, musculoskeletal and orthopaedic care (physiotherapy), and palliative care. Figure 1-1 shows the rough correlation between age, motor skills and SMA type in the natural history of the disease.

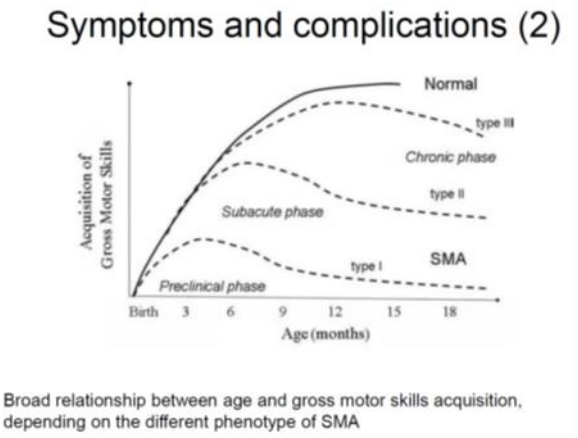

Figure 1-1: Progression by age and the SMA type [4]

1.1 Therapies for spinal muscular atrophy (SMA)

"neue" Therapien

Within the last years three disease-modifying (halting disease progression) treatments have been approved:

Spinraza®, Mai 2017, SMA (uneingeschränkt)

- Nusinersen (**Spinraza®**) by Biogen: EMA approval in May 2017 for the treatment of
  - patients with 5q spinal muscular atrophy (**SMA type 1 to SMA type 4**, without limitations).

Zolgensma®, Mai 2020, SMA1

- Onasemnogene abeparvovec (**Zolgensma®**) by Novartis: EMA approval in May 2020 for the treatment of
  - patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of **SMA type 1**, or
  - patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Evrysdi®, Mai 2021, SMA1-3

- Risdiplam (**Evrysdi®**) by Roche: EMA approval in May 2021 for the treatment of
  - patients with 5q spinal muscular atrophy (SMA) 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or
  - patients with one to four SMN2 copies.

1.2 Pivotal studies

1.2.1 Nusinersen (Spinraza®)

Mai 2017:

Zulassung von Nusinersen (Spinraza®)

In May 2017, nusinersen (Spinraza®, Biogen) was approved by the European Medicines Agency (EMA) for the treatment of chromosome 5q13(5q)-associated SMA [5]. Nusinersen is an antisense oligonucleotide (ASO), which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these 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 [5].

Eindämmung der Krankheitsprogression

Zulassungsstudien mit Nachbeobachtungen von 12-15 Monaten

The approval is based on two pivotal studies:

- ENDEAR [6], RCT, n=121 patients with SMA infantile onset, 12 months follow-up with an extension study SHINE, open label, n=89 patients.
- CHERISH [7], RCT, n=126 patients with SMA later onset, 15 months follow-up with an extension study SHINE, open label, n=20.
- Two further studies were conducted for non-eligible (in the pivotal studies) patients (EMBRACE [8]) and pre-symptomatic patients (NURTURE [9]).

Lumbalpunktion: 6 Behandlungszyklen im 1. Behandlungsjahr und 3 Zyklen in den Folgejahren

Nusinersen (Spinraza®) is injected into the cerebrospinal fluid by lumbar puncture at regular intervals. The drug is injected on day 0, 14, 28 and 63 and every four months. Six cycles are assumed in the first year of treatment and three cycles in subsequent years. In addition to lumbar puncture, peridural anaesthesia or long-term analgesia (implanted drug pump for continuous intrathecal application) may be necessary. Before administering nusinersen, an appropriate amount of cerebrospinal fluid is taken in advance [5].

1.2.2 Onasemnogene abeparvovec (Zolgensma®)

Mai 2020: Zulassung von Onasemnogene abeparvovec (Zolgensma®) Einschleusen des Gens SMN1 Zulassungsstudien mit Nachbeobachtungen von 14 Monaten

In May 2020, onasemnogene abeparvovec (Zolgensma®, Novartis) was approved by the EMA for the treatment of patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1 or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. Onasemnogene abeparvovec is a gene therapy designed to introduce a functional copy of SMN1 in the transduced cells to address the monogenic root cause of the disease. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons [10].

The approval is based on three pivotal studies

- START (CL-101)[11, 12], Phase 1, n=12 patients SMA1, 14 months follow-up.
- STR1VE (CL-303)[13], Phase 3 open label, single arm, n=22 patients with SMA 1 and 2 copies of SMN2, 14 months follow-up.
- SPR1NT (CL-304), Phase 3 open label, single arm, n=29 pre-symptomatic SMA patients with 2 (n=14) or 3 (m=15) SMN2 copies, completed (no publication yet).

Gentherapie: einmalige Verabreichung

- Further clinical studies are STRONG (Phase 1, dose finding, 3 SMN2 copies) and SMART (Phase 3b, over a 12 FU, ongoing).

Onasemnogene abeparvovec (Zolgensma®) is a one-time single-dose intravenous infusion. Patients receive a dose of nominal 1.1 x 1014 vg/kg. The total volume is determined by patient body weight [10].

1.2.3 Risdiplam (Evrysdi®)

Mai 2021:

Zulassung von Risdiplam (Evrysdi®)

In May 2021, risdiplam (Evrysdi®, Roche) was approved by the EMA for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, type 2 or type 3 or with one to four SMN2 copies. Risdiplam is a SMN2 pre-mRNA splicing modifier designed to treat SMA caused by mutations of the SMN1 gene in chromosome 5q that lead to SMN protein deficiency. Risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production of functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels [14].

SMN2-Modifikator fördert Bildung von funktionellem SMN-Protein

Zulassungsstudien mit Nachbeobachtungen von 12 Monaten

The approval is based on two pivotal studies:

- FIREFISH (Part 1, dose-finding, n=21), Part 2, phase 2-3, open-label study [15, 16], n=41 with symptomatic infantile onset SMA 1 patients, 12 months follow-up.
- SUNFISH (Part 1, dose-finding), Part 2, RCT, n=180 SMA 2 und SMA 3 patients, 12 months follow-up.
- Further clinical studies are JEWELFISH (pre-treated with another SMA-targeting therapy SMA patients, n=174, any age, SMA 1 to3, ongoing), RAINBOWFISH (pre-symptomatic babies, n=25, ongoing).

tägliche orale Einnahme

The recommended once daily dose of Evrysdi® is determined by age and body weight. Evrysdi® is taken orally once a day after a meal at approximately the same time each day [10].

1.2.4 Further compounds: Branaplam and Reldesdesemtiv

weitere Therapien in Erprobung (Phase 1/2): Branaplam und Reldesdesemtiv

Two further compounds are in the pipeline: Branaplam and Reldesdesemtiv. Branaplam (LMI070 and NVS-SM1 in Phase 1/ 2) is an experimental drug, developed by Novartis, aiming at increasing the amount of functional survival of motor neuron protein. Reldesdesemtiv (CK-2127107, Phase 2), developed by Cytokinetics in collaboration with Astellas, is a fast skeletal muscle troponin activator (FSTA) also investigated in patients with amyotrophic lateral sclerosis.

All clinical trials (pivotal and further studies, completed or ongoing) on Spinraza®, Zolgensma® (and combination therapies), Evrysdi®, Branaplam and Reldesdesemtiv are displayed in Table A 1.

1.3 Patient characteristics and results in pivotal trials

Patient*innen-Charakteristika:

Pts. in Spinraza-Studie ENDEAR älter und mit schlechterer Prognose

Studien wegen Studienpopulation und Ausschlusskriterien schwer vergleichbar

SMA1-Patient*innen-Charakteristika:

SMA1-Ergebnisse der Zulassungsstudien:

Verbesserung bei motorischen Fähigkeiten, nicht aber bei Bedarf nach Beatmung und Ernährung

Besides nusinersen (Spinraza®) now two more treatments are available for patients with spinal muscular atrophy. Detailed information on patient characteristics and in-/exclusion criteria in the pivotal trials, as well as results can be found in Table A 2 to Table A 4 for Spinraza®, in Table A 5 to Table A 7 for Zolgensma® and in Table A 8 to Table A 10 for Evrysdi®. Differences in the patient characteristics of the study populations hamper a comparison:

- while in ENDEAR (Spinraza®) SMA type 1 patients with the need for invasive ventilatory support were included, those patients were explicitly excluded in STR1VE (Zolgensma®) and FIREFISH (Evrysdi®),
- while in ENDEAR (Spinraza®) SMA type 1 patients with the need for nutritional support via tracheostomy were included, those patients were explicitly excluded in STR1VE (Zolgensma®) and FIREFISH (Evrysdi®),
- infants in STR1VE (Zolgensma®) had an initial higher CHOP-INTEND (motor-skills score) than those in ENDEAR (Spinraza®) and FIREFISH (Evrysdi®),
- accordingly, children in ENDEAR were older and had a worse prognosis than infants in STR1VE (Zolgensma®).

The results (see Table 1-3 and Table 1-4) from the pivotal trials with short follow-up show clinically meaningful improvements in motor skills in SMA type 1 patients, especially those with early treatment initiation, as well as a stabilisation of health status for SMA types 2 to 4. While motor skills improved in SMA type 1 patients, no changes or deterioration in the need for invasive or non-invasive ventilation support and in the need for nutritional support were observed.

Table 1-3: Summary of pivotal trials for SMA1 patients

Pivotal trial	ENDEAR [6] (n=80)	STR1VE [13] (n=22)	FIREFISH [15] (n=41)
Duration of trial	13m	14m	12m
Patient characteristics at baseline			
Age (months)	23.3 (7.4-34.6)	3.7 (0.5-5.9)	5.3 (2.2-6.9)
Age at symptom onset (weeks)(range)	7.9 (2-18)	7.6	6 (4-12)
Ventilatory support (%)	21 (26)	0 (100)	1 (5)
Nutritional support (%)	7(9)	0 (100)	2 (5)
HINE-2	1.29±1.07	n.r.	1.0 (0-5)
CHOP-INTEND	26.63±8.13	32.0 ±9.7	22.0 (8-37)
Results at end of trial (n=73)			
Permanent ventilatory support (%) NIV	18 (25)	4 (18) 7 (32)	2 (10)
Nutritional support • gastrostomy tube • nasojejunal tube	n.r.	3 (14) 2 (9) 1 (5)	7 (17)
HINE-2 responder (+ ≥ 2 points)** (%) • Sitting without support • Stands with support	39 (54)	n.r.	32 (78) 10 (25) 9 (22)
CHOP-INTEND responder (+≥ 4 points) (%)	52 (71)	21 (95)	37 (90) 23 (56)
Motor milestones (%) (n=73) • Head control • Roles from back to sides • Sits without support 30 sec • Sits without support/pivots 10 sec • Standing	 16 (22) 7 (10) 4 (5) 2 (3) 1 (1)	 17*/20 (85) 13/22 (59) 13/22 (59) 14/22 (64) n.r.	 6 (15) 4 (10) 12 (29)
AE (%) SAE (%)	77 (96) 45 (56)	22 (100) 10 (45)	41 (100) 24 (59)
Death (%)	13 (16)	1 (5)	3 (7)
Withdrawals (%)	2 (3)	2 (9)	0

2pts had head control at baseline, ** ≥ 2 points HINE-2 increase in ability to kick OR ≥ 1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking AND improvement in more categories of motor milestones than worsening, * Permanent ventilatory support defined as tracheostomy or ventilatory support for at least 16 hours per day.*

Table 1-4: Summary of pivotal trials for SMA 2-3 patients

Pivotal trial	CHERISH [7] (n=84)	SUNFISH [14] (n=120)
Duration of trial	15m	12m
Patient characteristics at baseline		
Age (years)	4 (2-9)	9 (2-25)
SMN2 Copy number (%) 2 3 4 unknown	 6 (7) 74 (88) 2 (2) 2 (2)	SMN2 n.r. SMA2 (71) SMA3 (29)
Disease duration (months)	39.3 (8-94)	n.r
Motor milestones ever achieved (%) • Sits without support • Ability to walk without support • Ability to walk indepenently ≥15 ft (4,5 meter)	 84 (100) 20 (24) 0	n.r
HFMSE	22.4±8.3	n.r
WHO motor milestones achieved	1.4±1.0	n.r
RULM	19.4±6.2	20.1
MFM32		46.1
Results at end of trial		
HFMSE HFMSE responder (+ ≥ 3 points) (%)	+3.9 48 (56.8)	n.r
WHO new motor milestones achieved*	13 (19.7)	n.r
RULM	+4.2	+1.61
MFM32** MFM32 responder (+ ≥ 3 points) (%)	n.r	+1.36 44 (38.3)

* n=66, **n=115

1.4 Conclusions in HTA-reports

Summarizing the results of HTA institutions (IQWiG/ GER and CADTH/ CA: nusinersen, onasemnogene abeparvovec and risdiplam; NICE/ UK: nusinersen and SMC/ UK: onasemnogene abeparvovec) which conducted assessments of the compounds, they come to the following conclusions:

Ergebnisse von HTAs

IQWiG (Germany) [17-20]:

- On **nusinersen** (Spinraza®): an indication of a major added benefit in comparison with best supportive care (BSC) in children with early onset of disease (in the first six months of life). In contrast, an added benefit in comparison with BSC in SMA later onset 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.
- On **onasemnogene abeparvovec** (Zolgensma®): no added benefit proven for any of the four types of SMA patients (pre-symptomatic, SMA1, SMA2 and SMA3) due to lack of data.

  On **risdiplam** (Evrysdi®): a hint 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, SMA2 and SMA3).

IQWIG, DE:
Spinraza®
Zusatznutzen (ZN) für SMA1 (early onset)
ZN-Anhaltspunkt für prä-symptomatische Pts.
kein ZN: SMA2+3

Zolgensma®
kein ZN in Ermangelung an Daten

Evrysdi®
ZN für SMA1
kein ZN: SMA2+3

CADTH (Canada) [21-23]:

- **Nusinersen (Spinraza®)** is recommended with clinical criteria and/or conditions (and reduction in prize) for:
  - Pre-symptomatic patients with 2-3 SMN2 copies or patients have had 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 12 years of age or younger with symptom onset after six months of age, and never achieved the ability to walk independently; if patient is not currently requiring permanent invasive ventilation.
  - Treatment should be discontinued if, prior to the fifth dose or any subsequent dose of nusinersen: there is no demonstrated achievement or maintenance of motor milestone function (as assessed using age-appropriate scales: Hammersmith Infant Neurological Examination/ HINE -2, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders /CHOP INTEND, or HFMSE) since treatment initiation in patients who were pre-symptomatic at the time of treatment initiation; or there is no demonstrated maintenance of motor milestone function (as assessed using age-appropriate scales: HINE -2, CHOP INTEND, or HFMSE) since treatment initiation in patients who were symptomatic at the time of treatment initiation; or permanent invasive ventilation is required.

CADTH, CA:

Spinraza®
prä-symptomatische Pts. (2-3 SMN2 Kopien)
SMA1 < 7 Monate
SMA2 12 Jahre)
ohne Bedarf nach IV Beatmung

Therapieabbruch bei Non-Respondern (HINE-1, HFMSE, CHOP INTEND) und nicht bei Bedarf von invasiver Beatmung

Zolgensma® SMA1 prä-symptomatisch oder symptomatisch (1-3 SMN2 Kopien) ≤ 6 Monate nicht bei Bedarf von IV oder NIV Beatmung

- **Onasemnogene abeparvovec (Zolgensma®)** is recommended with clinical criteria and/or conditions (and reduction in prize) for:

  Patients who are symptomatic or pre-symptomatic with one to three copies of the SMN2 , 180 days of age or younger OR not currently requiring permanent feeding or ventilatory support (either invasive or non-invasive).

Risdiplam (Evrysdi®) symptomatische, nicht ambulante Pts. 2-7 Monate (2 SMN2 Kopien) 7 Monate -25 Jahre (2-3 SMN2 Kopien) ohne Bedarf nach IV Beatmung

Therapieabbruch, vgl oben

Evrysdi® soll NICHT in Kombination mit Zolgensma® oder Spinraza® gegeben werden

- **Risdiplam (Evrysdi®)** is recommended with clinical criteria and/or conditions (and reduction in prize) for:
  - Patients, who are symptomatic and either aged between 2 months and 7 months, have a body weight greater than the third percentile and genetic documentation of 2 copies of the SMN2 gene OR aged 7 months and up to 25 years, who are non-ambulatory and have genetic documentation of 2 or 3 copies of the SMN2 gene; if patient is not currently requiring permanent invasive ventilation.
  - Treatment should be discontinued, if there is no demonstrated achievement in, or maintenance of, motor milestone function (as assessed using an age-appropriate measurement) after treatment initiation in patients aged between 2 months and 2 years at the time of treatment initiation; OR if there is no demonstrated maintenance of motor function (as assessed using an age-appropriate measurement) after treatment initiation in patients who were aged between 2 years and 25 years at the time of treatment initiation; OR if permanent invasive ventilation is required.
  - Risdiplam should not be used in combination with nusinersen or onasemnogene abeparvovec.

NICE (England) [24] and SMC (Scotland) [25]

SMA präsymptomatiosch, SMA1-3 nur in MEA

- **Nusinersen (Spinraza®)** is recommended as treatment option for
  - pre-symptomatic SMA, or SMA type 1, 2 or 3, and
  - the conditions in the managed access agreement are followed.

nicht bei Bedarf nach permanenter NIV oder IV Beatmung, nur in MEA

- **Onasemnogene abeparvovec (Zolgensma®)** is recommended as treatment option for:
  - 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in babies, only if:
    - they are 6 months or younger, or
    - they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team.

  It is only recommended for these groups if:

- permanent ventilation for more than 16 hours per day or a tracheostomy is not needed.
- the company provides it according to the commercial arrangement.

For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable that onasemnogene abeparvovec is allocated to babies in whom treatment brings at least a 70% chance of acquiring the ability to sit independently.

- presymptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies. It is recommended only if the conditions in the managed access agreement are followed.

- **Risdiplam (Evrysdi®)** assessment is in progress.

1.5 Costs of therapies

hohe Kosten werden mit F&E Ausgaben gerechtfertigt

The therapy costs range from 2 million euros (one-time) for Zolgensma® and annual therapy costs of 85,000 euros (Evrysdi®) to 300,00 euros (Spinraza®) - if monotherapy is used. Combination therapies (Zolgensma® plus Spinraza® or Zolgensma® plus Evrysdi®) are correspondingly even more cost-intensive.

The costs for the medication are justified by the market authorization holders with high R&D expenditures.

Excursus: Public investments in research

hohe öffentliche F&E der Grundlagen-forschung für SMA-Therapien

A recent report looked at public research funding of basic research for these new SMA therapies [26]. The basic research was primarily conducted by public research organisations and charities. Based on a document from the National Institute of Neurological Disorders and Stroke (NINDS), the stages of the development of nusinersen could be traced in detail (see Figure 1-2). It was possible to identify > 40 publicly, but also philanthropically funded projects. In total, funding for SMA R&D amounting to 165 million euros (of which 20 million euros was directly nusinersen product-related) was found.

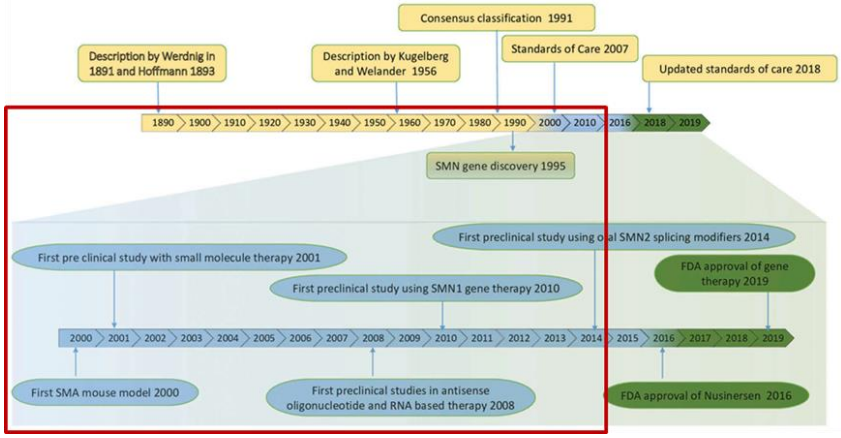

Figure 1-2: Basic research and preclinical development of SMA-therapies [27]

1.6 Objectives and scope of update report

Bericht 2020: nur FU Daten zu Spinraza® bei Pts. ≥ 6J

dieser Bericht 2021: ≥ 12 Monate FU zu Spinraza® & Zolgensma® bei Pts. SMA1 bis 3

In 2020, the AIHTA published a report on the evidence of ≥ 12 months follow-up of Nusinersen/ Spinraza® in „late onset" SMA-patients ≥ 6 years [28]. This present report aims at synthesizing the evidence

- on ≥ 12 months follow-up:
- of nusinersen/ Spinraza® and
- of onasemnogene abeparvovec/ Zolgensma® as monotherapies or
- as combination therapies.

It is NOT the intention to make a comparison of the three approved treatments.

In a second step, all data from Austrian patients documented in SMArtCARE will be collected and summarized in context of the available evidence presented in this report.

2 Methods

2.1 PICO question

2 Forschungsfragen

Research questions (RQ):

- RQ1: Which endpoints are reported in published studies and which instruments are used to measure these endpoints?
- RQ2: What medium- and long-term outcomes (≥ 12 months) on SMA therapies for SMA type 1, SMA type 2+3, and SMA type 4 are reported in the included studies?

Endpunkte und deren Messung

Ergebnisse zu Endpunkten ≥ 12 Monaten

2.2 Inclusion criteria

Table 2-1 provides a summary of the criteria for the inclusion of relevant studies.

Table 2-1: Inclusion criteria

Population	Patients with • SMA type 1 • SMA type 2+ 3 (+ 4)
Intervention	Nusinersen (Spinraza®), Onasemnogene abeparvovec (Zolgensma®), Combination therapies of Nusinersen + Onasemnogene abeparvovec Risdiplam (Evrysdi®)
Comparators	Standard of care (SoC)/ Best supportive care (BSC)
Outcomes	Outcomes with ≥12 months follow-up • Motor endpoints (HINE(-2), CHOP INTEND, HFSME, RULM) • Quality of life endpoints • Safety endpoints (adverse events: AEs, SAEs)
Study design	Any study design: retrospective, prospective case series, registry studies
Publication period	2017 until May 2021
Language	German, English

2.3 Systematic literature search

systematische Suche im Juni 2021

The systematic literature search was conducted between 11th-14th June 2021 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- Centre for Reviews and Dissemination (CRD: DARE, NHS-EED, HTA)

- International Network of Agencies for Health Technology Assessment (INAHTA)

546 Zitate identifiziert

The systematic search was limited to articles published in English or German. After the removal of duplicates, 546 citations were screened by title and abstract. By hand-search, two additional publications could be identified. Finally, 26 citations were included.

26 Zitate eingeschlossen

The specific search strategy employed for each database can be found in the Appendix.

Suche in Studienregistern

Furthermore, to identify ongoing studies, a search in two clinical trials registries (ClinicalTrials.gov; EU Clinical Trials) was conducted on the 12th August 2021 that identified 30 potentially relevant trials on the three approved compounds and combination therapies (Table A 1).

2.3.1 Flow chart of study selection

Literaturauswahl

Overall 546 hits were identified. Titles and abstracts were reviewed by two researchers (JE, CW) independent of each other and potentially relevant articles were retrieved and assessed for inclusion. In case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1. The final selection of full-text articles was based on the a priori established inclusion criteria presented in Table 2-1.

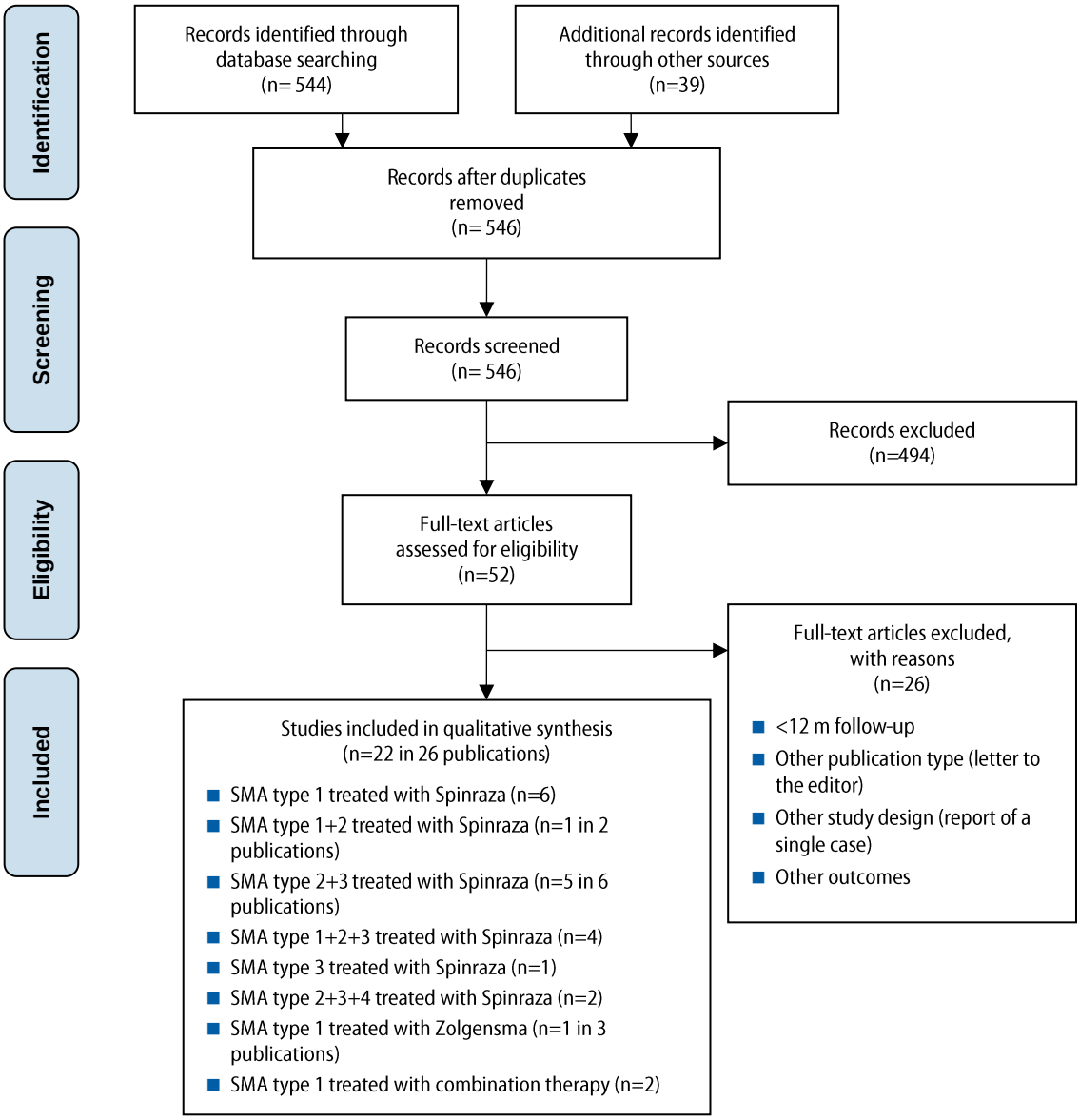

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.3.2 Analysis

Extraktion der Daten

One reviewer systematically extracted relevant data from the included studies into data extraction tables. A second reviewer cross-checked the data extraction tables with the data source and validated them for accuracy.

Bewertung der Studienqualität IHE checklist

The studies were systematically assessed for internal validity and risk of bias (RoB) by two researchers (JE, CW) independently, using the Institute of Health Economics (IHE) Risk of Bias checklist for case series [29]. Results are presented in the Appendix Table A 11 to Table A 16.

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**

2.3.3 Synthesis

qualitative Synthese

The questions were answered in plain text format. Results were summarised in, Table 3-2, Table 3-5, and Table 3-8.

No quantitative analysis of outcomes was performed due to the heterogeneity of the studies.

minimale klinisch-relevante Unterschiede

Minimal clinically important differences (MCID) were considered when this information was available for a certain outcome and applied values are reported in the results.

3 Results

3.1 Study characteristics

For the assessment of medium- and long-term outcomes (≥ 12 months) efficacy and safety of nusinersen, onasemnogene abeparvovec, or combination therapies, 22 studies (in 26 publications) met our inclusion criteria and were included in the present analysis. Nineteen studies (21 publications) assessed nusinersen, one study (three publications) assessed onasemnogene abeparvovec and two studies assessed combination therapy of nusinersen and onasemnogene abeparvovec. The onasemnogene abeparvovec and combination therapies studies enrolled exclusively patients with SMA type 1. The nusinersen studies included patients of various SMA types: six studies were on SMA type 1, one study on SMA type 1 and 2, four studies on SMA type 1 to 3, five studies on SMA type 2 and 3, one study on SMA type 3 alone, and two studies on SMA type 2 to 4.

22 Studien mit Ergebnissen ≥ 12 Monaten eingeschlossen: 19 zu Spinraza®, 1 zu Zolgensma®, 2 zur Kombinations-therapie

The number of patients enrolled in the included studies ranged from five to 123. The SMA type 1 nusinersen studies included in total 225 patients. The two nusinersen publications on SMA type 1 and 2 included 123 patients of which 34 were SMA type 1 and 89 SMA type 2 (presumably, participants of one study were part of the other study, therefore considered together in the analysis). The SMA type 1 to 3 nusinersen studies included 121 patients, of which 30 were SMA type 1, and 92 SMA type 2 and 3. SMA type 2 and 3 nusinersen studies enrolled 264 patients (there was one double publication). One study, which included only SMA type 3 patients, enrolled six of them. The SMA type 2 to 4 nusinersen studies included 34 patients. The onasemnogene abeparvovec study enrolled 12 patients. Combination therapies studies enrolled 18 patients.

insgesamt 774 SMA Patient*innen zu Spinraza®: 289 SMA1 485 SMA 2+3+4

12 Pts zu Zolgensma® 18 Pts zur Kombinationstherapie

Patient age: six studies enrolled only adult patients, three studies enrolled only children, and thirteen studies enrolled mixed population in terms of age.

3 Studien nur zu Kindern, 6 Studien zu Erwachsenen, 13 gemischte Pt-Population

The follow-up period of the included studies ranged from 12 months to 5.2 years. However, only one study followed up patients until 5.2 years. The majority of studies looked at a period of 12-24 months. Fourteen studies reported losses to follow-up due to various reasons (e.g. death, no observed benefit, did not tolerate lumbar puncture). One study did not report the losses to follow-up. In seven studies all patients could be followed-up until the pre-defined study end.

Nachbeobachtung: 12 Monate bis 5,2 Jahre, meist max 12-24 Monate

All of the included studies were of an observational, non-comparative design. Four studies used a historical cohort as a control group. Sixteen studies had a prospective study design (in two of them with double publications, a retrospective analysis was also published on the same or partly the same study populations), five studies were retrospective, and in one study, it was unclear if the study was conducted prospectively. The studies were conducted in various countries (USA, Australia, Germany, France, Poland, Belgium, Italy, Slovenia, Czech Republic, Israel, Brazil, Singapur); mainly in a single centre, however, eleven were multicentre studies.

22 ein-armige Beobachtungs-studien, 4 mit historischen Kontrollgruppen

Eleven publications reported on efficacy outcomes only, one study reported on safety outcomes only. Fourteen publications reported on both types of outcomes. The most commonly reported outcomes were CHOP INTEND,

Endpunkt-Messung mit CHOP INTEND, HINE-2, HFMSE

HINE-2, HFMSE, respiratory support, nutritional support and adverse events (including serious adverse events).

7 Hersteller-finanzierte Studien
21/26 Publikationen von Autor*innen mit Interessenskonflikten durch Honorare von Herstellerfirmen

In 21 publications, authors reported they had conflict of interest (honoraria from Ionis Pharmaceuticals and Biogen; Avexis and Roche, Novartis, etc.); in five publications, authors declared that they had no conflict of interest; and in one publication, conflict of interest was not reported on. Seven studies were manufacturer funded; six studies were funded by a research grant, a research institute/foundation or a non-profit organisation. Five studies reported no funding and four studies did not report if they received funding.

einige Doppelpublikationen

Double publication on the same study cohort or part of the cohort occurred in three instances: Gomez-Garcia et.al. reported on all French patients, while Audic et.al. reported on a smaller French cohort. The NCT02122952 study population was reported on in three publications (Lowes et.al. and two publications by Al-Zaidy et.al.). A part of the CS2 study cohort (NCT01703988, NCT02052791) was also reported on in two publications (Darras et.al. and Montes et.al.).

Further details on study characteristics of the included studies can be found in Table 3-1.

Verzerrungsrisiko: moderat, weil ein-armig, unverblindet, CoI

Most studies had a moderate risk of bias (RoB) because they were single-arm, and open-label (unblinded), often manufacturer-funded and written by authors with conflicts of interests (consultants of the manufacturers). High RoB was awarded for the studies, which were conducted retrospectively and did not report on the funding, or the conflict of interest of study authors. Detailed RoB assessment (on study level) is included in the Appendix (Table A 11 to Table A 16).

Table 3-1: Included studies (≥ 12 month follow-up, SMA1- SMA4): study characteristics

Authors/ country	n Pts.	Age	FU Period (m)	Funding + CoI	Endpoints measured
nusinersen (Spinraza®)					
SMA 1					
Acsadi et. al. 2021 [8] (USA, Germany)	20	Cross-over group: 28.7 m (24.5–65.3) 16.7 Nusinersen group continuing from Part 1: 16.7 m (7.3–48.6)	28	Funding: Biogen, Ionis Pharmaceuticals 11/11 authors with CoI - AveXis, Biogen, Genentech, Novartis, Roche, Sarepta, etc.	Respiratory support HINE-2 CGI-C AEs and SAEs
Aragon-Gawinska et. al. 2020 [30] (France, Poland, Belgium, UK)	53	21.9 m - 23.3 m	14	Funding: Association Institute of Myology 3/9 authors with CoI – Biogen, Roche, Avexis, Cytokinetics	HINE-2 CHOP INTEND
Lavie et.al. 2021 [31] (Israel)	20	13.5 m (1 m - 184 m)	24	Funding: Biogen CoI: None declared.	Respiratory support Respiratory hospitalisation AEs and SAEs
Mendonca et. al. 2021b [32] (Brazil)	21	5 m – 120 m	6-24	Funding: None declared. 2/5 authors with CoI - Biogen	CHOP-INTEND HINE-2 Respiratory support Nutritional support AEs
Modrzejewska et.al. 2021 [33] (Poland)	26	4.79 y (2 y - 15 y)	18-26	Funding: n.r. 1/13 authors with CoI - Biogen	CHOP INTEND Respiratory support Nutritional support AEs
Pane et.al. 2019 [34] (Italy)	85	2 m - 15 y 11 m	12	Funding: Famiglia SMA 13/23 authors with CoI – Biogen/Ionis Pharmaceuticals	HINE-2 CHOP INTEND Caregiver evaluation/parent reported questionnaires
SMA 1+ 2					
Audic et. al. 2020 [35] (France)	34 SMA 1 89 SMA 2 = 123	3 m – 16 y	12	Funding: French Network of Neuromuscular Disorders (FILNEMUS) CoI: None declared.	HINE-2 CHOP INTEND (children < 2 y); MFM20 (children 2- 5 y), MFM32 INTEND (children > 6 y) Nutritional support Respiratory support CGI-I AEs and SAEs
Gómez-García de la Banda et. al. 2021 [36] (France)	2 SMA 1 14 SMA 2 =16	3.5 y - 11.5 y	14	Funding: n.r. 4/12 authors with CoI - Biogen, Roche, Avexis, PTC Therapeutics, Novartis	MFM HINE-2 Respiratory muscle tests and lung function data
SMA 1+2+3					

Chachko et.al. 2021 [37] (Australia)	7 SMA 1 12 SMA 2 9 SMA 3 = 28	1.17 y (0.1 – 12.7)y	12	Funding: Biogen CoI: None declared.	Pulmonary function CHOP INTEND RULM HFSME AHI
Kariyawasam et. al. 2020 [38] (Australia)	6 SMA 1 10 SMA 2 4 SMA 3 = 20	4 m -20y	13.8 (4 - 33.5)	Funding: Scholarships, Hospital Foundation 1/7 authors with CoI - Biogen	CMAP MUNE LSMUP HFSME or CHOP INTEND
Osredkar et. al. 2020 [39] (Slovenia, Czech Republic)	16 SMA 1 32 SMA 2 13 SMA 3 = 61	2 m – 19 y	14	Funding: Slovenia -University Medical Centre Ljubljana research grant 20180153 CoI: None declared.	CHOP INTEND HFMS HFMSE MFM
Veerapandiyan et.al 2020 [40] (USA)	1 SMA 1 4 SMA 2 7 SMA 3 = 12	22 y (12 y – 52 y)	17.4 (4 - 26)	Funding: n.r. 2/7 authors with CoI – Biogen, Avexis, Sarepta, Santhera, Pfitzer, PTC, Strongbridge, NIH, FDA, MDA, PCORI, NeuroNEXT, CDC	RULM 6MWT AEs
SMA 2+3					
Darras et.al. 2019 [41] (USA)	11 SMA 2 17 SMA 3 = 28	2 y – 15 y	~32	Funding: Biogen, Ionis Pharmaceuticals With CoI - AveXis, Biogen, Bristol-Myers Squibb, Cytokinetics, Marathon, PTC, Roche, Santhera, Sarepta; NIH/National Institute of Neurologic Disorders and Stroke, Slaney Family Fund for SMA, SMA Foundation, Working on Walking Fund; Fibrogen, PTC, Roche, Santhera, Sarepta, Summit, Genentech, Muscular Dystrophy Association, Eunice Kennedy Shriver National Institute for Child Health and Human Development, Scholar Rock, Otonomy; Myotonic Dystrophy Foundation, ALS Association, ALS Finding a Cure, Neuraltus, Excel Scientific Solutions, Metafora, Sanofi, Department of Defense, Hope for Children Research Foundation, NIH, Mallinckrodt, Ultragenyx	HFMSE ULM 6MWT CMAP MUNE AEs, SAEs
Montes et.al. 2019 [42] (USA)	1 SMA 2 13 SMA 3 = 14		35	Funding: Biogen 14/15 authors with CoI - 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,	6MWT

				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	
Hagenacker et.al. 2020 [43] (Germany)	20 SMA 2 37 SMA 3 =57	16 y - 65 y	14	Funding: none declared. 22/31 authors with CoI - Biogen, Hoffmann–La Roche, Cytokinetics, Desitin Pharma, Novartis, Teva, Akcea Therapeutics, Alnylam Pharmaceuticals, Pfizer, Roche, Avexis, CSL Behring, Grifols, SMArtCARE, BIAL, AbbVie, Bayer, Santhera, Daiichi Sankyo, PTC Therapeutics, AB Science, GlaxoSmithKline, Orion Pharma, Tau Rx Therapeutics, Mitsubishi, and scholarships (Helmholtz Foundation, Federal Ministry of Education and Research, Innovationsausschuss des G-BA, German Neuromuscular Society, Schilling-Stiftung, Young Faculty Program of Hanover Medical School, German Israeli Foundation for Scientific Research and Development, EU Joint Programme for Neurodegenerative Disease Research)	HFMSE RULM 6MWT AEs, SAEs
Maggi et. al. 2020 [44] (Italy)	13 SMA 2 103 SMA 3 = 116	34 y (18 y – 72 y)	14	Funding: none declared. 19/41 authors with CoI - Sanofi Genzyme, Biogen, PTC, Sarepta, Santhera, Pfizer, Roche, CSL Behring, ITALFARMACO, PIAM, Boheringer, Novartis, Alnylam, Akcea, Catalyst, Alexion, ARGENX , Biomarin, LT3, NICO, SUMMEET, GALEN SYMPOSION; LT3, PREX; I & C; Spark, Lupin	HFMSE RULM 6MWT FVC AEs
Mendonça et al. 2021a [45] (Brazil)	14 SMA 2 27 SMA 3 = 41	10.6 y (10.3)	24	Funding: none declared. 2/7 authors with CoI - Biogen	HFMSE or CHOP-INTEND
Moshe-Lilie et. al. 2020 [46] (USA)	9 SMA 2 13 SMA 3 = 22	36 y (20 y - 71 y)	24	Funding: none declared. 2/6 authors with CoI - Sarepta. Acceleron, Akcea, Alexion, Alnylam, Argenx, Biogen, CSL Behring, Cytokinetics, Sanofi-Genzyme	MRC HFMS AEs
SMA 3					
Yeo et. al. 2020 [47] (USA, Singapur)	6 SMA3	29.9 y (24.9 y – 56.5 y)	17 (14 - 21)	Funding: n.r. 1/5 authors with CoI - Cure SMA, Biogen, AveXis, Roche	HFMSE RULM PedsQL Fatigue scale SMAFRS 6MWT and 10MWT

					AEs
SMA 2+3+4					
Binz et. al. 2020 [48] (Germany)	6 SMA 2 11 SMA 3 1 SMA 4 = 18	≥ 18y	14	Funding: Open access funding by Projekt DEAL. No targeted study funding. 5/8 authors with CoI – Biogen, Novartis, Jain Foundation, Cytokinetics, Desitin Pharma, Roche, Teva	FSS MFI HRQoL 6MWT HFMSE RULM
De Wel et. al. 2020 [49] (Belgium)	14 SMA 3 2 SMA 4 =16	37.1 (20 y – 66 y)	14	Funding: partially Biogen 1/9 authors with CoI - Alnylam, Biogen, CSL Behring, Sanofi-Genzyme	Hand grip strength RULM MRC 6MWT HFMSE SF-36 AEs, SAE
onasemnogene abeparvovec (Zolgensma®)					
SMA 1					
Al-Zaidy et. al. 2019a [50] (USA)	12	3.4 m (0.9 m - 7.9 m)	24	Funding: AveXis, Inc. CoI: n.r.	Respiratory support Nutritional support Motor milestones
Al-Zaidy et. al. 2019b [51] (USA)	12	3.4 m (0.9 m - 7.9 m)	24	Funding: AveXis, Inc., NN101- NINDS (U01NS079163), Cure SMA, Muscular Dystrophy Association, and SMA Foundation 15/17 authors with CoI: AveXis, Inc. Sarepta Therapeutics, Exonics Therapeutics, Biogen, Roche	CHOP INTEND AEs, SAEs
Lowes et. al. 2019 [52] (USA)	12	1.8 m - 5.1 m	24	Funding: AveXis, Inc. 12/16 authors with CoI - AveXis, Roche, F. Hoffmann-LaRoche AG, Sarepta Therapeutics, Exonics Therapeutics	Respiratory support Nutritional support CHOP INTEND
Combination therapy nusinersen (Spinraza®) + onasemnogene abeparvovec (Zolgensma®)					
SMA 1					
Harada et. al. 2020 [53] (USA)	5	17 m - 29 m	19.2 (8-27.2)	Funding: n.r. 4/10 authors with CoI - AveXis, Biogen, Sarepta, PTC therapeutics, Audentes, Cytokinetics, Novartis, NIH, Muscular Dystrophy Association, CureSMA, Genentech, NS Pharma, Pfizer, AMO Pharma, MedLink	CHOP INTEND HINE AEs
Mendell et.al. 2021 [12] (USA)	13	38.9 m (25.4 m – 48 m)	5.2 y (4.6-6.2) y	Funding: Novartis Gene Therapies 7/12 authors with CoI:- Novartis Gene Therapies, Milo Biotech, Catalyst, AveXis, Sarepta, Gene Therapy Immersion Training	AEs, SAEs

				Program, ATOM International, Nationwide Children's Hospital, Casimir	

6MWT = 6 minute walk test, 10MWT = 10 minute walk test, AE = adverse event, AHI = Apnoea-Hypopnoea Index, CGI-C = Clinical Global Impressions scale - Global Improvement, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, CMAP = compound muscle action potential, CoI = conflict of interest, ECG = electrocardiogram, FSS = fatigue severity scale, FVC =forced vital capacity, HFMSE =Hammersmith Functional Motor Scale Expanded for SMA, HINE = Hammersmith Infant Neurological Examination, HRQoL = health-related quality of life, LSMUP = largest single motor unit potential, MFI = multidimensional fatigue inventory, MFM = motor function measure, MRC = Medical Research Council, MUNE = motor unit number estimation, n.r. = not reported, PedsQL = pediatric quality of life, OS = overall survival, RULM = revised upper limb module for SMA, SAE = serious adverse event, SF-36 = 36-Item Short Form Survey, SMAFRS = spinal muscular atrophy functional rating scale, WHO-MGRS = WHO Multicentre Growth Reference Study.

3.2 Outcomes: clinical effectiveness and safety

Endpunkte und deren standardisierte Messung

The following instruments [54, 55] measure the treatment outcomes in SMA patients:

- SMA 1 patients: CHOP INTEND, HINE-2
- SMA 2 and 3 patients: HFMSE, 6MWT, (R)ULM, MFM, MRC

CHOP INTEND: motorische Entwicklung bei Kindern (bis 4J)

MID: ≥ 4 Pkte

The CHOP INTEND scale (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) was developed to evaluate the motor skills of children with SMA 1 from three months to over four years, although it is not limited to this age range. CHOP INTEND is a 16-item scale. Most items can be scored just by watching a baby or young child. Each item (e.g. spontaneous arm movement, handgrip, head control etc.) is graded on a scale of 0 to 4 (0=no response; 4=complete response) with a total possible score of 64 [56]. The CHOP INTEND is a validated instrument; the clinical relevance threshold (MCID) is 4 points.

HINE-2: motorische Entwicklung bei Kindern (bis 2 J)

MID: ≥ 2 Pkte

The HINE-2 score (Hammersmith Infant Neurological Examination) is only used in children up to the age of two years. It is a physiotherapy-based assessment. Most items can be scored just by watching a baby or young child. HINE measures eight aspects of motor ability, developmental tasks a baby is expected to be able to do (voluntary grasp, head control, ability to kick whilst lying on back, rolling, sitting, crawling, standing, and walking). Each item is scored up to four points. The total score is 26 [57]. The HINE is a validated instrument; the clinical relevance threshold (MCID) is 2 points.

HFSME: motorische Entwicklung bei Kindern/ Jugendlichen/ Erwachsenen

MID: ≥ 3 Pkte

The HFSME scale (Hammersmith Functional Motor Scale-Expanded): A change (or stabilisation) in motor function in children (≥ 24 months), adolescents and adults with SMA type 2 and 3 is measured with the HFSMSE scale. The HFSMSE consists of a 33-item list of motor tasks (chair sitting, standing supported, standing unsupported, etc.); each item is scored from 0 to 2 points). The total score is 66 [58]. The HFSMSE is a validated instrument; the clinical relevance threshold (MCID) is 3 points.

MFM motorische Entwicklung bei Kindern/ Jugendlichen/ Erwachsenen

MID: n.r.

MFM (Motor Function Measure) is a quantitative generic neuromuscular functional scale, targeting motor abilities in individuals with a wide spectrum of weakness distribution and severity. The MFM can be used for ambulatory and non-ambulatory children and adults aged 6 - 62 years, and for all levels of severity of the disease. The MFM in its classic form (MFM32) is suitable for children older than 6 years and a modified version with 20 items (MFM20 version) has been validated for children under 6 years of age, however it is most useful for children who can sit without support. Each item is scored from 0 (not able to initiate movement) to 3 (full performance of a task), and thus, 60 points are the maximum score on the MFM20 scale. [59, 60].

6MWT: Leistungsfähigkeit beim Gehen

MID: ≥ 30 Meter

The 6MWT (6-minute walk test) is a diagnostic tool primarily used in cardiology and pulmonology to determine a patient's performance. The patient walks on ground level for six minutes with the aim of walking as far as possible according to his/her own performance. For SMA type 2 and 3 patients, a clinically relevant change is considered to be an improvement of ≥ 30 metres in walking ability.

The **(R)ULM** (Revised Upper Limb Module) is a disease-specific assessment tool designed to evaluate upper limb function in SMA patients. RULM is a revised version of the shorter ULM questionnaire developed for the motor assessment of non-ambulatory SMA children. The RULM measures upper limb functionality over 20 items with different constructs than the HFMSE. (R)ULM is seen as a complement to the HFMSE, especially for weak and non-ambulatory patients. A clinically relevant change (MCID) is considered to be an improvement of ≥ 2 points.

(R)ULM: Funktionalität der oberen Extremitäten

MID: ≥2 Pkte

The **MRC** scale (Medical Research Council) is a scale to assess muscle strength by manual muscle testing on a scale of 0 to 5 in relation to the maximum expected for that muscle (grade 0=no movement observed, grade 5=muscle contracts normally against full resistance). In comparison to an analogue scale the MRC scale is more reliable and accurate for clinical assessment in weak muscles (grades 0-3) while an analogue scale is more reliable and accurate for the assessment of stronger muscles (grades 4 and 5) [61].

MRC: Muskelstärke

MID: n.r

3.2.1 Nusinersen in SMA type 1

Six prospective observational studies [8, 30-34] with 225 patients were included for the assessment of efficacy and safety of Nusinersen in SMA type 1 patients. One study had a cross-over design [8], while five studies were single-arm. In one study [33] all patients could be followed-up until the pre-defined last visit.

6 prospektive Fallserien mit insgesamt 225 SMA1 Patient*innen

Mortality, discontinuation

In five studies loss to follow-up occurred due to death or stopping of treatment. In Lavie et.al. [31] two patients died due to sleep apnoea as a result of massive aspiration, one stopped treatment after 14 months due to respiratory exacerbations related to infections, as well as to aspirations, which eventually led to anoxic brain injury. The three patients had different baseline characteristics in terms of need for respiratory support (use of assisted ventilation < 16 hours a day by one patient, > 16 hours a day by another patient and ≥16 hours a day by the third patient). Aragon-Gawinska et.al. [30] reported the death of two patients due to respiratory failure unrelated to treatment, and one withdrawal due to of lack of motor gain and respiratory degradation. Three patients were lost to follow-up without any particular reason. Mendonca et.al. [32] reported the death of one patient due to pulmonary infection and loss to follow-up of the majority of patients by the end of the follow-up period (17 of 21 patients lost at 24 months). The reasons for the losses to follow-up were not described in detail. At month 24, follow-up data was not available for any of the 14 patients who were on invasive ventilation at baseline, at 18 month follow-up data was available only for six of the 14 patients. In Acsadi et. al.[8] one patient died in the first part of the study, before the open label cross-over study period could start. This patient was in the sham study arm. All other patients from the sham arm continued in part two and received nusinersen. Every patient from the nusinersen group from part one continued the treatment in part two. In Pane et.al. [34] four patients stopped treatment after 6 months, four patients died, one was lost without any particular reason and 14 patients moved to other treatment

in allen 6 Studien berichtet

9 Todesfälle unter Therapie

6 Therapieabbrüche

35 lost to FU

centres. Those who discontinued treatment had reasons such as not having met improvement expectations, burden of procedure or concomitant disease.

Motor endpoints

CHOP INTEND in 4 Studien gemessen, in nur 3 Studien FU berichtet:

100% (von 185 Pts) erreichten ≥ 4 Pkte (MID) Ø +5-8 Punkte bei FU

CHOP INTEND scores were measured at baseline in four studies [30, 32-34]; data at follow-up were reported in three of them [32-34], while one study indicated only motor milestone achievements, without any exact scores on the CHOP INTEND scale [8]. MCID of at least 4 points on the CHOP INTEND scale was reached in all three studies. Motor skills improved from baseline 13.4±9.8 [32], 15.66±13.48 [34] and 19.11±14.28 [33] to +6.6/+14 (at 18 months: 7 patients/ at 24 months: 3 patients) [32], to 21.14±18.23 (+5.48) [34] and to 26.50±18.04 (18-26 months, +7.39) [33]. In Mendonca et.al. [32], at the 12 month follow-up, in patients with disease duration 12-24 month and on invasive respiratory support, there was a decrease of 0.6 points. At 18 and 24-month follow-up, scores increased again, but data was available for less patients. In this study motor milestone achievements showed no improvement for over 70% of patients, less than 10% achieved sitting and 14% achieved head control.

HINE-2 in 4 Studien gemessen, in nur 3 Studien FU berichtet 67-100% ≥ 2 Pkte (MID) Ø +1,5 - ≥ 2 Pkte bei FU

HINE-2 was reported in four studies [8, 30, 32, 34], however, in one study [30] follow-up data was not reported and another study [32] reported no follow-up values, only the proportion of patients reaching at least two points improvement (MCID). Motor skills improved from baseline 7.6±5.4 [8], 0.69±1.23 [34], 0-4 [32] to 13±2/ 15±2 (+5.4 at 22 months: 14 patients /+7.4 at 34 months: 5 patients), and to 2.16±3.58 (+1.47 at 12 months) [34]. Patients reached the MCID threshold in two studies [8, 32]. In the study without exact follow-up values, 1 of 5 patients (20% at 12 months), 1 of 7 (14% at 18 months) and 2 of 3 (67% at 24 months) reached the MCID [32]. In the other study [8], 93% of patients were HINE-2 responders, however 100% of the patients achieved the MCID threshold (the criteria to be classified as HINE-2 responder were stricter).

Quality of life endpoints (respiratory support, nutritional support, caregiver evaluation)

in 5 Studien erhoben, in nur 4 Studien FU berichtet

Respiratory support, both invasive (IV) and non-invasive (NIV), was reported in five studies [8, 31-34], but follow-up data was available only in four of them [31-34]. There was no significant change in the number of patients needing NIV, in one study however, the patients not requiring NIV at baseline (20%) all progressed to needing NIV <16 hours a day [31]. IV via tracheostomy was initiated in some more patients compared to baseline by last follow-up visit in two studies [33, 34].

invasive und nicht-IV Unterstützung der Atmung: bei FU kein Unterschied oder Verschlechterung

Nutritional support was reported in five studies [30-34], in four with follow-up data with no significant change between baseline and follow-up values [31-34].

Unterstützung bei der Nahrungsaufnahme bei FU kein Unterschied

Caregiver evaluations were collected and reported in three studies [8, 32, 34]. Any improvement was reported by caregivers´ and investigators´ evaluation equally (100%), while much improvement was reported more often by caregivers (64%) than by investigators (43%) [8]. In another study overall stability was reported in 11/72 (15%) patients, general increase in function in 61/72 (85%), improvement in motor function in 53/61 (87%), and combination of motor, respiratory and swallowing functions in 8/61 (13%) [34]. In the third evaluation of improvements provided by caregivers a reduction in recurrent infections and a decreased need for secretion aspiration was reported for 60% of patients in need for invasive respiratory support [32].

Evaluation der Betreuer*innen: gewisse Verbesserungen

Safety endpoints

Adverse events were reported in four of the six studies [8, 31-33], most frequently reported AEs were post-puncture headache, post-lumbar puncture syndrome and respiratory tract infections (two studies reported AEs in 100% of patients [8, 31]). Acsadi et. al [8] reported SAEs (64%), however not in detail (which events counted as serious).

unerwünschte Ereignisse: sehr häufig

3.2.2 Nusinersen in SMA type 1 + 2 and type 1 - 3

Five studies (in six publications) were identified for inclusion, of which one study (two publications) enrolled SMA type 1 and 2 [35, 36], and four enrolled SMA type 1 to 3 patients [37-40]. One study was of a retrospective design [35], another one [36] was a prospective observational cohort study with a historical control group, in which the treated SMA cohort was presumably part of the retrospective study's cohort. Four studies were prospective observational single arm studies [37-40]. The five studies included 66 patients with SMA type 1, 161 with SMA type 2 and 33 with SMA type 3.

5 Fallserien mit insgesamt 260 Patient*innen
SMA 1: 66 Pts.
SMA 2: 161 Pts.
SMA 3: 33 Pts.

Mortality, discontinuation

in 4 Studien berichtet

8 Todesfälle unter Therapie

3 Therapieabbrüche

nur 1 lost to FU berichtet, aber viele FU Daten nicht verfügbar

Four studies reported loss to follow-up due to death or other reasons [35, 37-39]. In Audic et.al. [35] six patients died (all SMA type 1), five of them before one year of treatment. Cause of death was reported only for the patient who died after one year of treatment (at 14 months due to cardiomyopathy). In Chachko et.al. [37] one SMA type 1 patient died because the parents opted for palliative care but continued to receive nusinersen and one patient with SMA type 3 had spinal surgery and was excluded from the analysis due to potential negative effects. In Osredkar et.al. [39] one patient died suddenly, probably due to cardiac arrest (the baseline characteristics of the patient were not reported) and one patient discontinued treatment due to not well tolerated nusinersen applications. One further study, Kariyawasam et.al. [38] reported that two patients did not tolerate the functional assessment at follow-up; therefore, data was not available for them. Veerapandiyan et.al. [40] did not report losses to follow-up, however, data was not available for one third of patients for one of the outcomes and 75% of patients for another outcome.

Motor endpoints

wenig einheitliche Berichterstattung in 4 Studien

CHOP INTEND was measured in four studies [35, 37-39], of which one study [35] measured it only for patients < 2 years of age, one study [37] measured it mainly in SMA type 1 patients, and two studies [38, 39] reported only the change from baseline without baseline data. Kariyawasam et.al. [38] used both CHOP INTEND and HFSME scales to define the improvement, as well as stability, but without further detailing how many patients were measured on each of the scales. Osredkar et.al. [39] used CHOP INTEND, HFMS(E), and MFM scores to define the improvement and decline in motor milestones. In Audic et.al. and Chachko et.al. [35, 37], the improvement from baseline to last follow-up exceeded the MCID.

CHOP INTEND SMA 1: Ø +15-16.5 (2 Studien) SMA 2: Ø +9 (1 Studie)

Motor skills improved (measured by CHOP INTEND) in SMA type 1 patients from 35.1 to 50.3 (+15.2 at 12 months: 14 patients <2 years) [35] and from 27.5 to 44.0 (+16.5 at 12 months: 5 patients) [37]. In SMA type 2 patients, motor skills improved from baseline 32.0 to 41.0 (+9 at 12 months: 1 patient) [37].

1 Studie mit SMA 1-3: 33% MID Verbesserungen, 67% stabil
1 Studie mit SMA 1-3 73% Verbesserung 26% keine Verbesserung oder Verschlechterung

In Kariyawasam et.al. [38] (SMA 1-3, age 4 months to 20 years) one third of the patients reached a clinically meaningful improvement, two thirds remained stable. The study did not detail the type of SMA, or the number of SMN2 copies of the patients who reached improvement, nor those of remaining stable. In Osredkar et.al. [39] there was a significant improvement in motor scales after 14 months of treatment in SMA patients type 1 and 2, while type 3 patients showed a trend towards improvement, but it was not statistically significant. 73 % of patients showed improvement, 12% no improvement and 14 % a decline [39].

HINE-2 scores were available in one study (two publications) two studies [35, 36]. In Audic et.al. [35] only for the patients < 2 years of age, for older than 2 years MFM scores were available. In Gomez-Garcia et.al. [36] HINE-2 and MFM scores were reported for the whole cohort. Motor skills improved (measured by HINE-2) in SMA type 1 patients from 7 (range 0-23) to 14.5 (range 7-25) (+7.5 at 12 months: 20 patients <2 years) [35] and in SMA type 1 and 2 from 8±5 to 9±5 (+1 at 14 months: 16 patients, >2 points in 7/16 patients) [35, 36]. The improvement in SMA type 1 patients reached the MCID threshold [35], while in SMA type 1 and 2 patients' HINE-2 scores improved by one point and only 7 of 16 patients (44%) reached the MCID threshold [36].

HINE-2 in 1 Studie gemessen
SMA 1: Ø +7,5
SMA 1+2: Ø +1

MFM scores were reported in Audic et.al. and Gomez-Garcia et.al. [35, 36]. Audic reported the MFM scores only for patients older than two years (68 patients). Motor skills improved (measured by MFM) from 42 (range 4-87) to 47 (range 6-78) (+5 at 12-month follow-up: 68 patients) and from 34±17 to 43±17 (+9 at 14-month follow-up: 30 patients).

MFM in 2 Publikationen
+5 bis +9

HFSME scores were reported in one study [37]; in which patients with SMA type 2 and 3 were evaluated with this scale, while SMA type 1 patients were measured with CHOP INTEND. In this study, SMA type 2 patients did not achieve the MCID of 3 points, however SMA type 3 patients achieved the MCID. Motor skills improved (measured by HFSME) in SMA type 2 patients from 32.0 to 34.0 (+2 at 12 months: 3 patients) and in SMA type 3 patients from 45.0 to 49.0 (+4 at 12 months: 8 patients) [37].

HFSME nur in 1 Studie
SMA 2: Ø +2
SMA 3: Ø + 4

RULM scores were reported in two studies [37, 40]. Results showed a clinically meaningful improvement only in one study in SMA type 2 patients and no improvement in SMA type 3 patients [40] and also no clinically meaningful improvement in the second study [37]. Upper limb functional skills improved (measured by RULM) in one SMA type 1 patient from 9.0 to 10.0 (+1 at 12 months: 1 patient) [37], in SMA type 2 patients from 8.5 to 9.0 (+0.5 at 12 months: 9 patients) and from 11.0 to 16.3 (+5.3 at 17.4 months: 3 patients) [37, 40] and in SMA type 3 patients from 17.5 to 18.4 (+0.9 at 17.4 months: 5 patients) [40].

RULM in 2 Studien berichtet
SMA 2: MID nur in 1 Studie

The 6MWT was used only in one study [40] in only one patient with reported improvement but no exact baseline and follow-up data. The 30-foot walk test, applied in the same study in two patients, did not show any improvements from baseline.

6MWT und 30-foot WT in 1 Studie
kein Unterschied in 30-foot WT, Verbesserung in 6MWT

in 4 Studien erhoben, in nur 3 Studien FU berichtet
IV und nicht-IV Unterstützung der Atmung (SMA 1+2): bei FU kein Unterschied oder Verschlechterung

2 Studien: Unterstützung bei der Nahrungsaufnahme bei FU n.s. Zunahme

Evaluation der Betreuer*innen: gewisse Verbesserungen

Quality of life endpoints (respiratory support, nutritional support, caregiver evaluation)

Respiratory support was reported in four publications (three studies) [35-37, 39], but follow-up data on NIV was not available in one of them [36]. In all studies, non-significant deterioration could be observed in NIV and stagnation in IV. The patients who started needing NIV during study period were SMA type 1 and 2.

Nutritional support baseline and follow-up data were available in two studies [35, 39] and showed non-significant increase in the number of patients requiring support during the follow-up period (two and one more patients requiring feeding support respectively).

Caregiver evaluations were collected and reported in two studies [35, 40]. In Audic et al. [35] the caregivers reported much (46%) or very much (6%) improved condition, no change (13%) or minimal improvement (35%), while worsening was not reported by any of the caregivers. In Veerapandiyan et al. [40] caregivers reported that 67 % of patients achieved improvements in endurance, fine hand movements and hand strengths and louder and clearer speech was reported in 42 % of patients.

Safety endpoints

unerwünschte Ereignisse: sehr häufig

AEs were related mainly to the lumbar puncture itself (comprised technical difficulties due to lumbar puncture, headache, post lumbar puncture syndrome, nausea and vomiting). AEs occurred in 20%-40% of patients [35, 39]. Two studies [36, 39] highlighted that no SAEs occurred.

3.2.3 Nusinersen in SMA type 2 + 3, type 3 and type 2 - 4

8 Fallserien mit insgesamt 341 Patient*innen
SMA 2: 93 Pts.
SMA 3: 245 Pts.
SMA 4: 3 Pts.

Five studies (six publications) were identified for inclusion with SMA type 2 and 3 patients, one study with only SMA type 3 patients, one study with SMA type 3 and 4 and one study with SMA type 2 to 4 patients. The SMA type 2 and 3 cohort in Montes et.al. [42] is part of the cohort reported on by Darras et.al. [41], hence the two studies are considered together. Five publications were prospective observational single arm studies, four publications had a retrospective study design (two of these retrospective studies included a historical control group). The included studies assessed in total 93 patients with SMA type 2, 245 with SMA type 3 and three patients with SMA type 4.

Mortality, discontinuation

Four studies reported loss to follow-up with reasons: one patient died of respiratory failure; five patients discontinued treatment due to lack of perceived benefit and poor tolerability of lumbar puncture and two patients withdrew because of adverse drug reactions (two further patients stopped treatment on patients' wishes without any particular reason).

in 4 Studien berichtet
1 Todesfall unter Therapie
9 Therapieabbrüche

Motor endpoints

CHOP INTEND was measured in one study [45] and only in those patients who were unable to sit at the time of baseline measurement. The scores in SMA type 2 and 3 patients improved but stayed below the clinically meaningful threshold both at 12-month follow-up (from 32.27 to 34.64, +2.37) and at 24-month follow-up to 35.69 (+3.41).

in 1 Studie gemessen
geringfügige Verbesserung: +3,41

HFMSE scores were measured in eight studies, however in one of the studies [46] baseline and follow-up values were not reported, only if there was change or no change in the scores. This study reported on only three of ten patients who received treatment, one of three patients improved (+12 points) and two remained stable at 24-month FU. Another study [44] reported clinically meaningful changes neither for SMA type 2 (at 14 months, +1.2), nor for the SMA type 3 patients (+2.85). Darras et.al. [41] reported an increase of 8.5 points at 28-month FU in SMA type 2 patients (in ten patients), and +10.8 at 38 months (in four patients). The SMA type 3 patients improved only marginally and below the threshold of clinically meaningful results (improved by +1.8 points at 28 months in 14 patients, remained stable at 38 months, however data was available only in six patients) [41]. In Hagenacker et.al. [43] 14-month follow-up showed also a clinically meaningful increase of 3.12 (2.06-4.19) points for the 61 patients who could be followed-up. The number of patients per SMA subtypes was not reported. Mendonca et.al. [45] reported changes below the clinically meaningful threshold, compared to the baseline value of 25.4 in the overall group of patients (SMA type 2 and 3): an increase of 1.47 at 12 months in 30 patients, and an increase of 1.6 at the 24-month follow-up. Results for SMA type 2 and 3 patients evolved differently at the 24-month follow-up: SMA type 2 patients improved by 4.5 points, which is over the MCID threshold, while SMA type 3 patients' scores declined by 1.0 point. Binz et.al. [48] also reported different directions in treatment effect at 14-month follow-up: the baseline value of 27.2 improved by 3.13 points in eight patients, while in seven patients the values decreased by 1.43 point. An improvement of 2.1 points was reported by De Wel et.al. [49] at 14-month follow-up compared to baseline value of 27.3 (19.8) in 16 patients. Five of the 16 patients (31%) experienced clinically meaningful improvement (≥ 3 points). In Yeo et.al [47], the mean improvement in six patients from baseline 35 (range 21-53) was 2 points (range 1-5). An improvement of at least 2 points was reached in three of six patients (50%) at 15-21 months, the other 50% of patients remained stable (with an improvement of 1 to 2 points) at 14-month follow-up.

HFMSE in 8 Studien erhoben

marginale Unterschiede

Stabilisierung, statt Verbesserung

sehr wenige Pts bei langfristigen FU-Erhebungen

kleine Verbesserungen, aber auch Verschlechterungen

Moshe-Lilie et.al. [46] reported MRC scores without baseline and FU values, only the change in the proportion of the maximum possible total score from baseline to FU. This increased by 2.5 and 3.9% at 12 and 24-month FU, respectively. One other study, De Wel et.al. [49] also used MRC scores as a measurement tool and reported a change of 2.5 points at 14-month FU.

MRC in 2 Studien

1 Studie berichtet zu Ansprechen in HFSME und RULM:

SMA 2: 20%
SMA 3: 51%

Motor milestone achievements in general were reported in one study [44], which defined HFMSE and RULM responders as having achieved at least a 3-point change and at least a 2-point change on the respective scale. HFMSE responders in SMA 2 patients were one of five patients (20%), in the SMA 3 patients it was 24 of 46 patients (51%). Within the subgroups of sitters and walkers in SMA 3 patients, this meant that 58% of the sitters and 48% of the walkers responded to the therapy. Considering RULM responders in the same subgroups, in the sitter group 52% of patients respond to therapy, in the walker subgroup, however only 16%.

RULM in 6 Studien erhoben

Stabilisierung, statt Verbesserung

sehr wenige Pts bei langfristigen FU-Erhebungen

RULM was measured in six studies. Two studies reported results per SMA type subgroups [41, 44]. Maggi et.al. [44] presented baseline data on 114 patients, however data was available only on 65 patients 14-month follow-up. The follow-up results did not reach MCID in any of the presented subgroups (SMA type 2: +1.6, SMA type 3 sitters and walkers: +1.47/+0.4 at 14 months). Darras et.al. [41] reported an increase of 3 points at 28-month follow-up (ten patients), and 4 points at 38 months (four patients), which are above the MCID for RULM. Hagenacker et.al. [43] reported joint results on SMA 2 and 3 patients. An increase from baseline to the FU-period of 14 months did not reach clinical significance (+1.09). De Wel et.al. [49] reported statistically and clinically non-significant increase (+1.1) at the 14-month follow-up on SMA type 3 and 4 patients jointly.

6 MWT in 5 Studien erhoben

+ 7 bis 98 Meter

6 MWT was reported in five studies. Baseline values ranged from 249-371 meters. Montes et.al. and Darras et.al. [41, 42], reporting on the same cohort, showed 98, respectively 92 meters change at 35 and 38-month follow-up, which exceeded the clinically meaningful improvement of 30 meters. It must be noted that Darras et.al. reported only on SMA type 3 patients, while for the SMA type 2 patients it was stated that one of eleven patients gained the ability to walk and improved 155 meters from baseline to FU. Data was not available on seven patients from the SMA type 3 subgroup at last follow-up visit. Hagenacker et.al. [43] measured the walking distance at 14 month after treatment and from an already higher baseline value patients gained 46 meters walking ability. One study [48] did not report follow-up results, one study [47] indicated that no statistically or clinically meaningful change occurred and one study [49] showed a minor increase of seven meters in walking ability.

5 Studien berichten zur Unterstützung der Atmung;

18-50% Pts brauchen Unterstützung bei Atmung

Quality of life endpoints (respiratory support, nutritional support, caregiver evaluation)

NIV was reported in five studies [44-46, 48, 49], however, follow-up data was not available in any of the studies. IV baseline data was reported in one study [46] but no follow-up data was available. Nutritional support baseline data was available in one study [48] without any follow-up data. The respiratory support baseline data showed that 18-54% of patients required some form of ventilation support.

Caregiver or self-evaluation was recorded in four studies [42, 47-49], fatigues was measured in there studies (in all three differently), activities of daily life was measured by SMAFRS in one study and in another study the SF-36 scale was used. On the SF-36 scale, no significant improvement but some stabilization (no change in 6 of 8 sub scores) could be shown [49]. SMAFRS showed a decline in four of six patients (66%) and stability or improvement in two of six (33%) [47]. The same study showed heterogeneous results in fatigue (measured by the PedsQL multidimensional fatigue scale). The two other studies measuring fatigue both reported improvements: -3.8% at 35 month follow-up (where a positive value represent fatigue) [42] and from baseline 4.31 to 3.87 at 14-month follow-up (measured on the fatigue severity scale, where a score of seven is the maximum and a score over 4 means abnormal fatigue) [48].

4 Studien berichten zu Lebensqualität

zumeist Stabilisierung, Verschlechterung, aber auch kleine Verbesserung (bei wenigen)

heterogene Ergebnisse auch bei Müdigkeit

Safety endpoints

All but two studies reported on safety endpoints [41, 43-47, 49]. Two of the studies highlighted that no serious adverse events occurred [39, 49]. In one of the studies [46], one patient died shortly after treatment initiation due to respiratory failure. Adverse events occurred in 40-100% of patients. The most frequent adverse events were related to the lumbar puncture itself, e.g. headache, lower back pain, post-lumbar puncture syndrome, nasopharyngitis, upper respiratory tract infection, nausea and vomiting.

unerwünschte Ereignisse: sehr häufig (40-100% der Pts)

3.2.4 Onasemnogene abeparvovec in SMA type 1

Three publications were included [50-52]. All three published results of the same study (NCT02122952), analysing 12 SMA type 1 patients with a follow-up of 24 months. One of the three studies [51] compared results of the intervention group with a cohort of untreated SMA type 1 patients and a group of healthy individuals.

1 Studie in 3 Publikationen: 12 SMA 1 Pts. 24 Monate FU

Mortality

None of the patients was lost to follow-up and all treated patients survived the 24-month follow-up period.

keine Todesfälle

Motor endpoints

Regarding change in the CHOP INTEND scores from baseline, all subgroups (early dosing/ low motor group, early dosing/ high motor group, late dosing group) reached the clinically meaningful improvement threshold with the biggest change of +35 points in the early dosing/low motor group and the lowest change of +16.3 points in the early dosing/high motor group. The mean change of the whole treatment group was +28.3 points. All but one patient achieved the milestone sit without support for at least 5 seconds, and nine patients achieved sitting for at least 30 seconds. Those who achieved standing without support (two patients) were the ones who could also walk alone. Al-Zaidy et.al. 2019a [50] added a statement about longer than 24 month follow-up where it is claimed that eleven patients achieved sitting

CHOP INTEND alle Subgruppen große motorische Gewinne: Ø +28,3

nach 24 Monaten: 11/12 können sitzen ≥ 5 Sek 9/12 können ≥ 30 Sek 2/12 stehen ohne Unterstützung

without support for at least 30 seconds and two more patients achieved the milestone standing with support.

Quality of life endpoints (respiratory support, nutritional support, caregiver evaluation)

NIV Beatmung: +3 Pts während Hospitalierung, 0 nach 24 Monaten keine IV Beatmung Unterstützung bei Ernährung: +1 in 24 Monaten

Two patients needed NIV at baseline (both from the late dosing group), which increased to five over the course of the follow-up period during hospitalizations. Upon discharge, the patients did not require support any more. Invasive respiratory support was not needed at both baseline and end of study. Nutritional support was needed in five patients at baseline, which increased to six by the end of the study.

Safety endpoints

100% der Pts haben Nebenwirkungen, davon 10% SAE

In terms of safety, only one of the publications reported adverse events, which occurred in all patients. Of 275 AEs 53 (19%) were serious, however, most of these were not associated with the treatment itself.

3.2.5 Combination therapies: Nusinersen and Onasemnogene abeparvovec in SMA type 1

2 Studien zu Kombinations-therapien: 18 Pts.

Two studies were identified for the assessment of combination therapies [12, 53]. In these two studies eighteen patients were included, all had SMA type 1. They had a follow-up of 19.2 months [53] to 5.2 years [12].

Mortality, discontinuation

keine Todesfälle

No death were reported.

1 Studie: Beginn mit Spinraza® + Zolgensma®

1 Studie: Beginn mit Zolgensma® + Spinraza®

In Harada et.al. [53] five patients were analysed, four of them started treatment with nusinersen and switched to onasemnogene abeparvovec, while one patient started treatment with onasemnogene abeparvovec and switched to nusinersen. The four patients who started with nusinersen completed six to seven courses of nusinersen injections before the switch due to the continued need for respiratory and nutritional support, as well as lack of substantial improvements in speech and bulbar function after the initiation of nusinersen therapy. After six weeks of onasemnogene abeparvovec administration, three of the four patients continued nusinersen again. One patient did not continue nusinersen again because the patient achieved desired motor milestones and CHOP INTEND scores. The patient who started with onasemnogene abeparvovec switched to nusinersen after 2.5 months without any reasons reported for the switch. Mendell et.al. [12] was a

long-term follow-up study called START LTFU, in which patients from the START study who received onasemnogene abeparvovec were eligible to enter. Of the thirteen participants, seven received concomitant nusinersen treatment; six patients remained on onasemnogene abeparvovec. The primary objective of Mendell et.al [12] was to report on the long-term safety of onasemnogene abeparvovec, and not to analyse combination therapies. Thus, the results were not reported separately for the subgroup who received nusinersen as concomitant therapy and for the subgroup who received only onasemnogene abeparvovec.

Motor endpoints and quality of life endpoints (respiratory support, nutritional support, caregiver evaluation)

Harada et.al. [53] reported CHOP INTEND and HINE-2 improvements. All participants (5 patients) improved on the CHOP INTEND scale and reached the MCID threshold ≥ 4 points. HINE-2 improvement data was available in two of five patients, both of them reaching MCID. Regarding motor milestone achievements, at last follow-up visit, 40% of patients were able to sit independently and stand with support, another 40% were able to sit independently, 20% could only control head and kick legs. The study, however, did not report baseline motor functions.

1 Studie (5 Pts): CHOP INTEND + HINE-2
100% MID bei CHOP INTEND
40% MID bei HINE-2
40% sitzen + stehen (mit Unterstützung)

Although in Mendell et.al. [12] the primary endpoints were safety endpoints, the study reported respiratory support and motor milestone achievements for a subset of study participants. The therapeutic dose group achieved no change in respiratory support by the end of the follow-up period and 80% (eight of ten patients) of the patients in this group remained stable in motor milestones. However, the remaining 20% achieved the ability to stand with support. These patients did not receive nusinersen.

1 Studie (13 Pts)
keine Veränderung bei Bedarf nach Beatmung
20% stehen (mit Unterstützung)

Safety endpoints

Mendell et.al. [12] reported serious adverse events in eight patients (62 %), none of which resulted in study discontinuation. Harada et.al. [53] reported one serious (liver failure) and two milder (mild liver enzyme elevations) adverse events. In both studies, all patients survived until last follow-up.

AE/ SAE sind häufig

Table 3-2: Included studies on efficacy and safety of nusinersen in SMA1

Author	Acsadi et. al. 2021 [8]	Aragon-Gawinska et. al. 2020 [30]	Lavie et. al. 2021 [31]	Mendonca et. al. 2021b [32]	Modrzejewska et. al. 2021 [33]	Pane et. al. 2019 [34]
n pts. (SMN2 copy number, n pts)	20 Group continuing Nusinersen: 14 (SMN2 copy number 2: 3, 3: 11) Cross-over group: 6	53 (SMN2 copy number ≤ 2: 28)	20 (SMN2 copy number 2: 13, 3: 1, unknown: 6)	21 (SMN2 copy number 2: 18, 3: 3)	26 (SMN2 copy number 2: 16, 3: 9, 4: 1)	85 (SMN2 copy number 1: 2, 2: 61, 3: 18, unknown: 4)
Non-sitter/sitter/walker at baseline, n	n.r.	32/15/n.r.	20/0/0	n.r.	n.r.	n.r.
Follow-up (m)	28	14	24	6 – 24	18 - 26	12
Loss to follow-up, n	1 pt in the sham group died in Part 1.	2 pts died, 1 withdrawn, 3 lost to FU	2 pts died, 1 stopped treatment (suffered anoxic brain injury)	1 pt died, 14 pts lost to FU at 12 m, 17 pts lost to FU at 24 m	0	85 pts at 12 m FU: 4 pts stopped treatment after 6 m (2 due to not meeting expectations, 1 due to burden of procedure, 1 due to concomitant disease). 4 pts died, 1 missed a follow-up appointment, 14 moved to other centres and their data was not included in the 12 m FU. 4 additional pts were included.
Results						
CHOP INTEND Baseline At FU	n.r.	Baseline: Sitters: 33.7 Non-sitters: 26.9 At FU: 15/47 pts were able to sit independently, scores not reported	n.r.	Baseline: 13.4 ± 9.8 (2-33) At 12 m FU (n=5): +5.9 Pts with disease duration <12 m and on NIV: +12.7 IV: +18 Pts with disease duration 12-24 m and on NIV: +15 IV: -0.6 Pts with disease duration >24 m and on NIV: +3	Baseline: 19.11 ± 14.28 At FU: 26.50 ± 18.04	Baseline: 15.66 ± 13.48 At FU: 21.14 ± 18.23

				IV: +2.7 At 18 m FU (n=7): +6.6 At 24 m FU (n=3): +14		
HINE-2 Baseline (SD or estimation) At FU	Baseline: Group continuing Nusinersen: 7.6 (± 5.4) Cross-over group: 6.7 (± 5.0) At 659-day FU[1]: Group continuing Nusinersen (n=14): 13 ± 2 Cross-over group (n=6): 9 ± 2 At 1018-day FU: Group continuing Nusinersen (n=5): 15 ± 2 Cross-over group: n.r.	Baseline: Sitters: 3.07 Non-sitters: 1.23 At FU: Sitters: n.r. Non-sitters: n.r.	n.r.	Baseline: 0-4 At FU: Improvement of ≥2 points: At 12 m FU: 1/5 pts At 18 m FU: 1/7 pts At 24 m FU: 2/3 pts	n.r.	Baseline: 0.69 ±1.23 At FU: 2.16 ± 3.58
Motor milestone achievements, n (%)	HINE-2 responders: Group continuing Nusinersen: 13/14 (93) Cross-over group: 5/6 (83)	n.r.	n.r.	No improvement: 15/21 (71.4) 2/21 sitting (9.5) 1/21 sitting with support (4.7) 3/21 head control (14.3)	n.r.	n.r.
Respiratory support, NIV, n (%) Baseline At FU	Baseline: Group continuing Nusinersen: 3/14 (21) Cross-over group: 4/7 (57) At FU: n.r.	n.r.	Baseline: <16 h/d: 4/20 (20) ≥16 h/d: 4/20 (20) None: 4/20 (20) At FU: <16 h/d: 8/20 (40) ≥16 h/d: 3/20 (15) None: 0/20 (0) [1 pt died at 18 m]	Baseline: 7/21 (33.3) At FU: 7/21 (5/7 pts reduced daily hrs of NIV, 1/7 pts increased hrs)	Baseline: 5/26 (19.2) >16 h/d: 13/26 (50) At FU: 5/26 (19.2) >16 h/d: 11/26 (42.3)	Baseline: <10 h/d: 8/85 (9.4) >10 h/d: 19/85 (22.3) At FU: <10 h/d: n.r. >10 h/d: 20/85 (23.5).

[1] Since exact numbers are not reported in Acsadi et.al. 2021, the numbers are based on estimations from Figure 2, C in [8]

Respiratory support, IV, n (%) Baseline At FU	Baseline: Group continuing Nusinersen: 0 Cross-over group: 0 At FU: Group continuing Nusinersen: 0 Cross-over group: 0	n.r.	Baseline: ≥16 h/d: 8/20 (40) via tracheostomy At FU: 7/20 (35) [1 pt died 36 months]	Baseline: 14/21 (66.6) At FU: 14/21 (1/14 pt reduced daily hrs of IV)	Baseline: 13/26 (50) via tracheostomy At FU: 16/26 (61.5) via tracheostomy	Baseline: 8/85 (9.4) via tracheostomy At FU: 10/85 (11.7) via tracheostomy
Nutritional support, n (%) Baseline At FU	n.r.	Baseline: Sitters: 13/15 (86.7) gastrostomy Non-sitters: 22/32 (68.7) (9 nasogastric tube, 13 gastrostomy) At FU: n.r.	Baseline: Oral feeding: 7/20 (35) Gastrostomy tube: 12/20 (60) Nasogastric tube: 1/20 (5) At FU: Died: 2/20 (10) Improved: 1/20 (5) No improvement: 16/20 (80)	Baseline: 18/21 (85) gastrostomy alone 2/21 (9.5) gastrostomy + oral feeding 1/21 (5.5) oral feeding At FU: No changes.	Baseline: 15/26 (57.7) required nasogastric tube or gastrostomy At FU: 13/26 (50)	Baseline: 42/85 (49.4) inserted/ planned gastrostomy At FU: 49/85 (57.6) required gastrostomy
Caregiver evaluation/subjective improvements	Caregiver evaluation (CGI-I) vs. Investigator evaluation[2] of the continuing Nusinersen group: Much improvement: 64% vs. 43% Any improvement: 100% vs. 100% No worsening: 100% vs. 100% Caregiver evaluation (CGI-I) vs. Investigator evaluation of the cross-over group:	n.r.	n.r.	Reduction in recurrent pulmonary infections and decreased need for secretion aspiration throughout the day: 60% of IV pts	n.r.	Decrease in function: 0 Overall stability: 11/72 General increase in function: 61/72 Overall perception of improvement due to: Improvement in motor function: 53/61 (85.24[3]%); Combination of factors including motor, respiratory, and swallowing: 8/61 (13.11%)

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

[3] Own calculation: 86.9% (as opposed to 85.24% calculated by study authors).

	Much improvement: 83% vs. 17% Any improvement: 100% vs. 100% No worsening: 100% vs. 100%					
Adverse events, n (%) Any AE SAE	Group initially randomized to Nusinersen: 14/14 (100) Cross-over group: 6/6 (100) No disconinuation or withdrawal SAEs: Group initially randomized to Nusinersen: 9/14 (64) Cross-over group: 4/6 (67)	n.r.	Respiratory complications: 0 Routine MIE in 20/20 (100) pts	Temporary intubation due to sedation during drug infusion: 1/4 pts (25) Post-puncture headache: 3/140 procedures (2.4)	Post-lumbar puncture syndrome: in 4/26 pts (15.38) Respiratory tract infection: 4/26 (15.38) Increased liver enzymes after gastrointestinal infections: 2/26 (7.69) Unsealed puncture site with temporary CFS leakage: 2/26 (7.69)	n.r.

6 MWT = 6-minute walk test, AE = adverse event, CFS = cerebrospinal fluid, CGI-I = Clinical Global Impression – Improvement scale, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, HINE-2 = Hammersmith Infant Neurological Examination Modul 2, IV = invasive ventilation, MIE = mechanical insufflation-exsufflation, NIV = non-invasive ventilation, n = number, n.r. = not reported, m = month, SAE = serious adverse event, SMA = spinal muscular atrophy

Table 3-3: Included studies on efficacy and safety of nusinersen in SMA 1+ 2

Authors	Audic et. al. 2020 [35]	Gómez-García et. al. 2021[4] [36]
n pts. (SMA type n pts) (SMN2 copy number, n pts)	123 (34 SMA1, 89 SMA2) (SMN2 copy number 2: 18, 3: 96 4: 3, unknown: 6)	30 Nusinersen group: 16 (2 SMA1, 14 SMA2), (SMN2 copy number 3: 16) (historical) control group: 14
Non-sitter/sitter/walker at baseline, n	n.r.	2/14/n.r.
Follow-up (m)	12	14
Loss to follow-up, n	5 SMA1a/b pts died before 1 y of treatment, 1 SMA 1c died after 1 y of treatment	n.r.
Results		
CHOP INTEND Baseline At FU	Baseline: Pts <2 y (n=14): 35.1 At FU: Pts <2 y (n=14): 50.3	n.r.
HINE-2 Baseline At FU	Baseline: Pts <2 y (n=20): 7 (0–23) At FU: Pts <2 y (n=20): 14.5 (7-25)	Baseline: Nusinersen group: 8 ± 5 Control group: n.r. At FU: Nusinersen group: 9± 5 (7 pts > 2 points) Control group: n.r.
MFM Baseline At FU	Pts >2 y (n=68) Baseline: 42 (4-87) At FU: 47 (6-78)	Baseline: Nusinersen group: 34 ± 17 Control group: n.r. At FU: Nusinersen group: 43 ± 17 Control group: n.r.
Respiratory support, NIV, n (%) Baseline At FU	Baseline: 45/123 (36.6) At FU: 47/123 (38.2)	Baseline: Nusinersen group: 9/16 (56.25) Control group: 6/14 (42.8) At FU: Nusinersen group: n.r.

[4] Nusinersen treated cohort (n=16) potentially part of the cohort of 123 pts in Audic et.al. [35]. Audic et.al. claims that all French pts were screened and the two centres participating in the study by Gomez-Garcia et.al. were part of the French centres where those pts were screened.

		Control group: n.r.
Respiratory support, IV, n (%) Baseline At FU	n.r.	Baseline: Nusinersen group: 1/16 (6.25) via tracheostomy Control group: n.r. At FU: Nusinersen group: n.r. Control group: n.r.
Nutritional support, n (%) Baseline At FU	Baseline: 14/123 (11.4) At FU: 16/123 (13)	Baseline: Nusinersen group: 2/16 (12.5) Control group: n.r. At FU: Nusinersen group: n.r. Control group: n.r.
Caregiver evaluation/subjective improvements	Minimally, much or very much worse (ratings 5, 6, 7) condition: 0 % No change (rating 4): 13% Minimal improvement (rating 3): 35% Much improved condition (rating 2): 46% Very much improved condition (rating 1): 6%	n.r.
Adverse events, n (%) Any AE SAE	95 AEs in 25/123 (20) pts: technical difficulties in lumbar puncture 55/95 (57.9) with fluoroscopic guidance required in 17 cases, headache 23/95 (24.2), post lumbar puncture syndrome 6/95 (6.3), nausea and vomiting 4/95 (4.2), asthenia 4/95 (4.2), back pain 2/95 (2.1), fever 1/92 (1)	AE: n.r. SAEs: 0

AE = adverse event, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, HINE-2 = Hammersmith Infant Neurological Examination Module 2, IV = invasive ventilation, NIV = non-invasive ventilation, n = number, n.r. = not reported, m = month, MFM = motor function measurement, SAE = serious adverse event, SMA = spinal muscular atrophy, y = year

Table 3-4: Included studies on efficacy and safety of nusinersen in SMA 1 - 3

Author	Chachko et.al. 2021 [37]	Kariyawasam et. al. 2020 [38]	Osredkar et. al. 2020 [39]	Veerapandiyan et. al. 2020 [40]
n pts. (SMA type n pts) (SMN2 copy number, n pts)	28 (7 SMA1,12 SMA2, 9 SMA3) (SMN2 copy number 2: 4, 3: 23, 4: 1)	20 (6 SMA1, 10 SMA2, 4 SMA3) (SMN2 copy number 2: 3, 3: 16)	61 (16 SMA 1, 32 SMA 2, 13 SMA 3) (SMN2 copy number 2: 11, 3: 38, 4: 12)	12 (1 SMA1, 4 SMA2, 7 SMA3) (SMN2 copy number 2: 2, 3: 2, 3-4: 1, 4: 1, unknown: 6)
Non-sitter/sitter/walker at baseline, n	n.r.	5/13/2	55/6[5]	9/3[6]
Follow-up (m)	12	13.8 (4–33.5)	14	17.4 (4–26)
Loss to follow-up, n	1 pt died, 1 lost-to follow-up	2 pts lost-to follow-up/ did not tolerate the functional assessment at FU	1 pt died, 1 discontinued treatment	n.r.
Results				
CHOP INTEND Baseline At FU	Baseline: 5/6 SMA1pts: 27.5 1/12 SMA2 pts: 32.0 At FU: 5/6 SMA1 pts: 44.0 1/12 SMA2 pts: 41.0	n.r.	n.r.	n.r.
HFSME Baseline At FU	Baseline: 3/12 SMA2 pts: 32.0 8/8 SMA3 pts: 45.0 At FU: 3/12 SMA2 pts: 34.0 8/8 SMA3 pts: 49.0	n.r.	n.r.	n.r.
Motor milestone achievements, n (%)	n.r.	CHOP INTEND or HFSME change from baseline[7]: 5/20 pts. (25): non-sitters 13/20 pts. (65): sitters	Imrovement: 43/59 (72.9) No overall improvement: 7/59 (11.9) Decline: 8/59 (13.6) Geometric means: baseline and at FU SMA1: 17 (±5.1) – 27.5 (± 4.7) SMA2: 30.0 (±2) – 33.8 (±2.1)	n.r.

[5] Defined as non-ambulatory/ambulatory, without any further definition of the terms.

[6] Defined as non-ambulatory/ambulatory, without any further definition of the terms.

[7] ≥4-point increase or decrease on CHOP INTEND scale or ≥3-point increase or decrease on HFSME scale defined as improvement. Stability defined as change < 4 resp. < 3 points.

		2/20 pts (10): walkers (independently or with support) At FU: Remained stable: 12/18 (67) Improvement: 6/18 (33)	SMA3: 65.8 (±1.6) – 78.0 (±1.3)	
RULM Baseline At FU	Baseline: 1/6 SMA1 pts: 9.0 9/12 SMA2 pts: 8.5 At FU: 1/6 SMA1 pts: 10.0 9/12 SMA2 pts: 9.0	n.r.	n.r.	Baseline (n=7): 14.7± 9.9 SMA2 pts (n=3): 11.0 SMA3 pts (n=4): 17.5 At FU (n=8): 17.6 ± 8.9 SMA2 pts (n=3): 16.3 SMA3 pts (n=5): 18.4
Respiratory support, NIV, n (%) Baseline At FU	Baseline: NIV at night: 11/28 (39.3) At FU: NIV at night: 16/26 (61.5)	n.r.	Baseline: NIV at night: 8/61 (13.1) NIV at night and day: 4/61 (6.6) At FU: NIV at night: 11/61 (18.0) NIV at night and day: 5/61 (8.1)	n.r.
Respiratory support, IV, n (%) Baseline At FU	Baseline: 0/28 (0) At FU: 0/28 (0)	n.r.	Baseline: SMA 1: 4/61 (6.6) At FU: SMA 1: 4/61 (6.6)	n.r.
Nutritional support, n (%) Baseline At FU	n.r.	n.r.	Baseline: 8/61 (13.1) At FU: 9/61 (14.7)	n.r.
6 MWT, 30 foot walk test Baseline At FU	n.r.	n.r.	n.r.	6 MWT (n=1): Improvement from baseline to FU. 30 foot walk test (n=2): No improvement from baseline to last FU.
Caregiver evaluation/subjective improvements	n.r.	n.r.	n.r.	Most frequently reported improvements: Endurance, fine hand movements/hand strength: 8/12 (66.6) Louder and clearer speech: 5/12 (41.6)

Adverse events, n (%) Any AE SAE	n.r.	n.r.	AEs: 24/61 pts (39.3): lumbar pain: 10/61 (16.4), headache: 8/61 (13.1), cerebral spinal fluid leakage: 4/61 (6.5), vomiting: 4/61 (6.5), irritability: 2/61 (3.3), rash at the site of LP: 1/61 (1.6), leg paraesthesia: 1/61 (1.6) SAEs: 0	Post LP headache: 8/87 (9) in 5 pts (2 pts had >1 occurrence); Site pain post LP: 5/87 (5.7) in 4 pts, No headache, site pain, bleeding, or infection was reported with cervical punctures. 1 patient developed a generalized tonic clonic seizure, and was determined to have primary generalized epilepsy.

6 MWT = 6-minute walk test, AE = adverse event, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, HFSME = Hammersmith Functional Motor Scale Expanded, LP = lumbar puncture, IV = invasive ventilation, n = number, NIV = non-invasive ventilation, n.r. = not reported, m = month, RULM = Revised Upper Limb Module, SAE = serious adverse event, SMA = spinal muscular atrophy

Table 3-5: Included studies on efficacy and safety of nusinersen in SMA 2+ 3

Author	Darras et. al. 2019 [41] (ISIS-396443-CS2: NCT01703988, NCT02052791)	Montes et. al. 2019 [42] (ISIS-396443-CS2: NCT01703988, NCT02052791)	Hagenacker et. al. 2020 [43]	Maggi et. al. 2020 [44]	Mendonça et al. 2021a [45]	Moshe-Lilie et. al. 2020 [46]
n pts. (SMA type n pts) (SMN2 copy number, n pts)	28 (11 SMA2, 17 SMA3) (SMN2 copy number 2: 1, 3: 21, 4: 6)	14 (1 SMA2, 13 SMA3) (SMN2 copy number 2: 9, 3: 5)	173 (at 14 m FU: 20 SMA2, 37 SMA3) (SMN2 copy number 2: 4, 3: 21, 4: 21, unknown:11)	116 (13 SMA 2, 103 SMA 3) (SMN2 copy number 2: 5, 3: 36, 4: 54, unknown: 21)	78 (34 SMA2, 44 SMA3) Nusinersen group: 41 (SMN2 copy number 2: 3, 3: 25, 4: 2) Control group (historical cohort of untreated SMA pts): 37 (SMN2 copy number 3: 32, 4: 5)	22 (9 SMA2, 13 SMA3) Nusinersen group: 10 Control group: 12 (SMN2 copy number 3: 13, 4: 5, unknown: 4)
Non-sitter/sitter/walker at baseline, n	0/28/13	0/14/13	n.r.	SMA 3 pts: 0/51/52	n.r./n.r.[8]/7 in the Nusinersen group and 6 in the control group	20/2[9]
Follow-up (m)	32	35	14	14	24	24
Loss to follow-up, n	4 pts did not complete treatment. No patient discontinued treatment due to AEs.	n.r.	61 pts remained for 14 m FU. 2 pts withdrew on pts' wish, 2 pts withdrew due to adverse drug reactions, for the rest of the missing pts no reason described.[10]	2 pts stopped due to lack of benefit and tolerability of lumbar puncture	At 24 m 4 pts were lost in the Nusinersen group without any particular reason. No patient discontinued treatment due to AEs.	1 pt died of respiratory failure after treatment, 3 pts. discontinued treatment due to lack of improvement
Results						
CHOP INTEND Baseline	n.r.		n.r.	n.r.	Baseline: Nusinersen group (n=11): 32.27 (5.78)	n.r.

[8] Formally not reported, but authors state that patients were evaluated with CHOP INTEND if they were unable to sit. That is at least 11 patients.

[9] Defined as non-ambulatory/ambulatory, without any further definition of the terms.

[10] In the 6 m analysis 124 pts were included, SMA type 1: 2, SMA type 2: 45, SMA type 3: 77, SMA type 4:0. SMN2 copy numbers of the 124 pts are 2: 7, 3:48, 4: 41, 5: 2, 6: 2 and unknown: 24).

At FU					Control group (n=37): n.r. At 12 m FU: Nusinersen group (n=11): 34.64 (6.91) Control group (n=37): n.r. At 24 m FU: Nusinersen group (n=7): 35.69 Control group (n=37): n.r.	
HFMSE Baseline At FU	n.r.	Baseline: n.r. At FU: Nusinersen group (n=3): Improvement of 12 points: 1/3 pts Stable: 2/3 pts Control group: n.r.	Baseline: 24.65 (21.83) At 14 m FU: +3.12 (2.06–4.19) 27.77 (23.47)	Baseline (n=116): 22.5 (0–64) SMA 2 (n=13): 0 (0-9) SMA 3 sitters (n=51): 9 (0-40) SMA 3 walkers (n=52): 50.5 (17-64) At 14 m FU (n=49): SMA 2 (n=5): +1.2 (2.68) SMA 3 sitters (n=19): +3.53 (3.67) SMA 3 walkers (n=27): +2.37 (2.22) SMA3 total (n=46): +2.85 (2.93)	Baseline: Nusinersen group (n=30): 25.4 (17.2) Control group (n=37): 24.9 (18.0) At 12 m FU: Nusinersen group: 26.87 SMA 2: +3.12 (1.26) SMA 3: no change Control group: 23.19 SMA 2: −1.45 (0.9) SMA 3: -2.0 (0.12) At 24 m FU: Nusinersen group: 27 SMA 2: +4.5 (1.91) SMA 3: −1.0 (0.58) Control group: 20.97 SMA 2: −3.4 (0.24) SMA 3: −4.65 (0.19)	Baseline: 38.0 (3.3) SMA2: 21.3 (2.9) SMA3: 48.9 (3.0) At 28 m (850 d) FU SMA2 (n=10): + 8.5 SMA3 (n=14): +1.8 At 38 m (1150 d) FU: SMA2 (n=4): + 10.8 (4.3) SMA3 (n=6): +1.8 (0.9)
Motor milestone achievements, n (%)	n.r.		n.r.	HFMSE responders[11]: 25/51 (49) pts: SMA2: 1/5 (20) SMA3: 24/46 (51) (sitters: 11/19, walkers: 13/27) RULM responders[12]: 17/49 (35) pts: SMA2: 3/5 (60)	n.r.	n.r.

[11] at least 3-point HFMSE change from baseline

[12] at least 2-point RULM change from baseline

				SMA3: 14/44 (32) (sitters: 10/19, walkers: 4/25)		
MRC Baseline At FU	n.r.		n.r.	n.r.	n.r.	Baseline and FU data: n.r. Change (%) in the proportion of a maximum possible total score from baseline to FU: Nusinersen group: +2.5% at 12 m FU, +3.9% at 24 m FU Control group: decline in 3 pts: 2.5% to 3.8%
RULM Baseline At FU	n.r.	Baseline (n=10): SMA2: 11.9 (0.9) SMA3: 16.0 (1.2) At 28 m (850 d) FU: SMA2+ 3 (n=10): +3 At 38 m (1150 d) FU: SMA2+ 3 (n=4): + 4.0 (2.4)	Baseline: 23.85 (12.16) At 14 m FU: +1.09 (0.62–1.55) 23.95 (12.42)	Baseline (n=114): 29 (0–37) SMA2 (n=12): 2.5 (0-22) SMA3 sitters (n=51): 20 (0-34) SMA3 walkers (n=51): 37 (25-37) At 14 m FU (n=49): SMA2 (n=5): +1.6 (1.52) SMA3 sitters (n=19): +1.47 (2.5) SMA3 walkers (n=25): +0.4 (1.83) SMA3 total (n=44): +0.86 (2.18)	n.r.	n.r.
6 MWT (m) (median, range) Baseline At FU	Baseline: 250.5 (0–563) At 35 m (1050 d) FU: + 98.0	Baseline (n=12): SMA3: 253.3 (50.7) At 38 m (1150 d) FU: SMA3 (n=5): + 92.0 (21.5) SMA2: 1/11 pts gained ability to walk (+154.5 from baseline)	Baseline: 371.43 (210.34) At 14 m FU: +46 (25.4–66.6) 403.0 (225.7)	n.r.	n.r.	n.r.

Respiratory support, NIV n (%)	n.r.		n.r.	Baseline: 21 (18.1) At FU: n.r.	Baseline: Nusinersen group, nightly ventilation: 22/41 (53.6) Control group: n.r. At FU: Nusinersen group: n.r. Control group: n.r.	Baseline: Nusinersen group: 4/10 (40) Control group: 4/12 (33.3) At FU: Nusinersen group: n.r. Control group: n.r.
Respiratory support, IV, n (%)	n.r.		n.r.	n.r.	n.r.	Baseline: Nusinersen group: 2/10 (20) Control group: 0/12 (0) At FU: Nusinersen group: n.r. Control group: n.r.
Nutrirional suppport, n (%)	n.r.		n.r.	n.r.	n.r.	n.r.
Caregiver evaluation/subjective improvements	n.r.	Fatigue: Baseline: 38.2 (47.1) At 35 m (1050 d)FU: -3.8%	n.r.	n.r.	n.r.	n.r.
Adverse events, n (%) Any AE SAE	28/28 (100) pts had ≥1 AE. The most common AEs: post-LP syndrome: 16/28 (57), headache: 13/28 (46), nasopharyngitis: 12/28 (43), upper respiratory tract infection: 12/28 (43), puncture site pain: 11/28 (39), back pain: 9/28 (32), scoliosis: 8/28 (29), pyrexia: 7/28 (25), joint contracture: 6/28 (21), rhinorrhea: 6/28 (21), vomiting: 6/28 (21).	n.r.	AE in 82/173 (47%) Most frequent AEs: headache: in 61/173 (35) pts, back pain: in 38/173 (22) pts, nausea: 19/173 (11) pts SAEs: 0	AEs in 48/116 (41.4) pts: Postprocedure headache (observed at least once): in 43/116 (37.1) pts Lumbar pain: in 10/116 (8.6) pts Renal colic: in 1/116 (0.9) pts	13 AEs, mainly post-puncture headache and lower back pain. In the group where sedation was used: 2 episodes of respiratory depression and 2 episodes of extreme tachycardia (>180 bpm).	Post-puncture headache: 5 pts; Bacterial meningitis requiring hospital admission and long-term antibiotics: 1 pt. Death due to respiratory failure (due to pneumonia) shortly after treatment initiation: 1 Recurrent pneumonia: 3 (patients stopped treatment)

	SAEs: in 5/28 (18) pts: post-LP syndrome: 2/5, lower respiratory tract infection, respiratory distress, and viral pneumonia: 1/5, acute respiratory failure and respiratory syncytial viral pneumonia: 1/5, vesicoureteral reflux and pyelonephritis: 1/5					

6 MWT = 6-minute walk test, AE = adverse event, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, HFSME = Hammersmith Functional Motor Scale Expanded, LP = lumbar puncture, IV = invasive ventilation, n = number, NIV = non-invasive ventilation, n.r. = not reported, m = month, MRC = Medical Research Council, RULM = Revised Upper Limb Module, SAE = serious adverse event, SMA = spinal muscular atrophy

Table 3-6: Included studies on efficacy and safety of nusinersen in SMA 2-4

Author	Binz et. al. 2020 [48]	De Wel et. al. 2020 [49]	Yeo et. al. 2020 [47]
n pts. (SMA type n pts) (SMN2 copy number, n pts)	18 (6 SMA 2, 11 SMA 3,1 SMA 4) (SMN2 copy number ≥4: 10, <4: 8)	16 (14 SMA 3, 2 SMA 4) (SMN2 copy number 3: 13, 4: 2, 5: 1)	6 (6 SMA 3) (SMN2 copy number ≥3: 6)
Non-sitter/sitter/walker at baseline, n	9/9[13]	9/7[14]	n.r./4[15]
Follow-up (m)	14	14	17 (14-21)
Loss to follow-up, n	0	0	0
Results			
CHOP INTEND Baseline At FU	n.r.	n.r.	n.r.
HFSME Baseline At FU	Baseline: 27.2 (25.3) At FU: Improvement (n=8): +3.13 (4.05) Stable/ deteriorating (n=7): -1.43 (1.4)	Baseline: 27.3 ± 19.8 At FU: 29.4 ± 19.9	Baseline: 35 (21-53) At FU: Improvement of >2 points (15-21 m FU): 3/6 pts (50), Stable (improvement of 1 to 2, 14 m FU): 3/6 pts(50) Mean HFMSE improvement (14 m FU): 2 (1- 5)
MRC Baseline At FU	n.r.	Baseline: 36.9 ± 10.3 At FU: 39.4 ± 8.40	n.r.
RULM Baseline At FU	Baseline (n=18): 23.4 (11.8) At FU (n=14): No change: 11/14 (78.6) Improvement: 3/14 (21.4)	Baseline: 27.1 ± 8.10 At FU: 28.2 ± 8.41	Baseline: 31.5 (22-37) At FU: Improvement of >2 (15-18 m FU): 2/6 pts (33) Stable (improvement of 0 to 2): 4/6 pts (67) Mean RULM improvement (14 m FU): 1.8 (0-3)

[13] Defined as non-ambulatory/ambulatory, where ambulatory means being able to walk without support for at least 10 meters.

[14] Defined as non-ambulatory/ambulatory, without any further definition of the terms.

[15] Defined as functional non-ambulatory/ambulatory, where ambulatory means being able to walk with or without support for at least 10 meters.

6 MWT (m)/ 10 MWT (s) Baseline At FU	6 MWT: Baseline (n=9): 345.4 (169) At FU: n.r.	6MWT: Baseline: 296 ± 199 At FU: 303 ± 211	Baseline: 6 MWT: 249 (74-429) 10 MWT: 10 (6-19) At FU: no statistically or clinically meaningful change.
Respiratory support, NIV n (%)	Baseline: 4 (22.2) At FU: n.r.	Baseline: 3 (18.8) At FU: n.r.	n.r.
Respiratory support, IV, n (%)	n.r.	n.r.	n.r.
Nutrirional suppport, n (%)	Baseline: 1 (5.6) via PEG At FU: n.r.	n.r.	n.r.
Caregiver evaluation/ subjective improvements	Fatigue (FSS)(n=15): Baseline: 4.31 At FU (n=14): 3.87	SF-36: n.s. improvement Stabilization: no change in 6/8 subscores	Activities of daily living (measured by SMAFRS): Decline: 4 pts Stability or improvement: 2 pts Fatigue (PedsQL Multidimensional Fatigue Scale): no trend, heterogeneous results
Adverse events, n (%) Any AE SAE	n.r.	255 AEs[16]: Back pain: 72 (28.2) Headache: 28 (11) Post LP headache: 11 (4.3) Blood patch: 3 (1.2) Fatigue: 45 (17.6) Increased appetite: 25 (1) Myalgia: 21 (8.2) Agitation: 22 (8.6) Nausea: 12 (4.7) Dizziness: 10 (3.9) Proteinuria: 6 (2.3) SAE: 0	12 AEs in 6/6 (100) pts: Post LP headache, fall related injuries, recurrent pressure sores, recurrent cellulitis due to chronic lymphedema SAEs: 2

6 MWT = 6-minute walk test, AE = adverse event, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, HFSME = Hammersmith Functional Motor Scale Expanded, LP = lumbar puncture, IV = invasive ventilation, n = number, NIV = non-invasive ventilation, n.r. = not reported, m = month, MRC

[16] The percentages are own calculations (occurrence of each AE/total number of AEs). De Wel et. al. calculated the occurrence of each AE in relation to the total number of administered Nusinersen injections.

= Medical Research Council, PedsQL = Pediatric Quality of Life, PEG = percutaneous gastrostomy tube, RULM = Revised Upper Limb Module, SAE = serious adverse event, SMA = spinal muscular atrophy, SMAFRS = Spinal Muscular Atrophy Functional Rating Scale

Table 3-7: Included studies on efficacy and safety of onasemnogene abeparvovec in SMA1

Author	Al-Zaidy et. al. 2019 a [50] (NCT02122952)	Al-Zaidy et. al. 2019 b [51] (NCT02122952)	Lowes et. al. 2019 [52] (NCT02122952)
n pts. (SMN2 copy number, n pts)	12 (SMN2 copy number 2: 12)	55 (AVXS-101 group: 12, Untreated SMA1 group: 16, Healthy group: 27)	12 (Early dosing/low motor group: 3, Late dosing group: 6, Early dosing/high motor group: 3) (SMN2 copy number 2: 12)
Non-sitter/sitter/walker at baseline, n	n.r.		
Follow-up (m)	24		
Loss to follow-up, n	0		
Results			
CHOP INTEND Baseline At FU	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: 56.5 Untreated SMA1 group: 5.3 ≥4.0 point improvement: AVXS-101 group: 12/12 (100) 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)
Motor milestone achievements, n (%)	Sit without support for ≥5 s and full head control: 11/12 (92) Sit without support for ≥10 s: 10/12 (83) Sit without support for ≥30 s: 9/12 (75) Able to roll: 9/12 (75) Able to crawl, pull to stand, stand and walk independently: 2/12 (17) Continued long-term FU (>24 m): Sit without support for ≥30 s: 11/12 (92), able to stand with support: 4 /12 (33)	AVXS-101 group: Sit without support for ≥5 s: 11/12 (92) Sit without support for ≥10 s: 10/12 (83) Sit without support for ≥30 s: 9/12 (75) Stand without support: 2/12 (17) Walk alone: 2/12 (17) Untreated SMA1 group: Sit without support for ≥5 s: 0/16 (0) Sit without support for ≥10 s: 0/16 (0) Sit without support for ≥30 s: 0/16 (0) Stand without support: 0/16 (0) Walk alone: 0/16 (0)	Sit without support for ≥5 s: 11/12 (92) Sit without support for ≥30 s: 9/12 (75) Stand without support: 2/12 (16.7)
Survival, n (%)	12/12 (100)	AVXS-101 group: 12/12 (100) Untreated SMA1 group: 8/16 (50) Healthy group: n.r.	12/12 (100)

Respiratory support, NIV, n (%) Baseline At FU	Baseline: 2/12 (17) Over the FU period: 5/12 (41.7)* *3 pts required NIV during hospitalization and returned to no support upon discharge	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: 2/3 (66.7) Late dosing group: n.r. Early dosing/high motor group: n.r.
Respiratory support, IV, n (%) Baseline At FU	Baseline: 0 (0) At FU: 0 (0)	n.r.	n.r.
Nutritional support, n (%) Baseline At FU	Baseline: 5/12 (42) At FU: 6/12 (50)	Baseline: AVXS-101 group: 5/12 (42) Untreated SMA1 group: 7/12 (44) Healthy group: 1/12 (4) At FU: n.r.	Baseline: Early dosing/low motor group: 3/3 (100) Late dosing group: 2/6 (33.3) Early dosing/high motor group: 0/3 (0) At FU: Early dosing/low motor group: 0/3 (0) Late dosing group: n.r. Early dosing/high motor group: n.r.
Adverse events, n (%) Any AE SAE	n.r.	275 AEs in 12/12 (100) pts, of which 53 SAEs in 10/12 (83) pts. Adverse event associated with treatment: 4 in 3 pts , Most frequent other AEs: Upper respiratory tract infection: 28 in 10 pts, Pyrexia: 12 in 7 pts, Vomiting: 11 in 8 pts, Pneumonia: 14 in 7 pts , Cough: 11 in 5 pts, Rhinovirus infection: 10 in 4 pts	n.r.

AE = adverse event, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, LP = lumbar puncture, IV = invasive ventilation, n = number, NIV = non-invasive ventilation, n.r. = not reported, m = month, SAE = serious adverse event, SMA = spinal muscular atrophy

Table 3-8: Included studies on efficacy and safety of combination therapy of nusinersen and onasemnogene abeparvovec in SMA1

Author	Harada et. al. 2020 [53]	Mendell et. al. 2021 [12]
n pts. (SMN2 copy number, n pts)	5 (1 pt started with onasemnogene abeparvovec and continued with Nusinersen, 4 pts started with nusinersen and continued with onasemnogene abeparvovec, 3 of them returned to Nusinersen) (SMN2 copy number 2: 5)	13 (Low dose group: 3, Therapeutic dosing group: 10) (SMN2 copy number 2: 13)
Non-sitter/sitter/walker at baseline, n	n.r.	n.r.
Follow-up (m)	19.2 (8-27.5)[17]	5.2 (4.6-6.2) yrs
Loss to follow-up, n	0	0
Results		
CHOP INTEND (range) Baseline At FU	Baseline (n=2): 15-18 At last FU (n=5): ≥ 4 point improvement: 5 (100)	n.r.
HINE-2 (range) Baseline At FU	Baseline (n=2): 0-2 At last FU (n=2): Improvement: 8-10	n.r.
Motor milestone achievements, n (%)	Able to sit independently, stand with support: 2/5 (40) Able to sit independently: 2/5 (40) Able to control head and kick legs: 1/5 (20)	Therapeutic dose group: Achieved to stand with support: 2/10 (20) Stable/ no decline: 8/10 (80)
Survival, n (%)	5/5 (100)	13/13 (100)
Respiratory support, NIV, n (%) Baseline At FU	Baseline: 3/5 (60) At FU: n.r.	Baseline: Low dose group: n.r. Therapeutic dose group: 4/10 (40) At FU: Low dose group: n.r. Therapeutic dose group: 4/10 (40)
Respiratory support, IV, n (%) Baseline At FU	Baseline: 2/50 (40) At FU: n.r	Baseline: Low dose group: n.r. Therapeutic dose group: 0/10 (0) At FU: Low dose group: 1/3 (0)* Therapeutic dose group: 0/10 (0)*

[17] Own calculation.

		*defined as permanent ventillation
Adverse events, n (%) Any AE SAE	Milder liver enzyme elevantions/transient thrombocytopenia: 2/5 (40) Liver failure: 1/5 (20)	SAEs in 8/13 pts (62), none of which resulted in study discontinuation. The most frequently reported SAEs: acute respiratory failure 4/13 (31), pneumonia 4/13 (31), dehydration 3/13 (23), respiratory distress 2 (15), bronchiolitis 2 (15)

AE = adverse event, CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, FU = follow-up, HINE-2 = Hammersmith Infant Neurological Examination Module 2, IV = invasive ventilation, n = number, NIV = non-invasive ventilation, n.r. = not reported, m = month, SAE = serious adverse event, SMA = spinal muscular atrophy

4 Discussion

4.1 Summary of Findings

Evidenz aus kleinen, einarmigen unverblindeten Studien

The available evidence is from small, open-label, single-arm studies. The lack of randomisation, in particular, weakens the internal validity of the findings. Furthermore, due to the observational descriptive study designs, no statistical conclusions could be drawn. The lack of blinding of patients, investigators and outcome assessors also weakens the certainty of the evidence, as they might have certain expectations, which might lead to bias.

Verzerrungsrisiko durch Erwartungshaltung, auch: fehlende Daten von vielen Pts

Missing data due to loss of follow-up or any other reason must be accounted for to reduce the risk of bias, which normally favours the intervention, as patients who do not do well on the intervention tend to withdraw from the study. This could be observed in the majority of the studies in particular. Furthermore, five of 19 studies (i.e. six of 21 publications) on nusinersen were financed by Biogen, the one study on onasemnogene abeparvovec by Avexis; the majority of authors of the 26 publications declared multiple conflicts of interests with the manufacturer in question (Biogen & Ionis Pharmaceuticals for nusinersen, AveXis & Roche for onasemnogene abeparvovec).

Hersteller-finanzierte Studien und Interessenskonflikte der Autor*innen

22 Studien in 26 Publikationen zu 774 SMA Patient*innen

Twenty-two studies reporting on ≥ 12 months follow-up data could be identified. Those 22 studies (in 26 publications) reported clinical data on 840 SMA patients, of which 289 SMA type 1 patients and 521 SMA type 2 to 4 patients were treated with nusinersen, only 12 SMA type 1 patients with onasemnogene abeparvovec and 18 SMA type 1 patients received a combination therapy. Most studies measured the outcomes of SMA type 1 patients with HINE-2 and CHOP INTEND, while SMA type 2 to 4 patients were measured with HFSME, RULM and 6MWT. For each of these instruments a validated minimal important clinical difference (MCID) is defined. Only a few studies used different instruments such as MFM or MRC without MCID.

Datenerhebung mit validierten Instrumenten

SMA1 – Spinraza®: fast alle Pts. sprechen an, aber nur wenige mit bedeutenden Verbesserungen

keine Veränderungen beim Bedarf nach Beatmung und Unterstützung bei Ernährung

To summarize the outcomes of 225 SMA type 1 patients (in the studies on exclusively SMA type 1 patients) treated with nusinersen nine died (4 %) despite therapy with nusinersen, six withdrew due to lack of improvement (2.7 %) and 35 patients (16 %) were lost to follow-up (despite regular therapy). For those children that could be followed-up many data were lacking. Nevertheless, 100 % (of 185) patients reached ≥4 points (MCID) on CHOP INTEND, while less patients (67-100 %) reached ≥2 points (MCID) on HINE-2. Notable improvements were documented for some children (10-20 %: head control, sitting without support), but not all. No significant improvements or even worsening were reported on the need for respiratory (non-invasive ≥16 hours or invasive) or nutritional support. Some studies conducted caregiver evaluations and showed that caregivers tended to overestimate the treatment effect in contrast to investigator evaluations (64 % vs. 43 % [8]), resp. 50 % perceived a much or very much improved condition of their children [35] or 60 % less need for secretion aspiration [32].

SMA1 – Zolgensma® und/ oder Kombinations-therapie: 40-75% lernen sitzen, 20% stehen – in sehr kleinen Studien keine Veränderungen: Beatmung & Ernährung

At 24 months follow-up nine of the 12 SMA type 1 patients (75 %) treated with onasemnogene abeparvovec achieved sitting for at least 30 seconds and two patients (17 %) standing without support. All 18 patients (100 %) treated with a combination of onasemnogene abeparvovec and nusinersen reached ≥4 points (MCID) on CHOP INTEND, but only 40 % reached ≥2 points (MCID) on HINE-2, 40 % learned to sit without support and 20% could control the head or stand. No significant improvements or even worsening were reported on the need for respiratory (non-invasive ≥16 hours or invasive) or nutritional support.

SMA 2 bis 4 – Spinraza®

Stabilisierung, nicht Verbesserung

keine Veränderungen: Beatmung & Ernährung

To summarize the outcomes of 341 patients with later onset of the disease (SMA type 2 to 4) treated with nusinersen (in the studies which did not include SMA type 1 patients), one died (0.3 %) despite therapy, and nine withdrew due to lack of improvement (2.6 %). In contrast to improvements in SMA type 1 patients, those with later onset of the disease achieve a stabilisation or eventually small improvements (mostly below the MCID of ≥3 points on HFSME and MCID of ≥2 points on RULM), but also deterioration. No significant improvements or even worsening were reported for the need of respiratory (non-invasive ≥ 16 hours or invasive) or nutritional support. Some studies conducted caregiver or self-evaluations, and showed much or very much improvement (52% [35] and 67 % [40] in endurance and strength.

unerwünschte Ereignisse: sehr häufig

Adverse events were common in all studies (nearly 100 % of patients) that reported on it, be it with nusinersen or with onasemnogene abeparvovec. AEs of nusinersen were headache, lower back pain, post-lumbar puncture syndrome, nasopharyngitis, upper respiratory tract infection, nausea and vomiting. (S)AEs of onasemnogene abeparvovec were liver failure and liver enzyme elevations.

4.2 Interpretation

große Heterogenität der Studien behindert Vergleichbarkeit

The data on the effectiveness and safety of the SMA-therapies have to be treated with caution. Heterogeneity in the reported outcomes, lengths of follow-up and the outcome measures across studies is a major issue, often acknowledged by study authors themselves. This heterogeneity hampers comparability of study outcomes. Not only the outcome measures, but also the included populations were heterogeneous. Although SMA type 1 and SMA type 2 to 4 patients have vastly different baseline characteristics as well as different outlook of improvements in any type of outcome, they were often combined in the studies and most often not separately reported on.

4 Studien machen Vergleiche mit historischer Kohorte:

SMA1 versterben früher, SMA 2-4 verschlechtern sich

Reporting-Bias: viele Daten fehlen

Four studies [36, 45, 46, 51] compared their results with natural history cohorts to examine what would be the natural progression of the disease. However, two of these studies did not report follow-up data of the untreated groups for any of the outcomes of our interest [36, 46]. One study [45] reported follow-up data of HFMSE scores for the untreated group with some deterioration and another study reported that 50% of the untreated SMA type 1 patients died during the follow-up period, while in the surviving patients there was much deterioration in CHOP INTEND scores [51]. In the later onset SMA patients (type 2 to 4) motor functions, fatigue and activities of daily living showed either stabilisation or deterioration in contrast to the

natural cohort [45]. In particular in these studies and in these patients, respiratory and nutritional support was not well reported on, motor endpoints were reported but with few patients at follow-up. Especially in the later onset patients, any changes observed in a non-comparative study cannot be attributed to the intervention with certainty due to lack of blinding and severe bias due to selection bias, performance bias and reporting bias. The interpretation of the results is severely hampered by the many missing data of endpoints or of patients at follow-up. Additionally, publications on mixed SMA populations, not reporting detailed data for SMA subtypes, are not very informative.

in SMA 1: Zugewinne bei Muskelstärke, aber nicht bei dem Bedarf nach Beatmung oder Unterstützung bei Ernährung

In contrast to the improvement of motor functions and muscle strengths in SMA type 1 patients, pulmonary outcomes such as the incidence of respiratory failure and the need for ventilator support show less advantageous results, since they stay unchanged over time or even deteriorate. Additional bulbar dysfunction and nutritional support are important, since they reflect the risk of aspiration and the overall ability of these children to thrive [62].

SMA 1 mittelfristige Ergebnisse zeigen: je früher, desto besser SMN2 Kopien und Bedarf von Beatmung

The mid-term outcomes support the findings of the pivotal trials that the responses to the therapies vary due to multiple factors - one of which is the number of SMN2 copies, the other is the pulmonary and swallowing functioning – that are important for medical decision-making. Early treatment in pre-symptomatic children, with at least 2 or more intact SMN2 copies and no need for pulmonary support, seems to lead to the best outcomes. SMN2 is considered the most important phenotypic modifier of the disease.

Screening zur Früherkennung

The impact of newborn screening for early identification could change the trajectory of this severe disease. So far, nine screening programs have been established [63], further countries will follow.

keine Langzeit-Ergebnisse, viele offene Fragen Dauerhaftigkeit und Plateau für Verbesserungen

Nevertheless, clinical data on long-term outcomes are still not available. Some questions remain unanswered, such as uncertainties around stabilisation or further improvement over time, persistence of gained abilities, and additional patient characteristics for clinical decision-making. The periodic assessment over many years is of utmost necessity to answer these questions [62] to ascertain that those lost to follow up have not died or deteriorated over time and that only positive data of those patients that improved are published (and generalized). Due to the cost-intensity of these therapies, many countries reimburse them requiring patient data documentation.

3 weitere systematische Reviews zu Nusinersen

To our knowledge, this is the first systematic review on SMA-therapies focusing on mid-term (≥12 months) follow-up data and on more than nusinersen. While Albrechtsen et.al. [64] and Wadman et.al. 2019 [65] conclude that SMA type 1 patients show improvements in survival and motor function, Albrechtsen et.al. [64] state that the benefits for SMA type 2 and 3 patients are less evident. On the contrary, Wadman et.al. 2020 [66] conclude that nusinersen improves motor function in SMA type 2, based on moderate-certainty evidence. Unfortunately, we could not identify more than one clinical trial on mid-term data for onasemnogene abeparvovec for our systematic review.

Table 4-1: Current clinical developments in SMA[67]

Primary targeted cell	Motor neurons					Muscle		
Mechanism	*SMN* gene replacement	SMN2 splicing modification				Antimyostatin		Troponin activation
Pharmacological class	AAV9	Antisens	Splicing modifiers		β-adrenergic agonist	Recombinant protein	Monoclonal antibody	Heteroarylpyrimidine
Product name	Zolgensma	Nusinersen	Risdiplam	Branaplam	Albuterol	RO7239361	SRK-105	Reldesemtiv
Company	Avexis (Novartis)	Biogen	Roche	Novartis		Roche	Scholar Rock	Cytokinetics
Route of administration	IV (IT)	IT	Oral	Oral	Oral	SC	IV	Oral
Approval status	FDA	FDA/EMA			Off label			
Phase completed in patients	I	III in SMA1, III in SMA2, I in SMA3						II
Current studies	III in type 1, I in type 2		III in SMA1, III in SMA2/3	I/II	II		II	

SMN, survival motor neuron; AAV, Adeno associated virus; IT, intrathecal; IV, intravenous; SC, subcutaneous.

As displayed in Table 4-1, the current clinical developments indicate an expected increase in the number of disease-modifying drug treatments [67]. New treatments [67, 68], such as branaplam and reldesemtiv, as well as combination-therapies, not only of onasemnogene abeparvovec plus nusinersen [12, 53], but also onasemnogene abeparvovec plus risdiplam [69], will further enlarge the spectrum of treatment options for SMA patients. Several studies are ongoing (see Table A 1).

4.3 Limitations

There are several major limitations of the evidence:

Limitation der Evidenz:

- Small patient numbers, single-arm, open-label trials and the quality of the studies prone to numerous biases. Multicentre studies across jurisdictions and health cate systems might give substantial information on larger patient cohorts and the effectiveness in subgroups of patients. This should not be too difficult to set up due to the reimbursement requirements for data documentation and disease registries.

kleine Studien, unverblindet Verzerrungspotential

- Industry-funded studies and their reporting tend to focus on positive results. Unfortunately, only few authors have no conflict of interest. Independent studies and publications are needed.

Industrie-finanziert oder von Autor*innen mit CoI

- Some patient characteristics are not unified e.g. ambulatory patients or the ability to walk. Furthermore, some clinically relevant outcomes were not included in some studies, only positive data were reported.

nicht alle Outcomes vereinheitlicht

The major limitation of this systematic review is,

Limitation des systematischen Reviews:

- that –though a systematic search in several databases was conducted and limited to the few years since the approval of the therapies and to studies reporting ≥12 months follow-up – there is always a large time lag until long-term outcome data becomes available due to publication time of at least 6 months to 2 years. This limitation can only be overcome by regular (annual) updates of the available clinical data.

große Zeitverzögeung bei Publikationen, regemäßige Updates notwendig

5 Conclusions

No long-term data published by independent clinicians are available yet and many open questions remain. Nevertheless, the existing clinical data show that early treatment in (pre-) symptomatic children, with at least 2 or more SMN2 copies and no need for pulmonary support seems to lead to the best outcomes.

keine Langzeit-Daten aber Evidenz, dass früher Therapiebeginn zu besseren Ergebnisse führt

- Newborn screening is recommended.
- The evidence for later onset SMA types (SMA type 2 to 4) is less convincing.
- Since all three approved therapies are cost-intensive, it is recommended that reimbursement is based on clinical data and clear criteria for discontinuation in case of non-response. These criteria should be communicated to the parents of SMA-children.
- A regular (annual) update of published clinical data should be conducted to answer the many remaining open questions and to guide clinical decision-making.

Neugeborenen-Screening, Refundierung an Datendokumentation knüpfen mit Abbruch-Kriterien, regelmäßige Updates der klinischen Evidenz

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7 Appendix

7.1 Clinical trials

Table A 1: Clinical trials on Spinraza®, Zolgensma®, Evrysdi®, Branaplam and Reldesdesemtiv

ISIS 396443 (nusinersen, Spinraza®)			
NCT04587492	SMA	Observational, n=35, Metabolomic	Completed
NCT04404764	SMA2-3	Observational [Patient Registry], cross-sectional, n=155, Characterization of the clinical-epidemiological profile	Completed
NCT02865109	SMA1	Expanded Access Program (EAP)	No longer available
NCT02462759	SMA	Phase 2, n=21, safety, tolerability (**EMBRACE**)	Terminated
NCT02594124	SMA	Phase 3, n=292, long-term safety and tolerability (**SHINE**)	Active, not recruiting
NCT03709784	SMA2-3 (18-70 years)	Observational, n=48, safety, tolerability, effectiveness	Active, not recruiting
NCT02292537	SMA (later onset)	Phase 3, n=126 (**CHERISH**)	Completed
NCT02193074	SMA (infantile onset)	Phase 3, n=122 (**ENDEAR**)	Terminated
NCT02386553	SMA (pre-symptomatic)	Phase 2, n=25 (**NURTURE**)	Active, not recruiting
NCT01780246	SMA (CS1 cohort)	Phase 1, n=18, safety, tolerability, previously treated CS1	Completed
NCT02052791	SMA (CS2, CS10 cohort)	Phase 1, n=47, safety and tolerability, previously treated CS2, CS10	Completed
NCT01494701	SMA	Phase 1, n=28, safety, tolerability, and dose-range finding	Completed
NCT01703988	SMA	Phase 1/ 2, n=34, safety, tolerability, and dose-range finding	Completed
NCT01839656	SMA (infants)	Phase 2, n=21, efficacy, safety, tolerability, and pharmacokinetics	Completed
NCT03878030	SMA2-3 (adults)	Observational, n=12	Active, not recruiting
NCT04591678	SMA (adults)	Observational, n=15	Active, not recruiting
NCT04576494	SMA2-3	Observational, n=24 (NUSI-AD-5qSM)	Not yet recruiting
NCT04602195	SMA (2-6 years)	Observational, n=60 (NusiMFM)	Recruiting
NCT04159987	SMA2 (adults)	Observational, n=20 (SMAII)	Not yet recruiting
NCT04644393	SMA (2-6 years)	Observational, n=20 (RetroNusiMFM)	Not yet recruiting
NCT04825119	SMA1-4	Observational, n=110	Recruiting
NCT04419233	SMA	Observational, n=50 (PANDA)	Recruiting
NCT04317794	SMA	Observational, n=145 (STANDARD)	Recruiting

NCT04089566	SMA (infantile and later-onset)	Phase 2/3, n=152, dose-escalating (DEVOTE)	Recruiting
NCT04729907	SMA	Phase 3, n=152, extension study, long-term safety and tolerability (ONWARD)	Enrolling by invitation
EudraCT2018-004383-65	SMA2-3	Phase 2	Ongoing
AVXS-101 (onasemnogene abeparvovec, Zolgensma®)			
NCT02122952	SMA1 (CL-101)	Phase 1, n=15 (2 cohorts with different doses)	Completed
NCT03421977	SMA1 (CL-101)	Long-Term Follow-up Study for Patients CL-101, n=12 (**START**)	Active, not recruiting
NCT03837184	SMA1	Phase 3, n=2	Active, not recruiting
NCT04851873	SMA1	Phase 3b, n=24 (**SMART**)	Not yet recruiting
NCT03955679	SMA1	Managed Access Program (MAP)	n.r.
NCT03505099	SMA1 (CL-304, pre-symptomatic)	Phase 3, n=30 (**SPR1NT**)	Completed
NCT03306277	SMA1 (CL-303)	Phase 3, n=22 (**STR1VE**)	Completed
NCT03461289	SMA1	Phase 3, n=33 (**STR1VE-EU**)	Completed
NCT03381729	SMA (6-60 months)	Phase 1, n=51 (2 cohorts with different doses) (**STRONG**)	Suspended
RO7034067 (risdiplam, Evrysdi®)			
NCT02633709	Healthy Volunteers	Phase 1, n=33, safety, tolerability, pharmacokinetics/pharmacodynamics	Completed
NCT03920865		Phase 1, n=26, safety, tolerability, pharmacokinetics/pharmacodynamics	Completed
NCT02240355	SMA1-3 (up to 55 years)	Phase 1, n=9 (3 cohorts with different doses) (**MOONFISH**)	Terminated
NCT04718181	SMA (18-55 years)	Phase 1, n=268, bioavailability and bioequivalence of two different formulation	Recruiting
NCT03032172	SMA1-3 (6-60 months)	Phase 2, n=174, safety, tolerability, pharmacokinetics/pharmacodynamics (**JEWELFISH**)	Active, not recruiting
NCT02913482	SMA1	Phase 2/3, n=62 (**FIREFISH**)	Active, not recruiting
NCT02908685	SMA2-3	Phase 2/3, n=231 **(SUNFISH)**	Active, not recruiting
NCT03779334	SMA (pre-symptomatic)	Phase 2, n=25 (**RAINBOWFISH**)	Recruiting
NCT04256265	SMA1-2	Expanded Access Program (EAP)	n.r.
EudraCT2016-004184-39	SMA1-3	Phase 2, safety, tolerability, pharmacokinetics/pharmacodynamics	n.r.?
Combination-Therapies			
EudraCT2020-003492-18	SMA1	Phase 4, study of nusinersen with patients who received onasemnogene abeparvovec	Ongoing
NCT04488133	SMA1	Phase 4, n=60, study of nusinersen with patients who received onasemnogene abeparvovec (RESPOND)	Recruiting
LMI070 (branaplam)			
EudraCT 2014-002053-19	SMA1	First-in-human study of oral LMI070	Ongoing
NCT02268552	SMA1	Phase 1/ 2, n=40	Active, not recruiting

CK-2127107 (reldesemtiv)			
NCT02644668	SMA (≥12 years)	Phase 2, n=70, dose-finding	Completed
SMA Registries and long-term FU			
NCT04174157	SMA, all	Registry of patients with diagnosis of SMA, n=500 (pts from Compassionate Use Program (CUP), Managed Access Program (MAP), Expanded Access Program (EAP), Single Patient Investigational New Drug (IND) (SPI) or Named Patient Program (NPP))	Recruiting
NCT04042025	SMA1-3	Phase 4, n=308, Long-term follow-up study SMA 1-3	Enrolling by invitation

7.2 Pivotal trials

Table A 2: Patient characteristics of pivotal trials: nusinersen (Spinraza®): ENDEAR [6] and CHERISH [7]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nusinersen Group (N=80)	Control Group (N=41)
Female sex — no. (%)	43 (54)	24 (59)
Age at first dose — days		
Mean	163	181
Range	52–242	30–262
Age at symptom onset — wk		
Mean	7.9	9.6
Range	2–18	1–20
Age at diagnosis of spinal muscular atrophy — wk		
Mean	12.6	17.5
Range	0–29	2–30
Disease duration at screening — wk		
Mean	13.2	13.9
Range	0–25.9	0–23.1
Symptoms of spinal muscular atrophy — no. (%)		
Hypotonia	80 (100)	41 (100)
Developmental delay of motor function	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)
Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Use of ventilatory support — no. (%)	21 (26)	6 (15)
Use of a gastrointestinal tube — no. (%)	7 (9)	5 (12)
Total HINE-2 score†	1.29±1.07	1.54±1.29
CHOP INTEND score‡	26.63±8.13	28.43±7.56
CMAP amplitude — mV		
Peroneal	0.371±0.31	0.317±0.29
Ulnar	0.226±0.19	0.225±0.12

* Plus–minus values are means ±SD. CMAP denotes compound muscle action potential.
† Scores on Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) range from 0 to 26, with higher scores indicating better motor function.[13,14]
‡ Scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) range from 0 to 64, with higher scores indicating better motor function.[15,16]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Nusinersen (N=84)	Control (N=42)
Female sex — no. (%)	46 (55)	21 (50)
Age at screening — yr		
Median	4.0	3.0
Range	2–9	2–7
Age at symptom onset — mo		
Median	10.0	11.0
Range	6–20	6–20
Age at diagnosis of SMA — mo		
Median	18.0	18.0
Range	0–48	0–46
Disease duration — mo†		
Median	39.3	30.2
Range	8–94	10–80
SMN2 copy number — no. (%)		
2	6 (7)	4 (10)
3	74 (88)	37 (88)
4	2 (2)	1 (2)
Unknown	2 (2)	0
Motor milestones ever achieved — no. (%)‡		
Ability to sit without support	84 (100)	42 (100)
Ability to walk with support	20 (24)	14 (33)
Ability to walk independently, ≥15 ft	0	0
HFMSE score§	22.4±8.3	19.9±7.2
WHO motor milestones achieved¶	1.4±1.0	1.5±1.0
RULM score‖	19.4±6.2	18.4±5.7

* Plus–minus values are means ±SD. No formal statistical testing was performed to assess differences between trial groups in baseline characteristics. Percentages may not total 100 because of rounding. SMA denotes spinal muscular atrophy.
† Disease duration is a child's age at screening minus the age at symptom onset.
‡ These data do not reflect the maximal milestone achieved.
§ Hammersmith Functional Motor Scale–Expanded (HFMSE) scores range from 0 to 66, with higher scores indicating better motor function.[19]
¶ The six World Health Organization (WHO) motor milestones are sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone, and walking alone.[24]
‖ Revised Upper Limb Module (RULM) scores range from 0 to 37, with higher scores indicating better function.[25]

Table A 3: Inclusion and exclusion criteria in ENDEAR [6] and CHERISH [7]

Inclusion Criteria	
ENDEAR https://clinicaltrials.gov/ct2/show/NCT02193074	• CHERISH https://clinicaltrials.gov/ct2/show/NCT02292537
Be born (gestational age) between 37 and 42 weeks Be medically diagnosed with spinal muscular atrophy (SMA) Have Survival Motor Neuron2 (SMN2) Copy number = 2 Body weight equal to or greater than 3rd percentile for age using appropriate country-specific guidelines Be able to follow all study procedures Reside within approximately 9 hours ground-travel distance from a participating study center, for the duration of the study	Parent or guardian has signed informed consent and, if indicated per participant's age and institutional guidelines, participant has signed informed assent Be medically diagnosed with Spinal Muscular Atrophy (SMA) Have onset of clinical signs and symptoms consistent with SMA at greater than 6 months of age Be able to sit independently, but has never had the ability to walk independently Have Motor Function Score (Hammersmith Functional Motor Scale - Expanded) greater than or equal to 10 and less than or equal to 54 at Screening Be able to complete all study procedures, measurements and visits and parent or guardian and subject has adequately supportive psychosocial circumstances, in the opinion of the Investigator Have an estimated life expectancy of greater than 2 years from Screening, in the opinion of the Investigator Meet age-appropriate institutional criteria for use of anesthesia and sedation, if use is planned for study procedures For subjects who have reached reproductive maturity, satisfy study contraceptive requirements
Exclusion Criteria	
Hypoxemia (oxygen [O2] saturation awake less than 96% or O2 saturation asleep less than 96%, without ventilation support) during screening evaluation Clinically significant abnormalities in hematology or clinical chemistry parameters or Electrocardiogram (ECG), as assessed by the Site Investigator, at the Screening visit that would render the participant unsuitable for participation in the study Participant's parent or legal guardian is not willing to meet standard of care guidelines (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study	Respiratory insufficiency, defined by the medical necessity for invasive or non-invasive ventilation for greater than 6 hours during a 24 hour period, at Screening Medical necessity for a gastric feeding tube, where the majority of feeds are given by this route, as assessed by the Site Investigator Severe contractures or severe scoliosis evident on X-ray examination at Screening Hospitalization for surgery (i.e., scoliosis surgery, other surgery), pulmonary event, or nutritional support within 2 months of Screening or planned during the duration of the study Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period

	History of brain or spinal cord disease, including tumors, or abnormalities by magnetic resonance imaging (MRI) or computed tomography (CT) that would interfere with the LP procedures or cerebrospinal fluid (CSF) circulation Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system (CNS) catheter History of bacterial meningitis Dosing with IONIS-SMN Rx in any previous clinical study Prior injury (e.g., upper or lower limb fracture) or surgical procedure which impacts the subject's ability to perform any of the outcome measure testing required in the protocol and from which the subject has not fully recovered or achieved a stable baseline Clinically significant abnormalities in hematology or clinical chemistry parameters or electrocardiogram (ECG), as assessed by the Site Investigator, at the Screening visit that would render the subject unsuitable for inclusion Treatment with another investigational drug (e.g., oral albuterol or salbutamol, riluzole, carnitine, creatine, sodium phenylbutyrate, et.c), biological agent, or device within 1-month of Screening or 5 half-lives of study agent, whichever is longer. Treatment with valproate or hydroxyurea within 3-months of Screening. Any history of gene therapy, antisense oligonucleotide therapy, or cell transplantation. Ongoing medical condition that according to the Site Investigator would interfere with the conduct and assessments of the study. Examples are medical disability (e.g., wasting or cachexia, severe anemia, etc.) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures.

Table A 4: Results of pivotal trials: nusinersen (Spinraza®): ENDEAR [6] and CHERISH [7]

Efficacy Parameter	Spinraza treated Patients	Sham-control Patients
Survival		
Event-free survival[2]		
Number of patients who died or received permanent ventilation	31 (39%)	28 (68%)
Hazard ratio (95% CI)	0.53 (0.32 -0.89)	
p-value[6]	p = 0.0046	
Overall survival[2]		
Number of patients who died	13 (16%)	16 (39%)
Hazard Ratio (95% CI)	0.37 (0.18 – 0.77)	
p-value[6]	p=0.0041	
Motor function		
Motor milestones[3]		
Proportion achieving pre-defined motor milestone responder criteria (HINE section 2)[4,5]	37 (51%)[1] p<0.0001	0 (0%)
Proportion at Day 183	41%	5%
Proportion at Day 302	45%	0%
Proportion at Day 394	54%	0%
Proportion with improvement in total motor milestone score	49 (67%)	5 (14%)
Proportion with worsening in total motor milestone score	1 (1%)	8 (22%)
CHOP INTEND[3]		
Proportion achieving a 4-point improvement	52 (71%) p<0.0001	1 (3%)
Proportion achieving a 4-point worsening	2 (3%)	17 (46%)
Proportion with any improvement	53 (73%)	1 (3%)
Proportion with any worsening	5 (7%)	18 (49%)

[1]CS3B was stopped following positive statistical analysis on the primary endpoint at interim analysis (statistically significantly greater percentage of patients achieved the definition of a motor milestone responder in the Spinraza group (41%) compared to the sham-control group (0%), p<0.0001)
[2]At the final analysis, event-free survival and overall survival were assessed using the Intent to Treat population (ITT Spinraza n=80; Sham-control n=41).
[3]At the final analysis, CHOP INTEND and motor milestone analyses were conducted using the Efficacy Set (Spinraza n=73; Sham-control n=37).
[4]Assessed at the later of Day 183, Day 302, and Day 394 Study Visit
[5]According to Hammersmith Infant Neurological Examination (HINE) section 2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening, defined as a responder for this primary analysis.
[6]Based on log-rank test stratified by disease duration

	Spinraza treated Patients	Sham-control Patients
HFMSE score		
Change from baseline in total HFMSE score at 15 months[1,2,3]	3.9 (95% CI: 3.0, 4.9) p=0.0000001	-1.0 (95% CI: -2.5, 0.5)
Proportion of patients who achieved at least a 3 point improvement from baseline to month 15[2]	56.8% (95% CI:45.6, 68.1) P=0.0006[5]	26.3% (95% CI: 12.4,40.2)
RULM		
Mean change from baseline to month 15 in total RULM score[2,3]	4.2(95% CI: 3.4, 5.0) p=0.0000001[6]	0.5 (95% CI: -0.6, 1.6)
WHO motor milestones		
Proportion of patients who achieved new motor milestones at 15 months[4]	19.7% (95% CI: 10.9, 31.3) p=0.0811	5.9% (95% CI: 0.7, 19.7)

[1]CS4 was stopped following positive statistical analysis on the primary endpoint at interim analysis (statistically significant improvement from baseline HFMSE score was observed in Spinraza treated patients compared to the sham-control patients (Spinraza vs. sham-control: 4.0 vs. -1.9; p=0.0000002))
[2] Assessed using the Intent to Treat population (Spinraza n=84; Sham-control n=42); data for patients without a Month 15 visit were imputed using the multiple imputation method
[3]Least squares mean
[4] Assessed using the Month 15 Efficacy Set (Spinraza n=66; Sham control n=34); analyses are based on imputed data when there are missing data.
[5] Based on logistic regression with treatment effect and adjustment for each subject's age at screening and HFMSE score at baseline
[6]Nominal p value

Table A 5: Onasemnogene abeparvovec (Zolgensma®) - patient characteristics of pivotal trial: STR1VE [14]

	Patients (n=22)
Age, months	
Mean	3.7 (1.6)
Median	3.5 (2.7-5.3)
Range	0.5-5.9
Gestational age at birth, weeks	
Mean	39.0 (1.0)
Median	39.0 (39.0-39.0)
Range	37.0-41.0
Age at symptom onset, months	
Mean	1.9 (1.2)
Median	1.8 (1.0-3.0)
Age at diagnosis, days	
Mean	56.1 (98.6)
Median	67.0 (56.0-126.0)
Weight at baseline, kg	
Mean (range)	5.8 (3.9-7.5)
Median	5.8 (5.1-6.5)
Sex	
Female	12 (55%)
Male	10 (45%)
Race	
White	11 (50%)
Other	6 (27%)
Black or African American	3 (14%)
Asian	2 (9%)
Ethnicity	
Non-Hispanic or Latino	18 (82%)
Hispanic or Latino	4 (18%)
Clinical characteristics	
Reported swallowing thin liquid	22 (100%)
Reported feeding support	0
Reported ventilator support*	0
CHOP INTEND score at baseline	
Mean	32.0 (9.7)
Median	33.5 (24-38)
Range	18-52

**defined as requiring no daily ventilator support, excluding acute reversible illness and perioperative ventilation, from 2 weeks before screening up until baseline visit*

Table A 6: Inclusion and exclusion criteria in STR1VE [13] and SPR1NT

Inclusion Criteria	
STR1VE https://clinicaltrials.gov/ct2/show/NCT03306277	SPR1NT https://clinicaltrials.gov/ct2/show/NCT03505099
Participants with SMA Type 1 as determined by the following features: a. Diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 1 or 2 copies of SMN2 (inclusive of the known SMN2 gene modifier mutation (c.859G>C))2 The first 3 participants enrolled must meet the criteria for the Intent-To-Treat Population Participants must be < 6 months (< 180 days) of age at the time of onasemnogene abeparvovec-xioi infusion Participants must have a swallowing evaluation test performed prior to administration of gene replacement therapy Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule	Age ≤6 weeks (≤42 days) at time of dose Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test Compound muscle action potential (CMAP) ≥2mV at Baseline; centralized review of CMAP data will be conducted Gestational age of 35 to 42 weeks Patients with pre-symptomatic SMA Type 1 as determined by the following features: Patients with 2 copies of SMN2 (n ≥12) Patients with pre-symptomatic SMA Type 2 as determined by the following features: 3 copies of SMN2
Exclusion Criteria	
Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period Pulse oximetry < 96% saturation at screening while the participant is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes > 1000 m, oxygen saturation < 92% awake or asleep without any supplemental oxygen or respiratory support Pulse oximetry saturation may decrease to < 96% after screening provided that the saturation does not decrease by ≥ 4 percentage points Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing Participants with signs of aspiration/inability to tolerate non-thickened- liquids based on a formal swallowing test performed as part of screening. Participants with a gastrostomy tube who pass the swallowing test will be allowed to enroll in the study	Weight at screening visit <2 kg Hypoxemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) at the screening visit or for altitudes >1000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit Any clinical signs or symptoms at screening or immediately prior to dosing that are, in the opinion of the Investigator, strongly suggestive of SMA Tracheostomy or current prophylactic use or requirement of noninvasive ventilatory support at any time and for any duration prior to screening or during the screening period Patients with signs of aspiration/inability to tolerate nonthickened liquids based on a formal swallowing test performed as part of screening or patients receiving any non-oral feeding method

Participants whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus) Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening Severe non-pulmonary/respiratory tract infection within 4 weeks before administration of gene replacement therapy or concomitant illness that creates unnecessary risks for gene replacement therapy such as: a. Major renal or hepatic impairment b. Known seizure disorder c. Diabetes mellitus d. Idiopathic hypocalcuria e. Symptomatic cardiomyopathy Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy Anti-adeno-associated virus serotype 9 (AAV9) antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay. Should a potential participant demonstrate Anti-AAV9 antibody titer > 1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50 Clinically significant abnormal laboratory values (gamma glutamyl- transpeptidase [GGT], ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin [Hgb] < 8 or > 18 g/dL; white blood cell [WBC] > 20,000 per cmm) prior to gene replacement therapy Participation in recent SMA treatment clinical study (with the exception of observational Cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intent to treat SMA at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study Expectation of major surgical procedures during the study assessment period Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites Parent(s)/legal guardian(s) refuses to sign consent form Gestational age at birth < 35 weeks (245 days)	Clinically significant abnormalities in hematology or clinical chemistry parameters as determined by investigator or medical monitor Treatment with an investigational or commercial product, including nusinersen, given for the treatment of SMA. This includes any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation. Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards Biological mother with active viral infection as determined by screening laboratory samples (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C) • Biological mothers with clinical suspicion of Zika virus that meet Centers for Disease Control and Prevention (CDC) Zika virus epidemiological criteria including history of residence in or travel to a geographic region with active Zika transmission at the time of travel will be tested for Zika virus RNA. Positive results warrant confirmed negative Zika virus RNA testing in the patient prior to enrollment. Serious nonrespiratory tract illness requiring systemic treatment and/or hospitalization within 2 Weeks prior to screening Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 Weeks prior to dosing Severe nonpulmonary/respiratory tract infection within 4 Weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator or Sponsor medical monitor, creates unnecessary risks for gene replacement therapy such as: Major renal or hepatic impairment Known seizure disorder Diabetes mellitus Idiopathic hypocalciuria Symptomatic cardiomyopathy Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients Previous, planned or expected major surgical procedure including scoliosis repair surgery/procedure during the study assessment period Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy,

	plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 4 Weeks prior to gene replacement therapy AntiAAV9 antibody titer >1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay • Should a potential patient demonstrate AntiAAV9 antibody titer >1:50, he or she may receive retesting inside the 30-Day screening period and will be eligible to participate if the AntiAAV9 antibody titer upon retesting is ≤1:50, provided the <6 Week age requirement at the time of dosing is still met Biological mother involved with the care of the child refuses anti-AAV9 antibody testing prior to dosing

Table A 7: Results of pivotal trials: onasemnogene abeparvovec (Zolgensma®): STR1VE [13]

Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (months)	95% Confidence interval
Head control	17/20* (85)	6.8	(4.77, 7.17)
Rolls from back to sides	13/22 (59)	11.5	(7.77, 14.53)
Sits without support for 30 seconds (Bayley)	14/22 (64)	12.5	(10.17, 15.20)
Sitting without support for at least 10 seconds (WHO)	14/22 (64)	13.9	(11.00, 16.17)

* 2 patients were reported to have Head Control by clinician assessment at baseline.

Table A 8: Risdiplam (Evrysdi®) - patient characteristics of pivotal trials: FIREFISH [15], SUNFISH [14] (data are not published yet)

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.

Characteristic	All Infants (N=41)
Median age at enrollment (range) — mo	5.3 (2.2–6.9)
Sex — no. (%)	
Female	22 (54)
Male	19 (46)
Median age at onset of symptoms (range) — mo	1.5 (1.0–3.0)
Duration of disease*	
Median (range) — mo	3.4 (1.0–6.0)
≤3 mo — no. (%)	14 (34)
>3 mo — no. (%)	27 (66)
Motor measures†	
Median CHOP-INTEND score (range)	22.0 (8.0–37.0)
Median HINE-2 score (range)	1.0 (0.0–5.0)
Able to swallow — no. (%)	39 (95)‡
No pulmonary care — no. (%)§	29 (71)

* Shown is the time between the onset of symptoms and first treatment.
† Scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) range from 0 to 64, with higher scores indicating better motor function. Scores on Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) range from 0 to 26, with higher scores indicating better motor function. All the infants were assessed with the use of the CHOP-INTEND and HINE-2 at baseline. One infant had one item missing in the baseline HINE-2 score (walking item, which would be expected to be 0); this item score was imputed to 0. None of the infants had a missing item in the baseline CHOP-INTEND score.
‡ One infant was fed by tube at baseline owing to inadequate weight gain. The ability to swallow had not been assessed after enrollment in the study.
§ No pulmonary care was defined as no ventilatory support or airway clearance.

Table A 9: Inclusion and exclusion criteria in FIREFISH [15] and SUNFISH [14]

Inclusion Criteria	
FIREFISH https://clinicaltrials.gov/ct2/show/NCT02913482	SUNFISH https://clinicaltrials.gov/ct2/show/NCT02908685
Clinical history, signs or symptoms attributable to Type 1 SMA with onset after 28 days but prior to the age of 3 months Gestational age of 37 to 42 weeks Confirmed diagnosis of 5q-autosomal recessive SMA Participants has two survival motor neuron 2 (SMN2) gene copies, as confirmed by central testing Body weight greater than or equal to (>=) third percentile for age, using appropriate country-specific guidelines Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the Investigator	Confirmed diagnosis of 5q-autosomal recessive SMA Negative blood pregnancy test at screening and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation For Part 1: Type 2 or 3 SMA ambulant or non-ambulant For Part 2: 1) Type 2 or 3 SMA non-ambulant; 2) RULM entry item A greater than or equal to 2; 3) ability to sit independently as assessed by item 9 of the MFM
Exclusion Criteria	
Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer Concomitant or previous administration of SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy study Any history of cell therapy Hospitalization for pulmonary event within the last 2 months, or planned at the time of screening Presence of clinically relevant electrocardiogram (ECG) abnormalities before study drug administration Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases Participants requiring invasive ventilation or tracheostomy Participants requiring awake non-invasive ventilation or with awake hypoxemia (arterial oxygen saturation less than [<] 95 percent [%]) with or without ventilator support Participants with a history of respiratory failure or severe pneumonia, and have not fully recovered their pulmonary function at the time of screening Multiple or fixed contractures and/or hip subluxation or dislocation at birth Presence of non-SMA related concurrent syndromes or diseases	Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer Concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy either in a clinical study or as part of medical care Any history of cell therapy Hospitalization for a pulmonary event within the last 2 months or planned at time of screening Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator Presence of clinically significant electrocardiogram abnormalities before study drug administration from average of triplicate measurement or cardiovascular disease indicating a safety risk for participants as determined by the Investigator Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration

Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration Any inhibitor of cytochrome P450 (CYP) 3A4 and/or any Organic Cation Transporter 2 (OCT-2) and multidrug and toxin extrusion (MATE) substrates taken within 2 weeks and/or any inducer of CYP3A4 taken within 4 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing or participants (and the mother, if breastfeeding the infant) taking any nutrients known to modulate CYP3A activity and any known flavin containing monooxygenase (FMO) 1 or FMO3 inhibitors or substrates Prior use (at any time in the participants lives) and/or anticipated need for quinolones (chloroquine and hydroxychloroquine), thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study. Infants exposed to chloroquine, hydroxycholoroquine, thioridazine, vigabatrin, retigabine or drugs with known retinal toxicity given to mothers during pregnancy (and lactation) should not be enrolled. Recent history (less than 6 months) of ophthalmic disease that would interfere with the conduct of the study as assessed by an ophthalmologist Therapeutic use, defined as use for 8 weeks or longer, of the following medications within 90 days prior to enrollment: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase (HDAC) inhibitory effect, medications known to or suspected of causing retinal toxicity (deferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, and interferon) and medications with known phototoxicity liabilities (e.g., oral retinoids including over-the-counter [OTC] formulations, amiodarone, phenothiazines and use of minocycline)	Recently initiated treatment (within less than [<] 6 months prior to randomization) with oral salbutamol or another beta 2-adrenergic agonist taken orally Any prior use of chloroquine, hydroxychloroquine, retigabin, vigabatrin or thioridazine, is not allowed Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to Risdiplam or to the constituents of its formulation Recent history (less than one year) of ophthalmological diseases Participants requiring invasive ventilation or tracheostomy

Table A 10: Results of pivotal trial: risdiplam (Evrysdi®): FIREFISH [15], SUNFISH [14] (data are not published yet)

Efficacy Endpoints	Proportion of Patients N=41 (90% CI)
Motor function and development milestones	
BSID-III: sitting without support for at least 5 seconds	29.3% (17.8%, 43.1%) p <0.0001[a]
CHOP-INTEND: score of 40 or higher	56.1% (42.1%, 69.4%)
CHOP-INTEND: increase of ≥4 points from baseline	90.2% (79.1%, 96.6%)
HINE-2: motor milestone responders[b]	78.0% (64.8%, 88.0%)
HINE-2: sitting without support[c]	24.4% (13.9%, 37.9%)
HINE-2: supports weight or stands with support[d]	22.0% (12.0%, 35.2%)
Survival and event-free survival	
Event-free survival[e]	85.4% (73.4%, 92.2%)
Alive	92.7% (82.2%, 97.1%)
Feeding	
Ability to feed orally[f]	82.9% (70.3%, 91.7%)

Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Module 2 of the Hammersmith Infant Neurological Examination.

[a] p-value is based on a one-sided exact binomial test. The result is compared to a threshold of 5%.

[b] According to HINE-2: ≥2 point increase [or maximal score] in ability to kick, OR ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening is defined as a responder for this analysis.

[c] Sitting without support includes patients that achieved "stable sit" (15%, 6/41) and "pivots (rotates)" (10%, 4/41) as assessed by the HINE-2.

[d] Supports weight or stands with support includes patients that achieved "supports weight" (17%, 7/41) and "stands with support" (5%, 2/41) as assessed by the HINE-2.

[e] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Three patients met the endpoint of permanent ventilation before Month 12. All 3 patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline.

[f] Includes patients who were fed exclusively orally (28 patients overall) and those who were fed orally in combination with a feeding tube (6 patients overall) at Month 12.

Endpoint	Evrysdi (N = 120)	Placebo (N = 60)
Primary Endpoint:		
Change from baseline in MFM32 total score[1] at Month 12 LS mean (95%, CI)	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from placebo Estimate (95% CI) p-value[2]	1.55 (0.30, 2.81) 0.0156	
Secondary Endpoints:		
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12 (95% CI)[1]	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) Adjusted(unadjusted) p-value[3,4]	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in RULM total score[5] at Month 12 LS mean (95% CI)	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from placebo estimate (95% CI) Adjusted (unadjusted) p-value[2,4]	1.59 (0.55, 2.62) 0.0469 (0.0028)	

LS=least squares

1. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (Evrysdi n=115; placebo control n=59).
2. Data analysed using a mixed model repeated measure with baseline total score, treatment, visit, age group, treatment-by-visit and baseline-by-visit.
3. Data analysed using logistic regression with baseline total score, treatment and age group.
4. The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint
5. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (Evrysdi n=119; placebo control n=58).

7.3 Risk of bias assessments

Table A 11: Risk of bias assessment of included studies on efficacy of nusinersen in SMA type 1 – study level

Study reference/ID	Acsadi et. al. 2021	Aragon-Gawinska et. al. 2020	Lavie et. al. 2021	Mendonca et. al. 2021b	Modrzejewska et. al. 2021	Pane et. al. 2019
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	Unclear
3. Were the cases collected in more than one centre?	Yes	Yes	No	No	Yes	Yes
4. Were patients recruited consecutively?	Yes	Unclear	Unclear	Yes	No	No
Study population						
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes	No
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Partial	No	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	No	Yes	Yes	Yes	Yes	Yes
Intervention and co-intervention						
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
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	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	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	No	Yes	Partial	Yes	No
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	Yes	Yes	Partial	Yes
Overall Risk of bias	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk

Table A 12: Risk of bias assessment of included studies on efficacy of nusinersen in SMA type 1 + 2, SMA type 1 to 3 – study level

Study reference/ID	Chachko et.al. 2021	Kariyawasam et. al. 2020	Veerapandiyan et. Al. 2020	Osredkar et. al. 2020	Audic et. al. 2020	Gomez-Garcia et. al. 2019
Study objective						
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	No	Yes	Yes	Yes
Study design						
2. Was the study conducted prospectively?	Yes	Yes	No	Yes	No	Yes
3. Were the cases collected in more than one centre?	No	No	No	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Yes	Yes	Yes
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	No	Partial	Yes
7. Did patients enter the study at a similar point in the disease?	No	No	Yes	Yes	No	Yes
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	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	Partial	Yes	Partial	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	No	Yes	Yes	Yes	Yes
Statistical Analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Unclear	No	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	No	Yes	Yes	No
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	No	Partial	Yes	Yes	Yes
18. Were the adverse events reported?	No	No	Yes	Yes	Yes	Partial
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	No	Unclear	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	Partial
Overall Risk of bias	Moderate risk	High risk	High risk	Moderate risk	Moderate risk	Moderate risk

Table A 13: Risk of bias assessment of included studies on efficacy of nusinersen in SMA type 2+3 – study level

Study reference/ID	Darras et. al. 2019	Montes et. al. 2019	Hagenacker et. al. 2020	Maggi et. al. 2020	Mendonca et. al. 2021a	Moshe-Lilie et. al. 2020
Study objective						
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	No	Yes	No	No	No
3. Were the cases collected in more than one centre?	Yes	Yes	Yes	Yes	No	No
4. Were patients recruited consecutively?	Unclear	Unclear	Yes	Unclear	Yes	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	Yes	Yes	Yes	No
7. Did patients enter the study at a similar point in the disease?	Yes	Yes	Unclear	No	No	No
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	Partial
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	Unclear	Yes	Yes	Yes	No
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	No	Yes	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Partial	Yes	Yes	No	No
18. Were the adverse events reported?	Yes	No	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Unclear	Yes	No
Competing interests and sources of support						
20. Were both competing interests and sources of support for the study reported?	Yes	Partial	Yes	Yes	Yes	Yes
Overall Risk of bias	Low risk	High risk	Low risk	Moderate ris	Moderate risk	High risk

Table A 14: Risk of bias assessment of included studies on efficacy of nusinersen in SMA type 3 and SMA type 2 to 4 – study level

Study reference/ID	Yeo et.al. 2020	Binz et. al. 2020	De Wel et. Al. 2020
Study objective			
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study design			
2. Was the study conducted prospectively?	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	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?	Yes	Partial	Yes
7. Did patients enter the study at a similar point in the disease?	No	No	Unclear
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	Partial	Yes
Statistical Analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	No	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	Yes	Yes
18. Were the adverse events reported?	Yes	No	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?	Partial	Yes	Yes
Overall Risk of bias	High risk	Moderate risk	Moderate risk

Table A 15: Risk of bias assessment of included studies on efficacy of onasemnogene abeparvovec in SMA type 1 – study level

Study reference/ID	Lowes et. al. 2019	Al-Zaidy et. al. 2020b	Al Zaidy et. al. 2020a
Study objective			
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study design			
2. Was the study conducted prospectively?	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	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	No
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	No	No
Intervention and co-intervention			
8. Was the intervention of interest clearly described?	Yes	Yes	No
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	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?	No	Yes	No
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	Yes	Yes
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			
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Partial
Overall Risk of bias	High risk	Moderate risk	High risk

Table A 16: Risk of bias assessment of included studies on efficacy of combination therapy of nusinersen and onasemnogene abeparvovec in SMA type 1

Study reference/ID	Harada et. al. 2017	Mendell et. al. 2021
Study objective		
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?	No	No
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?	No	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	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?	No	No
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?	No	No
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?	Partial	Yes
Overall Risk of bias	High risk	Moderate risk

7.4 Search strategies

Cochrane	
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	#1 OR #2 OR #3 OR #4 OR #5 (Word variations have been searched)
#7	(Nusinersen*) (Word variations have been searched)
#8	(spinraza*) (Word variations have been searched)
#9	(biib 058) (Word variations have been searched)
#10	(biib058) (Word variations have been searched)
#11	(ionis smnrx) (Word variations have been searched)
#12	("isis 396443") (Word variations have been searched)
#13	(isis396443) (Word variations have been searched)
#14	("isis smnrx") (Word variations have been searched)
#15	(Onasemnogene*) (Word variations have been searched)
#16	("avxs 101") (Word variations have been searched)
#17	(avxs101) (Word variations have been searched)
#18	(Risdiplam*) (Word variations have been searched)
#19	(evrysdi*) (Word variations have been searched)
#20	("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)
#21	("rg 7916") (Word variations have been searched)
#22	(rg7916) (Word variations have been searched)
#23	(ro 7034067) (Word variations have been searched)
#24	(ro7034067) (Word variations have been searched)
#25	#7 OR #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 (Word variations have been searched)
#26	#6 AND #25 in Trials (Word variations have been searched)
84 Hits	

Embase		
No.	Query Results	Results
#86	#85 AND ([english]/lim OR [german]/lim)	370
#85	#30 OR #84	374
#84	#29 AND #83	311
#83	#58 NOT #82	4,717,467
#82	#59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81	3,442,283
#81	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,338,814
#80	.(rat:tt OR rats:tt OR mouse:tt OR mice:tt OR swine:tt OR porcine:tt OR murine:tt OR sheep:tt OR lambs:tt OR pigs:tt OR piglets:tt OR rabbit:tt OR rabbits:tt OR cat:tt OR cats:tt OR dog:tt OR dogs:tt OR cattle:tt OR bovine:tt OR monkey:tt OR monkeys:tt OR trout:tt OR marmoset*:tt) AND 'animal experiment'/de	2,133
#79	(rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*:ti) ANDn'animal experiment'/de	1,114,477

#78	(databases NEAR/5 searched):ab	46,248
#77	'update review':ab	116
#76	'we searched':ab AND review:tt	8
#75	'we searched':ab AND (review:ti OR review:it)	36,746
#74	.review:ab AND review:tt NOT trial:tt	331
#73	review:ab AND review:it NOT trial:ti	881,025
#72	('random cluster' NEAR/4 sampl*):tt	
#71	('random cluster' NEAR/4 sampl*):ti,ab	1,467
#70	'random field*':tt	
#69	'random field*':ti,ab	2,466
#68	nonrandom*:tt NOT random*:tt	1
#67	nonrandom*:ti,ab NOT random*:ti,ab	16,997
#66	'systematic review':tt NOT (trial:tt OR study:tt)	122
#65	'systematic review':ti NOT (trial:ti OR study:ti)	176,107
#64	'case control*':tt AND random*:tt NOT ('randomised controlled':tt OR 'randomized controlled':tt)	1
#63	'case control*':ti,ab AND random*:ti,ab NOT ('randomised controlled':ti,ab OR 'randomized controlled':ti,ab)	17,755
#62	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':tt OR 'randomized controlled':tt OR 'control group':tt OR 'control groups':tt)	136
#61	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab OR 'randomized controlled':ti,ab OR 'control group':ti,ab OR 'control groups':ti,ab)	136
#60	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':tt OR 'randomized controlled':tt OR 'randomly assigned':tt)	
#59	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab OR 'randomized controlled':ti,ab OR 'randomly assigned':ti,ab)	2,699
#58	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR 5,253,232 #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57	
#57	'human experiment'/de	548,357
#56	volunteer:ti,ab OR volunteers:tt	34,723
#55	volunteer:ti,ab OR volunteers:ti,ab	259,221
#54	(controlled NEAR/8 (study OR design OR trial)):tt	67
#53	(controlled NEAR/8 (study OR design OR trial)):ti,ab	387,706
#52	assigned:tt OR allocated:tt	
#51	assigned:ti,ab OR allocated:ti,ab	419,143
#50	crossover:tt OR 'cross over':tt	262
#49	crossover:ti,ab OR 'cross over':ti,ab	111,350
#48	(parallel NEXT/1 group*):tt	5
#47	(parallel NEXT/1 group*):ti,ab	27,543
#46	'double blind procedure'/de	185,142
#45	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):tt	69
#44	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab	246,793
#43	(open NEXT/1 label):tt	12
#42	(open NEXT/1 label):ti,ab	87,513
#41	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,309,498
#40	compare:tt OR compared:tt OR comparison:tt	546
#39	compare:ti OR compared:ti OR comparison:ti	561,276
#38	placebo:tt	1,737

#37	placebo:ti,ab	325,116
#36	'intermethod comparison'/de	273,835
#35	'randomization'/de	90,848
#34	random*:tt	4,541
#33	random*:ti,ab	1,668,458
#32	'controlled clinical trial'/de	433,926
#31	'randomized controlled trial'/de	661,702
#30	#29 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	211
#29	#5 AND #28	1,208
#28	#6 OR #7 OR #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 OR #27	1,385
#27	ro7034067	
#26	'ro 7034067	5
#25	rg7916	67
#24	'rg 7916'	18
#23	'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'	
#22	evrysdi	10
#21	'risdiplam'/exp	148
#20	charisma:tn	2
#19	'avxs101'	
#18	'avxs 101'	198
#17	zolgensma*	110
#16	onasemnogene*	366
#15	'onasemnogene abeparvovec'/exp	353
#14	'isis smnrx'	16
#13	isis396443	
#12	'isis 396443'	14
#11	'ionis smnrx'	1
#10	biib058	
#9	'biib 058'	
#8	spinraza*	242
#7	nusinersen*	1,065
#6	'nusinersen'/exp	989
#5	#1 OR #2 OR #3 OR #4	60,388
#4	werdnig NEAR/1 hoffmann	1,279
#3	kugelberg NEAR/1 welander	679
#2	'spin* musc* atroph*'	11,131
#1	'spinal muscular atrophy'/exp	59,237
Date: 11 Jun 2021		

MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to June 10, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to June 10, 2021>	
No	
1	exp Muscular Atrophy, Spinal/ (6615)
2	spin* musc* atroph*.mp. (8153)
3	*Muscular Disorders, Atrophic/ (406)
4	(Kugelberg adj Welander).mp. (205)
5	(Werdnig adj Hoffmann).mp. (335)
6	1 or 2 or 3 or 4 or 5 (10493)
7	Nusinersen*.mp. (808)
8	spinraza.mp. (180)
9	"biib 058".mp. (0)
10	biib058.mp. (0)
11	"ionis smnrx".mp. (4)
12	"isis 396443".mp. (6)
13	isis396443.mp. (0)
14	"isis smnrx".mp. (8)
15	Onasemnogene*.mp. (105)
16	zolgensma.mp. (80)
17	"avxs 101".mp. (48)
18	avxs101.mp. (0)
19	Risdiplam*.mp. (66)
20	evrysdi.mp. (13)
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".mp. (0)
22	"rg 7916".mp. (2)
23	rg7916.mp. (10)
24	"ro 7034067".mp. (0)
25	ro7034067.mp. (6)
26	7 or 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 (943)
27	6 and 26 (871)
28	limit 27 to clinical trial, all (35)
29	((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.) (5513187)
30	27 and 29 (343)
31	28 or 30 (347)
32	limit 31 to (english or german) (331)
33	remove duplicates from 32 (169)

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