Medicinrådet

Bilag til direkte indplacering af nusinersen højdosisregime (50/28 mg) i Medicinrådets evidensgennemgang vedrørende lægemidler til spinal muskelatrofi

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. nusinersen højdosisregime (50/28 mg)
2. Ansøgers endelige ansøgning vedr. nusinersen højdosisregime (50/28 mg)

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26.03.2026

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	Biogen
Lægemiddel	Spinraza (nusinersen)
Ansøgt indikation	Behandling af 5q spinal muskelatrofi (SMA)
Nyt lægemiddel / indikationsudvidelse	Nyt dosisregime

Prisinformation

Amgros har forhandlet følgende pris på to nye styrker af Spinraza (nusinersen):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Spinraza	12 mg	484.725,02	[redacted]	[redacted]	[redacted]	[redacted]
Spinraza	28 mg	614.612,97	[redacted]	[redacted]	[redacted]	[redacted]
Spinraza	50 mg	1.097.523,15	[redacted]	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros har en aftale på Spinraza 12 mg som løber indtil 31.07.2029 [redacted]

Information fra forhandlingen:

[redacted]

Konkurrencesituationen

Spinraza indgår i lægemiddelrekommandation og behandlingsvejledning vedr. lægemidler til SMA. Behandlingsvejledningen omhandler tre behandlinger Spinraza, Zolgensma (onasemnogene abeparvovec) og Evrysdi (risdiplam) som er vurderet ligeværdige indenfor forskellige patientpopulationer.

Baseret på vurderingsrapporten indplaceres det nye højdoseringsregime som et alternativ til den nuværende behandling med Spinraza i lavdosisregime. Det nye højdosisregime administreres færre gange i opstartsåret, mens antallet af doseringer er ens i de efterfølgende år.:
Det første år administreres i alt fire doser (to støddoser og to vedligeholdelsesdoser), mens det nuværende dosisregime kræver i alt seks doser der første år (fire støddoser og to vedligeholdelsesdoser). Antallet af vedligeholdelsesdoser (tre per år) de efterfølgende år er ens, jf. Tillæg til Medicinrådets evidensgennemgang vedrørende lægemidler til spinal muskelatrofi.

Lavdosisregime: støddosis 4*12 mg (dag 0, 14, 28 og 63) herefter 12 mg hver 4. måned.

Højdosisregime: støddosis 2*50 mg (dag 0 og 14) herefter 28 mg hver 4. måned.

Tabel 2 viser lægemiddeludgifterne til Spinraza for hhv. lavdosis og højdosis i opstartsåret.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient. ***Opstartsår:***

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/opstartsår (SAIP, DKK)
Spinraza (lavdosis)	12 mg	Støddosis: 12 mg på dag 0, 14, 28 og 63. Vedligeholdelse: 12 mg hver 4. måned	[redacted] (6 doser i opstartsåret)	[redacted]
Spinraza (højdosis)	28 mg og 50 mg	Støddosis: 50 mg dag 0 og 14. Vedligeholdelse: 28 mg hver 4. måned	[redacted] (2 doser á 50 mg i opstartsåret) [redacted] (2 doser á 28 mg i opstartsåret)	[redacted]

Tabel 3 viser lægemiddeludgifter til Spinraza for hhv. lavdosis og højdosis i et vedligeholdelsesår.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient. ***Vedligeholdelsesår.***

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling vedligeholdelsesår (SAIP, DKK)
Spinraza (lavdosis)	12 mg	Vedligeholdelse: 12 mg hver 4. måned	[redacted]	[redacted]
Spinraza (højdosis)	28 mg	Vedligeholdelse: 28 mg hver 4. måned	[redacted]	[redacted]

Status fra andre lande

Der er ingen information fra andre lande om anbefaling på de to vurderede nye styrker af Spinraza.

Opsummering

Leverandøren har ifm. lanceringen af disse nye styrker. De nye styrker skulle hjælpe patienterne så det bliver en lettere opstartsbehandling.

Application for the assessment of Nusinersen (Spinraza) (50/28 mg) by updating “Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til spinal muskelatrofi“

Contact information

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Abbreviations

AEs	Adverse events
CHOP INTEND	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CSF	Cerebrospinal fluid
DMT	Disease-modifying treatment
EMA	European Medicines Agency
EFS	Event free survival
HD	Higher dose
HFSME	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Exam-Part 2
HR	Hazard ratio
HRU	Healthcare resource utilization
IT	Intrathecal
LSM	Least-squares mean
NfL	Neurofilament levels
RULM	Revised Upper Limb Module
SD	Standard deviation
SE	Standard error
SMA	Spinal muscular atrophy
SMN	Survival motor neuron

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Spinraza®
Generic name	Nusinersen
Therapeutic indication as defined by EMA	Spinraza (50/28mg or 12/12mg) is indicated for the treatment of 5q Spinal Muscular Atrophy.
Marketing authorization holder in Denmark	Biogen
ATC code	M09AX07
Combination therapy and/or co-medication	NA
(Expected) Date of EC approval	19 January 2026
Has the pharmaceutical received a conditional marketing authorization?	NO
Accelerated assessment in the European Medicines Agency (EMA)	NO
Orphan drug designation (include date)	YES
Other therapeutic indications approved by EMA	NO
Other indications that have been evaluated by the DMC (yes/no)	NO
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	1 vial containing 28 mg (5.6 mg/ml) nusinersen 1 vial containing 50 mg (10 mg/ml) nusinersen

2. Summary table

[Provide the summary in the table below, maximum 2 pages.]

Summary	
Therapeutic indication relevant for the assessment	Spinraza (50/28mg or 12/12mg) is indicated for the treatment of 5q Spinal Muscular Atrophy.
Dosage regiment and administration:	Intrathecal injection of 50/28 mg, including a loading phase with two 50 mg doses administered 14 days apart, followed by a maintenance dose of 28 mg every 4 months (**50/28 mg dosage regimen**)
Choice of comparator [if any]	In our qualitative assessment of the safety of the **50/28 mg dosage regimen** the comparator will be the **low dosage regimen (12 mg) (1)** In the pivotal part B, of trail, DEVOTE the 50mg/28mg group compared to a **prespecified matched sham group from ENDEAR (2).** A comparison of the 50mg/28mg regimen and the 12mg regimen was not performed for the primary endpoint but was included as secondary outcomes (1).
Most important efficacy endpoints (Difference/gain compared to comparator)	The pivotal part B cohort met its primary endpoint, with a clinically and statistically significant improvement in change in CHOP INTEND score from baseline in infantile-onset patients observed with the 50mg/28mg group compared to the prespecified matched sham group from ENDEAR **(LSM difference: 26.19; 95% CI: 20.7 to 31.7, p<0.0001)** The assessment was conducted at Day 183 to match the design of ENDEAR and allow for a robust comparison for 50mg/28mg nusinersen against the sham control from ENDEAR. **Secondaries endpoints included in the treatment guideline:** Although DEVOTE (Part B) was designed to characterize directional differences between the 50mg/28mg and 12mg regimens, the comparison was not powered to demonstrate statistically significant differences between arms (1). Despite the relatively small study size, numerical improvements were demonstrated favouring the 50mg/28mg nusinersen regimen over the 12mg nusinersen regimen. **DEVOTE part B** In infantile-onset patients, compared to the 12mg nusinersen regimen, survival outcomes numerically favored the 50mg/28mg nusinersen regimen and a **30% reduction in risk of death or permanent ventilation was observed for the 50mg/28mg dose (overall survival HR: 0.730; 95% CI: 0.264 to 2.015; p=0.4821; event free survival HR: 0.701; 95% CI: 0.338 to 1.452; p=0.2775) , .** In Patients with later-onset SMA, motor function improvements, as measured by HFSME and RULM, numerically favored the 50mg/28mg nusinersen regimen over matched

	treated and sham groups from CHERISH (1). Least-squares mean (LSM) change from baseline to day 302 in HFMSE score: +3.3 (standard error 0.82, n=16, 50/28mg), +1.7 (standard error 0.55, n=32, matched 12/12mg), -0.3 (standard error 1.03, n=16, matched sham). Least-squares mean (LSM) change from baseline to day 302 in RULM score: +2.3 (standard error 0.61, n=16, 50/28mg), +1.8 (standard error 0.43, n=32, matched 12/12mg), 0.4 (standard error 0.66, n=16, matched sham). **DEVOTE part C** In a patient population, who were previously treated with the 12mg nusinersen regimen a mean **improvement of 1.8 (SD: 3.99) points on the Hammersmith Functional Motor Scale Expanded (HFMSE) and 1.2 (SD: 2.14) points on the Revised Upper Limb Module (RULM) was observed 10 months** after patients transitioned to receiving 50mg/28mg nusinersen.
Most important serious adverse events for the intervention and comparator	The 50mg/28mg nusinersen regimen was generally well tolerated and reported adverse events (AEs) were consistent with SMA and the known safety profile of the 12mg nusinersen regimen, with less frequent occurrence of serious AEs than in the 12mg nusinersen group. No treatment-related discontinuations were reported for the 50mg/28mg nusinersen regimen in the DEVOTE study and treatment-emergent adverse events were mild in severity. No cases of meningitis, hydrocephalus, renal failure or liver failure were reported, and no clinically relevant trends in hematology, blood chemistry, urinalysis, coagulation, vital signs or ECGs were detected. The 50mg/28mg nusinersen regimen was generally well tolerated, with reported AEs generally consistent with SMA and the known safety profile of the 12mg nusinersen regimen. Furthermore, with up to ten years of experience and thousands of patients treated globally, real-world evidence reassures that adminstration of 12mg nusinersen is associated with a favorable and well-tolerated long-term safety profile in individuals with SMA

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

SMA is a debilitating disease and persistent loss of motor function, muscle weakness, and disability affect all SMA patients across types, ages, and ambulatory status.

Figure 1 The Danish population, as described by the medicine council.

Type	Antal pt.	Nye pt. per år	Debut alder	Udviklingstrin (ubehandlet)	Overlevelse (ubehandlet)	SMN2-kopier [5]
0	-	-	Medfødt	Ingen	< 6 måneder	1
1	14[1]	1-2[1,2]	0-6 mdr.	Sidder aldrig	< 2 år	2-3
2	Ca. 90[2]	Ca. 2[2]	6-18 mdr.	Går aldrig	Fra 2 år til normal levetid[3]	3-4
3	Ca. 70[2]	1-2[3]	> 18 mdr.	Står og går, men bliver permanente kørestolsbrugere inden eller i voksenalder	Normal levetid	4
4	-	-	Voksen-alder[4]	Går i voksenårene	Normal levetid	4-5

Currently 3 treatments for SMA are recommended in the Danish SMA treatment guideline **(Medicinrådets behandlingsvejledning vedrørende lægemidler til spinal muskelatrofi (SMA)** - version 1.0").

Biogen applies for direct emplacement in the treatment guideline for SMA of treatment with nusinersen in the new dosing regimen 50/28 mg.

Ideally the new dosing regimen of 50/28 mg should be recommended as a treatment option for the same patient groups as the currently approved dosing regimen of 12 mg nusinersen. This dosing is already recommended, reimbursed and currently being used in Danish clinical practice.

In our pivotal study DEVOTE (part B, infantile onset SMA), the new dosing regimen 50/28 mg is compared to placebo, however there is a treatment arm with today's standard dose (12mg)' that is not powered to compare results on efficacy. Cost-comparison can be performed between the two dosing regimens of nusinersen 12mg and nusinersen 50/28 mg.

3.2 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Spinraza (50/28mg or 12/12mg) is indicated for the treatment of 5q Spinal Muscular Atrophy
Method of administration	Intrathecal injection
Dosing	Intrathecal injection of 50/28 mg, including a loading phase with two 50 mg doses administered 14 days apart, followed by a maintenance dose of 28 mg every 4 months (**50/28 mg dosage regimen**)

Overview of intervention	
Should the pharmaceutical be administered with other medicines?	NO
Treatment duration / criteria for end of treatment	Criteria for end of treatment is described in the current treatment guideline in "Tabel 1.7. STOP-kriterier ved tegn på manglede effekt af behandlingen"
Necessary monitoring, both during administration and during the treatment period	Monitoring is described in the current treatment guideline in "Tabel 1.6. Monitorering af effekt og bivirkninger for patienter i sygdomsmodificerende behandling for spinal muskelatrofi (SMA)" In the current guideline, in section 6.4 "Monitorering af effekt og bivirkninger", Tabel 6.2, lists the current level of monitoring. For high dose we expect the same level of monitoring as low dose
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Diagnostics is described in the current treatment guideline and includes a clinical diagnose and genetical verification of SMA type – this will remain the same for the 50/28mg regime.
Package size(s)	1 vial containing 28 mg (5.6 mg/ml) nusinersen 1 vial containing 50 mg (10 mg/ml) nusinersen

3.2.1 The intervention in relation to Danish clinical practice

Currently 3 treatments for SMA are recommended in the Danish SMA treatment guideline. While remarkable progress has been made in the treatment of SMA, living with SMA remains a high burden for the patients and some still experience suboptimal response to their treatments.

The current treatment options are all 1st generation treatments, that renders room for further development and improvement within treatment of this disease.

While exploring higher doses of other disease-modifying treatments are limited by toxicity concerns, in the DEVOTE study, the 50mg/28mg nusinersen regimen was generally well-tolerated, with reported adverse events generally consistent with SMA and the known safety profile of 12mg nusinersen (1, 3, 4)

The 50mg/28mg nusinersen regimen is expected to be a valuable part of the Danish treatment algorithm and could potentially address the remaining unmet needs for some patients and further optimize SMA treatment.

Both nusinersen regimens are indicated for a broad population of patients of any age and SMA type; the regulatory label of 50mg/28mg nusinersen permits its use among treatment-naïve and treatment-experienced patients.

- Patients treated with 12mg nusinersen may transition to the 50mg/28mg dose to maximize outcomes, upon clinicians' discretion.
- Newly diagnosed SMA patients eligible for nusinersen will initiate treatment on the 50mg/28mg nusinersen regimen.

Data supporting the use of 50mg/28mg nusinersen in SMA patients with previous EVRYSDI exposure will be collected in ASCEND (5)

4. Overview of literature

Table 1 Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period (days)
DEVOTE part A NCT04089566 REF 4 Finkel RS,et al J Neuromuscul Dis. 2023;10(5):813-23	An open-label dose escalation study to characterize safety and tolerability of the 28mg nusinersen regimen	302 days	Start: 26-03-2020 Completion: 30-05-2024	Participants aged 2–15 years with SMA symptom onset at ≥6 months life expectancy > 2 years	Nusinersen 28/28mg Intrathecal injection	None	AE (applies to all patient groups)	Primary: Safety and tolerability of nusinersen based on The incidence of treatment-emergent AEs (TEAEs), including serious AEs, and clinical and laboratory safety parameters.
Devote part B NCT04089566 REF 1 . Crawford T; et al.,. 29th Annual Congress of the World Muscle Society; 8-12 October; Prague, Czechia 2024.	A randomized, double-blind evaluation of the safety and efficacy of 50/28mg nusinersen in treatment-naïve infantile-onset (pivotal) and later-onset (supportive) participants	302 days	Start: 26-03-2020 Completion: 30-05-2024	Infantile onset SMA (N = 75) and later onset SMA (N = 24)	Nusinersen 50/28mg Intrathecal injection	ENDEAR matched sham DEVOTE 12/12mg	AE (applies to all patient groups) Outcome measures for SMA type 1 and pre-symptomatic infants, as well as for SMA type 2 and type 3.	Primary: CHOP-INTEND (183) Other secondaries: CHOP-INTEND (302), HINE-2 (change) (302) Later-onset: HFMSE (302), RULM (302)

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period (days)
REF 6. Crawford TO, et al. Muscular Dystrophy Association (MDA) – Clinical and Scientific Conference, March 16–19, 2025. Dallas, TX, USA. Poster data, manuscript submitted								
Devote part C NCT04089566 REF 1. Crawford T; et al.,. 29th Annual Congress of the World Muscle Society; 8-12 October; Prague, Czechia 2024.	An open-label, safety and efficacy evaluation in children and adults with infantile-onset or later-onset SMA who transitioned from the 12/12mg to the 50/28mg regimen	302 days	Start: 26-03-2020 Completion: 30-05-2024	Participants were aged between 4 and 65 years and had been receiving the approved 12/12 mg dose of nusinersen	Nusinersen 50/28mg Intrathecal injection	None	AE (applies to all patient groups) Outcome measures for SMA type 2 and type 3.	Primary: Adverse events and serious adverse events (302) Other secondary: HFMSE (302), RULM (302),

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period (days)
REF 6. Crawford TO, et al. Muscular Dystrophy Association (MDA) – Clinical and Scientific Conference, March 16–19, 2025. Dallas, TX, USA. Poster data, manuscript submitted				for a median of 3.9 years before entering Part C.				

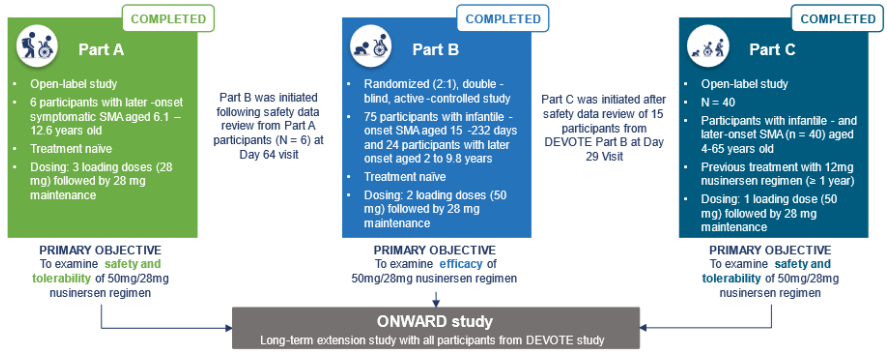
5. Clinical Question:

What evidence exists regarding potential differences in clinical outcomes between the 50/28 mg and 12/12 mg nusinersen dosing regimens in patients with SMA?

5.1 Efficacy of **50/28 mg nusinersen** compared to to **sham control** and **12 mg nusinersen** for patients SMA

5.1.1 Relevant studies

Figure 2. DEVOTE Study Design



SMA = spinal muscular atrophy Sources: (1,)

DEVOTE Study Design

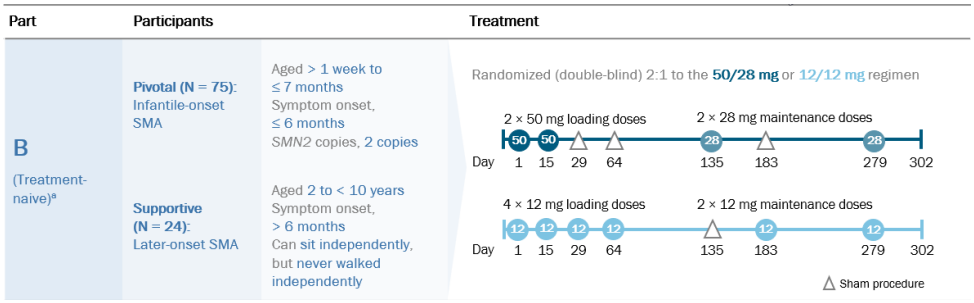
DEVOTE was a 3-part Phase 2/3 study evaluating efficacy, safety and tolerability of the 50mg/28mg nusinersen regimen.

Figure 3. Part A was the initial safety cohort

Part	Participants		Treatment
A (Treatment-naive)	Later-onset SMA (N = 6)	Aged 2–15 years Symptom onset, > 6 months Life expectancy, > 2 years	Open-label **28/28 mg** regimen 3 × 28 mg loading doses 2 × 28 mg maintenance doses Day 1 15 29 149 269 302

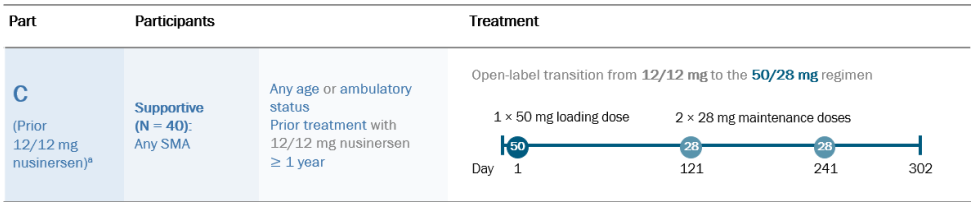
Part A was an open-label dose escalation study in a total of 6 treatment-naïve patients with later-onset SMA (age 2-15 years) to characterize safety and tolerability of the 28mg nusinersen regimen. All 6 patients received the higher dose. Safety findings in Part A supported further development of the 50mg/28mg nusinersen regimen in Parts B and C.

Figure 4. Part B was a RCT in treatment-naive participants, with a pivotal infantile-onset cohort and a supportive later-onset cohort



Part B was a double-blind, randomized controlled study including a total of 75 infantile-onset (age ≤7 months) and 24 later-onset (age 2 to <10 years) SMA patients to characterize efficacy and safety of the 50mg/28mg nusinersen regimen. Patients were randomized 2:1 to the 50mg/28mg nusinersen regimen or 12mg nusinersen regimen. In Part B, 50 infantile-onset and 16 later-onset patients received the 50mg/28mg dose, while 25 infantile-onset and 8 later-onset patients received the 12mg dose.

Figure 5. Part C was open-label with treatment-experienced participants transitioning from 12 mg nusinersen



Part C was an open-label study in 40 patients of any age (including adults) transitioning from the 12mg nusinersen regimen to the 50mg/28mg nusinersen regimen to characterize long-term safety, tolerability and efficacy of a the 50mg/28mg dose. Patients transitioned to the 50mg/28mg nusinersen regimen after at least 1 year of treatment with the 12mg nusinersen regimen.

The primary objective of the pivotal Part B (infantile treatment-naïve cohort) was to assess the efficacy of the 50mg/28mg nusinersen regimen. Data from Part A (safety), Part B later-onset, and Part C were intended as exploratory and supportive. (4).

Given the availability of approved DMTs at the time of DEVOTE initiation and the progressive nature of SMA, a placebo-controlled study was not considered ethical. In Part B of DEVOTE, to allow for a robust assessment of the efficacy and safety of 50mg/28mg nusinersen, a matched sham-controlled arm from ENDEAR was utilized (1).Inclusion / exclusion criteria for DEVOTE were almost identical to ENDEAR and an exhaustive matching algorithm facilitated a comparison of the ENDEAR sham and DEVOTE treatment arms.

The infantile-onset Part B study was powered to demonstrate superiority of 50mg/28mg nusinersen regimen over a matched sham arm, whilst secondary

comparisons versus the 12mg nusinersen regimen were also performed but were not powered to show superiority Part C was an open-label extension investigating treatment-experienced participants transitioning from 12 mg nusinersen.

5.1.2 Comparability of studies

Not applicable, as indirect comparison or NMA has been used in the application.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

The DEVOTE study enrolled a total of 145 patients across a range of ages and SMA types. In total, 112 patients received the 28 mg nusinersen regimen, distributed as follows: 6 patients in Part A, 66 patients in Part B, and 40 patients in Part C of the study (4,). The 12 mg nusinersen regimen was administered to 33 patients in Part B of DEVOTE.

Within the 28 mg nusinersen cohort, 52 patients had Infantile-Onset SMA (Parts B and C), and 60 patients had Later-Onset SMA (Parts A, B, and C). Additionally, 24 patients were aged over 18 years at the time of their first dose, and in Part C, the age at first dose ranged from 4 to 65 years. Both ambulatory and non-ambulatory patients were included in the study.

Overall, the DEVOTE population represents a broad spectrum of SMA patients, that are comparable to Danish patients eligible for treatment.

Baseline characteristics are described in detail in the tables below.

Table 2.1 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (DEVOTE part A)

Devote A	28/28 mg (n = 6)
Male, n (%)	5 (83)
Age at fi rst screening, years, range	6.1–12.6
Age at SMA diagnosis, months, range	8–36
CHOP-INTEND total score	9–139
SMN2 gene copies, n (%)	
3	3 (50)
4	3 (50)
Motor milestones ever achieved, n (%)	
Sitting without support	6 (100)
Standing without support	5 (83)
Walking with support	5 (83)
Walking without support	5 (83)
Motor milestones at screening, n (%)	
Sitting without support	6 (100)
Standing without support	3 (50)
Walking with support	3 (50)
Walking without support	3 (50)
Wheelchair use at screening, n (%)	4 (67)
Baseline HFMSE score,c range	6–63
Baseline RULM score,d range	7–37

Table 2.2 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (DEVOTE part B (Infantile-Onset))

Devote B (Infantile-Onset)				
		50/28 mg (n = 50)	12/12 mg (n = 25)	Matched sham (ENDEAR)[a] (n = 20)
Age at first dose, days		128.7 (64.06) [15–232]	115.5 (56.23) [20–217]	154.2 (55.70) [30–235]
Age at symptom onset, weeks		7.5 (5.26) [1–21]	5.8 (4.44) [2–20]	8.8 (5.11) [1–19]
Disease duration at informed consent, weeks		9.6 (5.29) [0–20]	9.1 (6.11) [0–25]	11.1 (4.92) [0–21]
CHOP-INTEND total score		20.9 (10.23) [5–56]	19.9 (9.63) [0–39]	23.6 (5.84) [11–33]
HINE-2 score		1.4 (1.36) [0–5]	1.4 (1.29) [0–4]	1.3 (1.02) [0–4]
Plasma NfL, pg/mL	N	40	22	20
	Mean (SD) [range]	304.7 (283.9) [78.6–1480.0]	329.4 (175.9) [83.9–678.0]	287.3 (140.4) [119.0–691.0]
	Geometric mean (95% CI)	253.3 (190.2, 291.0)	287.6 (225.9, 366.2)	260.3 (211.2, 320.9)
Geography,[b] n (%)	Asia-Pacific	20 (40)	8 (32)	2 (10)
	Europe	12 (24)	7 (28)	5 (25)
	North America	1 (2)	0	13 (65)
	South/Central America	17 (34)	10 (40)	0

Table 2.3 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (DEVOTE part B (Later-Onset))

Devote Part B, Later-Onset					
		50/28 mg (DEVOTE) (n = 16)	12/12 mg (DEVOTE) (n = 8)	Matched sham (CHERISH[a]) (n = 16)	Matched 12/12 mg (CHERISH[b]) (n = 32)
Age at first dose, years		6.1 (2.59) [2.1–9.8]	5.7 (3.00) [2.0–9.3]	5.1 (1.82) [2.1–7.5]	5.5 (1.83) [2.1–9.2]
Age at symptom onset, months		11.1 (4.11) [6.0–22.0]	9.9 (2.36) [7.0–15.0]	11.9 (3.85) [7.0–20.0]	10.7 (3.49) [6.0–18.0]
SMN2 copy number, n (%)	2	0	1 (13)	3 (19)	3 (9)
	3	15 (94)	7 (88)	12 (75)	28 (88)
	≥4	1 (6)	0	1 (6)	1 (3)
HFMSE score		20.3 (10.05) [10.0–42.0]	13.8 (4.59) [10.0–22.0]	21.4 (7.49) [13.0–34.0]	21.8 (8.60) [10.0–43.0]
RULM score		20.2 (5.31) [12.0–30.0]	14.9 (5.96) [4.0–25.0]	20.9 (4.99) [12.0–28.0]	20.6 (6.04) [11.0–33.0]
Plasma NfL, pg/mL	Mean (SD) [range]	15.0 (14.45) [3.1–58.6]	9.7 (3.32) [6.1–16.9]	14.0 (10.1) [5.3–46.4]	13.2 (9.6) [3.5–47.4]
	Geometric mean (95% CI)	10.9 (7.12, 16.59)	9.3 (7.14, 11.98)	11.8 (8.62, 16.22)	10.6 (8.16, 13.79)

Table 2.4 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (DEVOTE part C)

Devote Part C Median [range] or n (%)		Non-ambulatory (n = 19)	Ambulatory (n = 21)	Total (N = 40)
Age at first study dose, years		12.3 [4–60]	27.0 [6–65]	23.0 [4–65]
Child (< 18 years)		13 (68.4)	3 (14.3)	16 (40.0)
Adult (≥ 18 years)		6 (31.6)	18 (85.7)	24 (60.0)
Time on 12/12 mg nusinersen, years		3.8 [2–5]	3.9 [1–5]	3.9 [1–5]
Age of symptom onset, months		11.5 [4–36]	72.0 [12–192]	24.0 [4–192]
SMA Type				
Infantile-onset		2 (11)	0 (0)	2 (5)
Later-onset		17 (89)	21 (100)	38 (95)
SMN2 copy				
Number, n	2	2 (10.5)	1 (4.8)	3 (7.5)
	3	16 (84.2)	4 (19.0)	20 (50)
	4	0	14 (66.7)	14 (35)
	Other	1 (5.3)	2 (9.5)	3 (7.5)
Highest milestone achieved	Sat without support	15 (78.9)	0	15 (37.5)
	Stood without support	1 (5.3)	0	1 (2.5)
	Walked with support	3 (15.8)	0	3 (7.5)
	Walked (at least 15 feet) independently	0	21 (100)	21 (52.5)

5.2 Comparative analyses of efficacy and safety

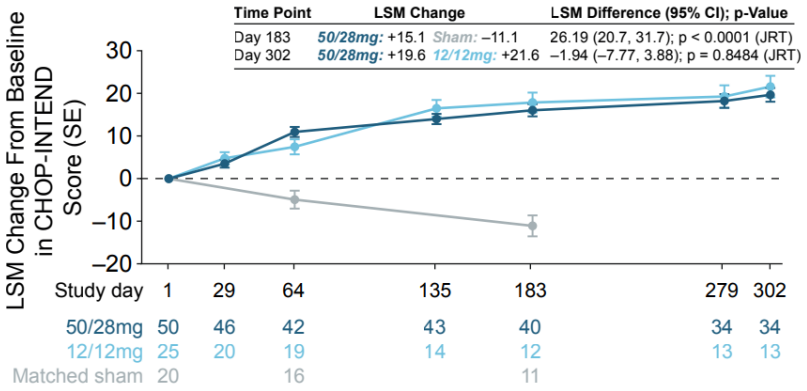
5.2.1 Efficacy and safety – results per study

DEVOTE part B (1)

The 50mg/28mg nusinersen regimen delivers significantly greater improvements in motor function compared to sham control, in children with infantile-onset SMA.

The pivotal part B cohort met its primary endpoint, with a clinically and statistically significant improvement in change in CHOP INTEND score from baseline in infantile-onset patients observed with the 50mg/28mg group compared to the prespecified matched sham group from ENDEAR (LSM difference: 26.19; 95% CI: 20.7 to 31.7, p<0.0001) (Figure 6.). The assessment was conducted at Day 183 to match the design of ENDEAR and allow for a robust comparison for 50mg/28mg nusinersen against the sham control from ENDEAR.

Figure 6. Change in CHOP INTEND in Infantile-Onset SMA

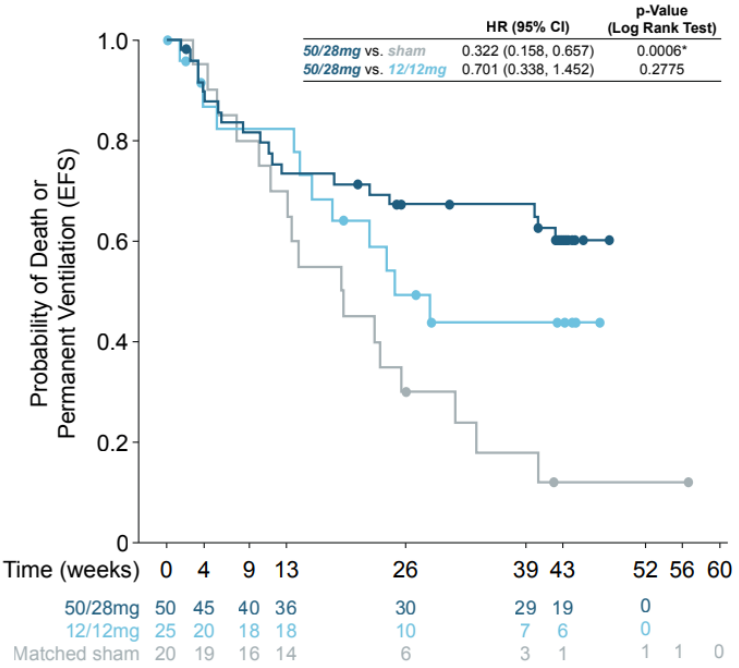


CHOP INTEND = The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; JRT = joint rank test; LSM = least-squares mean; SE = standard error. Source: (1)

In infantile-onset SMA, the 50mg/28mg nusinersen regimen numerically improves survival, reduces the risk of death, and decreases the need for permanent ventilation versus the 12mg nusinersen regimen.

In infantile-onset patients, the 50mg/28mg nusinersen regimen increased overall survival (overall survival HR: 0.279; 95% CI: 0.112 to 0.696; p=0.0012 [nominally significant]) and reduced the risk of death or permanent ventilation by 67.8% compared to the sham control group (event free survival HR: 0.322; 95% CI: 0.158 to 0.657; p=0.0006 [nominally significant]). Compared to the 12mg nusinersen regimen, survival outcomes numerically favored the 50mg/28mg nusinersen regimen and a 30% reduction in risk of death or permanent ventilation was observed for the 50mg/28mg dose (overall survival HR: 0.730; 95% CI: 0.264 to 2.015; p=0.4821; event free survival HR: 0.701; 95% CI: 0.338 to 1.452; p=0.2775) (Figure 7.).

Figure 7. Probability of Death or Permanent Ventilation (Event Free Survival) in Infantile-Onset SMA



Indicates nominally significant. CI = confidence interval; EFS = event free survival; HR = hazard ratio
Source: (1)

Compared with the 12/12 mg group, proportionately fewer participants in the 50/28 mg group were hospitalized or had serious respiratory events, and time spent in hospital was lower in the 50/28 mg group (figure 8)

Figure 8 hospitalizations due to SAEs and serious respiratory events Infantile-Onset SMA

	50/28 mg (n = 50)	12/12 mg (n = 25)
Hospitalizations due to SAEs		
Participants with no hospitalizations due to SAEs, n (%)	31 (62)	11 (44)
Adjusted annual rate of hospitalization due to SAEs,[a] (95% CI)	0.8 (0.51, 1.22)	1.4 (0.80, 2.27)
Mean proportion of time hospitalized due to an SAE, %	15.3	20.8
Serious respiratory events		
Participants with no serious respiratory events, n (%)	24 (48)	9 (36)
Adjusted annual rate of serious respiratory events,[a] (95% CI)	1.8 (1.17, 2.68)	2.1 (1.16, 3.72)

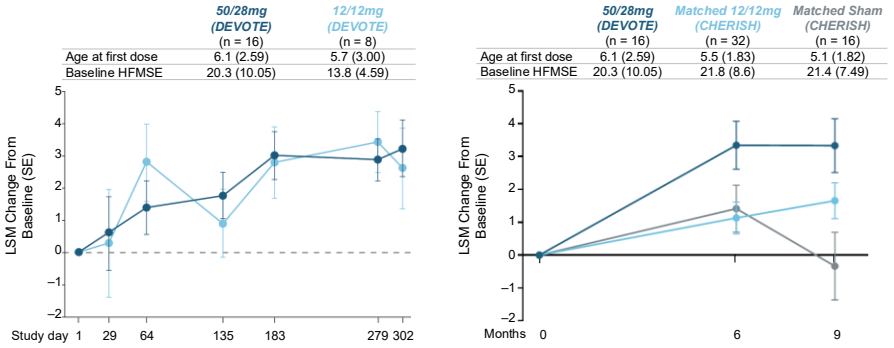
Source: (1, 6)

In later-onset SMA, the 50mg/28mg nusinersen regimen delivers numeric improvements in motor function when compared to the 12mg nusinersen regimen and matched treated and sham controls from CHERISH.

Additional evidence of improved motor function with the 50 mg/28 mg nusinersen regimen was observed in Part B of the DEVOTE study. Patients with later-onset SMA receiving the 50 mg/28 mg regimen demonstrated efficacy comparable to the 12 mg nusinersen dose at Day 302, based on HFMSE and RULM scores (Figures 9 and 10).

However, motor function improvements, as measured by HFSME and RULM, numerically favored the 50mg/28mg nusinersen regimen over matched treated and sham groups from CHERISH (1). Least-squares mean (LSM) change from baseline to day 302 in HFMSE score: +3.3 (standard error 0.82, n=16, 50/28mg), +1.7 (standard error 0.55, n=32, matched 12/12mg), -0.3 (standard error 1.03, n=16, matched sham). Least-squares mean (LSM) change from baseline to day 302 in RULM score: +2.3 (standard error 0.61, n=16, 50/28mg), +1.8 (standard error 0.43, n=32, matched 12/12mg), 0.4 (standard error 0.66, n=16, matched sham).

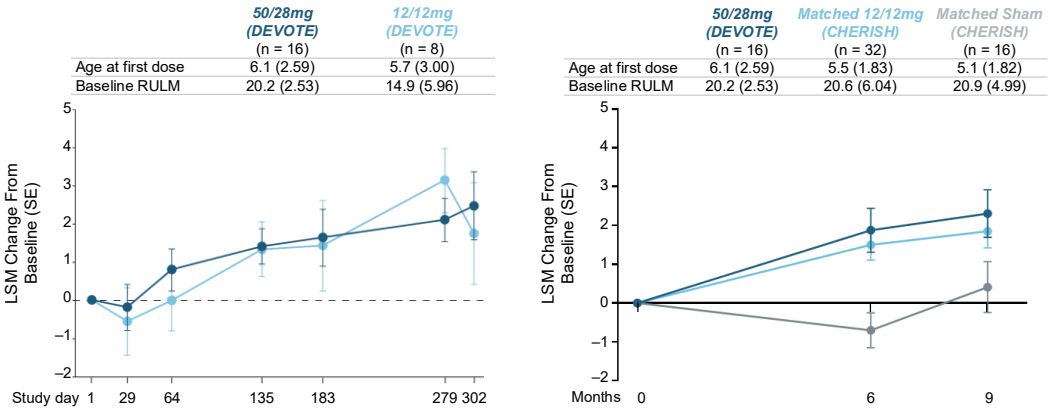
Figure 9. Mean Change in HFMSE Score in Later-Onset SMA*



*Data in the tables represent mean (SD). In the left panel, study Day 1 is baseline, and multiple imputation was used for missing data. In the right panel, data were based on multiple imputation and ANCOVA with treatment as a fixed effect and adjustment for each participants' age at first dose, baseline log plasma NfL, and baseline score. ANCOVA = analysis of covariance; HFMSE = Hammersmith Functional Motor Scale Expanded; LSM = Least-squares mean; NfL = Neurofilament levels; SD = standard deviation; SE = standard error

Sources: (1)

Figure 10. Mean Change in RULM Score in Later-Onset SMA*



*Data in the tables represent mean (SD). In the right panel, study Day 1 is baseline, and multiple imputation was used for missing data. In the right panel, data were based on multiple imputation and ANCOVA with treatment as a fixed effect and adjustment for each participants' age at first dose, baseline log plasma NfL, and baseline score.

ANCOVA = analysis of covariance; LSM = Least-squares mean; NfL = Neurofilament levels; RULM = Revised Upper Limb Module; SD = standard deviation; SE = standard error

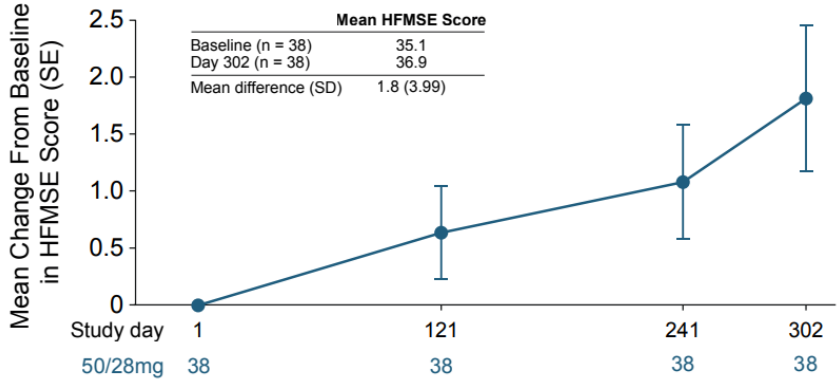
Source: (1).

DEVOTE part C (1)

The 50mg/28mg nusinersen regimen showed clinically relevant improvements in motor function in a diverse population of SMA patients previously well-treated with the 12mg nusinersen regimen, regardless of age and severity.

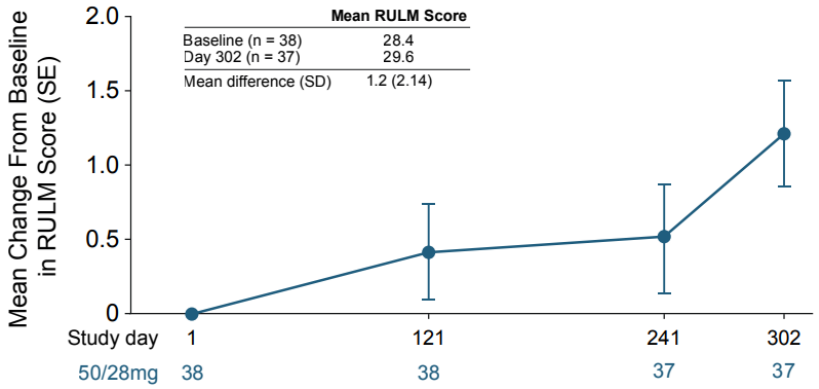
Supportive evidence in a diverse and highly treatment-experienced patient population, aged 4-65, who were previously treated with the 12mg nusinersen regimen for a median of 3.9 years before entering the study, highlight that patients can continue to achieve improvements with the 50mg/28mg nusinersen regimen after being treated on an existing therapy, regardless of age or severity. A mean improvement of 1.8 (SD: 3.99) points on the Hammersmith Functional Motor Scale Expanded (HFMSE) and 1.2 (SD: 2.14) points on the Revised Upper Limb Module (RULM) was observed 10 months after patients transitioned to receiving 50mg/28mg nusinersen (Figure 11 and 12).

Figure 11. Mean Change in HFMSE Score in Infantile- and Later-Onset SMA, Part C



HFSME = Hammersmith Functional Motor Scale Expanded; SD = standard deviation; SE = standard error; SMA = spinal muscular atrophy
Source: (1)

Figure 12. Mean Change in RULM Score in Infantile- and Later-Onset SMA



RULM = Revised Upper Limb Module; SD = standard deviation; SE = standard error; SMA = spinal muscular atrophy. Source: (1).

Safety:

Safety will be described in detail in section 5.2.2

Conclusion:

The 50mg/28mg nusinersen regimen delivers significantly greater improvements in motor function compared to sham control, in children with infantile-onset SMA.

Although DEVOTE Part B was designed to characterize directional differences between the 50mg/28mg and 12mg regimens, the comparison was not adequately powered to demonstrate statistically significant differences between arms.

Despite the relatively small study size, numerical improvements on respiratory events (OS, EFS), and hospitalizations were demonstrated favoring the 50mg/28mg nusinersen regimen over the 12mg nusinersen regimen.

In later-onset SMA, the 50mg/28mg nusinersen regimen delivers numeric improvements in motor function when compared to matched treated and sham controls from CHERISH

In DEVOTE part C, the 50mg/28mg nusinersen regimen showed clinically relevant improvements in motor function in a diverse population of SMA patients previously well-treated with the 12mg nusinersen regimen, regardless of age and severity.

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

DEVOTE Part A, B, C Safety Results (Infantile- and Later-Onset SMA)

The 50mg/28mg nusinersen regimen was generally well tolerated, with reported AEs generally consistent with SMA and the known safety profile of the 12mg nusinersen regimen (Figure 13). Among patients treated with the 50mg/28mg nusinersen regimen, there were no cases of meningitis, hydrocephalus, or renal/liver failure reported, and no clinically relevant trends related to hematology, blood chemistry, urinalysis, coagulation,

vital signs, or ECGs detected. The percentage of serious adverse events was lower with 50mg/28mg nusinersen compared to 12mg nusinersen, although it cannot be concluded that 50mg/28mg nusinersen leads to fewer serious adverse events. No new safety signals were reported across both treatment-naïve patients and those transitioning from 12mg nusinersen.

Figure 13. Summary of Adverse Events in DEVOTE Part A, B and C

Participants, n (%)	PART A	PART B					PART C
	Later-onset SMA	Infantile-onset SMA			Later-onset SMA		Infantile- and later-onset SMA
	50mg/28mg nusinersen regimen (n = 6)	50mg/28mg nusinersen regimen (n = 50)	12mg nusinersen regimen (n = 25)	Matched sham (ENDEAR study) (n = 20)	50mg/28mg nusinersen regimen (n = 16)	12mg nusinersen regimen (n = 8)	50mg/28mg nusinersen regimen (n = 40)
Any AE, n (%)	4 (67)	45 (90)	22 (88)	20 (100)	14 (87.5)	7 (87.5)	37 (92.5)
Severity[a], n (%)							
Mild	4 (67)	13 (26)	3 (12)	0	10 (62.5)	2 (25.0)	18 (45.0)
Moderate	1 (17)	10 (20)	5 (20)	2 (10)	3 (18.8)	4 (50.0)	14 (35.0)
Severe	2 (33)	22 (44)	14 (56)	18 (90)	1 (6.3)	1 (12.5)	5 (12.5)
Treatment-related AE[b], n (%)	0	3 (6)	1 (4)	4 (20)	1 (6.3)	0	8 (20.0)
SAE[c], n (%)	0	30 (60)	18 (72)	19 (95)	2 (12.5)	4 (50.0)	6 (15.0)
Treatment-related SAE, n (%)	0	0	1 (4)[d]	0	0	0	0
AE leading to treatment withdrawal, n (%)	0	0	0	NA	0	0	0
AE leading to study withdrawal, n (%)	0	10 (20)	6 (24)	11 (55)	0	0	0
AE leading to death, n (%)	0	10 (20)	6 (24)	11 (55)	0	0	0

AE = adverse event; ECG = electrocardiogram; NA = not assessed; SAE = serious adverse event;Sources: (1, 4, 6).

Postmarketing experience, nusinersen 12mg/12mg: Safety

Real-world evidence has been instrumental in elucidating the risk-benefit profile of nusinersen (12mg/12mg) in patients not included in the pivotal clinical trials (9). Safety events are detailed in Table 3, which also provides corresponding management recommendations. The label continues to recommend that clinicians evaluate urine protein, platelet count, and coagulation parameters at baseline and prior to each administration. While monitoring of platelet counts and coagulation studies remains necessary, there have been no documented instances of thrombocytopenia resulting in clinically significant bleeding. Similarly, although elevated urine protein levels were observed during clinical trials, no severe renal toxicity related to nusinersen has been reported. The side effect profile observed in real-world settings closely mirrors that identified in clinical trials. Adverse events associated with lumbar puncture (LP) procedures—such as headache, nausea, vomiting, back pain, and occasional cases of post-lumbar puncture syndrome (PLPS)—are among the most frequent. Rare incidences of meningitis and hydrocephalus have also been reported in patients treated with nusinersen. Notably, hydrocephalus has been detected at a fourfold higher rate in untreated SMA patients compared to unaffected controls, suggesting that these cases may be attributable to the underlying disease rather than to nusinersen itself. Consistent with clinical trial findings, respiratory infections remain common in real-world patient populations. Of particular note, a large adult cohort reported respiratory infections in only 5.4% of participants—a substantially lower incidence than observed in clinical trials .

This discrepancy underscores the likelihood that infection rates reported in paediatric trials are more closely associated with patient age and exposure factors than with the medication.

Overall, with up to ten years of experience and thousands of patients treated globally, real-world evidence demonstrates that adminstration of nusinersen is associated with a favorable and well-tolerated long-term safety profile in individuals with SMA.

Table 3, Reported side effects of Spinraza 12mg and suggested management considerations.

adapted from Matesanz and Finkel, 2025 (9)

Side effect	Comments/management
Thrombocytopenia/coagulation abnormalities	- Check platelet count and coagulation studies prior to each dose - If platelet count <50 µL, hold dose
Renal toxicity	- Quantitative spot urine protein testing at baseline and prior to each dose - If spot protein level > 0.2 g/L, repeat testing and consider further evaluation
Post lumbar puncture events (back pain, headache, and/or vomiting)	- Analgesics, anti-emetics, increased fluids - For severe cases, may require bed rest or IV caffeine - If repeated severe episodes continue despite supportive treatment, consider switch to alternative agent
Meningitis	- Rare cases reported - Complete repeat lumbar puncture with cell counts, protein, glucose, viral studies, and bacterial culture if patient develops clinical signs/symptoms concerning for meningitis - Start broad spectrum antibiotics while awaiting culture results - If recurrent episodes of aseptic meningitis, consider switch to alternative treatment - Consider brain imaging for hydrocephalus
Respiratory infections and atelectasis	- Rates of respiratory infections seen at similar rates between patients who received nusinersen and controls - Serious rates of atelectasis are higher in those treated with nusinersen compared to controls - Given decreased respiratory reserve in some patients with SMA, careful assessment of respiratory status should be performed by anesthesia/sedation team prior to each injection, and treatment should be postponed in those with active signs/symptoms of infection
Hydrocephalus	- Counsel patients on warning signs of hydrocephalus - Order CNS imaging if patient develops enlarging head circumference, vomiting not responsive to conservative management, irritability, lethargy

6. References

1. Crawford TO, Finkel RS, Mercuri E, Day JW, Montes J, del Mar Garcia Romero M, et al. Exploring higher doses of nusinersen in spinal muscular atrophy (SMA): final results from Parts B and C of the 3-part DEVOTE study. Presented at: The 29th Annual Congress of the World Muscle Society (WMS) October 08–12, 2024. Prague, Czechia.
2. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. The New England journal of medicine. 2017;377(18):1723-32.
3. Finkel RS, Ryan MM, Pascual Pascual SI, Day JW, Mercuri E, De Vivo DC, et al. Scientific rationale for a higher dose of nusinersen. Annals of clinical and translational neurology. 2022;9(6):819-29.
4. Finkel RS, Day JW, Pascual Pascual SI, Ryan MM, Mercuri E, De Vivo DC, et al. DEVOTE Study Exploring Higher Dose of Nusinersen in Spinal Muscular Atrophy: Study Design and Part A Results. J Neuromuscul Dis. 2023;10(5):813-23.
5. A Phase 3b Study to Evaluate Higher Dose Nusinersen (BIIB058) in Patients With Spinal Muscular Atrophy Previously Treated With Risdiplam. https://clinicaltrials.gov/study/NCT05067790. https://clinicaltrials.gov/study/NCT04089566?term=NCT04089566&rank=1.
6. Crawford TO, et al. Muscular Dystrophy Association (MDA) – Clinical and Scientific Conference, March 16–19, 2025. Dallas, TX, USA.

Appendix A. Main characteristics of studies included

Table 4. Main characteristic of studies included

Trial name: DEVOTE	NCT number: NCT04089566
Objective	The primary objectives of this study are to examine the clinical efficacy of nusinersen administered intrathecally at higher doses to participants with spinal muscular atrophy (SMA), as measured by change in Children's Hospital of Philadelphia-Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score (Part B); to examine the safety and tolerability of nusinersen administered intrathecally at higher doses to participants with SMA (Parts A and C).
Publications – title, author, journal, year	**DEVOTE Study Exploring Higher Dose of Nusinersen in Spinal Muscular Atrophy: Study Design and Part A Results** Finkel RS, et al. Journal of Neuromuscular Diseases 10 (2023) 813–823
Study type and design	DEVOTE was a 3-part Phase 2/3 study evaluating efficacy, safety and tolerability of the 50mg/28mg nusinersen regimen **Part A** was an open-label dose escalation study in treatment-naïve patients with later-onset SMA (age 2-15 years) All patients received the high dose. Participants received 3 loading doses of 28 mg of nusinersen, intrathecally (IT), on Days 1, 15 and 29 followed by 2 maintenance doses of 28 mg on Days 149 and 269. **Part B** was a double-blind, randomized controlled study including infantile-onset (age ≤7 months) and later-onset (age 2 to <10 years) SMA patients. Patients were randomized 2:1 to the 50mg/28mg nusinersen regimen or 12mg nusinersen regimen. Participants received following dosing: **12mg nusinersen group**: 4 loading doses of 12 mg of nusinersen, IT, on Days 1, 15, 29, and 64 followed by 2 maintenance doses of 12 mg on Days 183 and 279. Sham procedure was administered on Day 135 **50mg/28mg nusinersen group:** 2 loading doses of 50 mg of nusinersen, IT, on Days 1 and 15 followed by 2 maintenance doses of 28 mg on Days 135 and 279. Sham procedure was administered on Days 29, 64 and 183. **Part C** was an open-label study in patients of any age (including adults) transitioning from the 12mg nusinersen regimen to the 50mg/28mg nusinersen regimen. Patients transitioned to the 50mg/28mg nusinersen regimen after at least 1 year of treatment with the 12mg nusinersen regimen.

Trial name: DEVOTE	NCT number: NCT04089566
	Participants who had been receiving the 12 mg dose for at least 1 year prior to entry, received a single bolus dose of 50 mg of nusinersen, IT, on Day 1 (4 months after their most recent maintenance dose of 12 mg) followed by 2 maintenance doses of 28 mg on Days 121 and 241.
Sample size (n)	**Part A:** 28/28 mg Nusinersen (6) **Part B:** Infantile-Onset SMA: 12/12 mg Nusinersen (25) **Part B:** Infantile-Onset SMA: 50/28 mg Nusinersen (50) **Part B**: Later-Onset SMA: 12/12 mg Nusinersen (8) **Part B**: Later-Onset SMA: 50/28 mg Nusinersen (16) **Part C**: 50/28 mg Nusinersen (40)
Main inclusion criteria	Key Inclusion Criteria: Part A, B and C: - Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote) Part A: • Onset of clinical signs and symptoms consistent with SMA at > 6 months (> 180 days) of age (i.e., later-onset SMA) • Age 2 to ≤ 15 years, inclusive, at the time of informed consent Part B: • Participants with SMA symptom onset ≤ 6 months (≤ 180 days) of age (infantile onset) should have age > 1 week to ≤ 7 months (≤ 210 days) at the time of informed consent • Participants with SMA symptom onset > 6 months (> 180 days) of age (later onset): ○ Age 2 to < 10 years at the time of informed consent ○ Can sit independently but has never had the ability to walk independently ○ HFMSE score ≥ 10 and ≤ 54 at Screening Part C: - Currently on nusinersen treatment at the time of Screening, with the first dose being at least 1 year prior to Screening Part C Cohort 1: - Participants of any age (individuals ≥18 years of age at Screening must be ambulatory) Part C Cohort 2: • Participants ≥18 years of age at Screening (can be ambulatory or nonambulatory)

Trial name: DEVOTE	NCT number: NCT04089566
	• HFMSE total score ≥4 points at Screening • RULM entry item A score ≥3 points at Screening

Main exclusion criteria	Key Exclusion Criteria:
	Part A, B and C:
	• Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period
	• Presence of an implanted shunt for the drainage of cerebrospinal fluid (CSF) or of an implanted central nervous system (CNS) catheter
	• Hospitalization for surgery, pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose
	Part A:
	• Respiratory insufficiency, defined by the medical necessity for invasive or noninvasive ventilation for > 6 hours during a 24-hour period, at Screening
	• Medical necessity for a gastric feeding tube
	• Treatment with an investigational drug given for the treatment of SMA, biological agent, or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening or anytime during the study; any prior or current treatment with any survival motor neuron-2 gene (SMN2)-splicing modifier or gene therapy; or prior antisense oligonucleotide treatment, or cell transplantation
	Part B:
	• Treatment with an investigational drug including but not limited to the treatment of SMA, biological agent, or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening or anytime during the study; any prior or current treatment with any SMN2-splicing modifier or gene therapy; or prior antisense oligonucleotide treatment, or cell transplantation
	• Participants with SMA symptom onset > 6 months (> 180 days) of age (later onset):
	  ○ Respiratory insufficiency, defined by the medical necessity for invasive or noninvasive ventilation for > 6 hours during a 24-hour period, at Screening
	  ○ Medical necessity for a gastric feeding tube

Trial name: DEVOTE	NCT number: NCT04089566
	• Participants with SMA symptom onset ≤ 6 months (≤ 180 days) of age (infantile onset): Signs or symptoms of SMA present at birth or within the first week after birth Part C: • Concurrent or previous participation and/or administration of nusinersen in another clinical study • Concomitant or previous administration of any SMN2-splicing modifier (excluding nusinersen) or gene therapy, either in a clinical study or as part of medical care. • Concurrent or previous participation in any interventional investigational study for any other drug or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening
Intervention	**Part A:**: 28/28 mg Nusinersen **Part B:** 50/28 mg Nusinersen **Part C:** 12/50/28 mg Nusinersen
Comparator(s)	**Part B:** Infantile-Onset SMA: CS3B study (NCT02193074) sham control group and 12/12 mg nusinersen (Active Control Group) **Part B:** Later-Onset CS4 study (NCT02292537) matched sham, CS4 study (NCT02292537) matched 12/12 mg and 12/12 mg nusinersen (Active Control Group)
Follow-up time	302 days
Primary, secondary and exploratory endpoints	**Key efficacy endpoints** **Part B: Infantile-Onset SMA Endpoints (Study Day)** — **Comparator** Primary: CHOP- INTEND (183) — ENDEAR matched sham HINE-2 (Responder, Change) (183) — ENDEAR matched sham Plasma NfL (183) — ENDEAR matched sham CHOP - INTEND (302) — DEVOTE 12/12 mg HINE-2 (Change) (302) — DEVOTE 12/12 mg Plasma NfL (64) — DEVOTE 12/12 mg Event free survival/Overall survival — DEVOTE 12/12 mg ENDEAR matched sham

Trial name: DEVOTE		NCT number: NCT04089566
	HINE-1 suck/swallow (302)	DEVOTE 12/12 mg
	CGI-C (302)	DEVOTE 12/12 mg
	Part B: Later-Onset SMA	**Comparator**
	Endpoints (Study Day)	
	Plasma NfL (64)	DEVOTE 12/12 mg
	HFMS, RULM (302)	DEVOTE 12/12 mg CHERISH matched sham CHERISH matched 12/12 mg
	Part C	**Comparator**
	Endpoints (Study Day)	
	HFMS, RULM (302)	None
	Safety outcomes were primary outcome in Parts A and C and secondary in Part B and included: • Incidence of AEs and SAEs • Shifts from baseline in clinical laboratory parameters • Change from baseline in neurological examination outcomes • Change from baseline in growth parameters • Change from baseline in urine total protein	
Method of analysis	For the primary endpoint: Method of Estimation: Least square (LS) mean difference The Analysis of Covariance (ANCOVA) model used rank score as response, treatment as fixed effect and disease duration at screening, baseline Hammersmith Infant Neurological Examination (HINE) Section 2 (HINE 2), baseline CHOP INTEND total score as covariates.	
Subgroup analyses	No additional subgroups	
Other relevant information	An updated EPAR will be shared with the DMC once it is available -post EC decision	

Trial name: DEVOTE	NCT number: NCT04089566
	The DEVOTE manuscript is accepted for publication. The publication is expected during January 2026 and will be shared with the DMC once it is available.

Appendix B. Efficacy results per study

Results per study

Table 5 Results per study

Results of DEVOTE - NCT04089566											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in CHOP INTEND score from baseline - **Day 183** (infantile-onset) *LSM change from BL	50mg/28mg	50	42.9 (38.7 to 47.2)	26.06	(17.9, 34.2)	< 0.0001	NA	NA	NA	**Method of Estimation:** Least square (LS) mean difference **Statistical Test of Hypothesis**: ANCOVA models using joint-rank	REF 1 Crawford TO, et al (2024), REF 9 Crawford TO, et al (2025)
	Matched sham (ENDEAR)	20	16.9 (10.1 to 23.7)	26.19*	(20.7, 31.7) *						
Change in CHOP INTEND score from baseline - **Day 302** (infantile-onset) *LSM change from BL	50mg/28mg	50	38.3 (32.7 to 44.0)	1.0	(-9.3, 11.3)	0.8484	NA	NA	NA	**Method of Estimation:** Least square (LS) mean difference **Statistical Test of Hypothesis**: ANCOVA models using joint-rank	REF 1 Crawford TO, et al (2024), REF 9 Crawford TO, et al (2025)
	12/12 mg	25	37.3 (29.1 to 45.5)	–1.94*	(–7.77, 3.88) *						

Results of DEVOTE - NCT04089566											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in HINE-2 score **from baseline - Day 183)** **(infantile-onset)** *LSM change from BL	50mg/28mg	50	43.1 (39.0 to 47.2)	26.67	(18.8, 34.5)	<0.0001	NA	NA	NA	**Method of Estimation:** Least square (LS) mean difference **Statistical Test of Hypothesis**: ANCOVA models using joint-rank	REF 1 Crawford TO, et al (2024), REF 9 Crawford TO, et al (2025)
	Matched sham (ENDEAR)	20	16.5 (9.9 to 23.0)	3.9’	(2.5, 5.4) *						
Change in HINE-2 score from baseline - Day 302) **(infantile-**onset) *LSM change from BL	50mg/28mg	50	40.0 (35.1 to 44.9	6.12	(-2.69 to 14.94)	0.1734	NA	NA	NA	**Method of Estimation:** Least square (LS) mean difference **Statistical Test of Hypothesis**: ANCOVA models using joint-rank	REF 1 Crawford TO, et al (2024), REF 9 Crawford TO, et al (2025)
	12/12 mg	25	33.9 (26.9 to 41.0)	0.58*	(–1.89, 3.04) *						

Results of DEVOTE - NCT04089566											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Overall survival Screening up to Day 399 (infantile-onset)	50mg/28mg	50	NA (NA to NA), weeks	NA	NA	NA	HR: 0.279	0.112 to 0.696	0.0012	**Method of Estimation:** HR determined from Cox proportional hazards model adjusting for disease duration and baseline CHOP-INTEND **Statistical Test of Hypothesis:** log rank test stratified by disease duration (≤ 12 weeks or > 12 weeks).	REF 1 Crawford TO, et al (2024), REF 9 Crawford TO, et al (2025)
	Matched sham (ENDEAR)	20	33.6 (11.29 to NA), weeks								
	12/12 mg	25	NA (24.71 to NA), weeks	NA	NA	NA	HR: 0.730	0.264 to 2.015	0.4821		
Event-free survival (Time to death or Permanent ventilation) Screening up to Day 399 (infantile-onset)	50mg/28mg	50	NA (39.86 to NA), weeks	NA	NA	NA	HR: 0.322;	0.158 to 0.657;	0.0006	**Method of Estimation:** HR determined from Cox proportional hazards model adjusting for disease duration and baseline CHOP-INTEND **Statistical Test of Hypothesis:** log rank test stratified by disease duration (≤ 12 weeks or > 12 weeks).	REF 1 Crawford TO, et al (2024), REF 9 Crawford TO, et al (2025
	Matched sham (ENDEAR)	20	19.1 (10.00 to 31.29), weeks								

Appendix C. Comparative analysis of efficacy

Not applicable, no comparative analysis of efficacy. Was used in the application

Table 6 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird).	Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.	
Example: HRQoL		**–4.5**	−8.97 to −0.03	0.04	NA	NA	NA	HRQoL results for the studies included were synthesized using the standardized mean difference (SMD). The	

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
								estimated meta-analytical SMD of −0.3 (95% CI −2.99 to −0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate measure of HRQoL.	
Insert outcome 4									

Appendix D. Literature searches for the clinical assessment

D.1 Efficacy and safety of the intervention and comparator(s)

Not applicable, no Literature searches performed.

Table 7 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 3 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 4 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

Abbreviations:

D.1.2 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 5 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

D.1.3 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion.]

Table 6 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population		
Intervention		
Comparators		
Outcomes		

Study design/publication type	
Language restrictions	

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document.]

Table 7 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

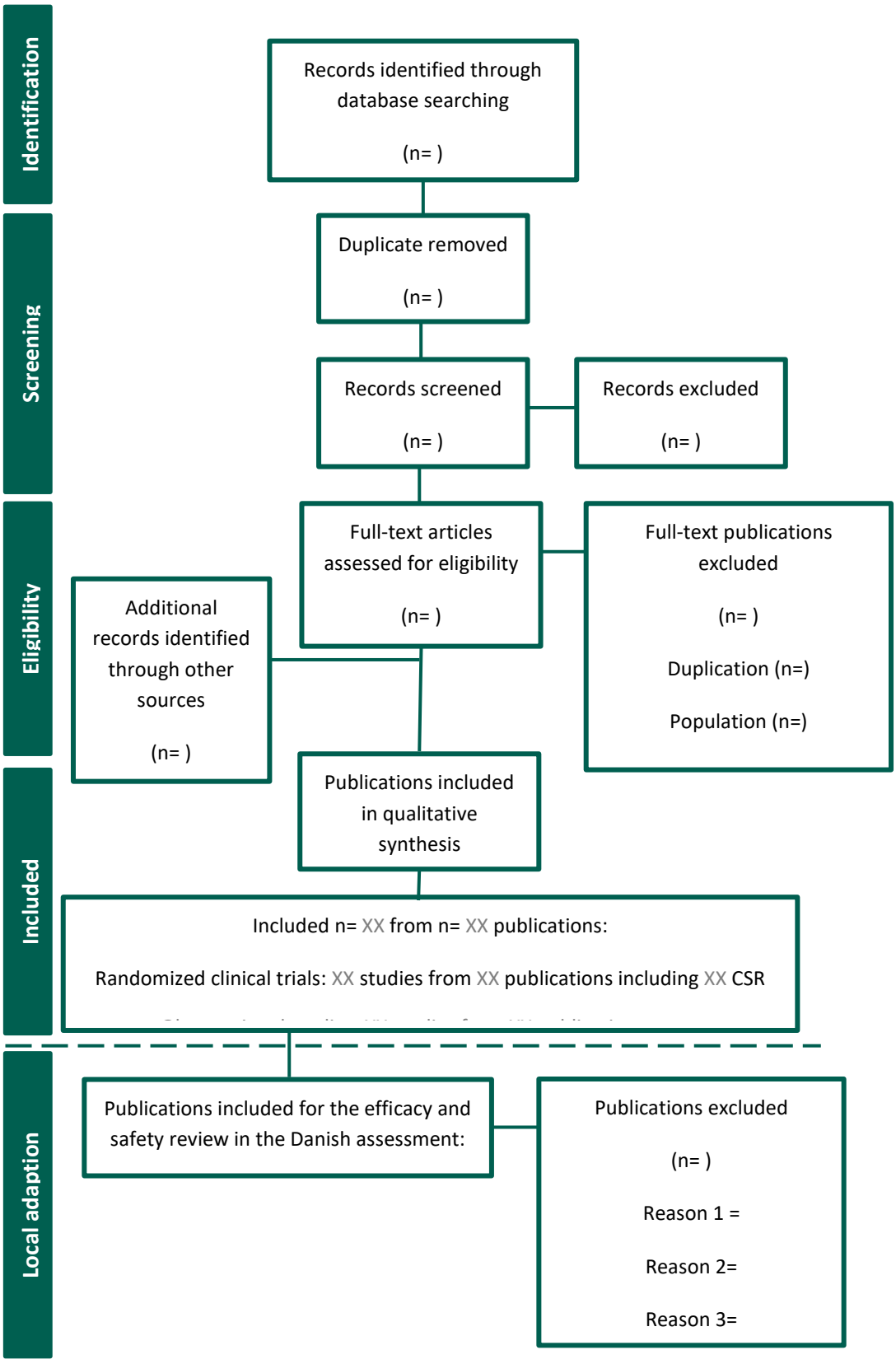
D.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

D.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.


Identification
Screening
Eligibility
Included
Local adaption
Records identified through database searching
(n=)
Duplicate removed
(n=)
Records screened
(n=)
Records excluded
(n=)
Full-text articles assessed for eligibility
(n=)
Full-text publications excluded
(n=)
Duplication (n=)
Population (n=)
Additional records identified through other sources
(n=)
Publications included in qualitative synthesis
Included n= XX from n= XX publications:
Randomized clinical trials: XX studies from XX publications including XX CSR
Publications included for the efficacy and safety review in the Danish assessment:
Publications excluded
(n=)
Reason 1 =
Reason 2=
Reason 3=

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