Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende risdiplam til behandling af spinal muskaltrofi

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. risdiplam til spinal muskelatrofi, version 1.0
2. Forhandlingsnotat fra Amgros vedr. risdiplam, version 1.0
3. Høringssvar fra ansøger, inkl. eventuel efterfølgende dialog vedr. lægemidlets værdi
4. Medicinrådets vurdering vedr. risdiplam til spinal muskelatrofi, version 1.1
5. Ansøgers endelige ansøgning
6. Tillæg til ansøgning (subgroups 10.8.2021)
7. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
8. Medicinrådets protokol for vurdering vedr. risdiplam til spinal muskelatrofi, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Risdiplam

Spinal muskelatrofi

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner. Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som standardbehandling, og udarbejder fælles regionale behandlingsvejledninger. Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

Dokumentets formål

Den sundhedsøkonomiske afrapportering indeholder Medicinrådets vurdering af de inkrementelle omkostninger pr. patient og budgetkonsekvenserne ved anbefaling. Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Den sundhedsøkonomiske afrapportering er udarbejdet efter *Metodevejledning for omkostningsanalyse af nye lægemidler og indikationsudvidelser i hospitalssektoren*.

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Indholdsfortegnelse

1. Begreber og forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekernes indkøbspris
SMA	Spinal muskelatrofi
SMN2	*Survival of motor neurons 2*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser

Patienter med SMA type 1

I det scenarie, Medicinrådet finder mest sandsynligt for patienter med SMA type 1, er de inkrementelle omkostninger for risdiplam ca. [redacted] DKK pr. patient sammenlignet med nusinersen over en behandlingsvarighed på 39 år. Når analysen er udført med apotekets indkøbspriser (AIP), er de inkrementelle omkostninger til sammenligning ca. -0,4 mio. DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af risdiplam som mulig standardbehandling vil være ca. [redacted] DKK i år 5 forudsat, at nogle patienter skifter fra nusinersen til risdiplam. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 0,6 mio. DKK i år 5.

Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år

I det scenarie, Medicinrådet finder mest sandsynligt for ikke-gående SMA type 2 og 3 i alderen 2-11 år, er de inkrementelle omkostninger for risdiplam ca. [redacted] DKK pr. patient sammenlignet med nusinersen over en behandlingsvarighed på 44 år. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 3,4 mio. DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af risdiplam som mulig standardbehandling til eksisterende patienter vil være ca. [redacted] DKK i år 5. Det omfatter patienter, hvoraf nogle allerede er i behandling med nusinersen. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 15,6 mio. DKK i år 5. Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af risdiplam som mulig standardbehandling til nydiagnosticerede patienter vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. -0,5 mio. DKK i år 5.

Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år

I det scenarie, Medicinrådet finder mest sandsynligt for ikke-gående SMA type 2 og 3 i alderen 12-25 år, er de inkrementelle omkostninger for risdiplam ca. [redacted] DKK pr. patient sammenlignet med best supportive care (BSC) over en behandlingsvarighed på 39 år. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 37,7 mio. DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af risdiplam som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Ingen af disse patienter er i nusinersenbehandling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 95,0 mio. DKK i år 5.

Patienter med SMA type 3, som har bevaret gangfunktion

I det scenarie, Medicinrådet finder mest sandsynligt for patienter med SMA type 3, som har bevaret gangfunktion, er de inkrementelle omkostninger for risdiplam ca. [redacted] DKK pr. patient sammenlignet med BSC over en behandlingsvarighed på 54

år. Når analysen er udført med AIP, er de inkrementelle omkostninger til sammenligning ca. 47,7 mio. DKK pr. patient.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af risdiplam som mulig standardbehandling vil være ca. [redacted] DKK i år 5. Ingen af disse patienter er i nusinersenbehandling. Når analysen er udført med AIP, er budgetkonsekvenserne ca. 56,9 mio. DKK i år 5.

Der er meget stor usikkerhed for den gennemsnitlige overlevelse for patienter med SMA type 1 og 2, da naturhistoriske data anvendes til at estimere overlevelsen og dermed behandlingsvarigheden. Endvidere er det antaget, at overlevelsen for SMA type 1 efter behandling vil svare til overlevelsen for SMA type 2. Overlevelsen for patienter med SMA type 2 og 3 har stor betydning for analysens resultat, da de inkrementelle omkostninger for alle sammenligninger næsten udelukkende er drevet af lægemiddelomkostningerne for risdiplam og nusinersen. Lægemiddelomkostninger vil derved akkumuleres over tid.

3. Introduktion

Formålet med analysen er at estimere de gennemsnitlige inkrementelle omkostninger pr. patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af risdiplam som mulig standardbehandling på danske hospitaler til spinal muskelatrofi.

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Roche. Medicinrådet modtog ansøgningen den 15. juni 2021.

3.1 Patientpopulation

5q spinal muskelatrofi (SMA) er en sjælden genetisk sygdom, der medfører muskelsvind og deraf nedsat muskelkraft. Trods sygdommens sjældenhed er SMA den hyppigste genetisk betingede årsag til dødsfald blandt spædbørn [1]. Incidensen i Skandinavien er estimeret til 1 ud af 6000 fødte børn [2].

Der er tale om et kontinuum af sværhedsgrader, der spænder fra få ugers overlevelse til progredierende forværring af motoriske funktioner over mange år. I praksis underinddeles sygdommen i fem stadier (SMA type 0-IV) ud fra tidspunkt for symptomdebut, motorisk udvikling og antal SMN2 (survival of motor neurons 2)-kopier [3,4].

Yderligere information om sygdomsområdet kan findes i Medicinrådets vurderingsrapport.

3.1.1 Komparator

Medicinrådet har vurderet den kliniske værdi af risdiplam på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 1, som ikke er i permanent ventilationsbehandling?

Klinisk spørgsmål 2:

Hvilken værdi har risdiplam sammenlignet med nusinersen for ikke-gående patienter med SMA type 2 og 3?

Klinisk spørgsmål 3:

Hvilken værdi har risdiplam sammenlignet med placebo for patienter med SMA type 2 og patienter med SMA type 3, som har mistet gangfunktionen?

Klinisk spørgsmål 4:

Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 3, som har bevaret gangfunktion?

4. Vurdering af den sundhedsøkonomiske analyse

I sin ansøgning har ansøger indsendt en sundhedsøkonomisk analyse, der består af en omkostningsanalyse og en budgetkonsekvensanalyse for hvert klinisk spørgsmål. I omkostningsanalysen estimeres de inkrementelle omkostninger pr. patient for risdiplam sammenlignet med nusinersen eller *best supportive care* (BSC). Medicinrådet vurderer nedenfor de sundhedsøkonomiske analyser, som ansøger har indsendt.

4.1 Antagelser og forudsætninger for modellen

For patienter med SMA type 1 antager ansøger, at der er ens effekt mellem risdiplam og nusinersen (klinisk spørgsmål 1).

For alle patienter med SMA type 2 og 3 antager ansøger, at der er en forskel i effekt mellem både risdiplam og nusinersen (klinisk spørgsmål 2) og risdiplam og BSC (klinisk spørgsmål 3). Ansøger har modelleret denne forskel i effekt på baggrund af SUNFISH part 2-studiet af risdiplam [5] og CHERISH-studiet af nusinersen [6]. Denne effektforskel har dog ikke betydning for estimeringen af omkostninger. Det skyldes at kun overlevelsen, har betydning for analysens resultat og overlevelsen antages at være ens ved behandling med risdiplam og nusinersen.

4.1.1 Modelbeskrivelse

Ansøger har indleveret en Markov-model, hvor modelstrukturen er ens for hvert klinisk spørgsmål. Modellen er opbygget til at kunne estimere omkostninger baseret på det

sygdomsstadie, patienten befinder sig i. Hvert stadie er forbundet med bestemte transitionssandsynligheder for sygdomsforbedring og død. Dog antager ansøger, at omkostninger og dødeligheden for hvert sygdomsstadie er ens, og derfor har sandsynlighederne for bevægelse mellem sygdomsstadierne ingen betydning for analysen resultat. Analysernes resultater er drevet af lægemiddelpriser og administration, da behandlingen antages at være livslang, er antagelserne om patienternes overlevelse afgørende for resultaterne. Modellen anvender overlevelseskurver til at estimere patientens gennemsnitlige overlevelse. Tiden estimeres ud fra OS-data, som den andel af patienter, der stadig er i live. Modellen har en cykluslængde på en måned.

Medicinrådets vurdering af ansøgers model
Sygdomsforløbet i modellen er en simplificering af SMA, da modellen ikke tager højde for udvikling i patienternes sygdomsforløb afhængig af motoriske færdigheder eller forskelle i omkostninger for hvert sygdomsstadie. Dette er potentielt en stor begrænsning for analyserne, da der kan være markant forskel på, hvor store omkostninger, der er forbundet med patienternes niveauer af motoriske færdigheder. Medicinrådet er dog opmærksom på, at der ikke findes tilstrækkelige data til at underbygge en mere detaljeret model. Medicinrådet vurderer derfor, at ansøgers model er acceptabel, da risdiplam vurderes at være ligeværdigt med nusinersen, og effekt og bivirkninger for risdiplam ikke adskiller sig fra placebo i de grupper, der i Danmark bliver tilbudt BSC, jf. vurderingsrapporten. Det vurderes således, at der ikke vil være forskel i andel af patienter i de forskellige sygdomsstadier mellem risdiplam, nusinersen og BSC, hvorfor omkostningerne hertil ikke vil være forskellig mellem behandlingsalternativerne og derfor ikke påvirke analysens resultater.

Medicinrådet accepterer ansøgers tilgang vedr. ansøgers model.

4.1.2 Modelantagelser og -beskrivelse

Ansøger har antaget en fordeling af alder, køn og type af SMA for hvert klinisk spørgsmål, som er baseret på data-on-file fra bl.a. studierne af risdiplam og naturhistoriske data for ubehandlede patienter. Baseret på disse data har ansøger udregnet en sammenhæng mellem patienternes vægt, alder og køn, hvorfra vægten for hver patientpopulation er estimeret. Patientkarakteristika for patientpopulationerne for hvert klinisk spørgsmål kan ses i Tabel 1.

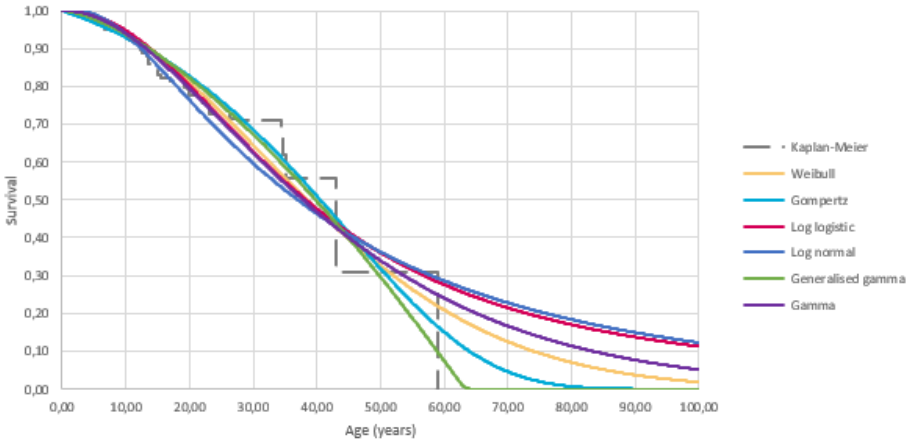
Tabel 1. Patientkarakteristika for de kliniske spørgsmål

Patientkarakteristika	Klinisk spørgsmål 1	Klinisk spørgsmål 2	Klinisk spørgsmål 3	Klinisk spørgsmål 4
Alder [år]	0,45 år	6,13 år	16,41 år	7,71 år
Kvinder	57 %	50 %	51 %	29 %
Vægt	4,9 kg	22,4 kg	51,0 kg	27,7 kg
Type I	100 %	0 %	0 %	0 %

Patientkarakteristika	Klinisk spørgsmål 1	Klinisk spørgsmål 2	Klinisk spørgsmål 3	Klinisk spørgsmål 4
Type II	0 %	79 %	57 %	0 %
Type III	0 %	21 %	43 %	100 %

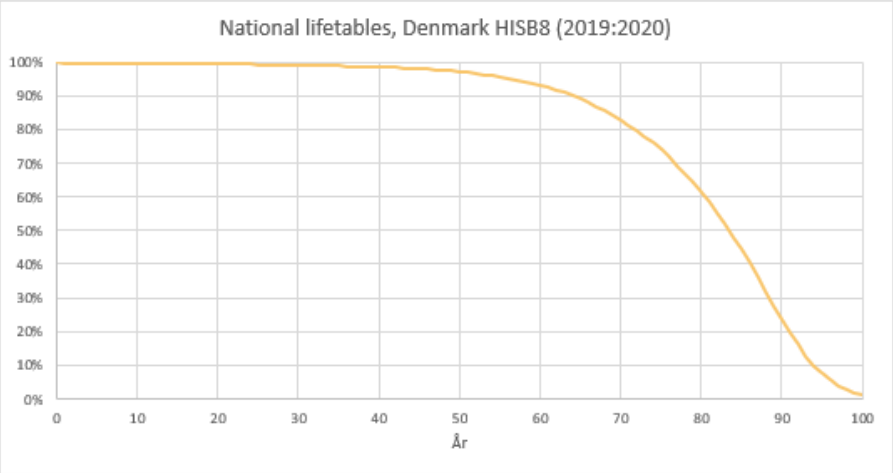
Da patienterne skal have livslang behandling, estimerer ansøger tiden i behandling med risdiplam, nusinersen eller BSC ved at anvende ekstrapolerede Kaplan-Meier (KM)-data for OS. Grundet overlevelsesdata med begrænset opfølgningstid anvender ansøger naturhistoriske overlevelsesdata fra patienter med SMA type 2 til at modellere overlevelsen. Ansøger har samlet naturhistoriske overlevelsesdata fra seks forskellige studier [7–13] i én samlet KM-kurve. Ansøger anvender en Gompertz funktion til at ekstrapolere overlevelsen, se Figur 1. Denne parametriske funktion er valgt, da ansøger vurderer, at Gompertz funktionen har det klinisk mest plausible forløb med et mere jævnt forløb til 0. Derudover er Gompertz funktionen også en af de parametriske funktioner, der, jf. AIC- og BIC-værdierne, har det bedste statistiske fit.

For patienter med SMA type 1 anvender ansøger ligeledes de naturhistoriske data fra SMA type 2-patienter som en proxy for overlevelsen for patienter med SMA type 1.



Figur 1. Ekstrapolerede funktioner for OS for patienter med SMA type 2

Ansøger antager, at patienter med SMA type 3 har normal levetid. Derfor modellerer ansøger overlevelsen for disse patienter baseret på den generelle befolknings mortalitetsrate fra Danmarks Statistik [14], se Figur 2.



Figur 2. Den generelle befolknings mortalitetsrate fra Danmarks Statistik

Medicinrådets vurdering af ansøgers modelantagelser

Fagudvalget vurderer, at ansøgers antagelser om patientkarakteristika for hvert klinisk spørgsmål overordnet stemmer overens med de danske patientpopulationer. Dog vurderer fagudvalget, at ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år vil være yngre end 6,1 år ved første dosering. Fagudvalget anslår, at patienterne vil være ca. 4,5 år ved første dosering. Gennemsnitsalderen for patienter med SMA type 3, som har bevaret gangfunktion, forventes derimod at være en del højere. Hertil anslår fagudvalget, at patienterne vil være ca. 27,5 år ved første dosering. For ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år estimerer fagudvalget, at en højere andel af patienterne har SMA type 2 svarende til ca. 70 %. Derudover vurderer fagudvalget også, at alle patientpopulationer skal være ligeligt fordelt mellem mænd og kvinder. Medicinrådet ændrer patientkarakteristika, således at disse stemmer overens med fagudvalgets vurdering, se Tabel 2.

Patienternes køn og alder er afgørende for deres vægt, hvilket betyder, at patienternes vægtfordeling ændres, når alderen og fordelingen af køn ændres. Dette har betydning for resultaterne af klinisk spørgsmål 1 og 2, da risdiplam gives vægtdoseret frem til patienterne vejer 20 kg.

Det er primært fordelingen mellem andelen af patienter med SMA type 2 og type 3, der har betydning for analysens resultat for klinisk spørgsmål 2 og 3, da patienter med SMA type 3 har længere overlevelse. Derfor vil en højere andel af patienter med SMA type 3 medføre en længere gennemsnitlig overlevelse og dermed behandlingsvarighed.

Tabel 2. Patientkarakteristika for de kliniske spørgsmål anvendt i Medicinrådets hovedanalyse

Patientkarakteristika	Klinisk spørgsmål 1	Klinisk spørgsmål 2	Klinisk spørgsmål 3	Klinisk spørgsmål 4
Alder	0,45 år	4,5 år	16,41 år	27,5 år
Kvinder	50 %	50 %	50 %	50 %

Patientkarakteristika	Klinisk spørgsmål 1	Klinisk spørgsmål 2	Klinisk spørgsmål 3	Klinisk spørgsmål 4
Vægt	5,0 kg	17,4 kg	51,4 kg	55,2 kg
Type I	100 %	0 %	0 %	0 %
Type II	0 %	79 %	70 %	0 %
Type III	0 %	21 %	30 %	100 %

Der er betydelig usikkerhed forbundet med overlevelsen for patienterne med SMA type 1 og 2. Fagudvalget forventer dog, at overlevelsen for patienter med SMA type 1, som modtager behandling, vil stige, så patienterne vil have en overlevelse, der formodentlig svarer til patienter med SMA type 2. Derfor accepterer fagudvalget ansøgers antagelser og vurderer, at overlevelsen for SMA type 2-patienter kan anvendes som proxy for patienter med SMA type 1.

Fagudvalget accepterer ansøgers anvendte overlevelseskurver for patienter med SMA type 2 og type 3. Fagudvalgets korrigeringer af gennemsnitsalder ved første dosering har indflydelse på den gennemsnitlige behandlingsvarighed. Derfor varierer den gennemsnitlige behandlingsvarighed i Medicinrådets hovedanalyse fra ansøgers hovedanalyse. Dette har mindre betydning for analysens resultat. For at undersøge betydningen af den valgte fremgangsmåde for ekstrapolering af de naturhistoriske overlevelsesdata for SMA type 2, udføres der en række følsomhedsanalyser. Estimater for behandlingsvarighed og overlevelse anvendt i Medicinrådets hovedanalyse er præsenteret i Tabel 3.

Tabel 3. Gennemsnitlig tid i behandling og samlet overlevelse

Population		Behandlingsvarighed [år]	OS [år]
SMA type 1, som ikke er i permanent ventilationsbehandling	Risdiplam	39,3	39,3
	Nusinersen	39,3	39,3
Ikke-gående patienter med SMA type 2 og 3 (2-11 år)	Risdiplam	44,0	44,0
	Nusinersen	44,0	44,0
Ikke-gående patienter med SMA type 2 og 3 (12-25 år)	Risdiplam	39,1	39,1
	BSC	39,1	39,1
SMA type 3, som har bevaret gangfunktion	Risdiplam	54,4	54,4
	BSC	54,4	54,4

Medicinrådet accepterer ansøgers tilgang vedr. modelantagelser. Dog korrigerer Medicinrådet enkelte patientkarakteristika, således disse stemmer overens med fagudvalgets vurdering af de danske patientpopulationer.

4.1.3 Analyseperspektiv

I overensstemmelse med Medicinrådets metoder har ansøger valgt et begrænset samfundsperspektiv til sin analyse. Analysen har en tidshorisont på 5 år, mens ansøger har valgt at lave en følsomhedsanalyse med en tidshorisont på 80 år svarende til livstid.

Omkostninger, der ligger efter det første år, diskonteres med en rate på 3,5 % pr. år. I følsomhedsanalysen, hvor tidshorisonten er 80 år, diskonteres omkostninger, der ligger efter år 35, med en rate på 2,5 % pr. år, mens raten falder til 2,5 % pr. år for omkostninger efter år 70.

Medicinrådets vurdering af ansøgers analyseperspektiv
Medicinrådet accepterer ikke ansøgers valgte tidshorisont. Dette skyldes, at SMA er en sygdom, som kræver livslang behandling, og analysens tidshorisont derfor skal være livslang for at opfange alle væsentlige forskelle i behandlingsomkostninger mellem risdiplam, nusinersen og BSC. En tidshorisont på 5 år vil derfor underestimere forskellen i omkostningerne mellem risdiplam og nusinersen. Tidshorisonten på 80 år er derimod lang nok til, at alle patienter forventes at være døde. Den gennemsnitlige modellerede overlevelse ses i Tabel 3. Medicinrådet vælger desuden at præsentere de inkrementelle omkostninger over en årrække på 1-25 år for hvert klinisk spørgsmål for at illustrere udviklingen i de inkrementelle omkostninger.

Medicinrådet accepterer ikke ansøgers valg vedr. analyseperspektiv, men vælger at øge tidshorisonten til 80 år i Medicinrådets hovedanalyse.

4.2 Omkostninger

I det følgende præsenteres ansøgers antagelser for omkostningerne i den sundhedsøkonomiske analyse af risdiplam sammenlignet med nusinersen og BSC. Ansøger har inkluderet lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger.

4.2.1 Lægemiddelomkostninger

Ansøger har, jf. *Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren,* estimeret lægemiddelomkostninger på baggrund af apotekernes indkøbspris (AIP).

Doseringen af risdiplam bestemmes af patientens alder og vægt:

- 2 måneder til < 2 år: 0,2 mg/kg oralt én gang dagligt
- ≥ 2 år (< 20 kg): 0,25 mg/kg oralt én gang dagligt
- ≥ 2 år (> 20 kg): 5 mg oralt én gang dagligt

Nusinersen gives som intrathekale støddoser på 12 mg på dag 0 og derefter på dag 14, 28 og 63. Herefter vedligeholdelsesdosis hver 4. måned.

Medicinrådets vurdering af ansøgers antagelser vedr. lægemiddelomkostninger
Medicinrådet har udskiftet AIP med sygehusapotekernes indkøbspris (SAIP), se Tabel 4.

Tabel 4. Anvendte lægemiddelpriser, SAIP (juni 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Betingede pris* [DKK]	Kilde
Risdiplam	0,75 mg/ml	80 ml	[redacted]	[redacted]	Amgros
Nusinersen	2,4 mg/ml	5 ml	[redacted]		Amgros

*Roche har tilbudt en pris betinget af at risdiplam bliver anbefalet til både patienter med SMA-type I, som ikke er i permanent respirationsbehandling ved opstart af behandling, samt patienter med SMA-type II under 6 år og patienter med SMA-type III under 6 år.

Jf. SPC'et for risdiplam skal risdiplam tages straks efter, at en dosering er klargjort. Hvis den ikke tages inden for 5 minutter, skal den kasseres fra den orale sprøjte, og en ny dosis skal forberedes. Derfor er der risiko for spild forbundet med risdiplam, som der ikke tages højde for i analysen.

De årlige lægemiddelomkostninger for risdiplam varierer derfor hvert år for de mindre patienter, som stiger i vægt.

Medicinrådet accepterer ansøgers valg vedr. lægemiddelomkostninger.

4.2.2 Hospitalsomkostninger

Administrationsomkostninger

Ansøger har inkluderet administrationsomkostninger for risdiplam og nusinersen i form af timeomkostninger for sundhedspersonale og DRG-takster. På hospitalet vil risdiplamopløsningen blive blandet af en sygeplejerske, hvorefter patienten får risdiplam udleveret. Ansøger antager, at det tager ca. 15 min. at blande op til 5 flasker risdiplam, derfor er der brugt 15 min. sygeplejersketid til administrationsomkostningerne for risdiplam.

Ansøger antager, at injektion med nusinersen kræver et administrationsbesøg på hospitalet. Hertil antager ansøger, at 1/3 af patienterne vil være i generel anæstesi, mens de resterende 2/3 af patienterne vil være i lokal anæstesi. Som enhedsomkostning for en injektion med nusinersen anvender ansøger 2021 DRG-taksten 09PR04 (Biopsi og væskeudsugning, overfladisk), hvilket giver en enhedsomkostning på 4.781 DKK.

Medicinrådets vurdering af ansøgers antagelser vedr. administrationsomkostninger
Fagudvalget mener ikke, at ansøger har anvendt den korrekte DRG-takst for injektion med nusinersen, idet procedurekoden biopsi og væskeudsugning overfladisk ikke dækker over administrationen. Medicinrådet vælger derfor at udskifte ansøgers valgte DRG-takst til 2021 DRG-taksten 01MA98 (MDC01 1-dagsgruppe, pat. mindst 7 år) på 3.353 DKK, jf.

Interaktiv DRG med diagnosekode: Spinal muskelatrofi og procedurekoden: Medicingivning ved intrathekal injektion. Fagudvalget mener derudover, at enhedsomkostningen til administration af nusinersen er for lav. Størstedelen af patienter, der behandles med nusinersen, skal i generel anæstesi. Medicinrådet vælger derfor at tilføje 2021 DRG-taksten 01MA98 (MDC01 1-dagsgruppe, pat. mindst 7 år) på 3.353 DKK til enhedsomkostningen for administration af nusinersen, jf. interaktiv DRG med diagnosekode: Spinal muskelatrofi og procedurekoden: Generel anæstesi, se Tabel 5. Denne ændring har mindre betydning for analysens resultat.

Tabel 5. Omkostninger til lægemiddeladministration

		Enhedsomkostning [DKK]	Kilde
Administration med risdiplam	Opblanding	554	Medicinrådets værdisætning af enhedsomkostninger
Administration med nusinersen	Ambulant besøg	3.353	2021 DRG-takst: 01MA98
	Generel anæstesi	3.353	2021 DRG-takst: 01MA98

Medicinrådet ændrer enhedsomkostningerne til administration med nusinersen i egen hovedanalyse.

Monitoreringsomkostning

Ansøger har inkluderet monitoreringsomkostninger i form af 2021 DRG-takster. Ansøger antager, at ressourceforbruget for monitorering af patienternes sygdomsforløb er ens mellem risdiplam, nusinersen og BSC. Patienter, der skal behandles med risdiplam eller nusinersen, forventes ikke at skulle have kontakter ud over ovenstående ambulante besøg.

Medicinrådets vurdering af ansøgers antagelser vedr. monitoreringsomkostninger
Medicinrådet vælger at ekskludere omkostninger til monitorering i Medicinrådets hovedanalyse, da der ikke er forskelle mellem risdiplam, nusinersen og BSC, og derfor ikke påvirker analysens resultater.

Medicinrådet ekskluderer monitoreringsomkostninger i Medicinrådets hovedanalyse.

Bivirkningsomkostninger

Ansøger har inkluderet omkostninger forbundet med bivirkninger og benytter frekvenser for bivirkninger af grad 3+ med en hyppighed over 5 %. For risdiplam og BSC har ansøger anvendt de rapporterede bivirkningsrater i SUNFISH Part 2-studiet, mens de rapporterede bivirkningsrater i CHERISH-studiet er anvendt for nusinersen. Enhedsomkostningerne brugt i forbindelse med de forskellige bivirkninger har ansøger baseret på 2021 DRG-takster.

Medicinrådets vurdering af ansøgers antagelser vedr. bivirkningsomkostninger
Jf. vurderingsrapporten vurderer fagudvalget, at der ikke er klinisk relevant forskel mellem risdiplam, nusinersen og BSC i hyppigheden af alvorlige bivirkninger. Omkostninger til bivirkninger ekskluderes derfor i Medicinrådets hovedanalyse.

Medicinrådet ekskluderer omkostninger til bivirkninger i Medicinrådets hovedanalyse.

4.2.3 Patientomkostninger

Ansøgers analyse indeholder omkostninger for både patienterne og deres pårørende. Patientomkostninger er estimeret på baggrund af administrations- og monitoreringsbesøg på hospitalet og inkluderer patientens og pårørendes effektive tid på hospitalet, ventetid og transporttid.

Ansøger antager, at administration med risdiplam tager ca. 5 min. for patienten/pårørende, da risdiplam er en oral opløsning. Patienter, der behandles med risdiplam, vil få lægemidlet udleveret ca. 8 gange om året, hvoraf to af udleveringerne vil ske i forbindelse med monitoreringsbesøg. De resterende 6 udleveringer vil patienten skulle hente på hospitalet. Hertil antager ansøger, at dette varer 30 min. pr. udlevering.

Ansøger antager, at patienten i gennemsnit er 6,75 timer på hospitalet, når patienten skal have injektion med nusinersen under generel anæstesi, mens patienter under lokal anæstesi vil være på hospitalet i 3,75 timer ved hver injektion. Derudover antager ansøger, at halvdelen af patienterne har to voksne/forældre med ved behandlingerne, mens den anden halvdel har én voksen/forælder med.

Ansøger anvender en enhedsomkostning for patienttid på 179 DKK pr. time og transportomkostninger på 100 DKK pr. besøg, jf. *Medicinrådets værdisætning af enhedsomkostninger*.

Medicinrådets vurdering af ansøgers antagelser vedr. patientomkostninger
Fagudvalget estimerer, at patienter, der behandles med nusinersen, vil være på hospitalet i 8 timer pr. injektion. Denne ændring har mindre betydning for analysens resultat.

Patienternes ressourceforbrug for risdiplam og nusinersen kan ses i Tabel 6.

Tabel 6. Estimat af effektiv patienttid

		Patienttid [minutter]
Risdiplam	Administration	5
	Udlevering af medicin	30
Nusinersen	Administration	480 (8 timer)

Medicinrådet accepterer ansøgers tilgang vedr. patientomkostninger men øger timeantallet til 8 timer pr. injektion med nusinersen i egen hovedanalyse.

4.3 Følsomhedsanalyser

Formålet med følsomhedsanalyserne er at undersøge usikkerhederne i analysen og de økonomiske konsekvenser af at justere de parametre, der er usikre.

Ansøger har udarbejdet en række følsomhedsanalyser, hvor hhv. effekten af variation i forskellige parametre undersøges, og hvor transitionssandsynlighederne, der bestemmer patienternes bevægelse mellem sundhedsstadier i modellen, varieres.

Følgende følsomhedsanalyser er derudover udført:

Tabel 7. Følsomhedsanalyser og beskrivelse

Følsomhedsanalyse	Beskrivelse
Ekstrapolering af OS for SMA type 2 – Weibull	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion Weibull
Ekstrapolering af OS for SMA type 2 – eksponentiel	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion eksponentiel
Ekstrapolering af OS for SMA type 2 – log-logistisk	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion log-logistisk
Ekstrapolering af OS for SMA type 2 – log-normal	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion log-normal
Ekstrapolering af OS for SMA type 2 – generalised gamma	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion generalised gamma
Ekstrapolering af OS for SMA type 2 – gamma	Data for OS ekstrapoleres ved anvendelse af den parametriske funktion gamma
Tidshorisont – 30 år	Tidshorisont ændres til 30 år
Tidshorisont – 50 år	Tidshorisont ændres til 50 år
Tidshorisont – 70 år	Tidshorisont ændres til 70 år
Pårørende – ingen	Antal pårørende til injektion med nusinersen sættes til 0
Pårørende – 1 stk.	Antal pårørende til injektion med nusinersen sættes til 1
Pårørende – 2 stk.	Antal pårørende til injektion med nusinersen sættes til 2

Medicinrådets vurdering af ansøgers valg af følsomhedsanalyser

Som tidligere beskrevet har ændringer i transitionssandsynlighederne ingen betydning for analysens resultat, da omkostninger og dødeligheden for hvert sygdomsstadie er ens. Medicinrådet vælger derfor ikke at præsentere disse følsomhedsanalyser. Ligeledes vurderer Medicinrådet ikke, at det er relevant at udarbejde følsomhedsanalyser med

alternative tidshorisonter, da tidshorisonten skal være så lang, at den opfanger alle forskelle i omkostninger mellem intervention og komparator.

Da patienternes dødelighed har betydning for analysens resultat, vælger Medicinrådet at præsentere følsomhedsanalyserne, hvor data for OS for SMA type 2 ekstrapoleres med forskellige parametriske funktioner. Fagudvalget vurderer, at størstedelen af ekstrapoleringerne ikke er klinisk plausible, og derfor vælger Medicinrådet kun at præsentere følsomhedsanalyser, hvor data for OS for SMA type 2 ekstrapoleres ved anvendelse af den parametriske funktion generalised gamma og Weibull. Disse to ekstrapoleringer ligger tættest på overlevelseskurven anvendt i Medicinrådets hovedanalyse.

Derudover vælger Medicinrådet også at præsentere ansøgers følsomhedsanalyser, der undersøger betydningen af antal pårørende til hver injektion med nusinersen. Det skal dog nævnes, at det eneste parameter, der har større indflydelse på resultaterne, er den pris, risdiplam indkøbes til.

Medicinrådet vælger at præsentere ansøgers følsomhedsanalyser, hvor overlevelsen for patienter med SMA type 2 undersøges samt antallet af pårørende.

4.4 Opsummering af basisantagelser

I Tabel 8 opsummeres basisantagelserne i henholdsvis ansøgers og Medicinrådets hovedanalyse.

Tabel 8. Basisantagelser for ansøgers og Medicinrådets hovedanalyse

Basisantagelser	Ansøger	Medicinrådet
Tidshorisont	5 år	80 år
Diskonteringsrate	1-35 år: 3,5 % 36-70 år: 2,5 % 71+ år: 1,5 %	1-35 år: 3,5 % 36-70 år: 2,5 % 71+ år: 1,5 %
Inkluderede omkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger	Lægemiddelomkostninger Hospitalsomkostninger Patientomkostninger
Behandlingsvarighed		
Klinisk spørgsmål 1:	4,67 år	39,3 år
Klinisk spørgsmål 2:	4,67 år	44,0 år
Klinisk spørgsmål 3:	4,65 år	39,1 år
Klinisk spørgsmål 4:	4,74 år	54,4 år
Overlevelse for SMA type 1	Anvende overlevelsen for SMA type 2	Anvende overlevelsen for SMA type 2

Basisantagelser	Ansøger	Medicinrådet
Parametriske funktioner for overlevelsen for SMA type 2		
Intervention:	Gompertz	Gompertz
Komparator:	Gompertz	Gompertz
Overlevelse for SMA type 3	Anvende den generelle befolknings mortalitetsrate	Anvende den generelle befolknings mortalitetsrate
Inkludering af spild	Nej	Nej

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Medicinrådets hovedanalyse bygger på samme antagelser som ansøgers hovedanalyse med undtagelse af de væsentligste ændringer, der fremgår af Tabel 8.

For alle fire populationer er de inkrementelle omkostninger drevet af forskelle i lægemiddelpriser, administration og behandlingsvarigheden. Behandling med risdiplam medfører højere omkostninger end behandling med nusinersen, når patienterne vejer over 20 kg. Det modsatte er tilfældet ved lav vægt, da risdiplam gives vægtdoseret til børn under 20 kg. Dette har især betydning for klinisk spørgsmål 1, da alle børn i denne population vejer under 20 kg, og i nogen grad også for klinisk spørgsmål 2, hvor en del af børnene vejer under 20 kg (gennemsnit 17,4 kg) ved behandlingsopstart. Da behandlingsvarigheden er behæftet med væsentlige usikkerheder, præsenteres de akkumulerede inkrementelle omkostninger over en årrække på 1-25 for alle fire populationer i diskussionen.

Patienter med SMA type 1

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor risdiplam sammenlignes med nusinersen for patienter med SMA type 1. I analysen bestemmes den gennemsnitlige behandlingsvarighed til at være 39 år, se Tabel 9. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient -0,4 mio. DKK.

Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor risdiplam sammenlignes med nusinersen for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år. I analysen bestemmes den gennemsnitlige behandlingsvarighed til at være 44 år, se Tabel 10. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 3,4 mio. DKK.

Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor risdiplam sammenlignes med BSC for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25. I analysen bestemmes den gennemsnitlige behandlingsvarighed til at være 39 år, se Tabel 11. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 37,7 mio. DKK.

Patienter med SMA type 3, som har bevaret gangfunktion

Den gennemsnitlige inkrementelle omkostning pr. patient bliver [redacted] DKK i Medicinrådets hovedanalyse, hvor risdiplam sammenlignes med BSC for patienter med SMA type 3, som har bevaret gangfunktion. I analysen bestemmes den gennemsnitlige behandlingsvarighed til at være 54 år, se Tabel 12. Er analysen udført med AIP, bliver den inkrementelle omkostning pr. patient 47,7 mio. DKK.

Tabel 9. Resultatet af Medicinrådets hovedanalyse ved sammenligning med nusinersen for patienter med SMA type 1, DKK, diskonterede tal

	Risdiplam	Nusinersen	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	33.331	431.282	-397.951
Patientomkostninger	134.496	236.671	-102.176
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 10. Resultatet af Medicinrådets hovedanalyse ved sammenligning med nusinersen for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år, DKK, diskonterede tal

	Risdiplam	Nusinersen	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	34.778	449.073	-414.295
Patientomkostninger	140.334	246.434	-106.100
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 11. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år, DKK, diskonterede tal

	Risdiplam	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	32.276	0	32.276

	Risdiplam	BSC	Inkrementelle omkostninger
Patientomkostninger	130.236	0	130.236
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 12. Resultatet af Medicinrådets hovedanalyse ved sammenligning med BSC for patienter med SMA type 3, som har bevaret gangfunktion, DKK, diskonterede tal

	Risdiplam	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	40.852	0	40.852
Patientomkostninger	164.844	0	164.844
Totale omkostninger	[redacted]	[redacted]	[redacted]

5.1.1 Resultatet af Medicinrådets følsomhedsanalyser

Ved samme antagelser som i Medicinrådets hovedanalyse for meromkostninger har Medicinrådet udført en følsomhedsanalyse på parametrene listet i Tabel 13.

Tabel 13. Resultatet af Medicinrådets følsomhedsanalyse sammenlignet med hovedanalysen, DKK

Scenarie		Inkrementelle omkostninger
Patienter med SMA type 1		
Resultatet af hovedanalysen		[redacted]
Overlevelse for SMA type 2	Generalised gamma	[redacted]
	Weibull	[redacted]
Antal pårørende	0	[redacted]
	1	[redacted]
	2	[redacted]
Patienter med SMA type 2 i alderen 2-11 år		
Resultatet af hovedanalysen		[redacted]
Overlevelse for SMA type 2	Generalised gamma	[redacted]
	Weibull	[redacted]

Scenarie		Inkrementelle omkostninger
Antal pårørende	0	[redacted]
	1	[redacted]
	2	[redacted]
Patienter med SMA type 2 i alderen 12-25 år		
Resultatet af hovedanalysen		[redacted]
Overlevelse for SMA type 2	Generalised gamma	[redacted]
	Weibull	[redacted]

6. Budgetkonsekvenser

Budgetkonsekvenserne pr. år er baseret på antagelsen om, at risdiplam vil blive anbefalet som mulig standardbehandling. Man ser derfor på to scenarier:

- Risdiplam bliver anbefalet som mulig standardbehandling af Medicinrådet til indikationerne, som denne analyse omhandler.
- Risdiplam bliver ikke anbefalet som mulig standardbehandling.

Budgetkonsekvenserne udgør forskellen mellem de samlede omkostninger i de to scenarier.

6.1 Estimat af patientantal og markedsandel

Ansøger har antaget, at:

- Patienter med SMA type 1, som ikke er i permanent ventilation: 12 patienter er kandidater til behandling med risdiplam. Derudover antager ansøger, at 2 nye patienter pr. år bliver diagnosticeret. Hvis risdiplam anbefales, forventer ansøger, at risdiplam vil have et markedsoptag på 50 % i år 1 stigende til 70 % i år 5. I år 1 vil 50 % af de patienter, som på nuværende tidspunkt behandles med nusinersen, skifte til risdiplam. Derudover vil 50 % af de nydiagnosticerede patienter opstartes i behandling med risdiplam.
- Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år: 36 patienter er kandidater til behandling med risdiplam. Derudover antager ansøger en incidens på 2 nye patienter pr. år. Hvis risdiplam anbefales, forventer ansøger, at risdiplam vil have et markedsoptag på 50 % i år 1 stigende til 60 % i år 5. I år 1 vil 50 % af de patienter, som på nuværende tidspunkt behandles med nusinersen, skifte til

risdiplam, og 50 % af de patienter, der behandles med BSC, vil påbegynde risdiplam. Derudover vil 50 % af de nye patienter opstartes i behandling med risdiplam.

- Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år: 42 patienter er kandidater til behandling med risdiplam. Derudover antager ansøger en incidens på 2 nye patienter pr. år. Hvis risdiplam anbefales, forventer ansøger, at risdiplam vil have et markedsoptag på 50 % fra år 1. Derudover vil 50 % af de nye patienter opstartes i behandling med risdiplam.
- Patienter med SMA type 3, som har bevaret gangfunktion: 20 patienter er kandidater til behandling med risdiplam. Derudover antager ansøger en incidens på 2 nye patienter pr. år. Hvis risdiplam anbefales, forventer ansøger, at risdiplam vil have et markedsoptag på 50 % fra år 1. Derudover vil 50 % af de nye patienter opstartes i behandling med risdiplam.

Medicinrådets vurdering af ansøgers budgetkonsekvensanalyse
Fagudvalget er blevet konsulteret i forhold til patientantal, hvis risdiplam anbefales som mulig standardbehandling, og hvis ikke risdiplam anbefales.

Fagudvalget estimerer, at 9 patienter med SMA type 1 forventes at være kandidater til behandling med risdiplam til den pågældende indikation. Fagudvalget mener, at det er relevant at opdele denne population i to budgetkonsekvensanalyser, så man kigger særskilt på hhv. eksisterende patienter og nydiagnosticerede patienter, da de eksisterende patienter med SMA type 1 allerede er i behandling med nusinersen. Jf. vurderingsrapporten vurderer fagudvalget, at der ikke er grund til at skifte fra nusinersen til risdiplam, hvis patienten er velbehandlet og ikke oplever betydelige bivirkninger eller komplikationer af nusinersen-behandlingen. Fagudvalget vurderer derfor, at ca. 50 % af patienterne vil skifte fra nusinersen til risdiplam ved en anbefaling af risdiplam, se Tabel 14. For de nydiagnosticerede patienter med SMA type 1 forventer fagudvalget, at de fleste patienter vil foretrække behandling med onasemnogene abeparvovec, således at hverken risdiplam eller nusinersen vil opnå et markedsoptag. Medicinrådet vælger derfor at ekskludere nydiagnosticerede patienter i budgetkonsekvensanalysen for patienter med SMA type 1.

Tabel 14. Medicinrådets estimat af antal eksisterende patienter pr. år for patienter med SMA type 1

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Risdiplam	5	0	0	0	0
Nusinersen	4	0	0	0	0
			Anbefales ikke		
Risdiplam	0	0	0	0	0
Nusinersen	9	0	0	0	0

Fagudvalget estimerer, at ca. 25 patienter med SMA type 2 og 3 i alderen 2-11 år vil være kandidater til behandling med risdiplam. Heraf er ca. 11 patienter på nuværende tidspunkt i behandling med nusinersen. Hertil mener fagudvalget også, at det er relevant at opdele denne population i to budgetkonsekvensanalyser, så man kigger særskilt på hhv. eksisterende patienter og nye patienter. For de 25 eksisterende patienter vurderer fagudvalget, at ca. 50 % af patienterne vil skifte til risdiplam, mens 25 % vil forblive på nusinersen, og 25 % vil forblive på BSC, se Tabel 15. For de nydiagnosticerede patienter med SMA type 2 (2 patienter pr. år) vurderer fagudvalget, at der vil være en ligelig fordeling for markedsoptaget mellem risdiplam og nusinersen, se Tabel 16.

Tabel 15. Medicinrådets estimat af antal eksisterende patienter pr. år for patienter med SMA type 2 og 3 i alderen 2-11 år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Risdiplam	13	0	0	0	0
Nusinersen	6	0	0	0	0
BSC	6	0	0	0	0
			Anbefales ikke		
Risdiplam	0	0	0	0	0
Nusinersen	11	0	0	0	0
BSC	14	0	0	0	0

Tabel 16. Medicinrådets estimat af antal nydiagnosticerede patienter pr. år for patienter med SMA type 2 og 3 i alderen 2-11 år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Risdiplam	1	1	1	1	1
Nusinersen	1	1	1	1	1
BSC	0	0	0	0	0
			Anbefales ikke		
Risdiplam	0	0	0	0	0
Nusinersen	2	2	2	2	2
BSC	0	0	0	0	0

Hvis risdiplam anbefales til patienter med SMA type 2 og 3 i alderen 12-25 år og patienter med SMA type 3 med gangfunktion, forventer fagudvalget, at alle patienter vil starte behandling med risdiplam. Medicinrådet ændrer derfor markedsoptaget ved en anbefaling af risdiplam til 100 %, se Tabel 17 og Tabel 18.

Tabel 17. Medicinrådets estimat af antal patienter pr. år for patienter med SMA type 2 og 3 i alderen 12-25 år

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Risdiplam	44	2	2	2	2
BSC	0	0	0	0	0
			Anbefales ikke		
Risdiplam	0	0	0	0	0
BSC	44	2	2	2	2

Tabel 18. Medicinrådets estimat af antal patienter pr. år for patienter med SMA type 3, som har bevaret gangfunktion

	År 1	År 2	År 3	År 4	År 5
			Anbefales		
Risdiplam	22	2	2	2	2
BSC	0	0	0	0	0
			Anbefales ikke		
Risdiplam	0	0	0	0	0
BSC	22	2	2	2	2

Ansøger har i modellen ikke taget højde for, at patienter, som fortsætter på behandling med nusinersen, blot fortsætter på vedligeholdelsesbehandling hver 4. måned. Medicinrådet retter dette i Medicinrådets budgetkonsekvensanalyser for patienter med SMA type 1 og patienter med SMA type 2 og 3 i alderen 2-11 år, hvor nusinersen indgår som en behandlingsmulighed.

Medicinrådet har udført sin egen budgetkonsekvensanalyse, hvor patientantallet stemmer overens med fagudvalgets forventninger. Derudover retter Medicinrådet doseringen for patienterne, som fortsætter behandling med nusinersen, således at omkostningerne til den øgede startdosering ikke inkluderes.

6.2 Medicinrådets budgetkonsekvensanalyse

Medicinrådet har korrigeret følgende estimater i sin budgetkonsekvensanalyse i forhold til ansøgers budgetkonsekvensanalyse:

- Patienter med SMA type 1: 9 patienter er kandidater til behandling med risdiplam, hvoraf risdiplam vil få et markedsoptag på ca. 50 % fra år 1.
- Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år: 25 patienter er kandidater til behandling med risdiplam, hvoraf ca. 50 % af patienterne vil skifte til risdiplam, mens 25 % vil forblive på nusinersen, og 25 % vil forblive på BSC.
- Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år: 100 % markedsoptag for risdiplam.
- Patienter med SMA type 3, som har bevaret gangfunktion: 100 % markedsoptag for risdiplam.

Patienter med SMA type 1, som ikke er i permanent ventilation

Medicinrådet estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med SMA type 1. Resultatet er præsenteret i Tabel 19. Budgetkonsekvenserne er ca. 0,6 mio. DKK i år 5, når analysen udføres med AIP.

Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år

Budgetkonsekvenserne er opdelt i nydiagnosticerede og eksisterende patienter, da en del af de eksisterende patienter allerede er i behandling med nusinersen.

Medicinrådet estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for eksisterende ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år. Resultatet er præsenteret i Tabel 20. Budgetkonsekvenserne er ca. 15,6 mio. DKK i år 5, når analysen udføres med AIP.

Medicinrådet estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for nydiagnosticerede patienter med SMA type 2. Resultatet er præsenteret i Tabel 20. Budgetkonsekvenserne er ca. -0,5 mio. DKK i år 5, når analysen udføres med AIP.

Anvendelse af risdiplam vil samlet resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for både eksisterende og nydiagnosticerede ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år.

Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år

Medicinrådet estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år. Resultatet er præsenteret i Tabel 22. Budgetkonsekvenserne er ca. 95,0 mio. DKK i år 5, når analysen udføres med AIP.

Patienter med SMA type 3, som har bevaret gangfunktion

Medicinrådet estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5 for patienter med SMA type 3, som har bevaret gangfunktion.

Resultatet er præsenteret i Tabel 23. Budgetkonsekvenserne er ca. 56,9 mio. DKK i år 5, når analysen udføres med AIP.

Tabel 19. Medicinrådets analyse af totale budgetkonsekvenser for patienter med SMA type 1, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 20. Medicinrådets analyse af totale budgetkonsekvenser for eksisterende ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 21. Medicinrådets analyse af totale budgetkonsekvenser for nye ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 22. Medicinrådets analyse af totale budgetkonsekvenser for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 23. Medicinrådets analyse af totale budgetkonsekvenser for patienter med SMA type 3, som har bevaret gangfunktion, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7. Diskussion

Behandling med risdiplam er forbundet med inkrementelle omkostninger på:

- [redacted] DKK sammenlignet med behandling med nusinersen for patienter med SMA type 1.
- [redacted] DKK sammenlignet med behandling med nusinersen for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år.
- [redacted] DKK sammenlignet med behandling med nusinersen for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år.
- [redacted] DKK sammenlignet med behandling med nusinersen for patienter SMA type 3, som har bevaret gangfunktion.

Sygdomsforløbet i modellen er en simplificering af SMA, da modellen ikke tager højde for udvikling i patienternes sygdomsforløb afhængig af motoriske færdigheder og forskelle i omkostninger forbundet med de forskellige stadier. Da Medicinrådet grundlæggende antager, at der ikke er forskel i effekt mellem risdiplam og komparator i korttidsstudier, og der ikke er data med længere opfølgningstid, som kan underbygge at effekten adskiller sig på længere sigt, og således retfærdiggøre en mere detaljeret model, accepterer Medicinrådet modellen. Dette er dog potentielt en stor begrænsning for analyserne, da der kan være markant forskel på, hvor store omkostninger, der er forbundet med patienternes niveauer af motoriske færdigheder, men der er ikke kliniske data for risdiplam, som kan belyse om det er tilfældet.

Der er meget stor usikkerhed for den gennemsnitlige overlevelse for patienter med SMA type 1 og 2, da naturhistoriske data anvendes til at estimere overlevelsen og dermed behandlingsvarigheden. Endvidere er det antaget, at overlevelsen for SMA type 1 efter behandling vil svare til overlevelsen for SMA type 2. Overlevelsen for patienter med SMA type 1 og 2, som samtidig modtager aktiv behandling kan potentielt være længere. Overlevelsen for patienter med SMA type 2 og 3 har dog minimal betydning for analysens resultat, da de inkrementelle omkostninger for alle sammenligninger næsten udelukkende er drevet af lægemiddelomkostningerne for risdiplam og nusinersen.

Risdiplam doseres vægtbaseret op til 20 kg, og derfor varierer de årlige lægemiddelomkostninger i de første par år for patienter under 20 kg. Dette har særlig betydning for klinisk spørgsmål 1, hvor patienterne i gennemsnit vejer under 20 kg ved behandlingsopstart. For de øvrige kliniske spørgsmål, hvor patienterne gennemsnitlig har en højere vægt, da vil de inkrementelle omkostninger stige allerede tidligere i behandlingsforløbet. For klinisk spørgsmål 1 og klinisk spørgsmål 2 gælder, at lægemiddelomkostningerne til nusinersen er dobbelt så høje det første år, hvilket udlignes jo længere tidshorisonten er. De akkumulerede inkrementelle omkostninger pr. år i modellens tidshorisont er vist for alle kliniske spørgsmål i Figur 3.

Figur 3. Akkumulerede inkrementelle omkostninger pr. år i modellen for hvert klinisk spørgsmål

Medicinrådets hovedanalyse tager ikke højde for de gener, det medfører for patienten og evt. påvirkning af livskvalitet, der følger med behandling af nusinersen og risdiplam. Jf. vurderingsrapporten har kan der være forskellige gener og ubehag forbundet med både nusinersen og risdiplam behandling. Den potentielle sundhedseffekt ved at undgå gene og ubehag, som behandlingerne kan medføre, har det ikke været mulig at kvantificere. Det er dog en mulighed, at Medicinrådet kan overveje, hvorvidt fordelen for patienterne ved at undgå behandlingsspecifikke gener og ubehag i sig selv skaber en yderligere værdi.

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9. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	27. oktober 2021	Godkendt af Medicinrådet

10. Bilag

10.1 Resultatet af ansøgers hovedanalyse

Patienter med SMA type 1

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 24.

Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 25.

Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 26.

Patienter med SMA type 3, som har bevaret gangfunktion

I ansøgers hovedanalyse bliver den inkrementelle omkostning pr. patient [redacted] DKK over en tidshorisont på 5 år. Resultaterne fra ansøgers hovedanalyse er præsenteret i Tabel 27.

Tabel 24. Resultatet af ansøgers hovedanalyse for patienter med SMA type 1, DKK, diskonterede tal

	Risdiplam	Nusinersen	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	28.109	99.169	-71.060
Patientomkostninger	41.963	48.623	-6.660
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 25. Resultatet af ansøgers hovedanalyse for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år, DKK, diskonterede tal

	Risdiplam	Nusinersen	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	28.094	99.127	-71.032
Patientomkostninger	41.942	48.602	-6.660

	Risdiplam	Nusinersen	Inkrementelle omkostninger
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 26. Resultatet af ansøgers hovedanalyse for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år, DKK, diskonterede tal

	Risdiplam	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	28.014	18.720	9.294
Patientomkostninger	41.829	11.179	30.650
Totale omkostninger	[redacted]	[redacted]	[redacted]

Tabel 27. Resultatet af ansøgers hovedanalyse for patienter med SMA type 3, som har bevaret gangfunktion, DKK, diskonterede tal

	Risdiplam	BSC	Inkrementelle omkostninger
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	28.579	19.075	9.503
Patientomkostninger	42.623	11.391	31.232
Totale omkostninger	[redacted]	[redacted]	[redacted]

10.2 Resultatet af ansøgers budgetkonsekvensanalyse

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som er inkluderet i omkostningsanalysen, dog uden patientomkostninger.

Patienter med SMA type 1, som ikke er i permanent ventilation

Ansøger estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 28.

Ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år

Ansøger estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 29.

Ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år

Ansøger estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 30.

Patienter med SMA type 3, som har bevaret gangfunktion

Ansøger estimerer, at anvendelse af risdiplam vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 5. Ansøgers estimat af budgetkonsekvenserne fremgår af Tabel 31.

Tabel 28. Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med SMA type 1, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 29. Ansøgers hovedanalyse for totale budgetkonsekvenser for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 30. Ansøgers hovedanalyse for totale budgetkonsekvenser for ikke-gående patienter med SMA type 2 og 3 i alderen 12-25 år, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 31. Ansøgers hovedanalyse for totale budgetkonsekvenser for patienter med SMA type 3, mio. DKK, ikke-diskonterede tal

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

Dato for behandling i Medicinrådet	27. oktober 2021
Leverandør	Roche
Lægemiddel	Risdiplam (Evrysdi)
EMA-indikation	5q spinal muskelatrofi

Forhandlingsresultat

Amgros har opnået følgende nye tilbud på risdiplam (Evrysdi):

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Forhandlet ny SAIP	Rabatprocent ift. AIP
Evrysdi	0,75 mg/ml	1 stk. (80 ml) pulver til oral opl.	62.378,77	[redacted]	[redacted]

Prisen er betinget af, at Medicinrådet som minimum anbefaler behandlingen til patienter med SMA-type I, som ikke er i permanent respirationsbehandling ved opstart af behandling, samt patienter med SMA-type II under 6 år og patienter med SMA-type III under 6 år.

Anbefales risdiplam (Evrysdi) ikke til ovenstående patienter indkøbes lægemidlet til AIP.

[redacted]

Vurdering af forhandlingsresultatet

[redacted]

Konklusion

[redacted]

Relation til markedet

[redacted]

Tabel 1: Sammenligning af årlige lægemiddelomkostninger for lægemidler til SMA

Lægemiddel	AIP	SAIP	Dosering	Lægemiddel-omkostning første år	Lægemiddel-omkostning efterfølgende år
Risdiplam (Evrysdi)	62.378,77	[redacted]	5 mg/kg dagligt (ved fuld dosis)	[redacted]	[redacted]
Nusinersen (Spinraza)	543.978,80	[redacted]	Første år: 6 doser Efterfølgende år: 3 doser	[redacted]	[redacted]
Onasemnogen abeparvovec (Zolgensma)	14.531.555,00	[redacted]	1 dosering	[redacted]	0

Status fra andre lande

Norge

Vurderingen er fortsat i gang.[1]

Sverige

Vurderingen er fortsat i gang.[2]

UK

Vurdering er fortsat i gang[3]. Prisforhandlinger pågår.

[1] https://nyemetoder.no/metoder/risdiplam
[2] https://janusinfo.se/nationelltinforandeavlakemedel/produktinfo/evrysdirisdiplam.4.29bf44e41784aa24ab4ce9da.html
[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10612/documents

8. september 2021

Medicinrådet

Att: Dorte Glintborg

dgl@medicinraadet.dk

Høringssvar fra Roche a/s Danmark vedrørende Medicinrådets vurdering af den kliniske merværdi af Evrysdi® (risdiplam) til behandling af spinal muskelatrofi (SMA).

Roche a/s har en række bemærkninger til den rådsgodkendte vurderingsrapport, som vi modtog d. 1. september 2021. Overordnet finder Roche ikke, at Medicinrådets konklusion er velunderbygget og har sammenhæng til den øvrige rapport.

Metodemæssig tilgang

Medicinrådet efterspørger i deres protokol data på en sammenligning mellem risdisplam og lægemidlet nusinersen i gruppen med SMA type 2 og 3 i alderen 2-11 år. Dette på trods af, at nusinersen ikke er dansk standardbehandling til patienter med SMA type 3 i alderen 2-11 år eller patienter med SMA type 2 i alderen 6-11 år (ikke anbefalet af Medicinrådet). Dermed strider både protokol og vurderingsrapport mod Medicinrådets metoder for vurdering af nye lægemidler, der tilsiger, at der for nye lægemidler skal sammenlignes med dansk standardbehandling.[i] Medicinrådet har således, for en substantiel del af de handicappede børn i netop ovenstående gruppe, sammenlignet med et ikke-anbefalet lægemiddel, men har alligevel udarbejdet en samlet konklusion på risdiplams effekt overfor dansk standardbehandling, dvs. overfor "ingen medicinsk behandling". I Medicinrådets konklusionen vedrørende risdiplam står således: "Medicinrådet vurderer, at der aktuelt ikke er påvist effekt af risdiplam for større børn og voksne med SMA type 2 og 3 i aldersgruppen 6-25 år. Opfølgningstiden i studiet (1 år) er for kort til at vise, om risdiplam kan

Roche a/s Industriholmen 59 2650 Hvidovre Tel. :36399826 Fax.:36399800 www.roche.dk CVR nr. 25230515

stabilisere sygdommen. Efter Medicinrådets kategorisering har risdiplam derfor ingen dokumenteret merværdi for disse patienter sammenlignet med ingen medicinsk behandling"[ii]
Sidstnævnte sammenligning er, for de 6-11 årige med SMA type 2 og type 3, ikke stillet som et klinisk spørgsmål eller kategoriseret og konkluderet på baggrund af i vurderingsrapporten. Det fremstår derfor uklart på hvilket datagrundlag, og med hvilke analyser, Rådet kommer til denne konklusion. Roche vil gerne opfordre Rådet til at tydeliggøre dette i vurderingsrapporten og præcisere det i Medicinrådets endelige konklusion, så det er tydeligt, hvad risdiplam sammenlignes med. Roche finder det vigtigt, da teksten ser ud til at være i modstrid med den konklusion fagudvalget kommer frem til i rapporten, hvor fagudvalget til SMA type 2 og 3 vurderer, at " risdiplam er *ligeværdigt* med nusinersen for patienter med SMA type 2 og 3 i aldersgruppen 2-11 år, som ikke har gangfunktion. Dette er baseret på en samlet vurdering af effekt og bivirkninger". Roche bemærker i øvrigt, at nusinersen har en *lille klinisk merværdi* over for ingen medicinsk behandling i den vurderingsrapport, der er udarbejdet for nusinersen for SMA type 2, og at nusinersen til behandling af SMA type 3 ikke kunne vurderes grundet manglende studiedata. [iii]

Med udgangspunkt i protokollen fra Medicinrådet har Roche leveret data på de sammenligninger, som Medicinrådet har efterspurgt. Det er disse data fagudvalget har forholdt sig til, kategoriseret og konkluderet på baggrund af. For gruppen med SMA type 2 og 3 i alderen 2-11 år, har man valgt *ikke* at basere vurderingen på effektmålet MFM-32, da denne motoriske skala ikke anvendes i det studie, som undersøger lægemidlet nusinersen, og derfor ikke kan danne grundlag for en sammenligning mellem risdiplam og nusinersen (Medicinrådets protokol s. 15). Roche finder det problematisk, at man ikke tager stilling til data for MFM-32, når Rådet så alligevel vælger at konkludere på risdiplams effekt over for ingen medicinsk behandling i aldersgruppen 6-11 år. Denne tilgang har man netop valgt for aldersgruppen 12-25 år, hvor MFM-32 er vægtet som et kritisk effektmål. Fremgangsmåden synes derfor ikke at være systematisk, og resultatet bliver desværre, at der tilsyneladende konkluderes på et ufuldstændigt datagrundlag i nogle af de aldersgrupper, der i dag ikke har adgang til medicinsk behandling i Danmark.

Håndtering af data, valg og fravalg af analyser

Medicinrådet skriver i deres konklusion, at opfølgningstiden i studiet (1 år) er for kort til at vise, om risdiplam kan stabilisere sygdommen. Denne bemærkning undrer Roche, da Medicinrådet jo netop har efterspurgt, at effektdata leveres ved 1 år (Medicinrådets protokol, s. 11)[iv]. Roche ville selvfølgelig havde foretrukket, at det havde været anført i protokollen, hvis fagudvalg og Råd fandt dette afgørende for at kunne foretage en retvisende vurdering. Roche *har* i øvrigt, og som supplement til ansøgningen (d. 28. juni 2021), indsendt data med 2-års opfølgning, og finder det bekymrende, hvis Medicinrådet ikke er forelagt de data.

Medicinrådet vælger ikke at anvende de indsendte MAIC-analyser som hovedresultat i sammenligningen mellem risdiplam og nusinersen i aldersgruppen 2-11 år. MAIC-analyserne er udarbejdet med det formål at korrigere for væsentlige forskelle i baselinekarakteristika mellem de inkluderede studier. I afsnittet, som vedrører databehandling og analyse, listes tre forhold, som gør, at Medicinrådet vælger kun at anvende resultaterne fra MAIC-analyserne som supplerende information i vurderingen (vurderingsrapporten s. 24-25). Et af argumenterne er, at Roche ikke har angivet baselinekarakteristika for den reducerede patientgruppe (populationen efter matching). Dette er imidlertid ikke korrekt - data før og efter matching fremgår af tabel 21 i den endelige ansøgning fra Roche. I stedet lægger Medicinrådet vægt på resultaterne fra indirekte sammenligninger udarbejdet ved brug af Buchers metode, som Roche efter forespørgsel fra Medicinrådet har indsendt som *supplerende* information. Roche gør i den endelige ansøgning opmærksom på, at resultaterne fra Buchers analyserne bør tolkes med stor forsigtighed, da der ikke tages højde for forskelle mellem studiepopulationerne. Slutteligt, ønsker Roche at påpege, at der for aldersgruppen 2-5 år og 6-11 år ikke er udarbejdet MAIC-analyser, hvilket der henvises til i vurderingsrapporten.

Forhold vedrørende administration

Roche noterer sig, at der på side 44 i vurderingsrapporten[v] foretages en vurdering af risdiplams administrationsmæssige fordele og ulemper ift. nusinersen. Under ulemperne fsva. risdiplam står: ”I og med, at det både er en alvorlig sygdom og en dyr medicin, forventer fagudvalget en høj grad af adhærens, men det er alligevel muligt, at patienter glemmer at tage medicinen, og der kan også være risiko for, at de ikke får anvendt eller opbevaret medicinen korrekt”. Roche finder denne antagelse spekulativ, idet størstedelen af patientgruppen må forventes at have klare ønsker om adgang til et virksomt lægemiddel med henblik på at opnå en højere livskvalitet. Herudover gør Roche opmærksom på, at de tre behandlingscentre i Danmark vil blive tilbudt redskaber, der vil understøtte patientens korrekte anvendelse og opbevaring af medicinen. I vurderingsrapporten anerkendes det, at administrationsvejen for risdiplam kan være en fordel hos patienter, hvor svær skoliose vanskeliggør den intratekale administration, ligesom at et skift fra nusinersen til risdiplam kan være en fordel, hvis patienten ikke er velbehandlet på nusinersen f.eks. oplever betydelige bivirkninger. Roche vil gerne opfordre Medicinrådet til at tydeliggøre at ovennævnte forhold, herunder udvikling af skoliose, kan opstå efter en årrække. Overvejelser vedrørende skift bør derfor ikke være knyttet op på en forhåndsdefineret aldersgruppe.

Sundhedsøkonomi

Roche har ingen bemærkninger til den fremsendte sundhedsøkonomiske afrapportering, ud over en positiv bemærkning om, at rapporten fremstår grundig og velargumenteret.

Med venlig hilsen

Kirsten Holdt Henningsen
Scientific Access Advisor
Mobil: +45 52409099
E-mail: kirsten.holdt@roche.com

Ditte Marie Clugston
Medical Writer
Mobil: +45 42142944
E-mail: ditte_marie.clugston@roche.com

Roche a/s

Industriholmen 59 | 2650 Hvidovre | Danmark
Telefon: +45 3639 9999 | Fax: +45 3639 9800
www.roche.dk

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[i] https://medicinraadet.dk/media/0xub45gk/h%C3%A5ndbog_for_medicinr%C3%A5dets_proces_og_metode_vedr-_nye_l%C3%A6gemidler_og_indikationsudvidelser_version_2-8_februar2021_adlegacy.pdf

[ii] https://medicinraadet.dk/media/omnfi0tv/medicinr%C3%A5dets-vurdering-af-risdiplam-til-spinal-muskelatrofi-vers-1-0-x_adlegacy.pdf

[iii] https://medicinraadet.dk/media/fofjbeuw/baggrund-for-medicinr%C3%A5dets-anbefaling-vedr-nusinersen-til-spinal-muskelatrofi-vers-2-0-med-bilag_adlegacy.pdf

[iv] https://medicinraadet.dk/media/5p2pyokx/medicinr%C3%A5dets-protokol-vedr-risdiplam-til-spinal-muskelatrofi-vers-1-0_adlegacy.pdf

[v] https://medicinraadet.dk/media/omnfi0tv/medicinr%C3%A5dets-vurdering-af-risdiplam-til-spinal-muskelatrofi-vers-1-0-x_adlegacy.pdf

Medicinrådet

Medicinrådets vurdering vedrørende risdiplam (Evrysdi) til behandling af spinal muskelatrofi

Version 1.1

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette bliver sammenfattet i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Dokumentoplysninger	
Godkendelsesdato	28. september 2021
Dokumentnummer	122876
Versionsnummer	1.1

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at risdiplam er en lige så god behandling som nusinersen til de patienter med SMA type 1 og 2, som i dag bliver behandlet med nusinersen. Det er typisk børn, der påbegynder behandling inden 6-årsalderen.

Medicinrådet vurderer, at der aktuelt ikke er påvist effekt af risdiplam for større børn og voksne med SMA type 2 og 3 i aldersgruppen 6-25 år. Opfølgningstiden i studiet er for kort til at vise, om risdiplam kan stabilisere sygdommen.

Risdiplam indtages oralt, mens nusinersen bliver indsprøjtet i det hulrum, som omgiver rygmarven. Derfor kan risdiplam være en fordel for nogle patienter, eksempelvis patienter med svær skoliose (rygskævhed) eller patienter, der oplever komplikationer ved indsprøjtningen af nusinersen. Der er ikke dokumentation for, at patienterne opnår bedre effekt ved at kombinere de to behandlinger.

Vurderingen er baseret på følgende kategoriseringer efter Medicinrådet metoder:

- For patienter med SMA type 1 kan værdien af risdiplam sammenlignet med nusinersen ikke kategoriseres, da datagrundlaget er sparsomt. Medicinrådet vurderer dog, at risdiplam er ligeværdigt med nusinersen.
- For patienter med SMA type 2 og 3 i alderen 2-11 år har risdiplam ingen dokumenteret merværdi sammenlignet med nusinersen. Det vil sige, at risdiplam også er ligeværdigt med nusinersen til disse patienter. Hos aldersgruppen 2-5 år er effekten af risdiplam også bedre end ingen medicinsk behandling, hvorimod effekten hos børn, der først påbegynder behandling i alderen 6-11 år, ikke er forskellig fra ingen medicinsk behandling.
- For patienter med SMA type 2 og 3, der påbegynder behandling i alderen 12-25 år, har risdiplam ingen dokumenteret merværdi sammenlignet med ingen medicinsk behandling.

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MEDICINRÅDET KATEGORISERER LÆGEMIDLERS VÆRDI I EN AF FØLGENDE KATEGORIER:

- **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.
- **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.
- **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.
- **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.
- **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

I nogle situationer er det ikke muligt at kategorisere lægemidlets samlede værdi. De situationer opstår, når evidensgrundlaget for vurderingen er for usikkert til at kategorisere værdien jf. Medicinrådets metoder (fx på grund af usikkerheder omkring effektforhold og spinkelt datagrundlag). Medicinrådet konkluderer da, at samlet værdi ikke kan kategoriseres. Medicinrådet vil i disse tilfælde argumentere for, om der er grund til at formode, at det nye lægemiddel er dårligere eller evt. bedre end gældende standardbehandling, eller der ikke er grund til at skelne mellem behandlingerne. Det sker på baggrund af det foreliggende datagrundlag og fagudvalgets kliniske erfaring. Vurderingen er forbundet med større usikkerhed end vurderinger, hvor lægemidlets værdi kan kategoriseres.

MEDICINRÅDET VURDERER KVALITETEN AF DE DATA, DER LIGGER TIL GRUND FOR VURDERINGEN AF LÆGEMIDLET (EVIDENSENS KVALITET) I EN AF FØLGENDE GRADE-KATEGORIER:

- **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.
- **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.
- **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.
- **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2. Begreber og forkortelser

6MWT:	Seks minutters gangtest (*six minutes' walk test*)
CHOP-INTEND:	*Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders*
EMA:	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR:	*European Public Assessment Report*
FDA:	*The Food and Drug Administration*
GRADE:	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HFSME:	*Hammersmith Functional Motor Scale Expanded*
HR:	*Hazard ratio*
ITT:	*Intention to treat*
MAIC:	*Match adjusted indirect comparison*
MFM-32	*Motor Function Measure scale*
OR:	*Odds ratio*
RCT:	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR:	Relativ risiko
RULM:	*Revised Upper Limb Module*
SD:	Standardafvigelse
SMA:	Spinal muskelatrofi
SMN:	*Survival motorneuron*

3. Introduktion

Formålet med Medicinrådets vurdering af risdiplam (Evrysdi) til spinal muskelatrofi er at vurdere den værdi, lægemidlet har sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Roche. Medicinrådet modtog ansøgningen den 15. juni 2021.

De kliniske spørgsmål er:

1. *Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 1, som ikke er i permanent ventilationsbehandling?*

2. *Hvilken værdi har risdiplam sammenlignet med nusinersen for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år?*

3. *Hvilken værdi har risdiplam sammenlignet med placebo for patienter i alderen 12-25 år, som har SMA type 2 eller SMA type 3, og har mistet gangfunktionen?*

4. *Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 3, som har bevaret gangfunktion?*

3.1 Spinal muskelatrofi

5q spinal muskelatrofi (SMA) er en sjælden genetisk sygdom, der medfører muskelsvind og deraf nedsat muskelkraft. Trods sygdommens sjældenhed er SMA den hyppigste genetisk betingede årsag til dødsfald blandt spædbørn. Incidensen i Europa er estimeret til 1 ud af 6000 fødte børn [1].

Sygdommen skyldes en gendefekt i *survival motorneuron 1* (*SMN1*), der betyder, at patienten ikke danner tilstrækkeligt af det SMN-protein, der sikrer fungerende motorneuroner i rygmarv og hjernestamme. SMN-proteinet dannes dog også via *SMN2*, som er til stede i genomet i et variabelt antal kopier, men kun ca. 10 % af det mRNA, som bliver transskriberet fra *SMN2,* bliver til funktionelt protein. Antallet af *SMN2*-kopier har derfor betydning for symptomdebut og sygdommens sværhedsgrad. Der er tale om et kontinuum af sværhedsgrader, der spænder fra få ugers overlevelse til progredierende forværring af motoriske funktioner over mange år. I praksis underinddeles sygdommen i fem stadier (SMA type 0-IV) ud fra tidspunkt for symptomdebut, motorisk udvikling og antal *SMN2*-kopier (Tabel 1) [1–3].

Tabel 1. Klinisk klassifikation af spinal muskelatrofi

Type	Antal pt.	Nye pt. per år	Debut alder	Udviklingstrin (ubehandlet)	Overlevelse (ubehandlet)	*SMN2* kopier
0	-	-	Medfødt	Ingen	< 6 måneder	1
1	9[1]	1-2[1,2]	0-6 mdr.	Sidder aldrig	< 2 år	2-3
2	Ca. 100[2]	Ca. 2[2]	6-18 mdr.	Går aldrig	Fra 2 år til normal levetid[4]	3-4
3	Ca. 100[3]	1-2[3]	> 18 mdr.	Står og går, men bliver permanente kørestolsbru-gere inden eller i voksenalder	Normal levetid	4
4	-	-	Voksen-alder[5]	Går i voksenårene	Normal levetid	4-5

1. Ifølge fagudvalget, 24. juni 2021, er der 9 patienter i aktuel behandling med nusinersen.
2. Oplyst på rcfm.dk (RehabiliteringsCenter for Muskelsvind), november 2018.
3. Oplyst på rcfm.dk (RehabiliteringsCenter for Muskelsvind), april 2019.
4. Ubehandlet er ca. 70 % i live ved 25-års alderen [3].
5. Litteraturen oplyser forskellige aldersgrænser. 21 år ifølge Burr et al 2020 [3]. 30-35 år ifølge EMA 2016 [1].

De kliniske karakteristika gælder for ubehandlede patienter. Indførsel af behandling med nusinersen i 2017 har gjort, at der nu er patienter, der opnår motoriske milepæle, der ikke tidligere var mulige. F.eks. vil der være patienter med SMA type 1, der opnår evnen til at sidde. Internationalt er man derfor begyndt at klassificere patienter som 'non-sitters', 'sitters' og 'walkers'.

3.2 Risdiplam

Risdiplam (Evrysdi) er en *SMN2 pre-mRNA splicing modifier,* der øger mængden af funktionelt SMN-protein.

Den godkendte EMA-indikation er:
Behandling af 5q spinal muskelatrofi (SMA) hos patienter, der er ældre end 2 måneder, som har:

- Den kliniske diagnose SMA type 1, type 2 eller type 3 *eller*
- 1-4 *SMN2*-kopier.

Fagudvalget præciserer, at det betyder, at patienterne har en bi-allelisk deletion og/eller mutation i *SMN1*-genet.

Risdiplam er et pulver, som sygehusapoteket eller sygehusafdelingen blander til en mikstur og udleverer til patienten. Det betyder, at patienten selv kan indtage medicinen derhjemme. Miksturen kan også gives via en sonde, hvis patienten ikke kan spise og drikke selv. Medicinen skal opbevares ved køleskabstemperatur og er maksimalt holdbar i 64 dage.

Tabel 2. Dosering af lægemidlet afhænger af alder og vægt

Alder og vægt	Dosis
Alder fra 2 mdr. til < 2 år	0,20 mg/kg dagligt
Alder ≥ 2 år:	
- Vægt < 20 kg	0,25 mg/kg dagligt
- Vægt ≥ 20 kg	5 mg dagligt

3.3 Nuværende behandling

Behandlingen af SMA varetages på tre centre i hhv. København, Aarhus og Odense. Målet med den aktuelle lægemiddelbehandling er at forsinke sygdomsprogressionen og derigennem øge patientens overlevelse, funktionsniveau og livskvalitet.

Ved SMA type 1 (non-sitters) er respirationssvigt den hyppigste dødsårsag [3]. Behandlingen handler derfor især om at nedsætte behovet for assisteret ventilation og derved øge muligheden for, at barnet overlever. Herudover tilstræber behandlingen, at barnet opnår de alderssvarende motoriske milepæle. Patienter med SMA type 1, som ikke er i permanent ventilationsbehandling, bliver i Danmark tilbudt nusinersen som standardbehandling iht. Medicinrådets anbefaling. Fra maj 2021 blev onasemnogene abeparvovec også anbefalet som mulig standardbehandling til disse patienter.

Ved SMA type 2 og 3 er målet primært at forbedre eller vedligeholde funktionsniveau og livskvalitet. Herunder både de grov- og finmotoriske funktioner. De grovmotoriske funktioner kan f.eks. betyde, at patienter med SMA type 2 (sitters) kan spise selv, kan vende sig selv, eller at patienter med SMA type 3 bevarer deres gangfunktion (walkers). De finmotoriske funktioner kan betyde, at patienten f.eks. kan anvende en computer eller styre et joystick på en elektrisk kørestol.

I Danmark bliver patienter med SMA type 2 tilbudt nusinersen som standardbehandling iht. Medicinrådets anbefaling, hvis deres symptomer er debuteret inden 2-års alderen, og sygdomsvarigheden er højst 4 år (svarende til alder < 6 år) ved tidspunkt for opstart af nusinersenbehandling. Det betyder i praksis, at børn og voksne over 6 år med SMA type 2 og 3 ikke aktuelt bliver tilbudt opstart af nusinersen eller anden sygdomsmodificerende behandling som standardbehandling. Der er aktuelt ingen randomiserede studier af nusinersen med patienter over 12 år.

I juni 2021 har Sundhedsstyrelsen anbefalet, at screening for SMA bliver indført som en del af det nationale screeningsprogram for sjældne sygdomme. Det betyder, at præsymptomatiske spædbørn med SMA og op til fire *SMN2*-kopier vil kunne behandles fra fødslen, inden de udviser symptomer på SMA. Denne mulighed gælder i øjeblikket for praktiske formål kun til søskende til børn med SMA, som diagnosticeres præ- eller neonatalt.

4. Metode

Medicinrådets protokol for vurdering vedrørende risdiplam (Evrysdi) til behandling af spinal muskelatrofi beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan Medicinrådet vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 SMA type 1 (non-sitters)

Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 1, som ikke er i permanent ventilationsbehandling?

5.1.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen omfatter to studier af risdiplam og ét studie af nusinersen.

For risdiplam har ansøger har poolet data for en delpopulation af 17 patienter fra fase 2-studiet FIREFISH del 1 [4] og den fulde population fra fase 3-studiet FIREFISH del 2 [5]. De poolede data er fortrolige *data-on-file*.

For nusinersen har ansøger inkluderet den fulde population fra ENDEAR, det randomiserede fase 3-studie for patienter med SMA type 1 [6].

Tabel 3. Oversigt over studier af patienter med SMA type 1

Publikationer	Klinisk forsøg	Studie/NCT-nummer	Intervention
Baranello 2021 [4]	Ukontrolleret studie	FIREFISH del 1	Risdiplam
Darras 2021 [5]	Ukontrolleret studie	FIREFISH del 2 /NCT02913482	Risdiplam
Finkel 2017 [6]	RCT	ENDEAR /NCT02193074	Nusinersen

FIREFISH-studiet er et ukontrolleret studie. Del 1 inkluderede 21 patienter [4], hvoraf de 17, som fik den terapeutiske dosis, blev inkluderet i ansøgers analyse. Del 2 inkluderede 41 patienter, som alle fik den terapeutiske dosis [5]. Opfølgningstiden var 2 år. Ansøger har poolet data med 1 års opfølgning fra de to studier. Patientgruppen udgør derfor 58 patienter.

ENDEAR er et randomiseret dobbeltblindet studie, hvor 121 patienter blev randomiseret 2:1 til nusinersen eller såkaldt shamkontrol. Nusinersenarmen udgør 80 patienter. Opfølgningstiden var ca. 13 måneder [6]. Studiet blev dog stoppet tidligere, hvilket har betydning for opgørelsen af de effektmål, der omhandler måling af funktionsniveau og motoriske milepæle, hvor der for en del af patienterne kun foreligger data for ca. 6 måneder.

Inklusionskriterierne i begge studier var børn med SMA type 1 med alder 1-7 måneder på tidspunktet for screening. Patienterne havde to SMN2-kopier og var ikke i permanent ventilationsbehandling på tidspunktet for inklusion (mere end 16 timer/døgn).

Tabel 4. Baselinekarakteristika

	Population risdiplam			Population nusinersen
	FIREFISH del 1	FIREFISH del 2	FIREFISH poolet	ENDEAR
Antal patienter	17*	41	58	80
Sygdomsvarighed ved screening, uger gennemsnit (range)	14,4 (5,3-23,3)	12,4 (1-22,9)	13,0 (1-23,3)	13,2 (0-25,9)
Alder ved symptomdebut, uger gennemsnit (range)	7,4 (4-13,1)	7,1 (4,1-13)	7,2 (4-13,1)	7,9 (2-18)

		Population risdiplam		Population nusinersen
	FIREFISH del 1	FIREFISH del 2	FIREFISH poolet	ENDEAR
Alder ved 1. dosis, dage gennemsnit (range)	170 (102-212)	159 (68-212)	163 (68-212)	163 (52-242)
CHOP-INTEND-score gennemsnit (range)	24 (16-34)	22 (8-37)	23 (8-37)	27 (NR)
HINE-2-score gennemsnit (range)	1 (0-2)	1,0 (0-5)	1,0 (0-5)	1,3 (NR)
Andel med behov for ventilationsstøtte n (%)	29 %	29 %	29 %	26 %
Andel med behov for hjælp til ernæring	6 %*	10 %	9 %	9 %

* 17 af i alt 21 patienter i FIREFISH del 1. De sidste 4 patienter er ikke inkluderet, fordi de fik en lavere dosis.
Brug af sonde blev ikke opgjort i dette studie. I stedet er angivet antal patienter, som ikke er i stand til at synke.

Patienterne, som indgår i det poolede datasæt for risdiplam, er sammenlignelige med de nusinersenbehandlede patienter med hensyn til alder og sygdomsvarighed ved 1. dosis samt behov for ventilationsstøtte og hjælp til ernæring (sonde). Til gengæld havde patienterne i risdiplamgruppen en lavere funktionsscore målt med CHOP-INTEND-score (forskel 4 point). HINE2-score var ikke væsentlig forskellig (0,3 point).

De 17 patienter fra FIREFISH del 1 blev inkluderet fra 5 forskellige lande (Belgien, Frankrig, Italien, Schweiz og USA). De 41 patienterne i FIREFISH del 2 blev inkluderet fra 10 forskellige lande. Heraf flest patienter fra Kina (11), Italien (10), Rusland (5), Frankrig (4) og Polen (4) [ref. EPAR]. Fagudvalget vurderer, at Danmark er mindre proaktive end f.eks. Italien med at tilbyde ventilationsstøtte til børn med SMA type 1. Det kan f.eks. betyde, at nogle af de dårligste patienter (som ikke er i permanent ventilationsbehandling i Danmark) var ekskluderet fra studiet (fordi de var i permanent ventilationsbehandling mere end 16 timer/døgn.

5.1.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Ansøger har sammenholdt data for risdiplam for 58 patienter, som indgik i to ukontrollerede studier med data for 80 patienter fra nusinersenarmen fra et randomiseret studie. Der er derfor ikke mulighed for en indirekte statistisk sammenligning via en fælles komparator (placebo). Der er således tale om en naiv

sammenligning af data for risdiplam og nusinersen, hvor datagrundlaget ikke er fuldstændig sammenligneligt, og der er derfor risiko for, at de konfidensintervaller, som ansøger har angivet, underestimerer den usikkerhed, der er forbundet med effektestimaterne. Fagudvalget vil derfor ikke basere sin konklusion på disse konfidensintervaller.

ENDEAR-studiet blev afsluttet tidligt, og tidspunktet for sidste måling af motoriske milepæle varierer derfor i praksis fra dag 183, 302 og 394. Da muligheden for at opnå motoriske milepæle, såsom at kunne sidde uden støtte, er stærkt afhængig af barnets alder på opgørelsestidspunktet, kan det få betydning, når man sammenligner med 12 måneders data for risdiplam. Ansøger har derfor også leveret et modificeret datasæt, hvor data for risdiplam for motoriske milepæle er opgjort op til 6 måneder før tidspunktet for data cut-off. Begge datasæt (6 og 12 måneder) vil indgå i fagudvalgets vurdering.

Bemærkninger til ansøgers MAIC-analyse

Ansøger har valgt at supplere den naive sammenligning af data med en *unanchored matching-adjusted indirect comparison* (MAIC)-analyse, hvor de 58 patienter fra risdiplamgruppen blev vægtet, så de bedre ligner de 80 patienter i nusinersengruppen. Patienterne blev matchet på tre kriterier: alder, sygdomsvarighed og CHOP-INTEND-score ved baseline. Ansøger konkluderer, at matchingen var succesfuld, samt at et højt antal patienter blev vægtet som 0 eller tæt på 0; konsistent med reduktionen i populationsstørrelsen (fra 58 patienter til 40,1 *effektive sample size*).

Fagudvalget bemærker, at matchingen udligner forskellen i CHOP-INTEND-score, mens alder og sygdomsvarighed i forvejen var identisk mellem de to grupper. Til gengæld medfører matchingen en betydelig reduktion i andel patienter i risdiplamgruppen, som havde behov for ventilationsstøtte ved baseline (fra 29 % til 20 %). Dermed bliver forskellen mellem grupperne større (20 % i risdiplamgruppen mod 26 % i nusinersengruppen med behov for ventilationsstøtte ved baseline). Fagudvalget vurderer, at denne forskel kan få betydning for tolkning af resultaterne. Særligt de effektmål, der angår patienternes risiko for at komme i permanent ventilationsbehandling. Dette kan introducere bias i estimatet fra MAIC-sammenligningen.

Fagudvalget har på denne baggrund valgt at se bort fra ansøgers MAIC-analyse, da den dels medfører en betydelig reduktion af en i forvejen meget lille populationsstørrelse, og der mindst er én væsentlig parameter (ventilationsstøtte), som der ikke er taget højde for.

5.1.3 Evidensens kvalitet

Da vurderingen af risdiplam er baseret på data fra ukontrollerede studier, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Medicinrådet har tidligere vurderet risiko for bias i det randomiserede studie af nusinersen som 'lav' (se Baggrund for Medicinrådet anbefaling af nusinersen).

På denne baggrund er evidenskvaliteten meget lav.

5.1.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Værdien af risdiplam sammenlignet med nusinersen kan ikke kategoriseres efter Medicinrådets metoder, da der er tale om et sparsomt datagrundlag fra to ukontrollerede studier af risdiplam.

Tabel 5. Resultater for klinisk spørgsmål 1. Risdiplam vs. nusinersen for patienter med SMA type 1

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Overlevelse	Andel pt. i live (5 %-point)	Kritisk	[redacted]	Ikke kategoriseres	[redacted]	Ikke kategoriseres	Ikke kategoriseres
Kombineret mortalitet eller permanent ventilations-behandling	Andel pt., som er døde eller anvender respirator > 16 timer/døgn (15 %-point)	Kritisk	[redacted]	Ikke kategoriseres	[redacted]	Ikke kategoriseres	Ikke kategoriseres
Permanent ventilations-behandling	Andel pt., som ikke anvender respirator > 16 timer/døgn (10 %-point)	Vigtigt	[redacted]	Ikke kategoriseres	Ikke beregnet	Ikke kategoriseres	Ikke kategoriseres
Motoriske milepæle (12 måneder)	Andel respondere på CHOP-INTEND (20 %-point)	Kritisk	[redacted]	Ikke kategoriseres	[redacted]	Ikke kategoriseres	Ikke kategoriseres
	Andel pt., der sidder iht. HINE-definition (10 %-point)	Vigtigt	[redacted]		[redacted]		
	Andel pt., der står eller går uden støtte (narrativt)	Vigtigt	Deskriptivt		[redacted] Ikke beregnet		
Alvorlige uønskede hændelser	Andel pt., som oplever mindst én hændelse (10 %-point)	Vigtigt	[redacted] %-point	Ikke kategoriseres	[redacted]	Ikke kategoriseres	Ikke kategoriseres

Ophør pga. bivirkninger	Andel pt., som ophører behandlingen pga. bivirkninger (10 %-point)	Vigtigt	[redacted]%-point	Ikke kategoriseres	[redacted]	Ikke kategoriseres	Ikke kategoriseres

Konklusion	
Samlet kategori for lægemidlets værdi	Kan ikke kategoriseres. Fagudvalget vurderer, at risdiplam er ligeværdigt med nusinersen baseret på en samlet vurdering af effekt og bivirkninger. Datagrundlag er dog for usikkert til, at værdien kan kategoriseres ved brug af Medicinrådets metoder.
Kvalitet af den samlede evidens	Meget lav - nye studier vil med høj sandsynlighed ændre effektestimaterne.

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

Overlevelse
Effektmålet overlevelse er kritisk for vurderingen af lægemidlets værdi for patienterne, fordi SMA type 1-patienter ubehandlet har en gennemsnitlig forventet levetid under to år.

- I risdiplamgruppen døde [redacted] efter 12 måneders opfølgning.
- I nusinersengruppen døde 13 af de 80 patienter (16,3 %) efter 13 måneders opfølgning.

Den relative forskel er ikke signifikant [redacted]. Den absolutte forskel [redacted] overstiger den mindste klinisk relevante forskel på 5 %-point.

Fagudvalget vurderer, at risdiplam har mindst lige så god effekt som nusinersen på overlevelse, men vurderingen er baseret på et sparsomt datagrundlag.

Kombineret mortalitet eller permanent ventilationsbehandling
Effektmålet kombineret mortalitet eller permanent ventilationsbehandling er kritisk for vurderingen af lægemidlets værdi for patienterne.

- I risdiplamgruppen var [redacted] enten døde eller i permanent ventilationsbehandling efter 12 måneder.
- I nusinersengruppen var det 31 af de 80 patienter (38,8 %) efter 13 måneder.

Den relative forskel er signifikant [redacted] Den absolutte forskel [redacted] overstiger den mindste klinisk relevante forskel på 15 %-point. Usikkerheden kan dog være større, end de angivne konfidensintervaller angiver, da datagrundlaget for de to lægemidler ikke er helt sammenligneligt.

Fagudvalget vurderer, at risdiplam har mindst lige så god effekt som nusinersen på det kombinerede effektmål død eller permanent ventilationsbehandling, men vurderingen er baseret på et sparsomt datagrundlag.

Permanent ventilationsbehandling
Effektmålet permanent ventilationsbehandling er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi det betyder, at patienten er afhængig af en respirator i mindst 16 timer i døgnet, fordi kraften i de muskler, der er nødvendige, for at patienten kan trække vejret, er svært nedsat. Samtidig er patienten mere modtagelig over for lungeinfektioner.

- I risdiplamgruppen var [redacted] i permanent ventilationsbehandling efter 12 måneder.
- I nusinersengruppen var det 18 af de 80 patienter (22,5 %) efter 13 måneder.

Ansøger har ikke beregnet de relative forskelle. Forskellen på [redacted] overstiger den mindste klinisk relevante forskel på 10 %-point til fordel for risdiplam.

Fagudvalget vurderer, at risdiplam har mindst lige så god effekt som nusinersen på effektmålet permanent ventilationsbehandling, men vurderingen er baseret på et sparsomt datagrundlag.

Motoriske milepæle
Motoriske milepæle omfatter:

1) CHOP-INTEND respondere (kritisk)
2) Evnen til at sidde uden støtte (vigtigt)
3) Evnen til at stå eller gå uden støtte (vigtigt).

CHOP-INTEND

CHOP-INTEND respondere (kritisk) er defineret som patienter, der opnår min. 4 point stigning på en skala, hvor max score er 64 point. Den indeholder 16 aktiviteter, som har relevans for alder før sidde-stadiet. Hver aktivitet scores fra 0-4 point. Fagudvalget har defineret, at den mindste klinisk relevante forskel i andel respondere er 20 %.

- I risdiplamgruppen opnåede [redacted] respons på CHOP-INTEND. Dette tal var det samme ved både 6 og 12 måneder.
- I nusinersengruppen opnåede 52 af 73 patienter (71 %) respons. Tidspunktet for sidste måling varierede fra ca. 6, 10 og 13 måneder pga. tidlig afslutning af studiet.

Den relative forskel er ikke signifikant [redacted]). Den absolutte forskel [redacted], overstiger ikke den mindste klinisk relevante forskel på 20 %-point.

Fagudvalget bemærker, at patienterne i risdiplamgruppen i gennemsnit havde en ca. 4 point lavere CHOP-INTEND- score ved baseline, hvilket potentielt kan have underestimeret resultatet for risdiplam.

Fagudvalget vurderer, at risdiplam har mindst lige så god effekt som nusinersen på CHOP-INTEND, men vurderingen er baseret på et sparsomt datagrundlag.

Evne til at sidde uden støtte

Evnen til at sidde uden støtte er meget afhængig af barnets alder på opgørelsestidspunktet. Ifølge WHO er 99 % percentilen 9,2 måneder for raske børn. Børnene var i gennemsnit ca. 3 måneder ved baseline og vil, uanset behandling, ikke opnå lige så hurtig evne til at sidde som raske børn. Forskelle i opfølgningstiden (6 eller 12 måneder) kan derfor få stor betydning for sammenligningen af resultaterne.

Der findes flere metoder/redskaber til at opgøre effekten, hvilket kan give forskellige resultater. Her er effektmålet for begge lægemidler, vurderet med HINE 2, patienter, der opnår *stabel sit eller pivot*, iht. den definition, der blev anvendt i ENDEAR-studiet af nusinersen.

- I risdiplamgruppen opnåede [redacted] evnen til at sidde uden støtte efter 6 måneder målt med HINE-2 (*stable sit eller pivot)*.
- Efter 12 måneder var tallet for risdiplam steget til [redacted].
- I nusinersengruppen opnåede 6 af de 73 patienter (8 %) evnen til at sidde uden støtte baseret på sidste måling, som i praksis var efter hhv. 6, 10 eller 13 måneder, afhængig af hvor længe patienterne var blevet fulgt, inden studiet blev afbrudt.

Den relative forskel mellem risdiplamdata for 6 måneder er ikke signifikant forskellig fra nusinersen [redacted] Den absolutte forskel [redacted] overstiger ikke den mindste klinisk relevante forskel på 10 %-point. Tallet kan dog være understimeret for risdiplam, da nogle af patienterne i nusinersengruppen blev fulgt længere end 6 måneder.

Sammenholdt med 12 måneders data for risdiplam ([redacted]) stiger forskellen mellem risdiplam og nusinersen til [redacted]. Dette tal risikerer til gengæld at overestimere effekten for risdiplam ift. nusinersen, da flere patienter kan sidde selv, alene fordi de nu er blevet ældre.

Fagudvalget vurderer, at risdiplam har mindst lige så god effekt som nusinersen på børnenes evne til at sidde uden støtte, men vurderingen er baseret på et sparsomt datagrundlag.

Stå eller gå uden støtte

Medicinrådet har vurderet, at dette effektmål kun beskrives deskriptivt, idet vi forventer at det vil være et meget lille antal patienter, der kan stå eller gå uden støtte efter 1 års opfølgning. Herudover har Medicinrådet bedt om data ved 2 års opfølgning.

- I risdiplamgruppen kunne [redacted] stå med støtte efter 6 måneder. [redacted]patienter kunne stå med støtte efter 12 måneder, og den ene kunne også gå med støtte. Efter 24 måneder kunne 8 børn stå med støtte og to børn gå med støtte. Ingen børn kunne på det tidspunkt gå uden støtte.
- I nusinersengruppen kunne et barn stå med støtte efter 6 måneder, ved afslutning af ENDEAR-studiet. Ingen børn kunne gå.

Det er således få børn, der opnår evnen til at stå eller gå med støtte, men man kan ikke på denne baggrund udtale sig om forskellen mellem lægemidler. Ingen børn opnåede evnen til at gå uden støtte inden for 2 år.

Alvorlige uønskede hændelser (SAE)

Effektmålet alvorlige uønskede hændelser er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi de alle er alvorlige hændelser, som ikke nødvendigvis er relateret til behandlingen.

- I risdiplamgruppen oplevede [redacted] mindst en SAE inden for 12 måneder.
- For nusinersengruppen er antal patienter, der oplevede mindst en SAE opgivet for den fulde ITT-population til 61 ud af 80 patienter (76 %).

Den relative forskel er statistisk signifikant [redacted]. Den absolutte forskel [redacted] overstiger også den mindste klinisk relevante forskel på 10 % til fordel for risdiplam.

Fagudvalget vurderer, at risdiplam resulterer i færre SAE end nusinersen. Der er her typiske tale om SAE såsom pneumoni/ luftvejsinfektioner og respirationssvigt, som kan være relateret til selve sygdommen. Endvidere er vurderingen baseret på et sparsomt datagrundlag.

En oversigt over typen af de hyppigste ikke-alvorlige hændelser kan ses i afsnit 6.

Ophør pga. bivirkninger
Effektmålet ophør pga. bivirkninger er vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienter i behandling med nusinersen kan opleve ikke-alvorlige men generende bivirkninger, hvor det kan blive aktuelt at ophøre eller skifte til anden behandling.

- I risdiplamgruppen havde [redacted] ophørt behandlingen pga. bivirkninger efter 12 måneder.
- I nusinersengruppen ophørte 13 ud af 80 (16 %) i ITT-populationen behandlingen pga. bivirkninger.

Den relative forskel er ikke signifikant [redacted]. Den absolutte forskel [redacted] overstiger ikke den mindste klinisk relevante forskel på 10 %-point.

For nusinersen var der typisk tale om respirationssvigt og få tilfælde relateret til den intratekale behandlingsprocedure. Det har ikke været muligt at finde information i EPAR'en, om hvilken type af bivirkninger som specifikt ledte til behandlingsophør hos patienterne i risdiplamgruppen. Gastrointestinale bivirkninger er hyppige, men det er uvist, om det reelt medførte ophør med behandlingen med risdiplam.

En oversigt over typen af de hyppigste ikke-alvorlige hændelser kan ses i afsnit 6.

Fagudvalget vurderer, at der ikke er klinisk relevant forskel mellem risdiplam og nusinersen, med hensyn til hvor mange der ophører behandlingen pga. bivirkninger.

5.1.5 Fagudvalgets konklusion

Værdien af risdiplam sammenlignet med nusinersen til behandling af patienter med SMA type 1, kan ikke kategoriseres med Medicinrådet metoder, da datagrundlaget er sparsomt.

Fagudvalget vurderer, at risdiplam er ligeværdigt med nusinersen til behandling af patienter med SMA type 1, baseret på en samlet vurdering af effekt og bivirkninger.

For flere effektmål overstiger punktestimatet Medicinrådets grænse for mindste klinisk relevante forskel til fordel for risdiplam, og ingen effektestimater trækker i negativ retning.

Der kan dog være andre forskelle mellem de to lægemidler, som er relevante at tage i betragtning ved valg af lægemiddel. Disse bliver gennemgået i afsnit 6.

5.2 Ikke-gående SMA type 2 og 3 (sitters) i alderen 2-11 år

Hvilken værdi har risdiplam sammenlignet med nusinersen for ikke-gående patienter med SMA type 2 og 3 i alderen 2-11 år?

5.2.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen baserer sig på de to randomiserede studier (SUNFISH og CHERISH), der er angivet i protokollen. Data fra SUNFISH-studiet af risdiplam er endnu ikke publiceret, men fremgår af EMAs EPAR [7], FDAs clinical review [8] samt to kongrespostere [9,10]. De fleste af de subgruppedata for risdiplam, som Medicinrådet har bedt om, er *data-on-file,* der anvendes i overensstemmelse med Medicinrådets kriteriepapir for brug af upublicerede data.

Tabel 6. Oversigt over studier

Publikationer	Klinisk forsøg	NCT-nummer	Intervention
EMAs EPAR Evrysdi [7] FDAs clinical review [8] Mercuri 2020 [9] Oscoui 2021 [10]	RCT	SUNFISH del 2/ NCT02908685	Risdiplam
Mercuri 2018 [11]	RCT	CHERISH/NCT02292537	Nusinersen

SUNFISH del 2

SUNFISH del 2 er et dobbeltblindet placebokontrolleret RCT, som inkluderede i alt 180 patienter med SMA type 2 eller ikke-gående (nonambulante) patienter med type 3 i alderen 2-25 år. Opfølgningstiden er 2 år. Randomiseringen blev stratificeret for aldersgrupperne 2-5 år, 6-11 år, 12-17 år og 18-25 år med henblik på at inkludere minimum 45 patienter i hver aldersgruppe. Dog ikke mere end 30 patienter i aldersgruppen 18-25 år [7]. I dette kliniske spørgsmål indgår data for subpopulationen af 112 børn i alderen 2-11 år.

Inklusionskriterier var en RULM-indgangsscore >= 2 (kan løfte en eller begge hænder op til munden). Herudover skulle patienterne kunne sidde selvstændigt.

Eksklusionskriterier var aktuel eller tidligere behandling med en SMN2-målrettet behandling, invasiv ventilationsbehandling eller tracheostomi eller kirurgi for skoliose eller hoftefiksering gennemført inden for det sidste år eller planlagt inden for de næste 18 måneder.

Det primære effektmål var ændring i MFM32-score efter 12 måneder. Ændring i HFSME- og RULM-score var sekundære effektmål [7].

CHERISH

CHERISH er ligeledes et dobbeltblindet RCT, hvor der i kontrolgruppen blev anvendt såkaldt sham-kontrol. Studiet inkluderede i alt 126 børn i alderen 2-12 år med 'senere debut af SMA'. De kliniske karakteristika for de inkluderede patienter svarede i praksis til klassifikationen af SMA type 2 (jf. tabel 1). Enkelte patienter havde dog symptomdebut i alderen mellem 18 og 20 måneder (grænsen jf. tabel 1 er 18 måneder). Opfølgningstiden er ca. 15 måneder.

Yderligere inklusionskriterier var HSFME mellem 10 og 54. Eksklusionskriterier var svær skoliose, behov for ventilationsstøtte mere end 6 timer per døgn eller sonde.

Det primære effektmål var ændring i HSMFE-score efter 15 måneder. Ændring i RULM-score var et sekundært effektmål [11].

Tabel 7 viser baselinekarakteristika for SUNFISH-subgruppen med alder 2-11 år samt den fulde population fra CHERISH.

Tabel 7. Baselinekarakteristika: for aldersgruppen 2-11 år

	SUNFISH del 2 (2-11 år) *data-on-file*		**CHERISH [11]**	
	risdiplam	**placebo**	**nusinersen**	**sham-kontrol**
Antal patienter	76	36	84	42
Totalpopulation (andel %)	120 (63 %)	60 (60 %)	84 (100 %)	42 (100 %)
Alder 2-5 år	37	18	70	36
Alder 6-11 år	39	18	14	6
Alder ved screening, år median (range)	6,0 (2-11)	5,5 (2-10)	4,0 (2-9)	3,0 (2-7)

	SUNFISH del 2 (2-11 år) *data-on-file*		CHERISH [11]	
	risdiplam	**placebo**	**nusinersen**	**sham-kontrol**
Alder ved symptomdebut, mdr. median (range)	12,3 (1-38)	12,2 (6-84)	10,0 (6-20)	11,0 (6-20)
Sygdomsvarighed ved 1. dosis, mdr. median (range)	54,1 (5-130)	50,1 (0-107)	39,0 (8-94)	30,2 (10-80)
HFMSE-score, gennemsnit (SD)	18,5 (12,3)	20,4 (11,6)	22,4 (8,3)	19,9 (7,2)
RULM-score, gennemsnit (SD)	19,0 (7,2)	20,9 (6,8)	19,4 (6,2)	18,4 (5,7)
SMA type 2	80%	78 %	100 %	100 %
SMA type 3	20 %	22 %		
2 SMN2-kopier (andel %)	3 %	3 %	7 %	10 %
3 SMN2-kopier (andel %)	92 %	86 %	88 %	88 %
4 SMN2-kopier (andel %)	5 %	11 %	2 %	2 %
ikke kendt	0 %	0 %	2 %	0 %
Svær skoliose (kurvatur > 40 grader)	17 %	17 %	0 %	0 %

Alt i alt er subgruppen fra SUNFISH del 2-studiet i gennemsnit 2 år ældre, har ca. 14 måneder længere sygdomsvarighed end populationen fra CHERISH-studiet og inkluderer endvidere patienter med svær skoliose.

- Den ældste patient i SUNFISH var 11 år, mens den ældste i CHERISH var 9 år.
- 13 patienter (17 %) i risdiplamgruppen havde svær skoliose mod ingen i nusinersengruppen, da dette var eksklusionskriterium i CHERISH.
- Ca. 80 % af patienter i SUNFISH-subpopulationen har SMA type 2, og 20 % har non-ambulant SMA type 3, mens alle patienterne i CHERISH opfylder de kliniske kriterier for SMA type 2. Fagudvalget vurderer dog, at de inkluderede patienter med SMA type 3 funktionelt svarer til SMA type 2, da de har mistet gangfunktionen.

- En større del af patienterne i SUNFISH har 4 SMN2-kopier, mens flere i CHERISH (7 %) har 2 SMN2-kopier, som typisk fører til udvikling af SMA type 1.
- Patienterne i SUNFISH har lavere funktionsniveau målt på HFSME.
- Der er ikke forskel i RULM-score, som her er det kritiske effektmål for vurdering af effekten i denne population.

Forskellene mellem de aktive studiearme går dog i de fleste tilfælde igen i kontrolgrupperne, hvorfor det er muligt at tage højde for en del af forskellene ved en indirekte sammenligning via den fælles komparator (kontrolgrupperne).

Fagudvalget bemærker dog, at forskellen i HFSME-score ved baseline mellem risdiplam og nusinersen (forskel 3,9 point) ikke går igen i kontrolgrupperne, da disse ikke er forskellige mellem studierne.

RULM-score er ikke væsentlig forskelligt mellem risdiplam og nusinersenarmene (0,4 point), men der er en forskel mellem kontrolgrupperne på 2,5 point, hvilket kan få betydning ved den indirekte sammenligning via kontrolgrupperne.

Ansøger har ikke angivet baselinekarakteristika i ansøgningen for subgrupperne med alder 2-5 år og 6-11 år, da det ikke har været muligt at få oplyst disse for nusinersen. Medicinrådet har, på forespørgsel, den 10. august 2021 modtaget baselinedata for risdiplam for de to aldersgrupper. Udover forskel i alder havde patienterne i aldersgruppen 2-5 år kortere sygdomsvarighed ved 1. dosis (40 vs. 96 måneder), lavere RULM-score (18 vs. 20 point) sammenlignet med aldersgruppen 6-11 år. Ingen i aldersgruppen 2-5 år havde svær skoliose mod 33 % i aldersgruppen 6-11 år. Andelen af patienter med SMA type 3 i de to aldersgrupper var hhv. 11 og 28 % [*data-on file*].

5.2.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Medicinrådet har i protokollen bedt om data for børn i aldersgruppen 2-11 år fra SUNFISH del 2 med henblik på at foretage en indirekte statistisk sammenligning med den fulde population fra CHERISH (2-12 år) via den fælles komparator. Ansøger har iht. protokollen udført en Buchers analyse, som inkluderer alle patienter.

Ansøger har, som anvist i protokollen, også leveret data for aldersgrupperne 2-5 år og 6-11 år. Der er dog ikke oplysninger om baselinekarakteristika til at vurdere, om aldersgrupperne er sammenlignelige imellem lægemidlerne. Medicinrådet ser derfor bort fra de konfidensintervaller, som ansøger har angivet for de to subpopulationer.

Ansøger har herudover udført en MAIC-analyse med det formål at korrigere for forskelle i baselinekarakteristika mellem de to studier. I praksis ekskluderer ansøger de patienter fra SUNFISH del 2, som ikke opfylder følgende tre kriterier:

- Alder ved screening under 9 år (ældste barn inkluderet i CHERISH var 9 år)
- Ingen svær skoliose ved baseline (eksklusionskriterium i CHERISH)
- HFSME baseline-score < 10 (eksklusionskriterium i CHERISH).

Det medfører i praksis en reduktion af risdiplamgruppen med 41 ud af de i alt 112 patienter i aldersgruppen 2-11 år svarende til, at en tredjedel af patienterne ekskluderes fra analysen (tilbage er 71 patienter).

De fleste af de 41 patienter opfyldte mere end et kriterium for eksklusion. 7 patienter blev alene ekskluderet pga. alder, og 13 patienter blev ekskluderet alene pga. HFSME baseline < 10.

Hos små børn ses et tæt tidsmæssigt sammenfald mellem alder og sygdomsvarighed, og deraf sammenhæng mellem alder og effekt. Der er dog ikke dokumenteret en sammenhæng mellem alder og effekt hos ældre børn med SMA type 3, hvor sygdommen kan debutere over en længere årrække. Fagudvalget finder det derfor problematisk, at ansøger ekskluderer 7 patienter fra MAIC-analysen alene pga. af en marginal aldersforskel, som ikke har dokumenteret sammenhæng med effekten.

Ansøger har ikke taget højde for, at SMA type 2 progredierer hurtigst i en tidlig alder, mens patienter med type 3 progredierer i en senere alder. Ansøger har ikke angivet baselinekarakteristika for dette forhold i den reducerede patientgruppe, og det er derfor ikke muligt at se, hvordan forholdet imellem patienter med SMA type 2 og 3 ændrer sig efterfølgende.

På denne baggrund vil Medicinrådet anvende resultaterne af den indirekte sammenligning (Buchers analyse) som hovedresultat med de nævnte forbehold, at resultaterne i kontrolgrupperne for nogle effektmål er ens og for andre effektmål er forskellige. Ansøgers MAIC-analyse vil blive anvendt som supplerende information.

5.2.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Risiko for bias i SUNFISH del 2 i aldersgruppen 2-11 år er med forbehold for, at HMSME ved baseline er lavere i risdiplamgruppen ift. placebogruppen (se bilag 1). Risiko for bias i CHERISH er med forbehold for, at patienterne i nusinersengruppen havde en højere HFMSE-score ved baseline end placebogruppen. Da forbeholdene samlet set medfører en mulig risiko for hhv. at underestimere effekten af risdiplam og overestimere effekten af nusinersen, har fagudvalget nedgraderet evidensen med ét niveau pga. risiko for bias.

Herudover har fagudvalget nedgraderet yderligere ét niveau pga. den indirekte sammenligning mellem nusinersen og risdiplam, da det ikke har været muligt at tage tilstrækkelig højde for alle relevante forskelle mellem de to studier. Følsomhedsanalyserne ændrer dog ikke konklusionerne, hvorfor der kun nedgraderes med ét niveau for dette domæne. Evidensen for 'alvorlige hændelser', der er et vigtigt effektmål, nedgraderes yderligere ét niveau pga. upræcist estimat.

Evidensens kvalitet er lav, hvilket betyder, at nye studier med stor sandsynlighed kan ændre konklusionen.

Evidensen for subgrupperne med alder 2-5 år og 6-11 år er ikke vurderet systematisk, men må anses som værende af lavere kvalitet pga. manglende oplysninger om baselinekarakteristika og mindre *sample size* med deraf mere upræcise effektestimater.

5.2.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 2.

Tabel 8. Resultater for klinisk spørgsmål 2. Risdiplam vs. nusinersen for patienter med SMA type 2 og 3 (uden gangfunktion) i alderen 2-11 år

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
HFMSE	Forskel i point (3 point)	Vigtigt	[redacted]	ingen	-	-	Ingen
RULM	Forskel i point (2 point)	kritisk	[redacted]	ingen	-	-	ingen
Alvorlige uønskede hændelser	Andel pt., som oplever mindst én hændelse (10 %-point)	Vigtigt	[redacted]) %-point	ingen	[redacted]	ingen	ingen
Ophør pga. bivirkninger	Andel pt., som ophører behandlingen pga. bivirkninger (10 %-point)	Vigtigt	0	ingen	-	ingen	ingen
Livskvalitet	Point (5 point eller 0,5 SD) (angivet som EQ-5D-5L)	Kritisk	[redacted] *	ingen	-	-	ingen
Konklusion							
Samlet kategori for lægemidlets værdi	Ingen dokumenteret merværdi for risdiplam sammenlignet med nusinersen. Fagudvalget vurderer, at risdiplam er et ligeværdigt behandlingsalternativ sammenlignet med nusinersen på baggrund af data for effekt og bivirkninger.						
Kvalitet af den samlede evidens	Lav - nye studier kan med høj sandsynlighed ændre effektestimaterne.						

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.
*Data for livskvalitet er her angivet ift. placebo, da der ikke er data, der muliggør en komparativ analyse ift. nusinersen.

Hammersmith Functional Motor Scale Expanded (HFMSE)
Effektmålet Hammersmith Functional Motor Scale Expanded (HFMSE) anvendes i begge studier og kan derfor bruges til at sammenligne forskellen mellem risdiplam og nusinersen. Når effektmålet er defineret som vigtigt og ikke kritisk, skyldes det, at skalaen er mindre følsom for ændringer i arm- og håndfunktion, som har stor betydning hos patienter uden gangfunktion.

- For risdiplam steg HFSME med [redacted] med placebo efter 12 måneder (forskel [redacted].
- For nusinersen steg HFSME med 3,9 point ift. et fald på -1,0 point i kontrolgruppen efter 15 måneder (forskel 4,9 point).

Den indirekte statistiske sammenligning (Buchers analyse) viser en signifikant absolut forskel mellem risdiplam og nusinersen på [redacted]Den overstiger dog ikke den mindste klinisk relevante forskel på 3 point.

Resultatet af ansøgers MAIC-analyse er statistisk signifikant [redacted] men da forskellen også her er under 3 point, ændrer det ikke konklusionen.

Fagudvalget bemærker, at effekten af risdiplam og nusinersen ift. placebo kan være hhv. under- og overstimeret (jf. afsnit 5.2.3), da patienterne i risdiplamgruppen havde en lavere HFMSE-score ved baseline ift. placebo. Omvendt havde patienterne i nusinersengruppen en højere HMFSE-score ved baseline end shamkontrolgruppen. MAIC-analysen, som ekskluderer alle patienter med HFSME < 10, ændrer dog ikke væsentligt ved resultatet.

<u>Aldersgruppen 2-5 år</u>

- Effekten for risdiplam vs. placebo var [redacted]
- Effekten for nusinersen vs. placebo var [redacted].

Forskellen for risdiplam ift. nusinersen på [redacted]overstiger ikke den mindste klinisk relevante forskel på 3 point.

Der er ikke baselinekarakteristika for nusinersen for denne aldersgruppe. Fagudvalget kan derfor ikke vurdere, om forskellen er reel.

For risdiplam oplyser ansøger, at ingen i aldersgruppen 2-5 år havde skoliose, men at 9 af de 55 patienter (16 %) havde en baseline HFMSE under 10 point. Resultatet af analysen, hvor patienter med HFMSE<10 er ekskluderet, ændrer dog ikke konklusionen.

<u>Aldersgruppen 6-11 år</u>

- Effekten for risdiplam vs. placebo var [redacted]
- Effekten for nusinersen vs. placebo var [redacted].

Forskellen mellem risdiplam og nusinersen på [redacted] er dermed hverken statistisk signifikant eller over Medicinrådets grænse for klinisk relevans. Resultatet af analysen, hvor patienter med HFMSE<10, svær skoliose eller alder over 9 år er ekskluderet, ændrer ikke konklusionen.

Fagudvalget vurderer, at der ikke er klinisk relevant forskel mellem risdiplam og nusinersen i effekt på HFMSE i aldersgruppen 2-11 år. Heller ikke inden for subgrupperne 2-5 år og 6-11 år.

Risdiplam ift. placebo

Fagudvalget bemærker, at effekten af risdiplam på HFMSE ikke adskiller sig statistisk signifikant fra placebo i hverken den fulde SUNFISH-population eller specifikt i aldersgrupperne 2-11 år, 2-5 år og 6-11 år.

Revised Upper Limb Module (RULM)

Effektmålet *Revised Upper Limb Module* (RULM) er defineret som kritisk for vurderingen af lægemidlets værdi for patienterne, fordi RULM er egnet til at måle finmotoriske ændringer og evne til at klare dagligdags aktiviteter hos personer uden gangfunktion.

- For risdiplam steg RULM med [redacted] ift. placebo efter 12 måneder (forskel[redacted].
- For nusinersen steg RULM med 4,2 point ift. 0,5 point i kontrolgruppen efter 15 måneder (forskel 3,7 point).

Den indirekte statistiske sammenligning viser en forskel mellem risdiplam og nusinersen på [redacted] hvilket hverken er statistisk signifikant eller over Medicinrådets grænse for klinisk relevans, da forskellen er under 2 point.

Resultatet af MAIC-analysen er [redacted] og ændrer ikke konklusionen.

Aldersgruppen 2-5 år

- Effekten for risdiplam ift. placebo er af ansøger oplyst til [redacted] Tal fra FDAs gennemgang viser en signifikant effekt ift. placebo på 3,41 (1,55; 5,26, n = 55) [8].
- Effekten for nusinersen ift. placebo er af ansøger oplyst til [redacted].

Forskellen mellem risdiplam og nusinersen på [redacted]) er hverken statistisk signifikant eller over Medicinrådets grænse for klinisk relevans for aldersgruppen 2-5 år. Resultatet af ansøgers analyse, hvor patienter med HFMSE<10 er ekskluderet, ændrer ikke konklusionen.

Aldersgruppen 6-11 år

- Effekten for risdiplam ift. placebo er af ansøger oplyst til [redacted] Tal fra FDAs gennemgang viser en ikke-signifikant forskel ift. placebo på 1,07 (-0,81; 2,94 (n = 57) [8].

- Effekten for nusinersen ift. placebo var [redacted].

Forskellen mellem risdiplam og nusinersen på [redacted] er hverken statistisk signifikant eller over Medicinrådets grænse for klinisk relevans. Resultatet af ansøgers analyse, hvor patienter med HFMSE<10, svær skoliose eller alder over 9 år er ekskluderet, ændrer ikke konklusionen.

Fagudvalget vurderer, at der ikke er forskel mellem risdiplam og nusinersen i effekt på RULM i aldersgruppen 2-11 år, samt at effekten heller ikke ser ud til at være forskellig mellem lægemidlerne i subgrupperne 2-5 år og 6-11 år.

Risdiplam ift. placebo

Fagudvalget bemærker, at effekten af risdiplam i aldersgruppen 2-5 år var både statistisk signifikant og oversteg Medicinrådets grænse for klinisk relevans ift. placebo [8].

I aldersgruppen 6-11 år var effekten af risdiplam hverken statistisk signifikant eller oversteg Medicinrådets grænse for klinisk relevans ift. placebo [8].

Forklaringen kan være andre forskelle i baselinekarakteristika udover alder, da der var stor forskel på sygdomsvarighed og andel patienter med svær skoliose. Endvidere var andelen af patienter med SMA type 3 og RULM-score lavere i aldersgruppen 2-5 år sammenlignet med aldersgruppen 6-11 år (jf. afsnit 5.2.1).

Alvorlige uønskede hændelser (SAE)

- For risdiplam forekom mindst en SAE hos [redacted] af børnene i aldersgruppen 2-11 år, hvilket ikke var forskelligt fra placebo ([redacted]).
- For nusinersen blev mindst en SAE rapporteret hos 17 % mod 29 % i kontrolgruppen.

Den relative forskel mellem risdiplam ift. nusinersen er ikke signifikant [redacted] Den absolutte forskel [redacted]) %-point overstiger ikke den mindste klinisk relevante forskel på 10 %-point.

Typen af SAE er ikke specifikt opgjort for de 2-11 årige, men data for den fulde SUNFISH-population viser, at der typisk er tale om pneumoni eller andre luftvejsinfektioner, der kan være relateret til selve sygdommen [7].

Frekvensen af SAE ved behandling med risdiplam synes højere i aldersgruppen 2-5 år [redacted]%-point end i aldersgruppen 6-11 år ([redacted]Frekvensen i placebogrupperne var ens for de to aldersgrupper[redacted] vs. [redacted]). Der er ikke tal for nusinersen for SAE hos disse subgrupper.

Fagudvalget vurderer, at der ikke er forskel mellem risdiplam og nusinersen i hyppigheden af SAE.

Ophør pga. bivirkninger

Der var intet behandlingsophør pga. bivirkninger i nogle af studierne [7,11].

Fagudvalget har endnu ingen klinisk erfaring med risdiplam, men på baggrund af den kliniske erfaring med nusinersen er der meget få patienter, om nogen, der er ophørt med denne behandling pga. bivirkninger.

Fagudvalget vurderer, at der ikke er forskel mellem risdiplam og nusinersen, på hvor mange der ophører behandlingen pga. bivirkninger i aldersgruppen 2-11 år.

Livskvalitet
Effektmålet livskvalitet er kritisk for vurderingen af lægemidlets værdi for patienterne, da målet med at bedre patienternes funktionsniveau i sidste ende er, at patienterne opnår bedre livskvalitet. Herunder, at bivirkninger af behandlingen balanceres ift. effekten ift. den samlede livskvalitet for patienten.

Livskvaliteten for risdiplam hos aldersgruppen 2-11 år er målt med EQ-5D-5L rapporteret af forældre eller omsorgsperson. Der var ingen ændring fra baseline til 12 måneder for hverken risdiplam- eller placebogruppen og derfor heller ingen forskel mellem risdiplam og placebo[redacted].

Ansøger har ikke leveret data for nusinersen, da der, ifølge ansøger, ikke er data tilgængelige. Medicinrådet har tidligere modtaget *data-on-file*, men de er fortrolige. En kongresposter fra 2019 indeholder data for forældrerapporteret livskvalitet målt med redskabet *Pediatric Quality of Life Inventory* (PedsQL). Data for samlet livskvalitet viser et gennemsnitlig lille fald (< 1 point) i nusinersengruppen, mens shamkotrolgruppen falder ca. 6 point (aflæst på figur). Det medfører en forskel på 5,0 (0,7; 9,3) point for nusinersen ift. placebo [12].

Data for sygdomsspecifik livskvalitet af risdiplam ift. placebo foreligger ikke specifikt for aldersgruppen 2-12 år, men foreligger for den fulde studiepopulation i alderen 2-25 år og 12-25 år (se afsnit 5.3.4).

Fagudvalget kan ikke på det foreliggende datagrundlag vurdere, om der er forskel i livskvalitet mellem de to lægemidler.

Fagudvalget bemærker, at risdiplam ikke er vist at medføre bedre livskvalitet ift. placebo målt som generisk livskvalitet.

5.2.5 Fagudvalgets konklusion

I henhold til Medicinrådets metoder har risdiplam ingen dokumenteret merværdi sammenlignet med nusinersen for patienter med SMA type 2 og 3 i aldersgruppen 2-11 år, som ikke har gangfunktion.

Fagudvalget vurderer, at risdiplam er ligeværdigt med nusinersen for patienter med SMA type 2 og 3 i aldersgruppen 2-11 år, som ikke har gangfunktion. Dette er baseret på en samlet vurdering af effekt og bivirkninger.

For alle effektmål gælder, at ingen af punktestimaterne for forskellen mellem risdiplam og nusinersen overstiger den af Medicinrådet definerede mindste klinisk relevante forskel.

Der kan dog være andre forskelle mellem de to lægemidler, som er relevante at tage i betragtning ved valg af lægemiddel. Disse bliver gennemgået i afsnit 6.

Fagudvalget bemærker yderligere, at effekten på det kritiske effektmål RULM-score var signifikant og oversteg Medicinrådets grænse for klinisk relevans ift. placebo for aldersgruppen 2-5 år (der i dag tilbydes behandling med nusinersen), men ikke for aldersgruppen 6-11 år, som ikke aktuelt bliver tilbudt nusinersen som standardbehandling i Danmark. Tilsvarende resultater blev i øvrigt også set på studiets primære effektmål MFM-32 (se s. 37).

Der er således ikke data, der dokumenterer effekten af risdiplam i aldersgruppen 6-11 år. Opfølgningstiden i SUNFISH-studiet var relativt kort (12 måneder), Det er uvist, om effekt på RULM ville adskille sig fra placebo efter længere behandlingstid.

5.3 Ikke-gående SMA type 2 og 3 (sitters) i alderen 12-25 år

Hvilken værdi har risdiplam sammenlignet med placebo for patienter i alderen 12-25 år, som har SMA type 2 eller SMA type 3, og har mistet gangfunktionen?

5.3.1 Litteratur

Ansøgningen baserer sig på ikke-publicerede data for aldersgruppen 12-25 år, som indgik i SUNFISH del 2-studiet. Denne aldersgruppe udgør ca. en tredjedel af den fulde studiepopulation (studiet er tidligere beskrevet i afsnit 5.2.1). Medicinrådets vurdering af denne aldersgruppe er baseret på data fra en poster [9] samt fortrolige *data on-file*.

For beskrivelse af studiedesignet se klinisk spørgsmål 2, afsnit 5.2.1. Ansøger bemærker, at resultater for det primære endepunkt og flere nøgleendepunkter blev udforsket i subgrupperne, men at subgruppeanalyserne ikke er designet til/har tilstrækkelig statistisk styrke til at vise en forskel mellem risdiplam og placebo. Medicinrådet har derfor også angivet resultaterne for den fulde studiepopulation (2-25 år).

Opfølgningstiden i den randomiserede del af studiet er forholdsvis kort (12 måneder). Efter fagudvalget udarbejdede protokollen er der dog blevet præsenteret 2 års data for studiet [10]. Der er dog tale om ukontrollerede opfølgningsdata, da de patienter, som indgik i placebogruppen, efterfølgende blev tilbudt at skifte til risdiplam. Disse data vil derfor kun indgå som supplerende information.

Tabel 9 viser en oversigt over baselinekarakteristika for subgruppen af patienter i alderen 12-25 år.

Tabel 9. Baselinekarakteristika for subgruppen i alderen 12-25 år i SUNFISH del 2 *data-on-file*

	Risdiplam	Placebo
Antal patienter	44	24
Fuld population (andel %)	120 (37 %)	60 (40 %)

	Risdiplam	Placebo
Alder ved screening, år median (range)	15,5 (12-25)	15,0 (12-24)
Alder ved symptomdebut, mdr. median (range)	12,8 (0-57)	14,9 (7-135)
Sygdomsvarighed ved 1. dosis, mdr. median (range)	168,9 (132-275)	171,5 (34-271)
HFMSE-score, gennemsnit (SD)	12,0 (11,9)	11,0 (10,7)
RULM-score, gennemsnit (SD)	20,5 (7,3)	19,9 (6,6)
SMA type 2	52 %	67 %
SMA type 3	48 %	33 %
3 SMN2-kopier (andel %)	84 %	79 %
4 SMN2-kopier (andel %)	14 %	17 %
Andet/ikke kendt	2 %	4 %
Svær skoliose (kurvatur > 40 grader)	48 %	71 %

Fagudvalget vurderer, at der er færre patienter med svær skoliose i risdiplamgruppen end i placebogruppen (48 vs. 71 %), hvilket muligvis kan medføre en overestimering af effekten af risdiplam ift. placebo. Dette forhold går igen i den fulde studiepopulation, om end forskellen er mindre (28 vs. 38 %).

Risdiplamgruppen indeholder også en lidt større andel af patienter med SMA type 3, men fagudvalget vurderer, at det ikke har afgørende betydning for sammenligningen. I den fulde studiepopulation var der ikke forskel. Øvrige baselinekarakteristika er sammenlignelige mellem risdiplam og placebo.

5.3.2 Databehandling og analyse

I dette afsnit er ansøgers datagrundlag, databehandling og analyse for hvert effektmål beskrevet.

Data er opgjort som den absolutte forskel i antal point, som angivet i protokollen. Bivirkninger er opgjort som både absolut og relativ forskel for det dikotome effektmål

5.3.3 Evidensens kvalitet

Medicinrådet har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 2).

Medicinrådet har nedgraderet evidensen med ét niveau pga. forbehold for bias, da effekten af risdiplam kan være overestimeret ift. placebo pga. den skæve fordeling af patienter med skoliose, som ydermere er mere udtalt i aldersgruppen 12-25 år (se bilag 1).

De kritiske effektmål MFM-32, RULM og livskvalitet og de vigtige effektmål HMFSE og ophør pga. bivirkninger er nedgraderet med ét niveau for 'upræcist estimat', som følge af at der er få patienter i subgruppen med alder 12-25 år, særligt i placebogruppen.

Det vigtige effektmål 'alvorlige hændelser' er nedgraderet med to niveauer pga. upræcist estimat, da konfidensintervallet er meget bredt og omfatter værdier for både positive og negative konklusioner.

Evidensens kvalitet er lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.3.4 Effektestimater og kategorier

I tabellen herunder fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 3.

Tabel 10 Resultater for klinisk spørgsmål 3

Effektmål	Målenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
HFMSE	Forskel i point (3 point)	Vigtigt	[redacted]	Ingen	-	Ingen	Ingen
RULM	Forskel i point (2 point)	Kritisk	[redacted]	Ingen	-	Ingen	Ingen
MFM-32	Forskel i point (3 point)	Kritisk	[redacted]	Ingen	-[Tekst]	Ingen	Ingen
Alvorlige uønskede hændelser	Andel pt., som oplever mindst én hændelse (10 %-point)	Vigtigt	[redacted]	Ingen	[redacted]	Ingen	Ingen
Ophør pga. bivirkninger	Andel pt., som ophører behandlingen pga. bivirkninger (10 %-point)	Vigtigt	0	Ingen	-	Ingen	Ingen
Livskvalitet	Point (5 point eller 0,5 SD)	Kritisk	[redacted]	Ingen	-	Ingen	Ingen
Konklusion							
Samlet kategori for lægemidlets værdi	Ingen dokumenteret merværdi sammenlignet med placebo.						

Kvalitet af den samlede evidens	LAV – nye studier kan med høj sandsynlighed ændre konklusionen-

CI = konfidensinterval, HR = Hazard Ratio, OR = Odds Ratio, RR = relativ risiko.

HFMSE
HFMSE-score ved 12 måneder i aldersgruppen 12-25 år var [redacted]for risdiplam vs. [redacted]Forskellen mellem risdiplam og placebo var [redacted]og således hverken statistisk signifikant eller over grænsen klinisk relevans som defineret af Medicinrådet (< 3 point).

Data for den fulde studiepopulation (2-25 år)

Til sammenligning var forskellen i HFMSE i den fulde studiepopulation (alder 2-25 år) 0,58, hvilket hverken var statistisk signifikant eller oversteg den af Medicinrådet fastsatte grænse for klinisk relevans [9]. Opfølgningsdata viser en lille stigning i risdiplamgruppen (aflæst på figur < 1 point, n = 106) fra 1-2 år [10]. Det vides ikke, hvorvidt det skyldes en gennemsnitlig stigning blandt de tilbageværende patienter eller et frafald af de dårligste patienter. Der var en stigning i placebogruppen fra 8 til 12 måneder, men der er ikke data for det efterfølgende år.

RULM
RULM-score var[redacted]for risdiplam og [redacted]for placebo. Forskellen mellem risdiplam og placebo var [redacted]) og således hverken statistisk signifikant eller over Medicinrådets grænse for klinisk relevans (< 2 point).

Data for den fulde studiepopulation (2-25 år)

Til sammenligning var forskellen i den fulde studiepopulation (alder 2-25 år) 1,59, hvilket var statistisk signifikant, men også under de 2 point [9]. Opfølgningsdata viser en stigning i risdiplamgruppen (aflæst på figur < 1 point, n = 105) fra 1-2 år [10]. Der var stort set ingen ændring i placebogruppen de første 12 måneder, men der er ikke data efter 12 måneder.

Andelen af patienter med svær skoliose var lavere i risdiplamgruppen end i placebogruppen i både subgruppen og i den fulde population, hvilket muligvis kan medføre en overestimering af effekten.

Motor Function Measure scale (MFM-32)
Effektmålet *Motor Function Measure scale* (MFM-32) er kritisk for vurderingen af lægemidlets værdi for patienterne, fordi skalaen er valideret til at måle funktionsændringer hos patienter ≥ 6 år med neuromuskulære sygdomme, herunder SMA type 2 og 3. Den omfatter tre domæner: domæne 1 måler 'forflytning i stående stilling', domæne 2 måler 'funktion i ekstremiteter tæt på kroppen' (skuldre, overarme, hofter) og domæne 3 måler 'funktion i ekstremiteter længere væk fra kroppen' (underarme, hænder, fødder). Endelig adskiller skalaen sig fra HFMSE ved at være mere sensitiv for ændringer i finmotorikken og dermed mere følsom for ændringer hos patienter uden gangfunktion.

MFM-32-score var [redacted]for risdiplamarmen og [redacted]) for placebo. Forskellen mellem risdiplam og placebo

var [redacted] og således hverken statistisk signifikant eller over grænsen defineret af Medicinrådet for klinisk relevans (> 3 point).

Data for den fulde studiepopulation (2-25 år)

Til sammenligning var forskellen i den fulde studiepopulation (alder 2-25 år) 1,55, hvilket var statistisk signifikant, men også under de 3 point [9]. I aldersgruppen 2-5 år var forskellen til gengæld statistisk signifikant bedre end for placebo (3,03 CI; 0.71, 5.35), mens det samme ikke var tilfældet for aldersgruppen 6-11 år (1,58 CI; - 0.58, 3.74).

Opfølgningsdata viser ingen ændring i risdiplamgruppen (aflæst på figur < 1 point, n = 103) fra 1-2 år [10]. Der var stort set ingen ændring i placebogruppen de første 12 måneder, men der er ikke data efter 12 måneder.

Andelen af patienter med svær skoliose var lavere i risdiplamgruppen end i placebogruppen i både subgruppen og i den fulde population, hvilket muligvis kan medføre en overestimering af effekten.

Alvorlige uønskede hændelser (SAE)
Antal patienter, der oplevede mindst en SAE, var [redacted] for risdiplam og [redacted] for placebo. Den relative forskel var [redacted] og den absolutte forskel var [redacted] og således hverken statistisk signifikant eller over Medicinrådets grænse klinisk relevans (< 10 %-point) ift. placebo.

Data for den fulde studiepopulation (2-25 år)

Antallet af SAE i den samlede studiepopulation var 24 ud af 120 (20 %) for risdiplam og 11 ud af 60 (18 %) i placebogruppen og dermed heller ikke klinisk relevant forskellig [9]. Der er ikke oplysninger om det samlede antal SAE efter 24 måneder.

Ophør pga. bivirkninger
Der var ingen bivirkninger, der medførte ophør af behandlingen i hverken risdiplam- eller placebogruppen. Hverken i denne aldersgruppe fra 12-25 år eller i den samlede studiepopulation [9]. Der er ikke oplysninger herom efter 24 måneder.

Livskvalitet
Ansøger har rapporteret livskvalitetsdata målt med EQ-5D, der er et generisk redskab, der måler ikke-sygdomsspecifik livskvalitet. Det består af fem spørgsmål om sundhedsrelateret livskvalitet vedrørende gangfunktion, personlig pleje, sædvanlige aktiviteter (fx arbejde, studie, husarbejde, familie, fritidsaktiviteter), smerter og ubehag samt angst og depression.

Forskellen ift. fra placebo i EQ-5D-5L [redacted] var ikke statistisk signifikant. Der var desuden ingen ændring ift. baseline i nogen af grupperne [redacted].

Data for det sygdomsspecifikke redskab *Spinal Muscular Atrophy Independence Scale* (SMAIS) foreligger fra en posterpræsentation for den fulde studiepopulation (n = 169), samt for aldersgruppen 12-25 år (n = 69). Det fremgår, at skalaen omfatter 22 items,

men da det oprindelige SMAIS-redskab omfatter 29 items, antager fagudvalget, at der må være tale om det videreudviklede redskab SMAIS-ULM (*upper limb module*), der omfatter 22 items, hvor der for hver kan opnås mellem 0-3 point (max score 66). Redskabet måler patientens evne til at gennemføre daglige aktiviteter ved brug af arm- og håndfunktion, såsom at spise selv, børste tænder selv, skrive/holde på en pen.

Fagudvalget har ikke vurderet den kliniske relevans, da det kun har være muligt at finde sparsom information om redskabet. For den enkelte patient kan selv små forskelle betyde store forbedringer i livskvalitet, som f.eks. evnen til selv at kunne putte sin mad i munden eller sidde selvstændigt på toilettet.

Forskellen mellem risdiplam og placebo (aflæst fra figur ca. 1,6 vs. -0,9, forskel ca. 2,5 point) var statistisk signifikant i den fulde population, men ikke i subpopulationen med alder > 12 år (aflæst fra figur ca. 1.0 vs. -0,4 point, forskel ca. 1,4 point) [9].

5.3.5 Fagudvalgets konklusion

I henhold til Medicinrådets metoder har risdiplam ingen dokumenteret merværdi sammenlignet med nusinersen for patienter med SMA type 2 og 3 (sitters) i aldersgruppen 12-25 år.

Fagudvalget vurderer, at effekt og bivirkninger for risdiplam ikke adskiller sig fra placebo i aldersgruppen 12-25 år vurderet over 12 måneder.

Fagudvalget bemærker, at en opfølgningstid på kun et år er meget kort tid at vurdere effekten på SMA type 2 og SMA type 3 i denne aldersgruppe, hvor sygdommen progredierer langsomt over en længere årrække. Data med 2 års opfølgningstid viser en stabil effekt fra 12 til 24 måneder, men der er ikke tilsvarende data for placebo efter 12 måneder. Hos ubehandlede patienter progredierer sygdommen langsomt over en årrække. I perioder oplever patienter uændret forløb eller midlertidige forbedringer. Der er derfor behov for studier med længere opfølgningstid, hvis man skal påvise en stabiliserende effekt.

5.4 SMA type 3 med bevaret gangfunktion (walkers)

Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 3, som har bevaret gangfunktion?

5.4.1 Litteratur

Nedenfor beskriver og vurderer Medicinrådet den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøger anvender SUNFISH del 1, hvor der indgik syv patienter med bevaret gangfunktion, som blev behandlet med risdiplam. Ansøger har herudover søgt litteratur med søgestrengen fra protokollen og har udvalgt tre studier med en mulig historisk kontrolgruppe.

Der er stor variation i baselinekarakteristika, som kan have stor betydning for den gennemsnitlige effekt. Af EPAR'en fremgår, at seks patienter var mellem 2 og 11 år, og en patient var mellem 11 og 25 år [7]. Ifølge ansøger varierer alderen fra 4 til 24 år [*data-on-file*]. Sygdomsvarigheden ved start af behandling med risdiplam varierer fra ca. 2-3 år til ca. 22-23 år.

5.4.2 Databehandling og analyse

Da der er tale om data for en meget lille og heterogen patientgruppe, giver det ingen mening at sammenholde data systematisk med en historisk kontrolgruppe, hvor baselinekarakteristika ydermere ikke er sammenlignelige med risdiplampopulationen. Der var desuden ingen data for 6MWT, som var det effektmål, som fagudvalget specifikt ønskede data for hos denne patientpopulation med bevaret gangfunktion.

Derfor vil der kun være en kort gennemgang af de effektmål, som ansøger har leveret data på.

5.4.3 Evidensens kvalitet

Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen, der som udgangspunkt er at betragte som af meget lav kvalitet.

5.4.4 Effektestimater og kategorier

HFMSE
Effektmålet HFMSE er defineret som kritisk for patienter med SMA type 3 med bevaret gangfunktion. Den mindste klinisk relevante forskel blev fastsat til 3 point.

Data for de syv patienter behandlet med risdiplam viste en gennemsnitlig forbedring ift. baseline på [redacted] point efter 1 år og [redacted] point efter 2 års behandling.

Til sammenligning sås der i et studie af en ubehandlet gruppe med 130 patienter en stigning på 1,5 point hos patienter i alderen 2,5-7 år og et fald på 2,6 point hos patienter i alderen 7-29 år [13], hvilket indikerer, at alder ved behandlingsstart kan have betydning for resultatet.

Fagudvalget kan ikke, ud fra det meget sparsomme datagrundlag, vurdere værdien af risdiplam på effektmålet HFSME.

MFM-32
Effektmålet MFM-32 er defineret som vigtigt for denne population. Den mindste klinisk relevante forskel blev fastsat til 3 point.

Effekten er dog kun målt for tre af de syv patienter, da effekten hos de sidste fire (formentlig de yngste) blev målt med MFM-20. Alderen på de tre patienter er ikke oplyst.

Data for de tre patienter viste en gennemsnitlig forbedring i MFM-32 på [redacted] efter 1 år og [redacted] efter 2 år.

Til sammenligning sås et fald i en ubehandlet gruppe af 11 patienter i alderen 4,5 til 19 måneder med 11 patienter på 1,67 point [14].

Fagudvalget kan ikke, ud fra det meget sparsomme datagrundlag, vurdere værdien af risdiplam på effektmålet MFM-32.

6 minutters gangtest (6MWT)
Effektmålet 6 minutters gangtest (6MWT) er defineret som vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi testen kan belyse patienternes gangfunktion. For patienter med SMA-type 3 er det vist, at 6MWT er korreleret med andre motoriske funktionstest, herunder HFMSE.

Da der ikke er data, kan fagudvalget ikke vurdere effektmålet 6MWT.

Alvorlige uønskede hændelser og ophør pga. bivirkninger
Grundet data for kun syv patienter vil bivirkningsmålene blive belyst under klinisk spørgsmål 2 og 3, idet fagudvalget vurderer, at bivirkningerne ikke afhænger af, om patienten sidder eller går.

Livskvalitet
Data for EQ-5D-5L er baseret på *data-on-file* og er for de syv patienter beregnet til en [redacted]. Ændringen fra baseline er dermed numerisk en smule større end den ændring, der ses blandt patienterne med SMA type 2 og ikke-gående patienter med SMA type 3, men er meget mere usikker pga. det yderst sparsomme datagrundlag.

Der er ikke opgivet sammenlignelige livskvalitetsdata fra historiske kontrolgrupper.

Fagudvalget kan ikke, ud fra det meget sparsomme datagrundlag, vurdere værdien af risdiplam på effektmålet livskvalitet.

5.4.5 Fagudvalgets konklusion

Fagudvalget vurderer, at værdien af risdiplam ikke selvstændigt kan vurderes for patienter med SMA type 3 med bevaret gangfunktion, da datagrundlaget er meget sparsomt, og der ikke er data for 6MWT, som netop kunne bidrage med ekstra information ift. SMA type 3-patienter uden gangfunkton.

Derfor kategoriseres værdien samlet for patienter med SMA type 2 og 3 med og uden gangfunktion.

6. Andre overvejelser

Fordele og ulemper

Der er forskellige fordele og ulemper ved hhv. risdiplam og nusinersen, som kan have betydning ift. den enkelte patients præferencer eller være relevante, hvis patienten ikke

tåler behandlingen eller af andre væsentlige årsager ikke kan fortsætte med den, hvormed et skift fra nusinersen til risdiplam eller omvendt kan blive relevant.

Forskelle i bivirkningsprofilerne

Tabel 11 viser almindelige og meget almindelige bivirkninger af begge lægemidler, som angivet i de godkendte produktresuméer fra EMA. Efter markedsføring af nusinersen i 2017 er der rapporteret flere sjældne bivirkninger (se tabellen). Sjældne bivirkninger for risdiplam fremgår ikke af EMAs produktresumé (og ej heller FDAs), som endnu ikke er opdateret med ny sikkerhedsinformation efter markedsføring.

Tabel 11. Bivirkninger ved risdiplam vs. nusinersen

	Risdiplam	Nusinersen
Almindelige, meget almindelige	Diarre, kvalme, feber, hovedpine, udslæt, urinvejsinfektion, mundsår og ledsmerter	Hovedpine, opkastning og rygsmerter i relation til lumbalpunkturen
Sjældne, meget sjældne, hyppighed ikke kendt*	Ikke oplyst	Meningitis eller anden alvorlig infektion, aseptisk meningitis, kommunikerende hydrocephalus, overfølsomhedsreaktion

Kilde: Produktresuméerne. *Bivirkninger indberettet efter markedsføring.

Graviditet og amning

Risdiplam frarådes, iht. EMAs produktresumé, under graviditet og amning pga. manglende humane data. Hos fertile kvinder skal anvendes sikker kontraception. Risdiplam passerer placentabarrieren og udskilles i mælken hos rotter. Prækliniske studier medførte ikke nedsat fertilitet hos rotter, men medførte lavere fødselsvægt og forsinket udvikling.

Mænd, der ønsker at blive fædre, skal ifølge produktresuméet stoppe behandlingen med risdiplam mindst 4 måneder før befrugtning. Risdiplam nedsætter produktionen af sædceller hos hanrotter og -aber, hvilket formentlig skyldes en reversibel forstyrrelse af celledelingscyklus.

Nusinersen bør, iht. EMAs produktresumé, undgås under graviditet og amning, da der ikke er tilstrækkelige humane data. Risikoen for systemisk påvirkning er generelt mindre ved lokal (intratekal) behandling end ved systemisk behandling. Dyreforsøg tyder ikke på teratogen toksicitet hos mænd eller kvinder.

Praktiske forhold

Risdiplam kan indtages oralt hjemme hos patienten, hvilket både er mere sikkert og praktisk for patienten, der både undgår sygehusbesøg og de gener og komplikationer, der kan være forbundet med lumbalpunkturen. Det sparer samtidig tid på sygehusene. Administrationsvejen kan også være en fordel hos patienter, hvor svær skoliose vanskeliggør den intratekale administration.

Til gengæld er det ikke muligt at sikre, at patienten reelt får taget medicinen hver dag. I og med, at det både er en alvorlig sygdom og en dyr medicin, forventer fagudvalget en høj grad af adhærens, men det er alligevel muligt, at patienter glemmer at tage medicinen, og der kan også være risiko for, at de ikke får anvendt eller opbevaret medicinen korrekt. F.eks. hvis patienten er ude at rejse. Ifølge produktresuméet skal miksturen blandes af sundhedspersonale (sygehusafdeling/apotek), inden den udleveres til patienten. Miksturen har en holdbarhed på 64 dage, når den opbevares i køleskab ved 2-8 grader C. Derfor er det vigtigt, at sundhedspersonalet sikrer, at patienten/familien er oplært i både korrekt brug og opbevaring af medicinen (ved rette temperatur) og løbende følger op på adhærens.

Skift af behandling

Der er endnu ikke publicerede data, som belyser, hvordan det går patienter, der skifter fra nusinersen til risdiplam.

Fagudvalget vurderer, at der ikke er faglige årsager til at skifte fra nusinersen til risdiplam, hvis patienten er velbehandlet og ikke oplever betydelige bivirkninger eller komplikationer af nusinersenbehandlingen. Der er ikke belæg for at opnå bedre effekt ved at skifte behandling, da effekten af de to behandlinger er ligeværdig, og der ikke er dokumentation for bedre effekt ved at skifte.

For patienter, som er startet i risdiplambehandling, kan der i visse tilfælde også være grund til at skifte til nusinersen. F.eks. hvis patienten oplever vedvarende og betydelige bivirkninger af risdiplam (typisk gastrointestinale gener) eller svære problemer med adhærens til den daglige orale behandling. Det er i princippet også muligt at skifte tilbage til nusinersen igen. Hvis der er faglige årsager, der begrunder det.

Kombinationsbehandling

Der er ingen data, som belyser effekt og bivirkninger ved at kombinere risdiplam med nusinersen eller onasemnogene abeparvovec. Bivirkningsprofilerne ved de tre behandlinger er meget forskellige og hænger i høj grad sammen med, at lægemidlerne har forskellige administrationsveje.

Fagudvalget vurderer derfor, at der ikke er baggrund for at anvende kombinationsbehandling på nuværende tidspunkt.

STOP-kriterier

Medicinrådet har iht. protokollen bedt fagudvalget udarbejde STOP-kriterier for, hvornår behandlingen eventuelt bør ophøre (STOP-kriterier). Fagudvalget har her taget

udgangspunkt i de STOP-kriterier, der foreligger for nusinersen for patienter med SMA type 1 (fra det danske SMA-netværk) og SMA type 2 (fra Medicinrådet).

Alvorlige bivirkninger eller væsentlige gener hos patienter bør altid medføre overvejelser, om behandlingen skal ophøre, eller om det i særlige situationer vil være relevant at skifte til anden behandling.

For børn med SMA type 1 foreslår fagudvalget, at Medicinrådet anvender de samme STOP-kriterier som for nusinersen. Første tidspunkt for vurdering (efter 5. dosis) svarer for risdiplam til ca. 6 måneder efter 1. dosis.

For børn med SMA type 2 og 3 foreslår fagudvalget, at det, ift. de eksisterende STOP-kriterier for nusinersen, specifikt fremgår, at ikke-reversibel forværring, som skyldes udefra kommende årsager, såsom længerevarende infektion og deraf forværret almentilstand eller skolioseoperation, ikke skal føre til ophør af behandlingen.

Fagudvalget har ikke specifikt udarbejdet forslag til STOP-kriterier for børn over 6 år, idet effekten i studiet af den ældre aldersgruppe ikke adskilte sig statistisk signifikant fra placebo. Den langsomme sygdomsprogression i den ældre aldersgruppe gør det yderligere vanskeligt at udarbejde anvendelige STOP-kriterier. Hos gående patienter er der dog mulighed for at anvende 6MWT i vurderingen.

Tabellen nedenfor viser fagudvalgets forslag til STOP-kriterier ved manglende effekt.

Tabel 12. STOP-kriterier for behandlingen

Population	STOP-kriterier
SMA type 1	Forværring af symptomer uden tegn på stabilisering vurderet efter 6 måneder og efterfølgende hver 6. måned.
SMA type 2 og 3 2-5 år	Forværring af respirationsstatus eller grovmotorisk funktion vurderet efter 12 måneder og efterfølgende hver 4. måned, hvor forværringen ikke vurderes at være reversibel, som ved infektion eller efter skolioseoperation. • Forværring i respirationsstatus er baseret på tid med ventilator/døgn eller forværring i SaO2 målt uden ekstra tilførsel af ilt, vurderet over 3 uger. • Forværring i grovmotorisk funktion er vurderet på videodokumenteret score på HFMSE-skalaen i to på hinanden følgende målinger, i forhold til da patienten påbegyndte behandlingen.

7. Relation til behandlingsvejledning

Medicinrådet har ikke aktuelt en behandlingsvejledning for SMA. Da der nu er i alt tre lægemidler tilgængelige, kan der være grundlag for at udarbejde en behandlingsvejledning på området.

8. Bemærkning til fagudvalgets vurdering

Fagudvalgets to patientrepræsentanter har ønsket at følgende tilføjes til fagudvalgets konklusioner:

"Vi opfordrer indtrængende til at man lader tvivl om effekt i ældre børn og voksne komme patienterne til gode, fordi de nerver, der dør mens vi venter, ikke kommer tilbage selv med senere behandling.

Behandling med risdiplam kan startes og stoppes med kort varsel og uden større gener for sundhedspersonalet og vi opfordrer til at man i prisforhandlinger ser på muligheden for "no cure no pay-rabatter. På den måde betaler man kun for effekt, og man sikrer sig at patienterne ikke unødigt mister funktioner."

9. Referencer

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10. Fagudvalg og kontakt

Medicinrådets fagudvalg vedrørende spinal muskelatrofi

Forvaltningslovens § 3, stk. 2/§ 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Kirsten Svenstrup *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Afventer ny udpegning	Region Nordjylland
Afventer ny udpegning	Region Midtjylland
Charlotte Olesen *Overlæge*	Region Midtjylland
Niels Ove Illum *Specialeansvarlig overlæge*	Region Syddanmark
Jesper Nørregaard *Speciallæge*	Region Sjælland
Peter Born *Overlæge*	Region Hovedstaden
Søren Bisgård Johansen *Farmaceut*	Dansk selskab for sygehusledelse
Jón Trærup Andersen *Læge, lektor*	Dansk Selskab for Klinisk Farmakologi
Ulla Werlauff *Fysioterapeut, ph.d., leder af UC*	RehabiliteringsCenter for Muskelsvind
Lisbeth Koed Doktor *Patient/patientrepræsentant*	Danske Patienter
Thomas Koed Doktor *Patient/patientrepræsentant*	Danske Patienter
Deltager ikke	Dansk Pædiatrisk Selskab

Medicinrådets sekretariat
Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	28. september 2021	Medicinrådet har justeret formuleringen vedr. den metodemæssige kategorisering i konklusionen, samt foretaget nogle mindre præciseringer og rettelser i selve rapporten.
1.0	1. september 2021	Godkendt af Medicinrådet.

12. Bilag

Bilag 1: Cochrane – risiko for bias

Vurdering af risiko for bias ved Cochrane risk of bias tool 2.0.

Tabel 13. Vurdering af risiko for bias i SUNFISH del 2 (oplysninger fra EPAREN og ansøger)

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	**Lav**	Foregik centralt. Randomiseringen blev stratificeret efter aldersgrupperne 2-5 år, 6-11 år, 12-17 år og 18-25 år, hvilket sikrer en ligelig fordeling. Alder har betydning for prognosen.
Effekt af tildeling til intervention	**Forbehold**	Der er færre patienter med svær skoliose i risdiplamgruppen end i placebogruppen (28 vs. 38 %), hvilket muligvis kan medføre en overestimering af effekten af risdiplam ift. placebo. Forskellen i subgruppen 12-25 år (48 vs. 71 %) er mere udtalt, hvorimod der ikke er forskel i aldersgruppen 2-11 år. I aldersgruppen 2-11 år var HMFSE 1,9 point lavere i risdiplamgruppen end i placebogruppen, hvilket muligvis kan have understimeret effekten.
Manglende data for effektmål	**Lav**	Ifølge EPAREN blev hhv. 3 og 6 patienter ekskluderet fra analysen af hhv. RULM og MFM-32 pga. manglende data. Data for HFSME mangler for [redacted] patienter ifølge ansøgers oplysninger.
Risiko for bias ved indsamlingen af data	**Lav**	Patienter, investigator og øvrigt personale, som havde kontakt med patienterne, var blindet. Kun farmaceuten, som stod for fordelingen af medicinen, var ublindet.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Lav**	Ansøger har leveret de data, som Medicinrådet har bedt om.
Overordnet risiko for bias	**Forbehold**	Forbehold for fordelingen af patienter med svær skoliose er skæv i subgruppen med alder 12-25 år. Der er derfor risiko for at overestimere effekten af risdiplam ift. placebo. Forbehold for forskel i HMFSE i aldersgruppen 2-11 år med risiko for at underestimere effekten af risdiplam ift. placebo.

Tabel 14. Vurdering af risiko for bias i CHERISH (Mercuri 2018)

Bias	Risiko for bias	Uddybning
Risiko for bias i randomiserings-processen	Lav	Foregik centralt.
Effekt af tildeling til intervention	Forbehold	Patienterne i nusinersengruppen havde en højere HFMSE-score ved baseline end placebogruppen (2,5 point), hvilket muligvis kan medføre en overestimering af effekten af nusinersen ift. placebo.
Manglende data for effektmål	Forbehold	De fulde data for livskvalitet er ikke publiceret.
Risiko for bias ved indsamlingen af data	Lav	Patienter og forældre var blindet. Personale, der administrerede behandlingen, var ikke blindet. Personale, der administrede behandlingen, måtte ikke være primær investigator, studie-koordinator eller ´`outcome assessor`.
Risiko for bias ved udvælgelse af resultater, der rapporteres	Lav	Alle analyser er baseret på ITT-populationen.
Overordnet risiko for bias	Forbehold	Forbehold for forskel i HFMSE-score ved baseline. Der er derfor en vis risiko for at overestimere effekten af nusinersen ift. placebo.

Bilag 2: GRADE

Klinisk spørgsmål 2 – risdiplam sammenlignet med nusinersen til behandling af ikke-gående SMA type 3 med alder 2-11 år

Tabel 15. GRADE evidensprofil for klinisk spørgsmål 2

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	risdiplam	nusinernsen	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
RULM, ca 1 år									-			
2	RCT	Alvorlig[a]	ingen	Alvorlig[b]	Ingen	Ingen	76	84	-	[redacted]	⨁⨁◯◯ LAV	KRITISK
HMFSE, ca. 1 år												
2	RCT	Alvorlig[a]	ingen	Alvorlig[b]	Alvorlig[c]	Ingen	76	84	-	[redacted]	⨁⨁◯◯ LAV	VIGTIG
Alvorlige uønskede hændelser, ca. 1 år												
2	RCT	Alvorlig[a]	ingen	Alvorlig[b]	Alvorlig[c]	Ingen	76	84	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIG
Ophør pga. bivirkninger, ca. 1 år												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	risdiplam	nusinernsen	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
2	RCT	Alvorlig[a]	ingen	Alvorlig[b]	Ingen	Ingen	76	84	0	0	⨁⨁◯◯ LAV	VIGTIG
Livskvalitet, ca. 1 år									-			
2	RCT	Alvorlig[a]	ingen	Alvorlig[b]	Ingen	Ingen	76	84	-	[redacted]	⨁⨁◯◯ LAV	KRITISK
Kvalitet af den samlede evidens LAV[d]												

[a] Der er nedgraderet ét niveau, da der var nogle forbehold i vurderingen af risiko for bias.

[b] Der er nedgraderet ét niveau, da der var forskellei baselinekarakteristika, som kan have betydning for resultatet.

[c] Der er nedgraderet et niveau, da konfidensintervallet er meget bredt og indeholder én beslutningsgrænse.

[e] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Klinisk spørgsmål 3 - risdiplam sammenlignet med placebo til behandling af SMA type 2 og ikke-gående SMA type 3 med alder 12-25 år

Tabel 16. GRADE evidensprofil for klinisk spørgsmål 3

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	risdiplam	placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
MFM-32, 12 måneder												
1	RCT	Alvorlig[a]	ingen	ingen	Alvorlig[b]	ingen	44	24	-	[redacted]	⨁◯◯◯ MEGET LAV	KRITISK
RULM, 12 måneder												
1	RCT	Alvorlig[a]	ingen	ingen	Alvorlig[b]	ingen	44	24	-	[redacted]	⨁⨁◯◯ LAV	KRITISK
HFMSE, 12 måneder												
1	RCT	Alvorlig[a]	ingen	ingen	Alvorlig[b]	ingen	44	24		[redacted]	⨁⨁◯◯ LAV	VIGTIG
Alvorlige uønskede hændelser, 12 måneder												

Sikkerhedsvurdering							Antal patienter		Effekt			
Antal studier	Studie-design	Risiko for bias	Inkonsistens	Indirekthed	Unøjagtighed	Andre overvejelser	risdiplam	placebo	Relativ (95 % CI)	Absolut (95 % CI)	Sikkerhed	Vigtighed
1	RCT	Alvorlig[a]	ingen	ingen	Meget alvorlig[c]	ingen	44	24	[redacted]	[redacted]	⨁◯◯◯ MEGET LAV	VIGTIG
Ophør pga. bivirkninger, 12 måneder												
1	RCT	Alvorlig[a]	ingen	ingen	Alvorlig[b]	ingen	44	24	0	0	⨁⨁◯◯ LAV	VIGTIG
Livskvalitet, 12 måneder												
1	RCT	Alvorlig[a]	ingen	ingen	Alvorlig[b]	ingen	44	24	-	[redacted]	⨁⨁◯◯ LAV	KRITISK
Kvalitet af den samlede evidens LAV[d]												

[a] Der er nedgraderet ét niveau, da der var nogle forbehold i vurderingen af risiko for bias.

[b] Der er nedgraderet ét niveau pga. upræcist estimat (få patienter – særligt i placebogruppen).

[c] Der er nedgraderet to niveauer, da konfidensintervallet er meget bredt og indeholder både positive og negative konklusioner.

[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.

Application for the assessment of risdiplam for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older

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1. Basic information

Contact information	
Name	**Kirsten Holdt Henningsen**
Title Phone number E-mail	Scientific Access Advisor +45 52 40 90 99 kirsten.holdt@roche.com
Name	**Ditte Marie Clugston**
Title Phone number E-mail	Medical Writer +45 42 14 29 44 ditte_marie.clougston@roche.com
Name	**Anne Kolbye**
Title Phone number E-mail	Value Demonstration Expert +45 42 14 29 50 anne.kolbye@roche.com
Name	**Thomas Damborg**
Title Phone number E-mail	Rare Conditions Lead +45 42 14 29 76 thomas.damborg@roche.com
Name	**Oskari Virtanen**
Title Phone number E-mail	Nordic Medical Lead, Rare Conditions +358 40 754 5415 oskari.virtanen@roche.com

Overview of the pharmaceutical	
Proprietary name	EVRYSDI
Generic name	Risdiplam
Marketing authorization holder in Denmark	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen, Germany
ATC code	M09AX10
Pharmacotherapeutic group	Other drugs for disorders of the musculo-skeletal system
Active substance(s)	Risdiplam
Pharmaceutical form(s)	Powder for oral solution.
Mechanism of action	Risdiplam is a survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to survival motor neuron (SMN) protein deficiency. Risdiplam promotes SMN2 exon 7 inclusion.
Dosage regimen	Dosing regimen by age and body weight: ***Age and body weight*** — ***Recommended Daily Dose*** 2 months to < 2 years of age — 0.20 mg/kg ≥ 2 years of age (< 20 kg) — 0.25 mg/kg ≥ 2 years of age (≥ 20 kg) — 5 mg Dosage changes must be made under the supervision of a HCP. Treatment with a daily dose above 5 mg has not been studied. No data are available in infants below 2 months of age.

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (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.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	According to the SmPC Evrysdi must be reconstituted by a Healthcare Professional.
Combination therapy and/or co-medication	NA
Packaging – types, sizes/number of units, and concentrations	Evrysdi 0.75 mg/mL powder for oral solution is supplied as powder in an amber glass bottle. Each carton contains; one bottle, 1 press-in bottle adapter, two reusable 6 mL and two reusable 12 mL graduated amber oral syringes.
Orphan drug designation	On 26 February 2019, orphan designation (EU/3/19/2145) was granted by the European Commission to Roche Registration GmbH, Germany, for risdiplam for the treatment of spinal muscular atrophy.

2. Abbreviations

ACR	Assumed Control rate
AE	Adverse Event
BSC	Best Supportive care
CCOD	Clinical cut-off date
CHMP	Committee for Medical Products for Human Use
CHOP-INTEND	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence Interval
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D-5L	EuroQol-5D descriptive system - 5 level
ESS	Effective sample size
FSS	Fatigue severity scale
HCP	Health Care Professional
HFMSE	Hammersmith Functional Motor Scale
HINE-2	Hammersmith Infant Neurological Exam-Part 2

HRQoL	Health-related Quality of Life
ITC	Indirect treatment comparison
ITT	Intention-to-treat
MAIC	Matching-adjusted indirect comparison
MCID	Minimal clinically important difference
NA	Not applicable
NMA	Network meta-analysis
NR	Not reported
RCT	Randomized controlled trial
RULM	Revised upper limb module
SAE	Serious adverse event
SaO_2	Oxygen saturation as measured by blood analysis
SD	Standard deviation
SMA	Spinal Muscular Atrophy
SMN	Survival motor neuron
SmPC	Summary of product characteristics
TTE	Time-to-event
6MWT	6-minute walk test

3. Summary

INTRODUCTION

On March 26th, 2021, the European Commission (EC) has approved Evrysdi (risdiplam) for the treatment of 5q spinal muscular atrophy (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. The approval is based on results from FIREFISH (NCT02913482), a multicenter, single-arm, open-label study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in symptomatic infants with Type 1 SMA, and results from SUNFISH (NCT02908685), a multi-center, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in adult and pediatric participants with Type 2 and Type 3 SMA.

This application, submitted to the Danish Medicines Council on June 10th, 2021, provides the basis for the assessment of risdiplam in comparison with standard of care for SMA in Denmark, which currently, and depending on SMA-type, age and other factors, are either nusinersen or "best supportive care". The application is based on the clinical questions defined in the protocol from the Medicines Council, which includes SMA patients up to 25 years based on the SUNFISH trial. However, in both the FIREFISH and SUNFISH trials there is an effect on motor function measures and a >2-fold increase in median SMN-protein levels vs. baseline on risdiplam. From the JEWELFISH trial - which includes adults over 25 years, the same increase in median SMN-protein levels was observed, indicating that risdiplam may also be beneficial in SMA patients over 25 years [1].

Disease area: SMA is an autosomal recessive disease caused by mutations or deletions in the SMN1 gene on chromosome 5. In 94% of all SMA cases, this mutation involves a deletion in a segment known as exon 7. A mutation in the SMN1 gene leads to a deficiency of a motor neuron protein called SMN, which stands for "survival motor neuron." Deficiency of SMN causes progressive muscle denervation and skeletal muscular atrophy with overall

weakness and loss of motor functions. This may cause severe complications and can lead to death. SMA is the number one genetic cause of infant mortality. There are four types of SMA and prognosis is type-dependent with type 1 being the most severe form of SMA. Without treatment, many children with SMA 1 do not live past the age of 2 years. Type 2 is an intermediate form of SMA and prognosis depends on the severity of symptoms but children with Type 2 may have a normal life span. Type 3 is a milder form of SMA, and this type generally has an almost normal life expectancy. Type 4 is very rare and usually only causes mild muscle impairment [2].

The incidence in Europe is estimated to 1 out of 6000 newborn children [3].

Treatment in Denmark: Regarding children with SMA Type 1 the Medicines Council currently (May 2021) recommends nusinersen as standard treatment for children who fulfil the following criteria: have 2-3 SMN2-copies, were max. 6 months of age at symptom debut and is not in permanent respiratory treatment at treatment initiation.

Regarding children with SMA Type 2 the Medicines Council currently recommends nusinersen as standard treatment for children who fulfil the following criteria: have at least 2 SMN2-copies, were max 24 months of age at symptom debut, have had max. 4 years of disease duration at treatment initiation and have no assisted ventilation apart from a need during nighttime and > than 95% SaO2 without ventilation assistance.

For the remaining patients with SMA the current standard treatment in Denmark is “best supportive care” [4].

METHODS

There is no direct evidence comparing risdiplam with nusinersen (clinical question 1-2) and, similarly, no direct evidence comparing ambulatory SMA type 3 patients with no disease modifying treatment (clinical question 4). Consequently, indirect treatment comparisons had to be conducted for these clinical questions. For clinical question 3 direct evidence from the trial SUNFISH part 2 was used.

For clinical question 1, the evidence network in Type 1 SMA was “unanchored”. Therefore, standard network meta-analysis (NMA) methodology or the Bucher method as suggested by the Medicines Council Secretariat could not be applied. The only appropriate indirect analysis was a naive comparison and MAIC-analyses. The relative risk ratios were calculated based on the matched odds ratio in order to mitigate bias between data sources.

For clinical question 2, the outcomes HFMSE, RULM and SAEs were considered feasible for indirect treatment comparison in the subgroup aged 2-11. Analyses conducted used the MAIC and the Bucher method. Because of differences in placebo response on the HFMSE scale between trials, HFMSE data is presented narratively. CHERISH did not report on quality of life in this subgroup, and a comparison was therefore not possible. For the subgroups aged 2-5 and 6-11 years, ITC analyses for HFMSE and RULM were conducted by applying the Bucher method. CHERISH did not report on safety or quality of life in these two subgroups, thus a comparison was not possible.

Direct evidence was available for clinical question 3, and for the defined subgroup additional analysis was conducted for MFM-32, HFMSE and RULM, safety and quality of life.

For clinical question 4, a systematic literature review was performed to identify relevant studies for indirect treatment comparisons. Five studies were found eligible for inclusion based on the outcomes defined, but because SUNFISH part 1 did not include the 6MWT, only three of these studies could be used to compare with risdiplam. Due to very small sample sizes, and substantial indirectness in the evidence available, it only made sense to summarize the results for clinical question 4 using descriptive statistics.

CONCLUSION

Clinical question 1: Overall the results using the unanchored MAIC methodology suggested that risdiplam may be superior to nusinersen on a number of endpoints, including overall survival, ventilation-free survival, HINE-2 motor milestone response and proportion of patients achieving CHOP-intend >4 point increase. Safety endpoints were favourable for risdiplam or comparable to nusinersen. Results of the analysis using FIREFISH data suggest that risdiplam may be associated with fewer reports of AEs leading to discontinuation and any SAE compared to nusinersen.

Clinical question 2: Overall, all indirect treatment comparisons conducted showed no significant difference between risdiplam and nusinersen. In the subgroup aged 2-11, MAIC and Bucher analyses for RULM and SAE showed no significant difference between treatments. Because of substantial differences in baseline characteristics between the trial populations, it was not possible to draw conclusions on the HFMSE outcome based on a narrative comparison. In both SUNFISH part 2 and CHERISH, there were no treatment withdrawals due to an AE in any of the treatment arms. As no data on quality of life from CHERISH is available, a comparison was not possible for this endpoint. Data on EQ-5D assessed by a parent or caregiver from SUNFISH showed no statistically significant difference between risdiplam and placebo. In the subgroups aged 2-5 and 6-11 years, the Bucher analysis for HFMSE and RULM showed no significant difference between risdiplam and nusinersen. In conclusion, there is no evidence of a difference between risdiplam and nusinersen in SMA type 2 and 3 patients aged 2-11 in terms of efficacy and safety.

Clinical question 3: In SMA type 2 and 3 patients aged 12-25 the efficacy estimates of mean treatment difference in MFM-32, HFMSE, and RULM are favourable towards risdiplam. However, the confidence intervals include 0 and thus, the analyses cannot statistically differentiate between risdiplam and placebo. In regard to safety, the estimated differences indicate that risdiplam could be associated with higher reportings of SAE compared to placebo, but the confidence intervals also include estimates in which risdiplam would be associated with less reportings, and thus, the analysis cannot differentiate between risdiplam and placebo. There were no treatment withdrawals due to an AE in any of the treatment arms. Data on patient-reported EQ-5D showed no statistically significant difference between treatments. Overall, the analyses cannot differentiate between risdiplam and placebo in SMA type 2 and 3 patients aged 12-25 in terms of efficacy and safety.

Clinical question 4: The risdiplam study program (SUNFISH part I) included seven ambulatory patients with SMA type 3. Effects observed in these patients were compared to the very limited data available on natural history of ambulatory SMA type 3 patients. For the outcomes related to motor function (HFMSE and MFM-32), there was an observed effect difference between risdiplam and natural history data in favour of risdiplam and patients receiving risdiplam had on average increased [redacted]

However, study differences in population characteristics at baseline, combined with small sample sizes and differences in study follow-up made firm conclusions around effect differences for ambulatory SMA type 3 patients receiving risdiplam in comparison with no disease modifying treatment uncertain.

4. Literature search

Clinical question 1 - 3 did not require a literature search. In the preliminary application, Roche has informed the Medicines Council that the SUNFISH part 1 study includes a small group of patients with SMA type 3, who have retained gait function. As SUNFISH part 1 does not include a prospective control group, Roche has performed a literature search for a similar group of untreated patients with SMA type 3 and gait function with the aim to be used as a control group in the comparison with risdiplam.

The literature search for peer-reviewed published full-text articles used the search strings provided in the Medicines Council protocol, see Appendix 8.1. Electronic searches were carried out in PubMed and in CENTRAL (via Cochrane Library) on March 27, 2021 and April 5, 2021 respectively. The searches contain terms descriptive of the area as described in the search strings. The search in PubMed and CENTRAL resulted in 91 and 24 references, respectively. The Search Builder for both searches are in Appendix 8.1.

Two reviewers independent of each other screened the references by title and abstract according to the defined in- and exclusion criteria (Appendix 8.1) using a reference management tool. In total 95 references were excluded of which 8 were duplicates. 20 references were found potentially relevant based on title and abstract.

The included articles then went through a full-text review and 5 articles [5-9] were relevant for the assessment. PRISMA flow charts and a list of excluded studies are available in Appendix 8.1. Two of these five trials looked at the 6MWT as the only relevant outcome [7,9], but because SUNFISH part 1 did not assess participants with 6MWT comparison with risdiplam was not possible and therefore these studies were not described further. Consequently,

three trials on natural history could be used for clinical question 4. Characteristics and results of the studies are described in section 5.4.1 and 5.4.2.

4.1 List of relevant studies

Table 1 Relevant studies included in the assessment.

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Risdiplam in Type 1 spinal muscular atrophy, **Baranello et al**., N Eng J Med. 2021 Mar 11;384(10):915-923. doi: 10.1056/NEJMoa2009965. Epub 2021 Feb 24. Efficacy and safety of risdiplam in Type 1 spinal muscular atrophy, **Darras et al.,** Submitted.	FIREFISH (part 1) FIREFISH (part 2)	NCT02913482	December 24th, 2016 to November 17, 2023 (first results posted January 8, 2021)	Clinical question 1
Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. **Finkel et al. N Engl J Med. 2017** Nov 2;377(18):1723-1732. doi: 10.1056/NEJMoa1702752. PMID: 29091570 [10]	ENDEAR	NCT02193074	August 19th, 2014 to November 21st, 2016	Clinical question 1
Risdiplam in Type 2 and non-ambulant Type 3 Spinal Muscular Atrophy. **Mercuri et al.** Submitted.	SUNFISH	NCT02908685	October 20, 2016 to estimated September 2nd, 2023 (Primary completion date September 6th, 2019)	Clinical question 2, 3, 4
Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. **Mercuri et al. N Engl J Med. 2018** Feb 15;378(7):625-635. doi: 10.1056/NEJMoa1710504. PMID: 29443664 [11]	CHERISH	NCT02292537	November 24th, 2014 to February 20th, 2017	Clinical question 2
Natural history of Type 2 and 3 spinal muscular atrophy: 2-year NatHis-SMA study. **Annoussamy et al. Ann Clin Transl Neurol. 2021** Feb;8(2):359-373. doi: 10.1002/acn3.51281. Epub 2020 Dec 24. PMID: 33369268; PMCID: PMC7886049 [5]	2-year NatHis-SMA study	NCT02391831	May 2015 to May 2018	Clinical question 4

Clinical Variability in Spinal Muscular Atrophy Type III. **Coratti et al. Ann Neurol. 2020** Dec;88(6):1109-1117. doi: 10.1002/ana.25900. Epub 2020 Oct 2. PMID: 32926458 [8]	Clinical Variability in Spinal Muscular Atrophy Type III	Not available (trial not registered on ClinicalTrials.gov)	Unclear	Clinical question 4
Single-Blind, Randomized, Controlled Clinical Trial of Exercise in Ambulatory Spinal Muscular Atrophy: Why are the Results Negative? **Montes et al. J Neuromuscul Dis. 2015** Oct 7;2(4):463-470. doi: 10.3233/JND-150101. PMID: 27858749; PMCID: PMC5240606 [6]	Single-blind randomized, Controlled Clinical Trial of Exercise in Ambulatory Spinal Muscular Atrophy: Why are results negative?	NCT01166022	December 2010 to August 2014	Clinical question 4

4.2 Main characteristics of included studies

Main characteristics of the included studies for clinical question 1-3 and are presented in **Tables A2** in Appendix 8.2 and main characteristics of the included studies for clinical question 4 are presented in **Table 32-34** in section 5.4.1.

5. Clinical questions

5.1 What is the clinical benefit of risdiplam compared to nusinersen in SMA type-1 (non-sitters)?

5.1.1 Presentation of relevant studies

The clinical trials FIREFISH and ENDEAR are used in the comparison of risdiplam and nusinersen for clinical question 1 (the evidence network for SMA type 1). Detailed study characteristics of the two studies are in Appendix 8.2.

FIREFISH is an open-label, two-part, phase 2/3 dose-escalation/single-arm study. Part 1 is the dose-escalation part, while Part 2 is the confirmatory part at the dose selected based on the results from Part 1. ENDEAR is a double-blind phase 3 RCT.

FIREFISH is ongoing with a total treatment period of 24 months, followed by an open-label extension phase, while ENDEAR is complete and was terminated early. Both studies were conducted globally, across countries including Asia, Europe and the US. The number of sites that participated in the study was 31 in ENDEAR, 7 in FIREFISH Part 1 and 14 in FIREFISH Part 2.

Table 2 summarizes the baseline characteristics of the enrolled patients in ENDEAR and of the pooled Part 1 patients on pivotal dose and all Part 2 patients from FIREFISH. The patient characteristics of risdiplam are similar to those of the ENDEAR trial in terms of age and disease duration. The severity of disease at baseline was slightly worse in the FIREFISH patients as illustrated by the differences in baseline CHOP-INTEND (risdiplam vs nusinersen -4.16; vs sham -5.96) and HINE-2 scores (risdiplam vs nusinersen -0.36; vs sham -0.61).

Table 2 Baseline characteristics of patients in ENDEAR and FIREFISH

Baseline characteristic	Risdiplam (FIREFISH) N=58*	Risdiplam (FIREFISH part 1 'high dose' cohort) N=17	Risdiplam (FIREFISH part 2) N=41	Nusinersen (ENDEAR) N=80	Sham control (ENDEAR) N=41
Mean age at first dose in days (sd, [range])	163 days (44, [68-212])	170 days (43, [102-212])	159 days (45, [68-212])	163 days (NR,[52-242])	181 days (NR,[30-262])
Female gender	57%	65%	54%	54%	59%
Mean age at symptom onset in weeks (sd, [range])	7.2 weeks (3, [4-13.1])	7.4 weeks (2.9, [4-13.1])	7.1 weeks (3, [4.1-13])	7.9 weeks (NR,[2-18])	9.6 weeks (NR,[1-20])
Mean disease duration at screening in weeks (sd, [range])	13.0 weeks (5.9, [1-23.3])	14.4 weeks (5.9, [5.3-23.3])	12.4 weeks (5.9, [1-22.9])	13.2 weeks (NR,[0-25.9])	13.9 weeks (NR,[0-23.1])
Mean age at diagnosis in weeks (sd, [range])	12.7 weeks (6, [4-26.4])	13.9 weeks (6.1, [4-23.3])	12.2 weeks (6, [4-26.4])	12.6 weeks (NR, [0-29])	17.5 weeks (NR, [2-30])
Mean score on CHOP INTEND scale (sd, [range])	22.47 (6.79, [8-37])	24.29 (5.75, [16-34])	21.71 (7.1. [8-37]	26.63 (8.13, [NR])	28.43 (7.56, [NR])
Patients with nutritional support: Unable to swallow† /Gastrointestinal tube feeding	9%	6%	10%	9%	12%
Patients with ventilatory support	29%	29%	29%	26%	15%

Mean HINE-2 score (sd, [range])	0.93 (0.95, [0-5])	0.94 (0.56, [0-2])	0.93 (1.08, [0-5]	1.29 (1.07, [NR])	1.54 (1.29, [NR])
Mean CMAP negative peak amplitude (mV) - ulnar nerve (SD, [range])	0.199 (0.15, [0-0.8])	0.177 (0.1, [0.03-0.3])	0.21 (0.17, [0-0.8]	0.226 (0.19, [NR])	0.225 (0.12, [NR])
*Includes patients from the 'High-dose' (pivotal dose) cohort of Part 1 (n=17) and all patients from Part 2 (n=41) of FIREFISH †Baseline data on gastrointestinal tube feeding was not available for most patients in Part 1, as the questionnaire was only introduced 6 months after the start of the study. Ability to swallow was used as a proxy for tube feeding for these patients.					

5.1.2 Results per study

For clinical question 1, the Medicines Council has requested data on the following endpoints:

- Survival - Critical outcome
- Ventilation-free survival - Critical outcome
- Permanent ventilation - Important outcome
- Motorical milestones
    - CHOP-INTEND responders - Critical outcome
    - Ability to sit without support - Important outcome
    - Ability to stand or walk without support - Important outcome
- Serious adverse events - Important outcome
- Discontinuation due to adverse events - Important outcome

Results per study is presented in the **Tables A3** in Appendix 8.3. For FIREFISH, data is presented for all patients from Part 2 (N=41).

5.1.3 Comparative analyses

The following section contains a comparative analysis of risdiplam versus nusinersen, which the Scientific Committee has appointed as the relevant comparator in the assessment for SMA type 1 (non-sitters). In the absence of head-to-head clinical trial data, an indirect treatment comparison (ITC) has been conducted to evaluate the relative efficacy of risdiplam against nusinersen together with an assessment of potential bias from differences in reported baseline characteristics.

The evidence network in Type 1 SMA was "disconnected" or "unanchored". Therefore, standard network meta-analysis (NMA) methodology could not be applied. The Bucher method was also not feasible, as it requires a connected evidence network with a common comparator between trials - in this case sham procedure or placebo. Due to the single-arm design of the FIREFISH trial, it was necessary to apply a matching-adjusted indirect comparison (MAIC) methodology. In the analysis both unweighted (naive comparison) and weighted (MAIC) analysis are being presented.

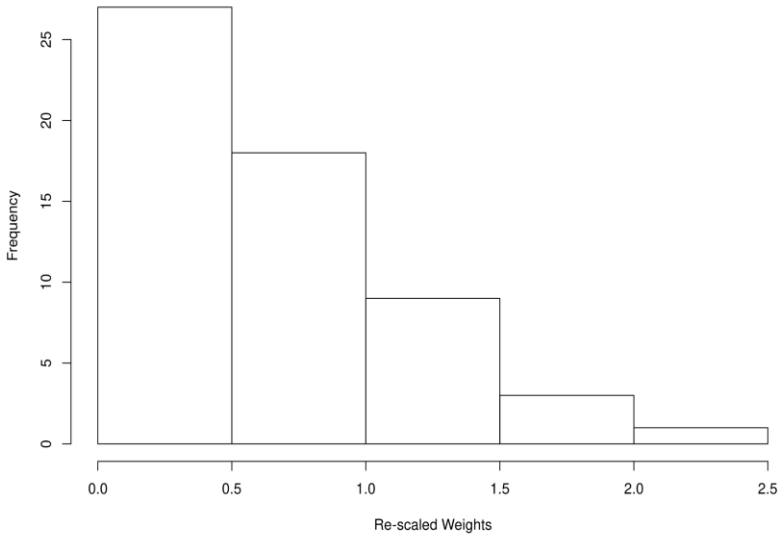
For the MAIC analyses, a literature review was undertaken to identify prognostic and predictive factors in Type 1 SMA. EMBASE and Medline databases were searched for randomized controlled trials (RCTs) and observational studies using SMA disease terms. [12] FIREFISH patients were matched to the ENDEAR nusinersen arm population on

three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The selection of characteristics was based on the availability of baseline characteristics in the trials, predictive and/or prognostic factors identified in the literature review as well as feedback from the internal medical team at Roche and external medical experts. Care was taken to not include too many matching factors in order to avoid overfitting and resulting in a small effective sample size (ESS). Table 3 provides an overview over key baseline characteristics of risdiplam before and after matching, compared to the ENDEAR baseline characteristics of nusinersen arm. The risdiplam baseline characteristics show that matching to the ENDEAR trial characteristics was successful. For all three selected matching factors (age at first dose, disease duration at screening and CHOP-INTEND score at baseline), risdiplam baseline characteristics post-matching were equal to the ENDEAR baseline nusinersen arm characteristics. The ESS was reduced to 40.1 from a total sample size of 58 FIREFISH patients. Figure 1 displays the distribution of the rescaled weights. A high number of patients received weights of zero or close to zero; consistent with the reduction in sample size.

Table 3 FIREFISH baseline characteristics pre and post ENDEAR-matching

Baseline characteristic	Pre-Matching: Risdiplam (Pooled FIREFISH)	Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to ENDEAR)	Nusinersen (ENDEAR)
Sample size (ESS)	58	58 (40.12)	80
Mean age at first dose in days	**163 days**	**163 days**	**163 days**
Female gender	57%	66%	54%
Mean age at symptom onset in days	51 days	51 days	55 days
Mean disease duration at screening in days	**91 days**	**92 days**	**92 days**
Mean age at diagnosis in weeks	12.7 weeks	13.3 weeks	14.3 weeks
Mean score on CHOP-INTEND	**22.47**	**26.63**	**26.63**
Mean HINE-2 score	0.93	1.18	1.29
Patients with ventilatory support	29%	20%	26%

Figure 1 Histogram of re-scaled weights in the ENDEAR-matched FIREFISH population



Outcomes considered of interest and feasible for the ITC included survival endpoints (event-free survival, overall survival), motor function endpoints (HINE-2, CHOP-INTEND) and safety endpoints (any AE leading to discontinuation, any SAE). The early termination of ENDEAR caused a shorter time period (280 days in the nusinersen arm) to assess the efficacy and safety of nusinersen compared to FIREFISH, for which a minimum of 12 months data are available. Hence, for binary endpoints analyses, a modified FIREFISH dataset comprising assessments up to six months prior to data cut (median time on study of 283 days) was used. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of risdiplam. However, as requested by the expert committee we have added ITCs using the FIREFISH 12-month data as a sensitivity analyses. For clinical question 1, the MAIC-analyses should be viewed as the suggested base case from a Roche perspective. The Medicines Council has, however, requested that absolute differences are calculated for each naïve comparison and for all sensitivity analyses. This is performed in the same way as for the MAIC-analyses and using the same ACRs.

Overall survival (critical outcome)

Time-to-event analyses were conducted on the overall survival endpoints and hazard ratios (HRs) were calculated based on a Cox proportional hazards model. For analyses of time-to-event endpoints (event-free survival, overall survival), all available data from the 12-month data cuts were used. Differences in follow-up duration are less relevant for survival analyses as information over all time points is taken into account, unlike in analyses of binary outcomes.

Analysis results of overall survival are provided in **Figure 1** and **Table 4.** In conclusion, the results of both unadjusted (naïve) analysis and MAIC analysis suggest that risdiplam might be more effective than nusinersen. [redacted]. Based on the latter HR and the OS-rate for nusinersen at 13 months of 83.8% in ENDEAR, the estimated absolute difference in OS-rate was [redacted], which exceeds the minimal clinically important difference (MCID) of 5% prespecified by the expect committee. Based on the HR for the naïve analysis, the estimated absolute difference in OS-rate was [redacted].

[redacted]

Table 4 Overall survival hazard ratios (MAIC vs ENDEAR)

Comparator (STUDY)	Naïve Comparison		MAIC	
	Pre-match Number of events / Sample Size	Hazard Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number of events / Sum of weights	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	[redacted]			
Nusinersen (ENDEAR)	13/80	[redacted]	13/80	[redacted]
Key: CI, Confidence Intervals (Bootstrap; N=1000 Bootstrap samples)				

Ventilation-free survival (critical outcome)

Time-to-event analyses were conducted on the ventilation-free survival endpoints and HRs were calculated based on a Cox proportional hazards model. For analyses of time-to-event endpoints (event-free survival, overall survival), all available data from the 12-month data cuts were used. Differences in follow-up duration are less relevant for survival analyses as information over all time points is taken into account, unlike in analyses of binary outcomes.

The analysis results of ventilation-free survival are provided in **Figure 3** and **Table 5.** In conclusion, the results of both unadjusted (naïve) analysis and MAIC analysis suggest that risdiplam might be more effective than nusinersen. [redacted] Based on the latter HR and the rate for nusinersen at 13 months of 61.3% in ENDEAR, the estimated absolute difference in ventilation-free survival-rate was [redacted], which exceeds the MCID of 15% prespecified by the expect committee. Based on the HR for the naïve analysis, the estimated absolute difference in ventilation-free survival-rate was [redacted].

[redacted]

[redacted]

Table 5 Ventilation-free survival hazard ratios (MAIC vs ENDEAR)

Comparator	Naïve Comparison	MAIC

(STUDY)	**Pre-match** Number of events / Sample Size	Hazard Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number of events / Sum of weights	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	[redacted]			
Nusinersen (ENDEAR)	31/80	[redacted]	[redacted]	[redacted]
Key: CI, Confidence Intervals (Bootstrap; N=1000 Bootstrap samples)				

Permanent ventilation (important outcome)

In FIREFISH permanent ventilation was defined by 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 or tracheostomy. A central, independent Permanent Ventilation Adjudication Committee determined time to permanent ventilation.

In ENDEAR permanent ventilation was defined as the use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event). The use of permanent assisted ventilation as of days 91, 182, 273, 364, and 394 was determined based on patient data from parental diaries and hospital records obtained at those visits. An independent end-point adjudication committee whose members were unaware of the group assignments adjudicated all events of permanent assisted ventilation.

Permanent ventilation as a single endpoint was not included in the ITC, but as a part of composite endpoint of ventilation free survival. Therefore the crude results from FIREFISH and ENDEAR of permanent ventilation endpoints from FIREFISH and ENDEAR studies are presented in **Table 6**.

[redacted] required permanent ventilation compared to 18 patients (22.5%) in ENDEAR. As no further analysis was done on this endpoint, it is difficult to draw any further conclusions.

Table 6 Permanent ventilation in FIREFISH (12 month data) and in ENDEAR final analysis

	Risdiplam (FIREFISH)		**Nusinersen/BSC (ENDEAR)**	
	FIREFISH Part 1 (n=17)*	FIREFISH Part 2 (n=41)	Nusinersen (n=80)	BSC (n=41)
Permanent ventilation (%)	[redacted]		18 (22.5)	13 (31.7)
*patients in a pivotal dose group				

CHOP-INTEND responders (critical outcome)

ITC analyses for CHOP-INTEND score improvement of at least 4 points were conducted using FIREFISH data with a modified dataset using the latest visit up to 6 months prior to datacut. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of risdiplam. The modified dataset using data up to 6 months prior to data cut has a median follow-up duration of **283 days**, which is similar to the follow-up of ENDEAR (**280 days** in the nusinersen arm). Hence, analyses with the modified data set are the primary analyses that will be weighted the most (the base case analyses).

In conclusion, results of the analysis using FIREFISH data up until 6 months prior to data cut are presented in **Table 7.** MAIC analysis results suggest that risdiplam may be more effective than nusinersen in terms of CHOP-INTEND score improvement of ≥4 points [redacted] The estimated absolute difference was [redacted], which exceeds the MCID of 20% prespecified by the expect committee. Naïve comparison results also suggest higher efficacy of risdiplam in CHOP-INTEND score improvement of ≥4 points outcome ([redacted].

Table 7 CHOP-INTEND results using FIREFISH data at the latest visit 6 months prior to data cut (MAIC vs ENDEAR)

Endpoint	Comparator (STUDY)	Naïve Comparison			MAIC		
		Pre-match Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number of responders / Sum of weights (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
CHOP-INTEND score improvement ≥4 points	Risdiplam ‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen§ (ENDEAR)	52/73 (71% [59;81]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ CHOP-INTEND score at the later of Days 0, 119, 182, 245, 301, 364 and 427

§ CHOP-INTEND score at the later of Days 183, 302 and 394

° Clopper-Pearson CIs

Sensitivity analysis: Results using 12-month FIREFISH data

Results of the analysis using 12 month FIREFISH data are presented in **Table 8**. These results are biased in favour of risdiplam, as patients had a longer time on study compared to ENDEAR which was terminated early (median time on study in the nusinersen arm was 280 days). However, results are presented here for completeness.

The MAIC analyses suggest that risdiplam may be more effective than nusinersen in terms of CHOP-INTEND score improvement ≥4 points ([redacted]). The same number of patients had a CHOP-INTEND score improvement of ≥4 points as in the base case analysis with the modified data cut. However, effect estimates are smaller in this analysis. The reason is that the individual patients achieving an improvement of ≥4 points were not the same in both dataset. Some patients achieved this improvement at an earlier visit and not at the 12-month visit and vice versa. As each patient is associated with their own weight, the MAIC ORs differ between the two analyses.

The same conclusions as in the MAIC analysis can be drawn from the naïve comparison ([redacted]), albeit smaller effect sizes.

Table 8 CHOP-INTEND results using FIREFISH data at the 12-months visit (MAIC vs ENDEAR)

Endpoint	Comparator (STUDY)	Naïve Comparison			MAIC		
		Pre-match Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number of responders / Sum of weights (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
CHOP-INTEND score improvement ≥4 points	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen§ (ENDEAR)	52/73 (71% [59;81]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ CHOP-INTEND score at 12 months

§ CHOP-INTEND score at the later of Days 183, 302 and 394

° Clopper-Pearson CIs

HINE-2 motor milestones: sitting (important outcome) and standing (important outcome)

ITC analyses were conducted for HINE-2 endpoints, including achievement of the following milestones: sitting without support (stable sits and pivots), and standing or walking (with support and unaided).

Analyses were conducted using FIREFISH data with a modified dataset using the latest visit up to 6 months prior to datacut. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of risdiplam. The modified dataset using data up to 6 months prior to data cut has a median follow-up duration of 283 days, which is similar to the follow-up of ENDEAR (280 days in the nusinersen arm).

Results of the analysis using FIREFISH data up until 6 months prior to data cut (median follow-up of 283 days) are presented in **Table 9**. MAIC results suggest that risdiplam might be superior in the sitting without support endpoint [redacted]. The estimated absolute difference was [redacted], which exceeds the MCID of 10% prespecified by the expect committee. The naïve analysis also suggests that risdiplam may be more effective than nusinersen in the sitting without support milestone ([redacted]. However, confidence intervals include ORs of <1. The analyses suggest that in terms of the standing with support milestone achievement nusinersen might be more effective than risdiplam ([redacted]), as no standing or walking milestones were recorded for risdiplam. This is not unexpected, as even children with normal motor function may not be able to stand or walk at that age.

Table 9 HINE-2 motor milestones using FIREFISH data at the latest visit 6 months prior to data cut (MAIC vs ENDEAR)

Milestone	Comparator (STUDY)	Naïve Comparison			MAIC		
		Pre-match Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number of responders / Sum of weights (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
Sitting without support (stable sits and pivots)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen§ (ENDEAR)	6/73 (8% [3;17]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing (with support and unaided)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen§ (ENDEAR)	1/73 (1% [0;7]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ HINE motor milestone achievement in infants at the later of Days 0, 119, 245 and 364

§ HINE motor milestone achievement in infants at the later of Days 183, 302 and 394

* ORs calculated using half-cell correction

° Clopper-Pearson CIs

Sensitivity analysis: Results using 12-month FIREFISH data

Results of the analysis using FIREFISH data at 12 months are presented in **Table 10**. These results are biased in favour of risdiplam, as patients had a longer time on study compared to ENDEAR. However, results are presented here for completeness.

The results suggest that risdiplam may be more effective than nusinersen in the MAIC analysis in terms of sitting without support ([redacted]. As expected the number of patients reaching this endpoint grew from 8 to 16 in the FIREFISH population when a longer follow-up was used. Point estimates of the standing milestone is also favourable towards risdiplam (OR >1) with the longer follow-up as 2 patients in the FIREFISH population reached this endpoint compared to 0 with the shorter follow-up used in our base case analysis, however there is considerable uncertainty around the estimate as the 95% confidence intervals include estimates that may favour nusinersen over risdiplam (OR <1).

Table 10 HINE-2 motor milestones using FIREFISH data at the 12-months visit (MAIC vs ENDEAR)

Milestone	Comparator (STUDY)	Naïve Comparison			MAIC		
		Pre-match Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number of responders / Sum of weights (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
Sitting without support (stable sits and pivots)	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen§ (ENDEAR)	6/73 (8% [3;17]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing (with support	Risdiplam‡ (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

and unaided)	Nusinersen§ (ENDEAR)	1/73 (1% [0;7]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

‡ HINE motor milestone achievement in infants at 12 months visit

§ HINE motor milestone achievement in infants at the later of Days 183, 302 and 394

° Clopper-Pearson CIs

24-month data on standing or walking (HINE-2 scale)

Patients in the FIREFISH trial further achieved motor milestones during the second year of treatment in both part 1 [13] and in part 2 [14]. In part 2 one patient cruised at month 24. No patients were able to walk without support. Data is summarized in a **Table 11.**

Table 11 Highest level of motor milestones achieved in HINE-2 items standing and walking at months 12 and 24 in FIREFISH part 1 and part 2.

	FIREFISH part 1 (N=17)*		FIREFISH part 2 (n=41)	
	12 month	24 month	12 month	24 month
Standing - supports weight	1 (5.9%)	4 (23.5%)	7 (17.1%)	5 (12.2%)
Standing - stands with support	0	1 (5.9%)	2 (4.9%)	6 (14.6%)
Walking - bouncing	0	0	1 (2.4%)	1 (2.4%)
Walking - cruising	0	0	0	1 (2.4%)

*patients in a pivotal dose group

Serious adverse events (important outcome) and discontinuation due to adverse event (important outcome)

Indirect treatment comparison analyses were conducted for safety outcomes: any AE leading to discontinuation and any serious AE. Analyses were conducted using FIREFISH data with a modified dataset using the latest visit up to 6 months prior to datacut. As ENDEAR had a shorter follow-up duration compared to FIREFISH, the analysis using 12-months data would be biased in favour of nusinersen (less time to observe and record adverse events). The modified dataset using data up to 6 months prior to data cut has a median follow-up duration of 283 days, which is similar to the follow-up of ENDEAR (280 days in the nusinersen arm).

Results of the analysis using FIREFISH data up until 6 months prior to data cut are presented in **Table 12**. The results suggest that risdiplam may be associated with fewer reports of adverse events leading to discontinuation and any SAE compared to nusinersen in both the naïve comparison and MAIC analysis. The OR for any AE leading to discontinuation estimated with the MAIC was [redacted]. The estimated absolute difference was [redacted]), which exceeds the MCID of 10% (in negative direction) prespecified by the expect committee. The OR for the naïve comparison was [redacted] and the absolute difference was [redacted] The OR for any SAE estimated with the MAIC was [redacted]. The estimated absolute difference was [redacted], which exceeds the MCID of 10% (in negative direction) prespecified by the expect committee. The OR for the naïve comparison was [redacted] and the absolute difference was [redacted]

In conclusion, safety endpoints were favourable for risdiplam or comparable to nusinersen (naïve comparison). Results of the analysis using FIREFISH data suggest that risdiplam may be associated with fewer reportings of AEs leading to discontinuation and any SAE compared to nusinersen.

Table 12 Safety results using FIREFISH data up until 6 months prior to data cut (MAIC vs ENDEAR)

Endpoint	Comparator (STUDY)	Naïve Comparison			MAIC		
		Pre-match Number of events / Sample size (% with AE [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number events / Sum of weights (% with AE [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
Any adverse event leading to discontinuation	Risdiplam * (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen (ENDEAR)	13/80 (16% [9;26]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious adverse event	Risdiplam (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen (ENDEAR)	61/80 (76% [65;85]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

*To align with the definition in ENDEAR, deaths were included as a reason for discontinuation

°Clopper-Pearson Cis

Sensitivity analysis: results using 12-month FIREFISH data

Results of the analysis using 12-month FIREFISH data are in **Table 13**. Results from this analysis would be biased in favour of nusinersen, as patients were followed-up for a shorter time in ENDEAR. The analyses suggest that risdiplam may be associated with fewer AEs leading to discontinuation compared to nusinersen in both the naïve comparison ([redacted]) and MAIC analysis ([redacted]) with the 95% confidence interval for OR including estimates below 1. The analyses also suggest that risdiplam may be associated with fewer serious AEs compared to nusinersen in both the naïve comparison ([redacted]) and MAIC analysis ([redacted]). For both analyses the 95% confidence interval for OR included estimates below 1.

Table 13 Safety results using 12-month FIREFISH data (MAIC vs ENDEAR)

Endpoint	Comparator (STUDY)	Naïve Comparison			MAIC		
		Pre-match Number of events / Sample size (% with AE [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)	**Post-match** Weighted number events / Sum of weights (% with AE [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
Any adverse event leading to discontinuation	Risdiplam (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen (ENDEAR)	13/80 (16% [9;26]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious adverse event	Risdiplam (FIREFISH)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nusinersen (ENDEAR)	61/80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		(76% [65;85]°)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)

°Clopper-Pearson CIs

5.2 What is the value of risdiplam compared to nusinersen in non-walking patients at age 2 to 11 with SMA type 2 and 3?

5.2.1 Presentation of relevant studies

SUNFISH is a double-blind, two-part, phase II/III randomized controlled trial (RCT). Part 1 is a dose-escalation part, while Part 2 is a confirmatory part at the dose selected based on the results from Part 1. The study includes patients with type 2 or non-ambulant type 3 SMA aged 2–25 years of age. CHERISH is a double-blind phase III RCT that includes patients with type 2 SMA aged 2-11 years of age. SUNFISH is ongoing with a total treatment period of 24 months, followed by an open-label extension phase, while CHERISH is complete with a total study duration of approximately 16 months. Both studies were conducted globally, across countries including Asia, Europe and the US. The number of sites that participated in the study was 24 in CHERISH and 42 in SUNFISH. Main characteristics of both trials are in **Tables A2** in Appendix 8.2.

Baseline characteristics of the patients in SUNFISH Part 2 and CHERISH are summarized in **Table 14**. Since SUNFISH Part 2 enrolled a much broader patient population, the patient characteristics at baseline of the SUNFISH trial are very different to those of the CHERISH trial. Patients in SUNFISH were older at screening, had a considerably longer disease duration, and lower HFMSE score than patients in CHERISH. Mean age at symptom onset was similar; however, the range of ages was larger in SUNFISH compared to CHERISH. In addition, CHERISH excluded patients with severe scoliosis, severe contractures and non-invasive ventilation for more than 6 hours during a 24-hour period, while such restrictions were not applied in SUNFISH. Gender, RULM score and SMN2 copy number were similar. (Data on file, [11]).

Table 14 Baseline characteristics in the ITT populations of SUNFISH Part 2 and CHERISH

Baseline characteristics	SUNFISH Part 2		CHERISH	
	Risdiplam (N = 120)	Placebo (N = 60)	Nusinersen (N = 84)	Sham (N = 42)
Female gender	51%	50%	55%	50%
Median age at screening in years (range)	9.0 (2–25)	9.0 (2–24)	4.0 (2–9)	3.0 (2–7)
Median age at symptom onset in months (range)	12.3 (0-57)	12.8 (6-135)	10.0 (6-20)	11.0 (6–20)
Median disease duration in months (range)[a]	95.8 (5–273)	92.2 (0–266)	39.3 (8–94)	30.2 (10–80)
Mean HFMSE baseline score (SD)	16.1 (12.5)	16.6 (12.1)	22.4 (8.3)	19.9 (7.2)
Mean RULM baseline score (SD)	19.6 (7.2)	20.5 (6.6)	19.4 (6.2)	18.4 (5.7)
SMN2 copy number				

% 2 copies	3%	2%	7%	10%
% 3 copies	89%	83%	88%	88%
% 4 copies	8%	13%	2%	2%
% Unknown	0%	2%	2%	0%
SMA type				
Type 2	70%	73%	NR	NR
Type 3	30%	27%	NR	NR
Severe scoliosis (curvature >40 degrees)	28%	38%	0%	0%

5.2.2 Results per study

As requested in the protocol provided by the Medicines Council, data on the following endpoints will be presented per study:

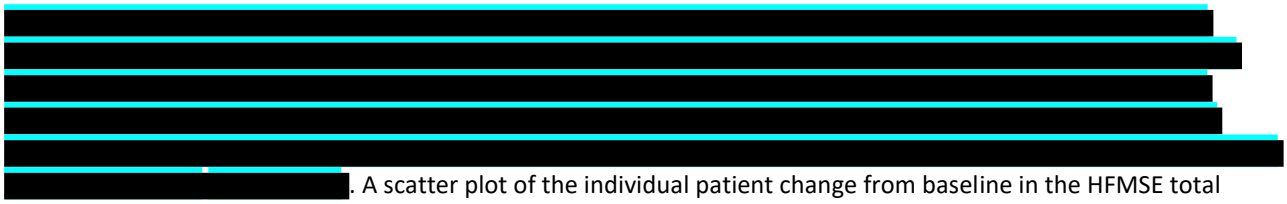
- Hammersmith Functional Motor Scale Expanded - Important outcome
- Revised Upper Limb Module - Critical outcome
- Serious adverse events - Important outcome
- Discontinuation due to adverse events - Important outcome
- Quality of life - Critical outcome

In SUNFISH Part 2, the ITT population is the primary analysis population for all efficacy analyses. The consistency of the primary efficacy endpoint and key efficacy endpoints were explored for the age subgroups: 2-5, 6-11, 12-17, and 18-25 years at randomization. Safety data up to the clinical cut-off date (CCOD) of September 6, 2019 were reported for all patients who received at least one dose of risdiplam or placebo. As of the CCOD, median duration of exposure to risdiplam was 365.0 days (100–392 days) and median exposure to placebo was 366.0 days (182–378 days). All outcomes are assessed using a 12-months efficacy and safety set. Additional efficacy and safety analyses for the age subgroup 2-11 years have been conducted for the purpose of this assessment. It should be noted that patient numbers are small in some subgroups, and that the study was not powered to demonstrate efficacy between subgroups.

In CHERISH, the ITT population is the primary analysis population for all efficacy analyses. Efficacy endpoints Hammersmith Functional Motor Scale Expanded (HFSME) and Revised Upper Limb Module (RULM) were explored for the age subgroups: 2-5 and 6-11 years at randomization. Again, it should be noted that patient numbers are small in some subgroups, and that the study was not powered to demonstrate efficacy between subgroups. Safety data up to the CCOD of August 31, 2016 were reported for all patients who received at least one dose of nusinersen or placebo. The length of treatment with nusinersen or sham-control ranged from 324–482 days. All outcomes are assessed using a 15-months efficacy and safety set.

Detailed efficacy and safety results are in **Tables A3** in Appendix 8.3.

Hammersmith Functional Motor Scale Expanded (important outcome)



. A scatter plot of the individual patient change from baseline in the HFMSE total

score at month 12 by age and SMA type (Type 2 or Type 3) and treatment (risdiplam or placebo) is presented in appendix 8.7.

At the final analysis of CHERISH (CCOD: August 31, 2016), the least-squares mean change from baseline in the HFMSE total score at 15 months in the ITT population was 3.9 (95% CI, 3.0 to 4.9) in the nusinersen arm and -1.0 (95% CI, -2.5 to 0.5) in the placebo arm. The mean treatment difference between nusinersen and placebo was 4.9 (95% CI to 3.1-6.7) [11,15]. Waterfall plots of the change from baseline in HFMSE total score at month 9, 12 and 15 by age subgroups 2-5 and 6-11 years are presented in the supplementary appendix in Mercuri et al. 2018 [11]. The plots are based on children with nonmissing values at 12 months and show individual patient change from baseline (suppl. Figure S3 in [11]).

Revised Upper Limb Module (critical outcome)

[redacted]. A scatter plot of the individual patient change from baseline in the RULM total score at month 12 by age and SMA type (Type 2 or Type 3) and treatment (risdiplam or placebo) is presented in appendix 8.7.

At the final analysis of CHERISH, the least-squares mean change from baseline in the RULM total score in the ITT population was 4.2 (95% CI, 3.4 to 5.0) in the nusinersen arm and 0.5 (95% CI, -0.6 to 1.6) in the placebo arm. The least-squares mean difference in change between nusinersen and placebo was 3.7 (95% CI, 2.3 to 5.0) [11]. Waterfall plots of the change from baseline in RULM total score at month 9, 12 and 15 by age subgroup 2-5 and 6-11 years are presented in the supplementary appendix in Mercuri et al. 2018. The plots are based on children with nonmissing values at 12 months and show individual patient change from baseline (suppl. Figure S5 in [11]).

Serious adverse events (important outcome)

[redacted]

In CHERISH, SAE data is only reported in the ITT population. As of the final analysis, 14 patients (16.7%) in the nusinersen arm and 12 patients (28.6%) in the placebo arm had experienced ≥ 1 serious AE.

[redacted] [11]).

[redacted]

MedDRA Preferred Term	SUNFISH Part 2		CHERISH	
	Risdiplam (N = 120)	Placebo (N = 60)	Nusinersen (N = 84)	Control (N = 42)
Pneumonia	[redacted]		2 (2%)	6 (14%)
Influenza	[redacted]		0	2 (5%)

Respiratory distress**	[redacted]		2 (2%)	2 (5%)
Fecaloma	[redacted]		0	2 (5%)
Dehydration	[redacted]		0	2 (5%)

*The events, classified according to MedDRA preferred terms, occurred in at least 5% of patients in either trial group.

**Respiratory outcomes in SUNFISH Part 2 were not classified as "respiratory distress", but all respiratory outcomes reported in SUNFISH Part 2 were <5%.

Discontinuations due to adverse events (important outcome)

[redacted](Data on file, [11]).

Quality of life (critical outcome)

Data on quality of life from CHERISH is not available. [redacted]

Table 16 EQ-5D utility score in subgroups aged 2-11, 2-5 and 6-11 years in SUNFISH Part 2

	Subgroup aged 2-11		Subgroup aged 2-5		Subgroup aged 6-11	
	Risdiplam (N=76)	Placebo (N=36)	Risdiplam (N=37)	Placebo (N=18)	Risdiplam (N=39)	Placebo (N=18)
Baseline total score, mean (SD)	[redacted]					
Change from baseline at Week 52, LS mean (SE) (95% CI)	[redacted]					
Difference from placebo, estimate (SE) (95% CI)	[redacted]					

5.2.3 Comparative analyses

In the absence of head-to-head clinical trial data, ITC analyses have been conducted to evaluate the treatment effects of risdiplam against nusinersen in the subgroups aged 2-11, 2-5 and 6-11 years.

ITC analyses were conducted using the MAIC and the Bucher method when possible. SUNFISH Part 2 enrolled patients that were excluded from CHERISH, such as adolescents and adults, patients with severe scoliosis and contractures. As a result, the connected network between risdiplam (SUNFISH Part 2) and nusinersen (CHERISH)

exhibits heterogeneity in terms of factors that were found to be predictive of outcome (age, SMN2 copy number, motor function at baseline) [12]. In general, it is important to adjust for differences in effect modifiers in indirect treatment comparisons, otherwise results will be biased. Following a recommendation by Signorovitch et al. [16], the ITC analyses were conducted on a subset of the SUNFISH population that would have met key CHERISH enrolment criteria:

- **Age at screening ≤ 9 years**: Adjustment for the age is very important, given that this is a key effect modifier in SMA patients [17]. Even in the subset, patients in SUNFISH were on average older than those in CHERISH. Keeping patients aged 10-11 years in the analysis set would increase the average age even further and, given that no patients older than 9 years were enrolled in CHERISH, the analysis would be biased to the detriment of risdiplam.
- **No severe scoliosis present at baseline:** Similarly, it is also important to remove patients with severe scoliosis from the analysis set. Severe scoliosis can limit the range of motion and therefore prevent detecting improvements in motor scale assessments [17]. Severe scoliosis was an exclusion criterion in CHERISH and not accounting for this difference to SUNFISH again biases the analysis to the detriment of risdiplam.
- **Baseline HFMSE score ≥ 10:** There is also evidence on baseline functional score impacting outcomes and therefore it is also important to adjust for the enrolment criteria in CHERISH of excluding patients with a baseline HFMSE score of <10.

Mean age and HFMSE baseline score were still slightly different in the SUNFISH subset compared to CHERISH. As age and baseline motor function were identified to be (potential) treatment-effect modifiers for motor function [17], anchored MAIC methodology was used for efficacy endpoints in the base case when possible. The Bucher methods were conducted as sensitivity analyses. There is a lack of evidence of treatment-effect modifiers for safety outcomes. Therefore, for the safety endpoint, the Bucher method was the base case analysis and MAIC the sensitivity analysis. In supplement, Roche has conducted additional ITC Bucher analyses including the full SUNFISH population within each subgroup upon request by the Medicines Council. Because of the important differences between trial populations, caution should be given in terms of interpretation of results.

For the subgroup aged 2-11, outcomes considered of interest and feasible for the ITC included RULM, HFMSE and SAEs. Because of differences in placebo response on the HFMSE scale between trials, main emphasis is on a narrative comparison of the HFMSE data. Results for quality of life are also compared in a narrative form because of differences in reporting. For the subgroups aged 2-5 and 6-11 years, ITC analyses for HFMSE and RULM were conducted by applying the Bucher method. CHERISH did not report on safety or quality of life in the two subgroups, and a comparison was therefore not possible.

The follow-up time of the available data cuts for the analysis was shorter in SUNFISH Part 2 than in CHERISH. For all outcomes, the primary data cut from SUNFISH Part 2 with a follow-up of at least 12 months was available, while CHERISH reports 15-months data.

Age subgroup 2-11

Baseline characteristics of patients in the SUNFISH Part 2 subgroup aged 2-11 years and CHERISH are presented in **Table 17**. Patients in the SUNFISH Part 2 subgroup were older than the patients in CHERISH, and 17% of patients had severe scoliosis at baseline compared to 0% in CHERISH. Due to these important differences, the ITC analyses were conducted on a subset of the SUNFISH population that would have met key CHERISH enrolment criteria. Out of a total of 112 patients, 41 patients were excluded from the analyses set (N=71). 18 patients were aged 10-11 years old. Of those, 11 had severe scoliosis and/or a baseline HFMSE score <10 (severe scoliosis only: N=3; baseline HFMSE <10 only: N=2; both severe scoliosis and baseline HFMSE <10: N=6). In the patients aged 2-9 years old, 23 had severe scoliosis and/or a baseline HFMSE score <10 (severe scoliosis only: N=2; baseline HFMSE <10 only: N=13; both severe scoliosis and baseline HFMSE <10: N=8). Of the remaining 71 patients in the subset, 3 patients had data missing for HFMSE and RULM, and were therefore not included in any of the ITC analyses (See Table S2 in Appendix 8.7). Using this SUNFISH subset (N=68), patient characteristics are more balanced. However, some imbalances remained (e.g. age at screening) or increased (e.g. RULM baseline score).

For the MAIC analyses, age at screening, SMN2 copy number and baseline motor function score were selected as matching factors as these are prognostic and/or predictive factors in type 2 SMA. Baseline characteristics pre- and post-matching and results are presented in the respective sections of each of the endpoints.

Table 17 Baseline characteristics in SUNFISH Part 2 age 2-11 subgroup versus CHERISH

Baseline characteristics	SUNFISH Part 2		CHERISH	
	Risdiplam (N = 76)	Placebo (N = 36)	Nusinersen (N = 84)	Sham (N = 42)
Female gender	51%	47%	55%	50%
Median age at screening in years (range)	**6.0 (2–11)**	**5.5 (2–10)**	**4.0 (2–9)**	**3.0 (2–7)**
Median age at symptom onset in months (range)	12.3 (1-38)	12.2 (6-84)	10.0 (6-20)	11.0 (6–20)
Median symptom duration in months (range)	54.1 (5–130)	50.1 (0–107)	39.0 (8–94)	30.2 (10–80)
Mean HFMSE baseline score (SD)	18.5 (12.3)	20.4 (11.6)	22.4 (8.3)	19.9 (7.2)
Mean RULM baseline score (SD)	19.0 (7.2)	20.9 (6.8)	19.4 (6.2)	18.4 (5.7)
SMN2 copy number				
% 2 copies	3%	3%	7%	10%
% 3 copies	92%	86%	88%	88%
% 4 copies	5%	11%	2%	2%
% Unknown	0%	0%	2%	0%
SMA type				
Type 2	80%	78%	NR	NR
Type 3	20%	22%	NR	NR
Severe scoliosis (curvature >40 degrees)	**17%**	**17%**	**0%**	**0%**

Hammersmith Functional Motor Scale Expanded (important outcome)

MAIC and Bucher analyses were conducted on the change in HFMSE from baseline at 12 months. However, differences in the placebo response between SUNFISH and CHERISH raise the question if the HFMSE data is comparable between trials. In the total SUNFISH Part 2 population, mean change from baseline at 12 months was 0.6 points in the placebo arm. In natural history, the mean 12-month change from baseline was reported to be -0.84 in non-ambulant Type 2 and 3 patients [18], a difference of 1.4 points compared to SUNFISH. The same pattern was observed in the SUNFISH subset (patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis). The mean change from baseline at 12 months was 1.7 in the placebo arm of the SUNFISH subset (before matching-adjustment), 2.1 in the placebo arm of the SUNFISH subset matching-adjusted to CHERISH and 0.2 in the sham arm of CHERISH. This is a difference between control arms of 1.5 points before matching-adjustment, which is increasing to 1.9 points after matching-adjustment. It is surprising that matching-

adjustment of the SUNFISH subset to CHERISH did not reduce differences in placebo response, despite successful matching of the three selected matching factors (age, baseline score, SMN2 copy number) in the placebo arm. Baseline characteristics and weight distribution after matching adjustment are presented in Appendix 8.7. These differences in placebo response on the HFMSE scale suggest potential for confounding due to trial differences that were unobserved or that could not be adjusted.

Therefore, main emphasis is placed on a narrative presentation of the HFMSE data (**Table 18**). [redacted] and in CHERISH, the mean treatment difference between nusinersen and sham was 4.9 (95% CI to 3.1-6.7) [11]. Because of the aforementioned substantial differences in baseline characteristics between the trial populations, it was not possible to draw conclusions on the HFMSE outcome.

Results from MAIC and Bucher analyses are provided upon request from the Danish Medicines Council (**Table 19 and 20).** For the subset aged 2-9 years (N=71), 3 patients had data missing for HFMSE because of discontinuation prior to the 12 months visit and were therefore not included in the analyses (Table S2). Imputation of missing data was not performed. Because of potential confounding, these results should be interpreted with caution. The analyses suggested that nusinersen may be superior to risdiplam in terms of change from baseline. Results are driven by the unusually high placebo response in SUNFISH. This is unexpected, as treatment-effect would be expected to be higher in a younger and stronger population [17]. In addition, Bucher ITC results using data from the full SUNFISH population aged 2-11 (N=112) are included for comparison purposes upon request from the Medicines Council (**Table 20**). For this population, HFMSE data at 12 months were not available for 4 patients due to study discontinuation prior to the 12 months visit. Therefore, these patients were not included in the analyses (Table S2).

Table 18 HFMSE change from baseline in SUNFISH Part 2 and CHERISH

Comparator (Study)	N	Change from baseline		Difference against control (95% CI)
		Intervention	Control	
Risdiplam (SUNFISH)	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	3.9 (3.0–4.9)	-1.0 (-2.5–0.5)	4.9 (3.1-6.7)

Table 19 Anchored MAIC HFMSE change from baseline at 12 months

Comparator (Study)	ESS/N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	3.3	0.2	3.1	Reference

[redacted]

Table 20 Bucher ITC HFMSE change from baseline at 12 months

Comparator (Study)	N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]					
[redacted]					
Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	3.7	0.7	3.0	Reference

[redacted]

Revised Upper Limb Module (critical outcome)

MAIC and Bucher analyses were conducted on the change in RULM from baseline at 12 months. The MAIC analysis is the base case analysis, as it reduces differences in patient characteristics between the SUNFISH subset and CHERISH. Notably, median age at screening was 5 years in the SUNFISH subset and 3-4 years in CHERISH. Given the differences in motor function development and treatment effects in patients younger versus older than 5 years [17] further adjusting for age at screening in the MAIC could reduce bias.

Baseline characteristics of the subset of the SUNFISH population before and after matching to the CHERISH means of the three matching factors age at screening, RULM baseline score and SMN2 copy number are presented in **Table 21** In the placebo arm, matching factors were perfectly matched to the means of CHERISH. However, the matching was at the expense of the ESS which was reduced to <10 patients from 25 patients in the placebo arm. In the risdiplam arm, matching to CHERISH baseline characteristics resulted in similar means, with small differences in the decimal points of mean RULM baseline score and mean SMN2 copy number. Differences to CHERISH were also reduced in other characteristics that were not directly matched for, such as age at symptom onset, symptoms duration and HFMSE baseline score. The ESS after matching was reduced to 28.3 from 43 patients in the risdiplam arm of the SUNFISH subset. The total ESS of both arms was estimated to be 37.1, a reduction of 45% from the total sample size of the SUNFISH subset (N=68). Stepwise exclusion of SMN2 copy number and baseline score as matching factors was tested in order to determine if the ESS could be increased. However, the reduction in the ESS was mainly driven by differences in age and removing matching factors had minimal impact on ESS.

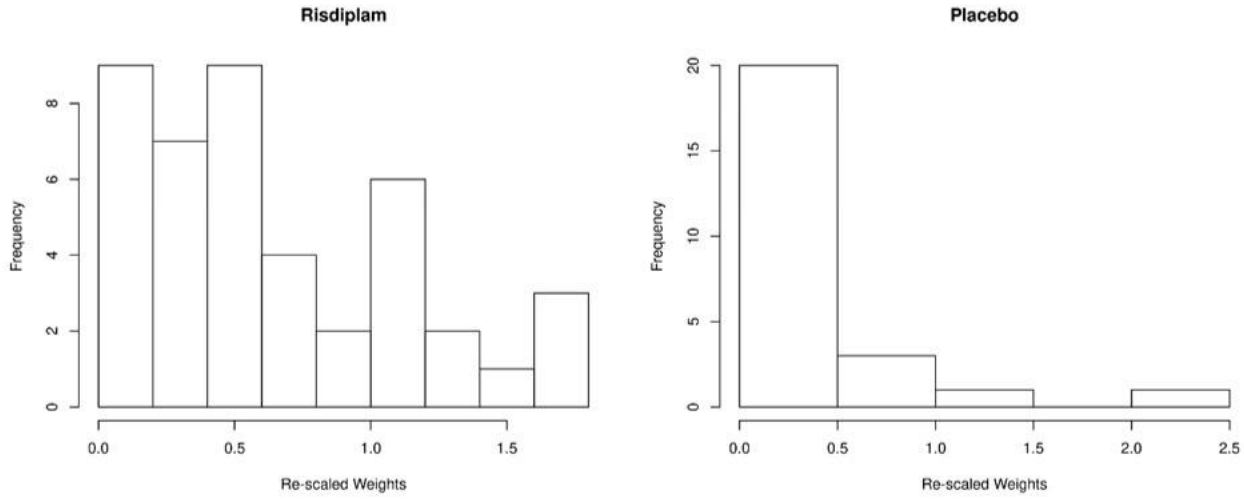
The distribution of weights was fairly even in the risdiplam arm, while in the placebo arm extreme weights of 0 or close to 0 occurred at a high frequency (**Figure 4**). This is consistent with the reduction of the ESS in the placebo arm. Results of the MAIC analyses must be interpreted with caution as very few individuals with a weight of ≥1 may dominate placebo outcomes. Statistical power to detect treatment differences will be decreased [19].

Table 21 Baseline characteristics in the SUNFISH Part 2 subset population versus CHERISH pre- and post-matching

Baseline characteristics	SUNFISH Part 2 subset [a] Pre-matching		SUNFISH Part 2 subset [a] Post-matching		CHERISH
	Risdiplam (N = 43)	Placebo (N = 25)	Risdiplam (N = 43, ESS: 28.3)	Placebo (N = 25, ESS: 8.8)	Nusinersen and sham (N = 121)
Female gender	53%	44%	61%	43%	53%
Median age at screening in years	**5.0**	**5.3**	**3.7**	**3.7**	**3.7[b]**
Median age at symptom onset in months	13.7	16.6	12.7	13.4	10.3[b]
Median symptom duration in months	46.3	46.3	31.6	30.7	36.0[b]
Mean HFMSE baseline score	24.21	23.12	21.99	22.36	21.57
Mean RULM baseline score	**21.65**	**22.28**	**19.11**	**19.07**	**19.07**
Mean SMN2 copy number	3.09	3.08	3.00	2.94	2.94
% 2 copies	0%	4%	0%	7%	8%
% 3 copies	91%	84%	100%	91%	88%
% 4 copies	9%	12%	0%	1%	2%
% Unknown	0%	0%	0%	0%	2%

[a] Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis. [b] In the absence of reported means, means for the overall CHERISH population were calculated as a weighted average of the medians for the purpose of these analyses.

Figure 4 Histograms of re-scaled weights in the CHERISH-matched restricted SUNFISH population



Comparison of control arms is recommended [16] in order to assess the potential for confounding due to differences in trials. Results of the control arms between the two studies showed similar responses between placebo and sham. The difference in the mean change from baseline at 12 months between the placebo arm outcome in the SUNFISH subset and the sham arm outcome in CHERISH was 0.5 points. This difference decreased to only 0.1 points after matching-adjusting to CHERISH, resulting in very similar control arm outcomes.

The estimated mean difference in change of RULM score at 12 months was [redacted] (**Table 22**). Given that we could not reliably identify and remove patients with severe contractures from the SUNFISH subset, this mean difference may be a conservative estimate. [redacted]

Sensitivity analysis was conducted using Bucher ITC with the SUNFISH subset. Bucher ITC results using data from the full SUNFISH population aged 2-11 (N=112) are included for comparison purposes upon request from the Medicine Council. For the full population, RULM baseline data was not available for 3 patients and RULM data at 12 months were not available for 4 patients due to study discontinuation prior to the 12 months visit. For the subset, 3 patients out of a total of 71 patients had data missing for RULM because of discontinuation prior to the 12 months visit (Table S2). Therefore, these patients are not included in the analyses. Imputation of missing data was not performed. Overall, point estimates across all methods showed comparable efficacy of risdiplam and nusinersen, with a numerically smaller improvement for risdiplam. Confidence intervals encompassed a mean difference of 0, and thus, it is not possible to differentiate between treatment effects (**Table 23**) (Data on file).

Table 22 Anchored MAIC RULM change from baseline at 12 months

Comparator (Study)	ESS/N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			[redacted]

Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	3.7	0.7	3.0	Reference

[redacted]

Table 23 Bucher ITC RULM change from baseline at 12 months

Comparator (Study)	N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]					
[redacted]					
Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	3.7	0.7	3.0	Reference

[redacted]

Serious adverse events

MAIC and Bucher analyses were conducted on the proportion of patients with serious AEs. The Bucher analysis is the base case analysis, as there are increased differences in the control arms after matching-adjustment and lack of evidence of treatment effect modifiers relating to AEs, indicating that the Bucher ITC may provide less biased results. Bucher ITC results using data from the full SUNFISH population aged 2-11 (N=112) are included for comparison purposes upon request from the Medicines Council.

In the SUNFISH subset that met some of CHERISH's enrolment criteria (age ≤9 years, baseline HFMSE score ≥10, no severe scoliosis), the proportion of patients that were reported to have any serious AE was higher in the placebo arm compared to risdiplam; similar to what was observed in CHERISH. OR suggest comparable reporting of any serious adverse events of risdiplam and nusinersen, although the point estimate provides a slightly higher OR for risdiplam [redacted]

In the sensitivity analysis, results from the MAIC suggested that risdiplam may be associated with a higher reporting of SAEs. However, results appear to be unstable as the upper limit of the confidence interval is very high (**Table 25**). The same matching factors as for the RULM endpoints were used (age at screening, SMN2 copy number, baseline RULM score). See baseline characteristics and weight distribution after matching adjustment under the description of the RULM endpoint.

Table 24 Bucher ITC results on any serious adverse event

Comparator (Study)	N	Proportion with any SAE		OR against control	OR against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	14 (17%)	12 (29%)	0.5	Reference

[redacted]

Table 25 Anchored MAIC results on any serious adverse event

Comparator (Study)	ESS/N	Proportion with any SAE		OR against control	OR against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			
Nusinersen (CHERISH)	126 (Nusinersen: 84; Sham: 42)	17%	29%	0.5	Reference

[redacted]

Quality of life

Data on quality of life from CHERISH is not available, and therefore a comparison with data from SUNFISH cannot be made. [redacted]

Age subgroup 2-5

CHERISH did not report on the baseline characteristics in the subgroup aged 2-5 years, therefore it is not possible to compare baseline characteristics in this subgroup. However, the enrolment criteria of CHERISH excluded patients

with severe scoliosis at baseline and those with a baseline HFMSE score <10. In the SUNFISH subgroup aged 2-5 years, 0% of patients had severe scoliosis, while 16% had a baseline HFMSE score <10. HFMSE is associated with a floor effect in weaker patients. Therefore the indirect analysis was conducted in a subset of the 2-5 years patient subgroup, excluding patients with a HFMSE score <10. 9 patients had a baseline HFMSE score <10 and no patients had severe scoliosis. Out of a total of 46 patients, 2 patients had data missing for HFMSE and 2 patients had data missing for RULM (Table S2). Bucher ITC results using data from the full SUNFISH population aged 2-5 are included for comparison purposes upon request from the Medicines Council. A total of 55 patients are in the full 2-5 age group, 3 patients had data missing for HFMSE and 3 patients had missing data for RULM (Table S2).

Importantly, data from CHERISH had to be extracted from the available charts for the purpose of the ITC, and the models could therefore not be adjusted by baseline age and baseline motor function (as individual patient data on those characteristics was not available). Data from CHERISH was only from those patients that reached the 12 months visit, and there was no imputation of missing data.

Hammersmith Functional Motor Scale Expanded (important outcome)

[redacted]). The point estimate is favourable towards nusinersen, and does exceed the MCID of 3 points prespecified by the expert committee. However, the confidence interval includes absolute differences below and above 0. Thus, the analysis cannot differentiate between risdiplam and nusinersen.

Table 26 Bucher ITC results on HFMSE change from baseline at 12 months

Comparator (Study)	N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
Nusinersen (CHERISH)	103 (Nusinersen: 68; Sham: 35)	3.97	0.66	3.31	Reference

[redacted]

Revised Upper Limb Module (critical outcome)

[redacted]
(Data on file). In conclusion, the point estimate is favourable towards risdiplam, but does not exceed the MCID of 2 points prespecified by the expert committee. The confidence interval includes absolute differences below and above 0, and thus, the analysis cannot differentiate between risdiplam and nusinersen.

Table 27 Bucher ITC results on RULM change from baseline at 12 months

Comparator (Study)	N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
Nusinersen (CHERISH)	103 (Nusinersen: 68; Sham: 35)	4.38	1.51	2.87	Reference

[redacted]

Age subgroup 6-11

CHERISH did not report on the baseline characteristics in the subgroup aged 6 and older, therefore it is not possible to compare baseline characteristics in this subgroup. However, the enrollment criteria of CHERISH excluded patients with severe scoliosis at baseline and those with a baseline HFMSE score <10. Further, the maximum age of the enrolled population was 9 years. In the SUNFISH subgroup aged 6-11 years, 32% of patients were aged >9 years, 33% had severe scoliosis, and 35% had a baseline HFMSE score <10. Age is an important treatment effect modifier, HFMSE is associated with a floor effect in weaker patients, and severe scoliosis can impact the range of motion (making it difficult to assess changes on motor function scales). Therefore, the indirect analysis was conducted in a subset of the 6-11 years patient subgroup, excluding patients aged >9 years, those with a HFMSE score <10 and those with severe scoliosis. 18 patients were aged >9 years. Of the remaining patients aged 6-9, 4 patients had a baseline HFMSE score <10 only, 2 had severe scoliosis only and 8 had both severe scoliosis and a baseline HFMSE score <10. Out of a total of 25 patients, 1 patients had data missing for HFMSE and 1 patients had data missing for RULM (Table S2). Bucher ITC results using data from the full SUNFISH population aged 6-11 are included for comparison purposes upon request from the Medicines Council. A total of 57 patients are in the 6-11 age group, 1 patient had data missing for HFMSE and 4 patients had data missing for RULM (Table S2). Again, data from CHERISH had to be extracted from the available charts for the purpose of the ITC, and the models could therefore not be adjusted by baseline age and baseline motor function. Data from CHERISH was only from those patients that reached the 12 months visit, and there was no imputation of missing data.

Hammersmith Functional Motor Scale Expanded (important outcome)

[redacted]

Table 28 Bucher ITC results on HFMSE change from baseline at 12 months

Comparator (Study)	N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
Nusinersen (CHERISH)	15 (Nusinersen: 9; Sham: 6)	-0.44	-0.83	0.39	Reference

[redacted]

Revised Upper Limb Module (critical outcome)

[redacted]

Table 29 Bucher ITC results on RULM change from baseline at 12 months

Comparator (Study)	N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]			
Nusinersen (CHERISH)	15 (Nusinersen: 9; Sham: 6)	-0.44	-1.83	1.39	Reference

[redacted]

5.3 What is the value of risdiplam compared to placebo in patients at age 12 to 25 with SMA type 2 and patients with SMA type 3, who have lost gait function?

5.3.1 Presentation of relevant studies

SUNFISH Part 2 is presented in section 5.2.1 and **Table A2** in Appendix 8.2. Baseline characteristics of the subgroup aged 12-15 years are presented in **Table 30** (Data on file).

Table 30 Baseline characteristics in SUNFISH Part 2 age 12-25 subgroup

Baseline characteristics	SUNFISH Part 2	
	Risdiplam (N = 44)	Placebo (N = 24)
Female gender	50%	54%
Median age at screening in years (range)	15.5 (12–25)	15.0 (12–24)
Median age at symptom onset in months (range)	12.8 (0-57)	14.9 (7-135)
Median time between onset of initial SMA symptoms to first treatment in months (range)	168.9 (132-275)	171.5 (34-271)
Mean HFMSE baseline score (SD)	12.0 (11.9)	11.0 (10.7)
Mean RULM baseline score (SD)	20.5 (7.3)	19.9 (6.6)
SMN2 copy number		
% 2 copies	2%	0%
% 3 copies	84%	79%
% 4 copies	14%	17%
% Unknown	0%	4%

SMA type		
Type 2	52%	67%
Type 3	48%	33%
Severe scoliosis (curvature >40 degrees)	48%	71%

5.3.2 Results per study

As requested in the protocol provided by the Medicines Council, data on the following endpoints will be presented per study:

- Hammersmith Functional Motor Scale Expanded - Important outcome
- Revised Upper Limb Module - Critical outcome
- 32-item Motor Function Measure - Critical outcome
- Serious adverse events - Important outcome
- Discontinuation due to adverse events - Important outcome
- Quality of life - Critical outcome

In SUNFISH Part 2, the ITT population is the primary analysis population for all efficacy analyses. The consistency of the primary efficacy endpoint and key efficacy endpoints were explored for the age subgroups: 2-5, 6-11, 12-17, and 18-25 years at randomization. Safety data up to the CCOD (September 6, 2019) were reported for all patients who received at least one dose of risdiplam or placebo. As of the CCOD, median duration of exposure to risdiplam was 365.0 days (100–392 days) and median exposure to placebo was 366.0 days (182–378 days). All outcomes are assessed using a 12-months efficacy and safety set.

Additional efficacy and safety analyses for the age subgroup 12-25 years have been conducted for the purpose of this assessment. It should be noted that patient numbers are small in the subgroup, and that the study was not powered to demonstrate efficacy between subgroups.

Detailed efficacy and safety results are presented in **Table A3** in Appendix 8.3.

32-item Motor Function Measure (critical outcome)

[redacted] (Data on file). [redacted] A scatter plot of the individual patient change from baseline in the MFM32 total score at month 12 by age and SMA type (Type 2 or Type 3) and treatment (risdiplam or placebo) is presented in appendix 8.7.

Hammersmith Functional Motor Scale Expanded (important outcome)

[redacted]

[redacted] (Data on file). [redacted] A scatter plot of the individual patient change from baseline in the HFMSE total score at month 12 by age and SMA type (Type 2 or Type 3) and treatment (risdiplam or placebo) is presented in appendix 8.7.

Revised Upper Limb Module (critical outcome)

[redacted] (Data on file). [redacted] A scatter plot of the individual patient change from baseline in the RULM total score at month 12 by age and SMA type (Type 2 or Type 3) and treatment (risdiplam or placebo) is presented in appendix 8.7.

Serious adverse events (important outcome)

As of the CCOD (6 September, 2019), 24 patients (20.0%) in the risdiplam arm and 11 patients (18.3%) in the placebo arm had experienced ≥ 1 SAE. [redacted] (data on file).

Overall, the analysis cannot differentiate between risdiplam and placebo. The point estimates indicate that risdiplam could be associated with higher reportings of SAE compared to placebo, but it is below the MCID of 10% prespecified by the expert committee. The confidence intervals also include estimates in which risdiplam would be associated with less resportings (RR below 1 and absolute difference below 0), and thus, the analysis cannot differentiate between risdiplam and placebo. In general the confidence intervals are wide, indicating that there is uncertainty associated with the estimates.

Discontinuations due to adverse events (important outcome)

In SUNFISH part 2, there were no treatment withdrawals due to an AE in any of the treatment arms (data on file).

Quality of life

[redacted]

Table 31 EQ-5D utility score in subgroup aged 12-25 years in SUNFISH Part 2

	Subgroup aged 12-25	
	Risdiplam (N=43)	Placebo (N=24)

Baseline total score, mean (SD)	[redacted]	
Change from baseline at Week 52, LS mean (SE) (95% CI)	[redacted]	[redacted]
Difference from placebo, estimate (SE) (95% CI)	[redacted]	

5.3.3 Comparative analyses

Results are described in the previous section (Results per study).

5.4 What is the value of risdiplam compared to placebo in patients with SMA type 3, who have retained gait function?

5.4.1 Presentation of relevant studies

The data presented in the following comes from a literature review on natural history data for ambulant SMA type 3 patients. Description of the literature search can be found in section 4 and Appendix 8.1.

The identified natural history data is compared to data available for the ambulant SMA type 3 patients treated with risdiplam. In the risdiplam clinical program, ambulant patients were enrolled into Study BP39055 (SUNFISH) Part 1 including 7 ambulant patients and 44 non-ambulant patients, and Study BP39054n (JEWELFISH) including 16 ambulant patients and 158 non-ambulant patients. For this clinical question only data from the 7 ambulant SMA type 3 patients in SUNFISH part 1 is included as the JEWELFISH study included patients previously treated with medication.

Outcomes defined relevant in the protocol provided by the Medicines Council for clinical question 4 were:

- Hammersmith Functional Motor Scale Expanded - Critical outcome
- 32-item Motor Function Measure - Important outcome
- 6 Minute Walk Test - Important outcome
- Serious adverse events - Important outcome
- Discontinuation due to adverse events - Important outcome
- Quality of life - Critical outcome

Of the outcomes defined as relevant, the SUNFISH Part 1 study collected data on HFMSE, MFM-32, SAEs, discontinuation due to AEs, and HRQoL, but because very few patients enrolled in the study were walkers, no data was collected on the 6MWT.

Literature review results

Five trials on natural history data were eligible for inclusion [5-9]. However, out of these, two publications only reported natural history study data on the 6MWT [7,9]. These two trials are not further described, as no comparison with risdiplam will be possible. Consequently, three trials were compared with the study on risdiplam. Additionally, the EPAR for risdiplam published on the EMA website was consulted [20]. The EPAR does not provide separate information on this patient population. An overview of the 4 included studies are presented in **Table 32.** The methods used per outcome for each study and the baseline characteristics of the patients are summarized in **Table 33** and **Table 34**, respectively.

Table 32 Overview of the four studies included in the assessment for clinical question 4

Trial name and identifier, author year	Study type	Study design, in - and exclusion criteria	Total number of patients in study and number of patients included for this review	Relevant outcomes reported	Follow-up
SUNFISH part 1 NCT02908685 	A Two Part, Multi-Center Randomized, Placebo-Controlled, Double-Blind Study	Study design, and in-and exclusion criteria for the SUNFISH trial (part I and II) is described in Table A2B	SUNFISH Part 1 included 51 patients; data available for the 7 ambulatory SMA type 3 patients is included in this review.	HFMSE MFM-32 Serious adverse events (SAE) Withdrawal due to adverse event QoL (assessed with EQ-5D and PedQL)	12 and 24 months
NatHis-SMA (2-year NatHis SMA-study) NCT02391831 Annousamy, 2021[5]	Prospective Study of the Natural History of Patients With Type 2 and 3 Spinal Muscular Atrophy (NatHis-SMA)	Prospective, longitudinal and open label (no masking) Main inclusion criteria: Type 2 or 3 spinal muscular atrophy genetically confirmed, and age superior or equal to 2 years old up to 30 years of age Main exclusion criteria: Previously treated with an investigational drug within 6 months prior to the recruitment in this study. Further in - and exclusion criteria are described on ClinicalTrials.gov	81 patients were included, data for the 19 ambulant SMA type 3 is included for this review	MFM-32	12 and 24 months
"Clinical Variability in Spinal Muscular Atrophy Type III" Coratti, 2020[8]	Cohort study (longitudinally)	Design rather unclear, Study states data is prospectively collected from retrospective data from the International SMA Registry Inclusion criteria: All patients with a genetically confirmed diagnosis of SMA and a clinically confirmed diagnosis of SMA type 3 Exclusion criteria: Data from patients participating in clinical trials or treated with disease modifying drugs	At baseline (first visit) 182 patients were included, of these 130 patients ambulant SMA type 3 are included for this review.	HFMSE	Ranged between 0.46 years and 13.34 years

"Single-blind randomized, Controlled Clinical Trial of Exercise in Ambulatory Spinal Muscular Atrophy: Why are results negative?" NCT01166022 Montes, 2015[6]	Single-Blind, Randomized, Controlled Clinical Trial	Evaluator-blinded, randomized, controlled trial of aerobic and strengthening exercise in 14 ambulatory SMA patients aged 8-50 years. Patients were randomised to exercise or control. Main inclusion criteria: Weakness and hypotonia consistent with the clinical diagnosis of SMA type 3. Laboratory documentation of homozygous absence of SMN1 exon 7. Ability to walk at least 25 meters without assistance. Aged 8 to 50 years at the time of enrollment. Further in- and exclusion criteria are described on ClinicalTrials.gov	14 ambulatory SMA type 3 patients were randomized, data from the 7 patients in the control arm is included for this review	HFMSE Serious adverse events (SAE) Withdrawal due to adverse event QoL (children assessed with PedsQLNM, adults assessed with SF36PH and SF36MH)	6 months

Table 33 Overview of methods of analysis per outcome

Trial	HFMSE	MFM-32	QoL	Safety (SAEs and withdrawal due to AEs)
SUNFISH Part 1	HFMSE Mean (SD) 95% CI (baseline, Mean change at wk 52 and wk 104).	MFM-32 Mean (SD) 95% CI (baseline, Mean change at wk 52 and wk 104).	EQ5D (baseline, mean change at week 52).	Frequency of SAEs and withdrawals during study period.
Annousamy, 2021	NR	MFM-32 Median total score, range, p-value and SRM (baseline, point change at wk 52 and wk 104)	NR	NR
Coratti, 2020	HFMSE Mean (SD) at baseline, average change in HFMSE score per year before and after age 7.	NR	NR	NR
Montes, 2015	HFMSE Mean (SD) at baseline and 6 months, and change over 6 months (%).	NR	SF-36 and PedsQL Mean (SD) at baseline and 6 months.	Frequency of AEs during study period.

Abbreviations: SD – Standard Deviation; SRM – Standardized response mean; NR – Not reported

Table 34 Baseline characteristics of for ambulatory SMA type 3 patients included in review

Baseline characteristics	SUNFISH Part 1 (N = 7)	Coratti 2020 (N=130)	Montes 2015 (N=7)	Annousamy 2021 (N=19)
Female gender	28.6%	54.6%	28.6%	NR
Median age at screening in years (range)	5.0 (4-24)	10.08 (2.5-28.67)	26.7 (10-48)	10.4 (4.5-19.2)
Median age at symptom onset (range)	22 months (8-27)	NR	6.4 years (1- 15)	22 months (17-32)
Mean HFMSE baseline score (SD)	50.00 (5.07)	51.68 (8.83)	54.0 (8.16)	NR
Mean MFM-32 baseline score (SD)	74.65 (6.28)[1]	NR	NR	84.4 (range 70.1- 90.6)[2]
SMN2 copy number				
% 2 copies	0 %	4.62%	NR	0 %
% 3 copies	57%	46.15%	NR	13/19
% 4 copies	43%	26.92%	NR	5/19
% Unknown	0 %	22.31%	NR	1/19

[1]Only three of the seven patients were assessed with this tool at all time points (due to a protocol deviation in SUNFISH part 1 some patients aged 4-5 years were assessed with MFM-20). [2]Only 11 of the 19 patients assessed with this tool (younger patients appr. 5 years and under were assessed with MFM-20).

Quality assurance in included studies

As requested by the Medicines Council in the protocol information available on quality assurance of assessment and scoring of the effect measures in the included studies are summarized below:

SUNFISH Part 1: [redacted]

Annousamy 2021: To minimize inter and intra site variability, the order in which each evaluation was to be performed was clearly stipulated in the protocol (link to the full S1 Protocol can be found in reference). Study sites were reminded to adhere to this schedule. Visits lasted 1 to 2 consecutive days depending on patient's age and fatigability [21].

Coratti 2020: No information was available.

Montes 2015: The study states that in order to ensure participating networks shared quality (reliability) in evaluation of the HFMSE scale, training and the same procedure manual. Individual evaluators were trained at in-person meetings and established reliability of the HFMSE. Evaluators also had regular annual refresher training with item scoring review.

5.4.2 Results per study

Data is presented narratively due to substantial differences in population characteristics (e.g. average age) (**Table 34**) and methods used to summarize the outcome measures and effect sizes (**Table 33**)**.**

Hammersmith Functional Motor Scale Expanded (critical outcome)

Three trials included information on change scores on the HFMSE-scale (SUNFISH data-on-file, Montes, 2015 and Coratti, 2020 [6,8]).

Due to the small sample size, it only makes sense to summarize the results from the study using descriptive statistics. Hence, we provide mean and standard deviation at baseline and for change scores for SUNFISH Part 1 and Montes 2015, and additionally for SUNFISH the 95% confidence intervals as reported in the study (**Table 35**). Note that the study by Coratti, 2020 [8]used a model accommodating different 12-months change effects for individuals under and above 7 years. The statistical analysis undertaken assessed the longitudinal changes of HFMSE using piecewise linear mixed-effect models, and this method of analysis is not comparable with the method used in the two other studies. In the Coratti study, a sensitivity analysis was undertaken to allow for differences in effect between walkers and non-walkers, but no differences were found. The Coratti 2020 study was conducted using data from five countries; however, this is not adjusted for in the analysis.

For ease of comparison we consider the mean changes provided in SUNFISH part 1 and Montes, 2015. There is a difference in mean changes between risdiplam and natural history data. The risdiplam group showed a small increase in mean HFMSE scores after 1 year [redacted] and after 2 years [redacted] whereas the control arm in Montes 2015 after 6 months remained stable. However, study differences in population characteristics at baseline, combined with very small sample sizes and differences in study follow-up period makes conclusion around effect differences uncertain.

Table 35 Results ambulatory SMA 3 on the HFMSE scale.

Trial	N	Baseline total score, Mean (SD) (95% CI)	Follow-up	Mean change (SD) 95% CI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Montes 2015	7	54 (8.16)*	6 months	54 (7.07)*
Coratti 2020	130	51.68 (8.83)*	Between 0.46 years and 13.34 years	12 months change < 7 years (adjusted, SE) : 1.5076 (0.3388) 12 months change > 7 years (adjusted, SE): -2.5911 (0.4074)

*95% CIs not reported

32-item Motor Function Measure (important outcome)

Two trials included information on change scores on the MFM-32 scales (SUNFISH data-on-file and Annousamy, 2021[5]).

Of the 7 ambulatory SMA 3 patients in SUNFISH part 1, three patients were assessed with the MFM-32 tool and four patients with the MFM-20 tool. Of the 19 ambulatory SMA 3 patients included in the NAt-His trial, 11 patients from appr. 6 years and above were assessed with the MFM-32 tool and the 8 younger patients with the MFM-20 tool. This is however, not consistently reported in the Nat-His article where one place states that the split was 10 MFM-32

versus 9 MFM-20 patients. However, patient level data in the supplements provides information on 11 patients assessed with MFM-32, which we extracted for this review. Due to the small sample size, it only makes sense to summarize the results from the study using descriptive statistics. Hence, we provide mean and standard deviation at baseline and for change scores and the 95% confidence intervals as reported in the SUNFISH part 1 study, and median total score, interquartile range (IQR) at baseline and median point change, range (min, max) and p-value as reported in the Nat-His trial (**Table 36**).

For ease of comparison, we consider the mean changes. There is a difference in mean changes between risdiplam and natural history data after 12 months [redacted] and after 24 months [redacted] in favour of risdiplam. However, there are considerable uncertainties around the effect differences due to the very small sample sizes, uncertainties around population characteristics and differences in analysis methods utilized.

Table 36 Results ambulatory SMA 3 on the MFM-32 scale

Results SUNFISH part 1 - MFM-32, N=3	
[redacted]	
[redacted]	
[redacted]	
Results Nat-His study - MFM-32, N=11	
Baseline median total score, IQR	84.4 (70.1–90.6)
Wk 52, median point change, range (min,max), p-value Mean change (SD)	-1.05 (-11.46, 2.09), 0.184 -1.67 (3.87)

SAEs and withdrawal due to AEs (important outcomes)

Two trials provided information on SAEs and withdrawals due to AEs (SUNFISH data-on-file and Montes, 2015 [6].

[redacted] No events led to withdrawal of study drugs. In natural history data included only the RCT by Moratti 2015 reports adverse events. This study does not report any SAEs or study withdrawal in the control group.

[redacted] In a control group of 7 patients from a previous RCT no SAEs or study withdrawal was reported. The very small sample size makes conclusions on SAEs and withdrawals due to AEs uncertain.

Quality of life (critical outcome)

Two trials provided information on quality of life using a variety of scales (SUNFISH data-on-file and Montes, 2015 [6].

Quality of life was assessed by the parent/caretakers of ambulatory patients in SUNFISH part 1 by EQ-5D-5L. An ITT-analysis was performed to account for missing values. [redacted]

In the natural history data included, only the RCT by Montes, 2015, reported data on quality of life. This study followed-up at 24 weeks. Quality of life results from the control arm are based on very few observations (from two to four patients or caretakers depending on scale) and no ITT-analysis was performed. Adult participants were assessed with SF-36 (physical and mental health) and Fatigue severity scale (FSS). Child participants/caretakers were assessed with PedsQL (Neuromuscular and fatigue scales). Baseline mean with standard deviations and mean change with standard deviations after 6 months are presented below, as reported in the study.

Results from SUNFISH Part 1

[redacted]

[redacted]

EQ-5D summary score	N	Mean	SD	Median	Min	Max
[redacted]						
[redacted]						
[redacted]						

Results from Montes, 2015

Data for SF-36 (physical and mental health) are shown in **Table 38**. Because only two out of seven participants filled in the SF-36 questionnaire, it is not possible to draw a meaningful conclusion on SF-36.

Table 38 Montes, 2015, adult participants assessed with SF-36

SF-36, mental health	N	Mean	SD
Baseline	2	54.2	2.32
Change from baseline at week 24	2	55.0	2.74
SF-36 physical health	**N**	**Mean**	**SD**
Baseline	2	39.4	0.29
Change from baseline at week 24	2	37.8	1.60

Data for Fatigue severity scale (FSS) is shown in **Table 39.** Because only four out of seven participants filled in the Fatigue Severity Scale, it is not possible to draw a meaningful conclusion based on this data.

Table 39 Montes, 2015, adult participants assessed with Fatigue severity scale (FSS)

Fatigue Severity scale	N	Mean	SD
Baseline	4	5.0	0.85
Change from baseline at week 24	4	5.4	1.04

Data for PedsQL (Neuromuscular and fatigue scales) are shown in **Table 40.** Because only three out of the child/caretakers participants filled in the PedsQL Scale, it is not possible to draw a meaningful conclusion based on this data.

Table 40 Montes, 2015, child participants/caretakers assessed with PedsQL

Outcome PedsQL, neuromuscular	N	Mean	SD
Baseline Child Parent	3	 85.3 83.0	 13.61 10.81
Change from baseline at week 24 Child Parent	3	 85.4 85.7	 9.40 9.61
Outcome PedsQL, Fatigue	**N**	**Mean**	**SD**
Baseline Child Parent	3	 81.7 75.9	 15.49 18.86
Change from baseline at week 24 Child Parent	3	 85.2 83.24	 12.12 14.43

Conclusion on quality of life

[redacted]

Based on the data available it is, however, not possible to conclude whether there are differences in quality of life in ambulatory SMA 3 patients receiving risdiplam compared to placebo. This is because the studies use different QoL-scales, very limited data is available on both the risdiplam treated patients and the natural history patients and scales are sometimes reported by patients, sometimes by caretakers. Additionally, the two studies included have different follow-up periods.

6. Other Considerations

6.1 Advantages with oral administration

A recent publication from January 2021 [22] summarizes a Europe-wide survey performed with the goal of understanding patients' treatment expectations, realities of daily living and access to clinical trials and therapy, and how this varied according to parameters such as age and disease severity. 1474 patients from 26 European countries

completed the survey. Results regarding willingness of participants to accept different routes of administration showed a higher willingness of participants to accept oral administration than intrathecal or intravenous administration and this was true in both the treated and untreated patient group (fig. 3 in article).

Similarly, a discrete choice experiment conducted to examine patient/caregiver preference for key attributes of treatments for spinal muscular atrophy (SMA) amongst patients (aged≥18 years) and caregivers of SMA patients with SMA types 1–4 showed that oral medication and one-time infusion were strongly preferred over repeated IT injections (RC: 0.80, 95% CI: 0.60–0.98 and RC: 0.51, 95% CI: 0.30–0.73, respectively). This publication also concludes that "For some patients, there may be willingness to trade off additional gains in efficacy for a change in route of administration from repeated intrathecal administration to oral medication" [23].

6.2 Combination with other treatments

There is no data on concomitant use of risdiplam with other SMA treatments. Regarding switching, The JEWELFISH study is a multi-center, exploratory, non-comparative, and open-label study to investigate the safety, tolerability, PK, and PK/PD relationship of risdiplam in adults, children and infants with Spinal Muscular Atrophy (SMA) previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime or AVXS-101. Results from the JEWELFISH study will be available later in 2021.

At this point there is safety data from the JEWELFISH study available from 173 patients. Results show that there have been no treatment-related AEs leading to withdrawal in JEWELFISH, with some patients receiving treatment for over 3 years. The abstracts published conclude the following:

The overall AE profile of risdiplam treatment in non-naïve patients is consistent with that of treatment-naïve patients. JEWELFISH have shown a sustained, >2-fold increase in median SMN protein levels versus baseline, which is consistent with treatment-naïve patients. Exploratory efficacy endpoints will be presented after all patients have been treated for a minimum of 1 year [1].

6.3 Stop-criteria

SMA type 1

There are no current Danish STOP-criteria for SMA type 1 defined for nusinersen. Roche suggests the same applies for risdiplam. It does not seem ethically justifiable to have predefined criteria due to the short life expectancy in this patient population.

SMA type 2 and SMA type 3

The current Danish STOP-criteria for Spinraza defines that the SMA-type 2 patient should stop treatment if the following applies:

- Deterioration in respiratory status based on needed time in ventilation treatment per day or deterioration in SaO2 measured without additional supply of oxygen assessed over 3 weeks, where the deterioration is not caused by infection.
- Deterioration in gross motor function assessed on the HFMSE scale in two consecutive measurements compared to when the patient started treatment.

In 2015, SMA Europe, an umbrella organization of SMA patient organizations across Europe, conducted a large-scale multinational survey to assess the impact of SMA on general well-being and the therapeutic expectations of patients with Type 2 and Type 3 SMA in Europe. Through this SMA Europe learnt that almost all respondents (96.5%) considered stabilization to be a positive outcome from treatment, regardless of disease status, age or geographical origin. The findings from 2015 were built upon with a second survey in 2019[24]. This survey confirms the finding of the 2015 survey by SMA Europe that individuals living with SMA consider stabilization of their current clinical state to be progress, with 96.6% of all participants in agreement and the proportion similar across stratified groups[22].

Consequently, Roche suggest that STOP-criteria are defined equally across "milder" SMA-types being SMA type 2 and type 3 regardless of age, and that treatment should be discontinued under the following circumstances:

Deterioration in respiratory status based on needed time in ventilation treatment per day or deterioration in SaO2 measured without additional supply of oxygen assessed over 3 weeks, where the deterioration is not caused by infection or a clinically meaningful deterioration in gross motor function assessed on both the HFMSE scale (3 points) and the MFM-32 (3 points) scale and assessed in two consecutive measurements compared to when the patient started treatment. The evaluation is suggested to be initiated after two years of treatment which is in line with the data from FIREFISH and SUNFISH where 2-year data showed continuous improvements.

7. References

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8. Appendices

8.1 Literature search

The literature search is performed for clinical question 4.

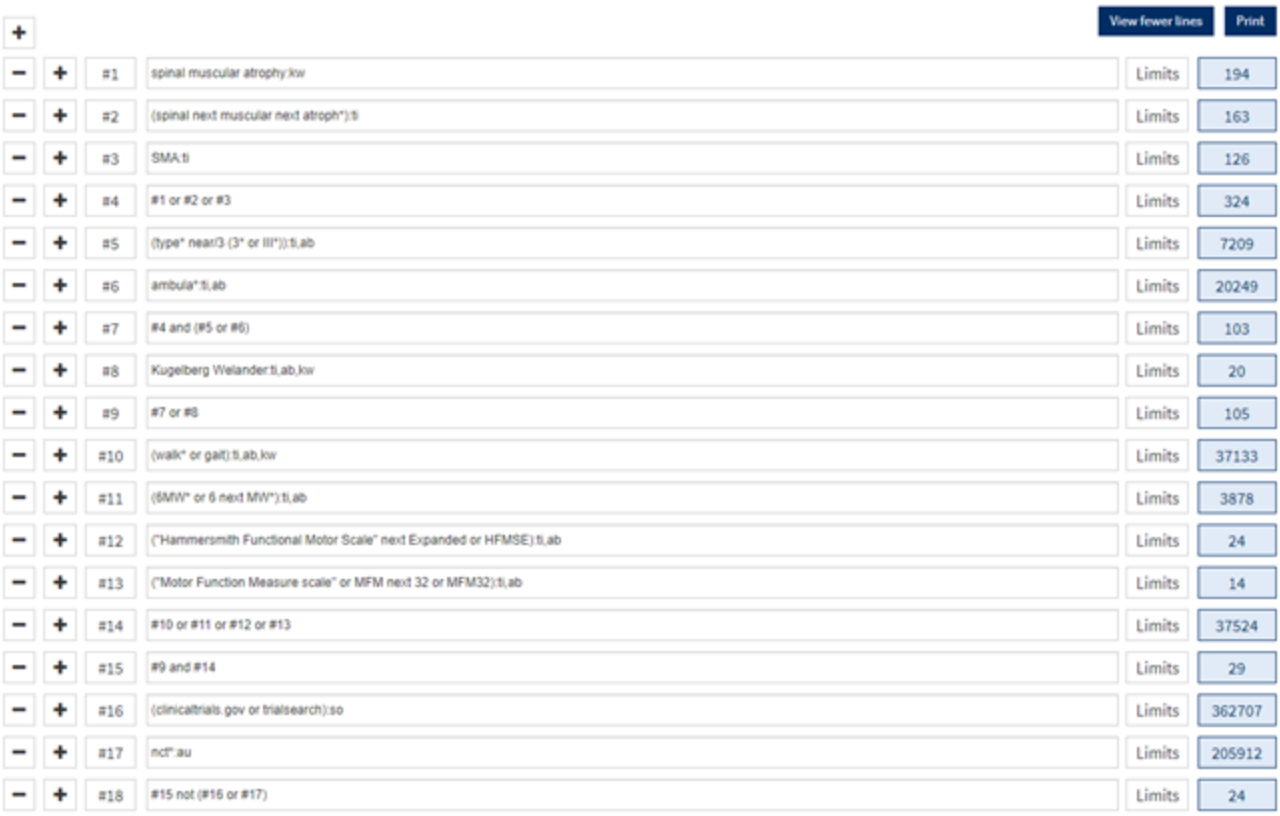
Table A1 Inclusion and exclusion criteria	
Inclusion criteria	**Population:** Patients with SMA type 3 who have maintained walking function. **Intervention**: Risdiplam (dosage according to SmPC) **Comparator:** No disease-modifying treatment **Outcomes:** At least one critical or important effect measure relevant for protocol: ● HFMSE ● MFM-32 ● 6MWT ● SAE ● Treatment discontinuation due to AEs ● QoL **Study design:** Randomised trials, observational studies **Language restrictions:** English **Other search limits or restrictions applied:** **Publication Date:** Year of publication 2010 – 2021 **Human/animal:** Human only
Exclusion criteria	**Population:** Populations irrelevant to protocol **Intervention:** Intervention irrelevant to protocol **Comparator:** N/A **Outcomes:** Outcome(s) out of PICO scope **Study design:** Case Reports, Comments, Editorials, Guidelines, Letters, News, Review articles, In vitro studies. **Language restrictions:** Other than English **Other search limits or restrictions applied:** **Publication Date:** Outside date limits **Human/animal:** Veterinary

Databases and search strategy

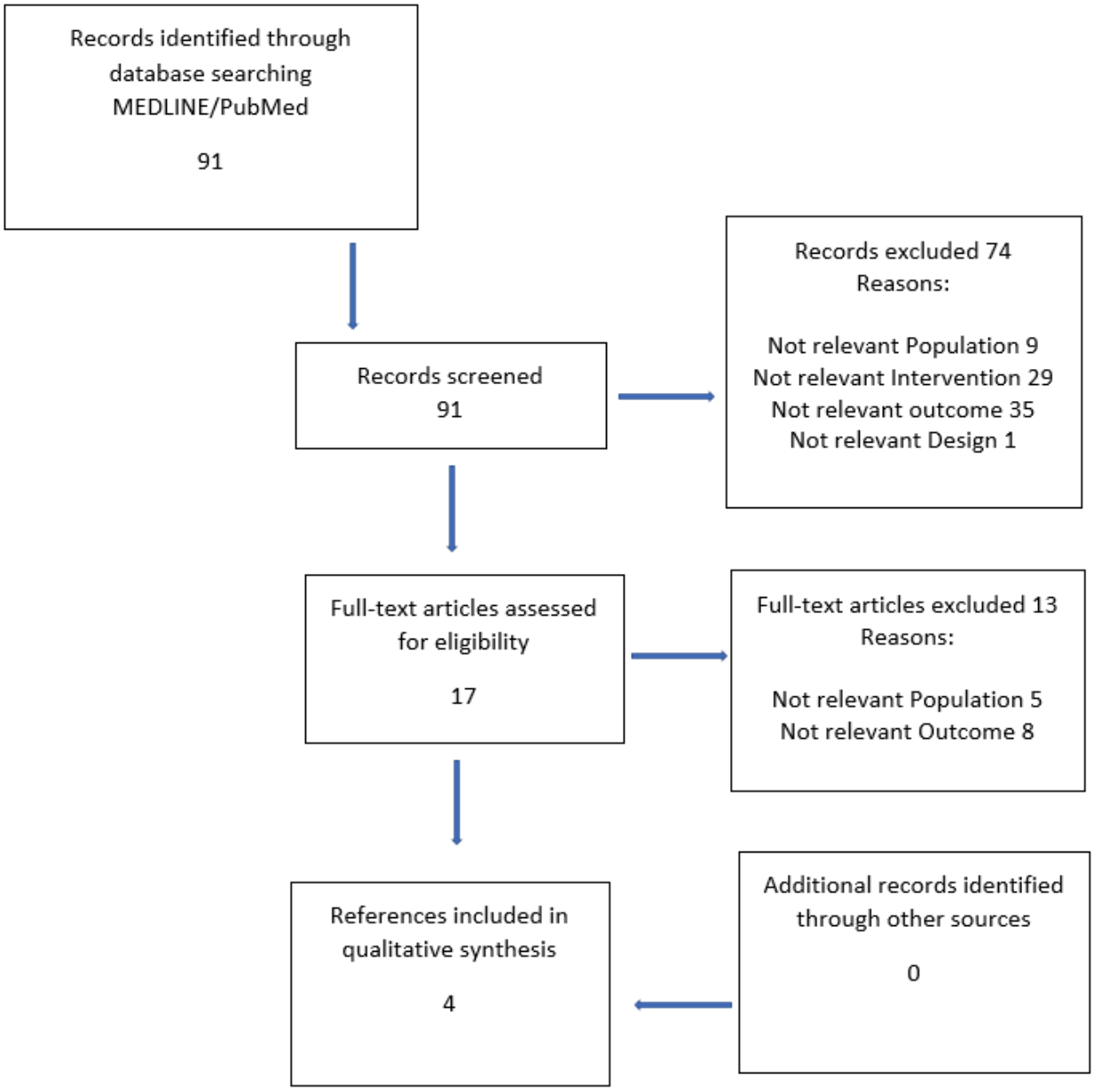
Figure S1 Screenshot of the Search Builder in PubMed.

Search	Actions	Details	Query	Results	Time
#19	···	>	Search: **#16 AND #17 AND #18**	91	11:18:05
#18	···	>	Search: **("2010/01/01"[Date - Publication] : "3000"[Date - Publication])**	12,388,429	11:17:53
#17	···	>	Search: **english[la] AND hasabstract**	20,122,566	11:17:20
#16	···	>	Search: **#14 NOT #15**	116	11:17:05
#15	···	>	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]**	6,767,783	11:16:34
#14	···	>	Search: **#9 AND (#10 OR #11 OR #12 OR #13)**	149	11:16:23
#13	···	>	Search: **Motor Function Measure scale[tiab] OR MFM-32[tiab] OR MFM32[tiab]**	32	11:16:13
#12	···	>	Search: **Hammersmith Functional Motor Scale Expanded[tiab] OR Expanded Hammersmith Functional Motor Scale[tiab] OR HFMSE[tiab]**	59	11:16:01
#11	···	>	Search: **6MWT[tiab] OR 6-MWT[tiab] OR 6MWD[tiab] OR 6-MWD[tiab]**	5,251	11:15:51
#10	···	>	Search: **Walking[mh] OR Walk Test[mh] OR Walking Speed[mh] OR Gait[mh] OR Gait Analysis[mh] OR walk*[tiab] OR gait[tiab]**	169,161	11:15:40
#9	···	>	Search: **#7 OR #8**	1,040	11:15:29
#8	···	>	Search: **Kugelberg-Welander*[tiab]**	210	11:15:19
#7	···	>	Search: **#4 AND (#5 OR #6)**	868	11:15:06
#6	···	>	Search: **ambula*[tiab]**	109,249	11:14:57
#5	···	>	Search: **type*[tiab] AND (3[tiab] OR 3A[tiab] OR 3A[tiab] OR III[tiab] OR IIIA[tiab] OR IIIB[tiab] OR IIIs[tiab])**	853,749	11:14:46
#4	···	>	Search: **#1 OR #2 OR #3**	6,627	11:14:15
#3	···	>	Search: **SMA[ti]**	1,121	11:14:04
#2	···	>	Search: **spinal muscular atroph*[ti]**	3,248	11:12:30
#1	···	>	Search: **Spinal Muscular Atrophies of Childhood[mh] OR Muscular Atrophy, Spinal[mh:noexp]**	5,117	11:12:17

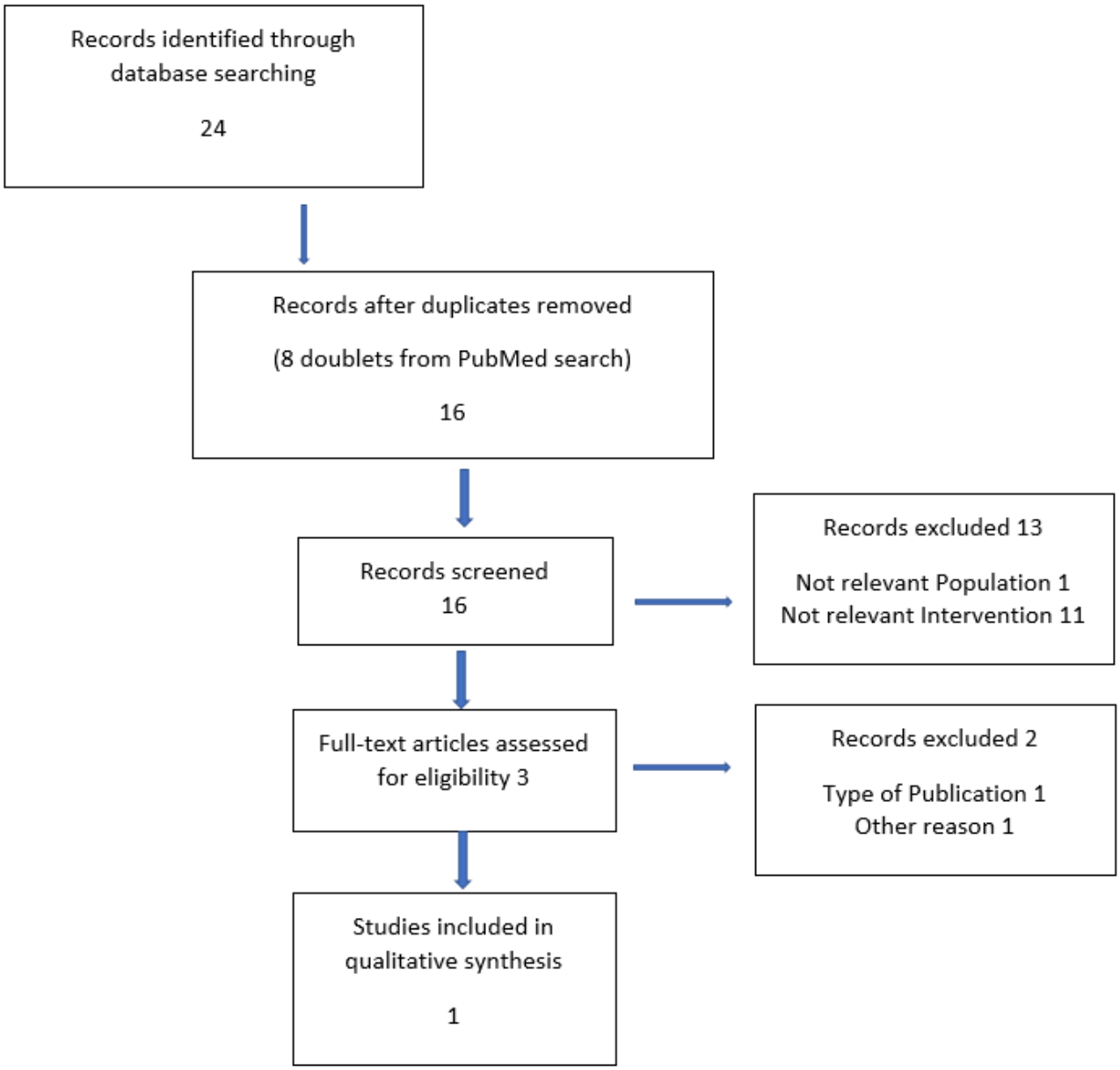
Figure S2 Screenshot of the Search Builder in CENTRAL (via Cochrane Library).



PRISMA Flow Diagram for PubMed Literature Search

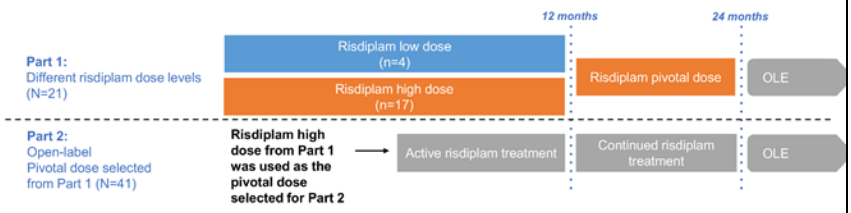


PRISMA Flow Diagram for CENTRAL (via Cochrane Library) Literature Search



8.2 Main characteristics of included studies

Note that tables have been created for the four main studies in the assessment (FIREFISH, SUNFISH, ENDEAR and CHERISH). The three studies included on natural history data use smaller subsets of the studies (ambulatory SMA 3 patients), and these studies and subsets are described in tables under clinical questions 4.

Table A2a Main study characteristics	
Trial name	FIREFISH
NCT number	NCT02913482
Objective	FIREFISH is a multicenter, single-arm, open-label study to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of risdiplam in symptomatic infants with Type 1 SMA (aged 1 to 7 months at enrollment).
Publications – title, author, journal, year	Risdiplam in Type 1 spinal muscular atrophy, **Baranello et al.**, N Eng J Med. 2021 Mar 11;384(10):915-923. doi10.1056/NEJMoa2009965. Epub 2021 Feb 24 (Part 1). Efficacy and safety of risdiplam in Type 1 spinal muscular atrophy, **Darras et al**. (Part 2). Submitted.
Study type and design	**Part 1** of FIREFISH is an open-label, dose-escalation study in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment) to select the dose for Part 2 based on safety, pharmacokinetics (PK), and pharmacodynamics (PD) data. **Part 2** of FIREFISH is an open-label, single-arm study over a 24-month treatment period, in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment), to assess the efficacy of risdiplam at the dose selected in Part 1. The primary analysis of Part 2 was conducted at 12 months of treatment. A single-arm, open-label study design was considered justified on ethical grounds and also in the context of the choice of the primary endpoint (proportion of infants sitting without support after 12 months of treatment), which is minimally subject to bias, and the known natural history of this endpoint (and developmental milestones) within the study population, as defined by the inclusion and exclusion criteria for this study.
Follow-up time	

<table>
<tr><td>Population (inclusion and exclusion criteria)</td><td>
<table>
<tr><td rowspan="2"> 
FIREFISH
Type 1 SMA</td><td>Inclusion criteria</td><td>• Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of SMN1.
• Clinical history, signs or symptoms attributable to Type 1 SMA after 28 days but prior to 3 months.
• Adequate nutrition at time of enrollment (with or without gastrostomy).
• Two copies of the SMN2 gene.</td></tr>
<tr><td>Exclusion criteria</td><td>• Concomitant or previous participation in an SMN2 targeting or gene therapy study.
• Participants requiring invasive ventilation or tracheostomy.
• Participants requiring awake non-invasive ventilation or with awake hypoxemia (SaO2˚<95%) with or without ventilator support.
• Hospitalization for a pulmonary event within the last 2 months or planned at the time of screening.
• Recent history (<6 months) of ophthalmologic disease.</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Part 1: Risdiplam - dose escalation study. Starting dose for first patient 0.00106 mg/kg. Dose level 1, target exposure AUC0-24h,ss 700 ng h/mL. Dose level 2, target exposure not exceeding the exposure cap of 2000 ng h/mL AUC0-24h,ss.

Part 2: Risdiplam starting dose levels:
Infants >1 month and below 3 months old at enrollment: 0.04 mg/kg.
Infants at least 3 months but below 5 months old at enrollment: 0.08 mg/kg.
Infants 5 months old or older at enrollment: 0.2 mg/kg.

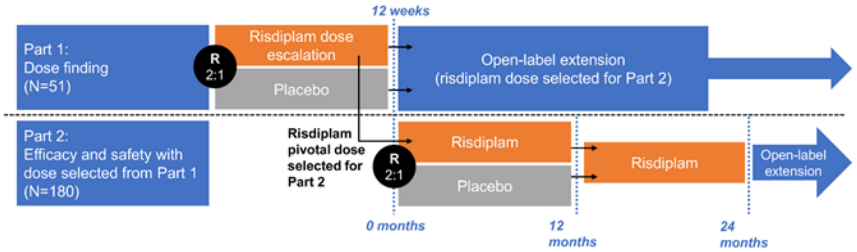
The dose was adjusted to a dose of 0.2 mg/kg within 1 – 2 months after enrollment into the study based on target exposure of mean 2000 ng h/mL AUC0-24h,ss.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th></th><th>FIREFISH (Part 2)</th></tr>
<tr><td>Characteristic</td><td>Risdiplam (n = 41)</td></tr>
<tr><td>Female sex – number (%)</td><td>22 (53.7%)</td></tr>
<tr><td>Age at enrollment, months, median (range)</td><td>5.32 (2.2–6.9)</td></tr>
<tr><td>Age at symptom onset, months, median (range)</td><td>1.45 (1.0–3.0)</td></tr>
<tr><td>Age at diagnosis of SMA, months, median (range)</td><td>2.79 (0.9–6.1)</td></tr>
<tr><td>Disease duration, months, median (range)</td><td>3.38 (1.0–6.0)</td></tr>
<tr><td>SMN2 copy number – number (%)</td><td></td></tr>
<tr><td>2</td><td>41 (100%)</td></tr>
<tr><td>CHOP-INTEND score, median (range)</td><td>22.0 (8.0–37.0)</td></tr>
<tr><td>BSID-III Gross Motor Scale total raw score, median (range)</td><td>2.0 (0.0–8.0)</td></tr>
<tr><td>HINE-2 score, median (range)</td><td>1.00 (0.0–5.0)</td></tr>
<tr><td colspan="2">BSID-III, Bayley scales of infant and toddler development – third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neurological Examination Module 2; SD, standard deviation; SMA, spinal muscular atrophy</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>The primary objectives for the study are as follows:

Part 1</td></tr>
</table>

	• To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in infants with Type 1 SMA, and to select the dose for Part 2. **Part 2** • To assess the efficacy of risdiplam measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the gross motor scale (defined as sitting without support for 5 seconds). Secondary objectives for **Part 2** of this study are as follows: • To assess the safety and tolerability of oral treatment with risdiplam. • To assess the pharmacokinetics of risdiplam. • To assess the PD effects of risdiplam (SMN2 mRNA, SMN protein). • To evaluate at 12 months of treatment with risdiplam the effect on motor development milestones, such as head control and rolling, as measured in the BSID-III gross motor scale. • To evaluate at 24 months of treatment with risdiplam the effect on sitting without support for 5 seconds and further motoHammersmith Infant Neurological Examination Module 2 (r development milestones, such as sitting without support for 30 seconds, crawling, standing alone, and walking, as measured in the BSID-III gross motor scale. • To assess the achievement of motor milestones at 12 and 24 months of treatment with risdiplam, as measured by the HINE-2). • To evaluate the proportion of infants who achieve a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at 12 months of treatment. • To evaluate the proportion of infants who achieve an increase of at least 4 points on their CHOP-INTEND score from baseline at 8 and 12 months of treatment. • To evaluate the proportion of infants who achieve head control at 8, 12, and 24 months of treatment (defined as a score of 3 or higher for item 12 of the CHOP-INTEND). • To assess the change from baseline in the total raw score of the BSID-III gross motor scale at 12 and 24 months of treatment. • To assess the proportion of infants who achieve a reduction of at least 30 degrees in phase angle at 12 months of treatment measured by respiratory plethysmography (RP). • To evaluate the proportion of infants who do not require invasive or non-invasive respiratory (e.g., bilevel positive airway pressure [BiPAP]) support at 12 and 24 months of treatment. • To assess at 12 and 24 months of treatment the proportion of infants who are alive without permanent ventilation, as defined by 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 or tracheostomy. • To assess the impact of treatment with risdiplam on time-to-event (death, permanent ventilation).
Method of analysis	For Part 2 of FIREFISH, the intention-to-treat population is the primary analysis population for all efficacy analyses, with the exception of weight-for-age and length/height-for-age percentiles, which were analyzed based on the safety population. As with Part 1, efficacy results from Part 2 were compared to, and put into context with, data describing the natural history of untreated infants with Type 1 SMA: in Part 2, hypothesis testing was used to compare efficacy endpoints with pre-defined performance criterion.

Subgroup analyses	Subgroup analyses were planned for the primary efficacy endpoint of the proportion of infants sitting without support for 5 seconds at Month 12 and the secondary efficacy endpoint of time to death or permanent ventilation. Subgroup analyses were also performed for the secondary efficacy endpoint of the proportion of infants who achieve a CHOP-INTEND score of 40 or higher at Month 12. Analyses were planned for the following subgroups: ● Age at enrollment (<5 months, >5 months) ● Sex ● Race/ethnicity ● Region (Europe, rest of world, and USA/Canada) ● Baseline CHOP-INTEND score (<median score, > median score) ● Baseline CMAP amplitude (1mV, 1mV [not performed because no patients had CMAP 1mV) ● Time between first treatment and onset of symptoms (<3 months, >3 months)

Table A2b Main study characteristics	
Trial name	SUNFISH
NCT number	NCT02908685
Objective	Multi-center, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of Risdiplam in adult and pediatric participants with Type 2 and Type 3 SMA. The study consists of two parts, an exploratory dose finding part (Part 1) of Risdiplam for 12 weeks and a confirmatory part (Part 2) of Risdiplam for 24 months.
Publications – title, author, journal, year	Risdiplam in Type 2 and non-ambulant Type 3 Spinal Muscular Atrophy, Mercuri et al. Submitted.
Study type and design	Part 1 of SUNFISH is a double-blind, randomized (2:1 risdiplam:placebo), exploratory, dose-finding study in patients with Type 2 and Type 3 (ambulant and non-ambulant) SMA to select the dose for Part 2 based on safety, PK, and PD. Part 2 is double-blind, placebo-controlled, and randomized (2:1 risdiplam:placebo), and investigates the efficacy and safety of risdiplam at the selected dose from Part 1 over a 24 month treatment period, in patients with Type 2 or Type 3 SMA (non-ambulant only, in order to minimize variability in changes in motor function and thereby increase the likelihood of detecting a treatment effect) aged 2 to 25 years. The primary analysis of Part 2 was conducted at the end of the 12 month randomized, double-blind risdiplam vs placebo period (i.e., before all patients

	completed the 24 month treatment period). Use of a placebo-control was considered necessary for a robust assessment of the safety, tolerability, and efficacy of risdiplam, especially given the variability of disease status and disease progression across patients. In order to limit the length of time that patients received placebo, all patients enrolled in SUNFISH were switched to active treatment as soon as possible according to the design of each part of the study.
Follow-up time	
Population (inclusion and exclusion criteria)	**Inclusion and exclusion criteria:** **Type 2/3 SMA** **Key inclusion criteria[34]** **Part 1 (N=51)** • Type 2 or ambulant and non-ambulant Type 3 SMA. • Confirmed genetic diagnosis of SMA. **Part 2 (N=180)** • Type 2 or non-ambulantType 3 SMA. • Confirmed genetic diagnosis of SMA. **Key exclusion criteria[34]** • Previous participation in an *SMN2* targeting study or gene therapy study. • Planned (within 18 months) or previous (within 1 year prior to study) surgery for scoliosis or hip fixation. SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Intervention	**Part 1**: 51 patients were enrolled in five cohorts in a staggered dose escalating design. Patients were randomized to either placebo or risdiplam at initially assigned doses of 0.02, 0.05 and 0.25 mg/kg for the age group of 2-11 years, and 3 and 5 mg for the age group of 12-25 years once daily. After patients in Part 1 completed the minimum 12-week double-blind treatment period, patients on placebo were switched to risdiplam at the dose tested in their cohort until the Independent Monitoring Committee selected the dose for Part 2. **Part 2:** 180 patients were randomised (2:1) to receive either risdiplam (at the pivotal dose of 5 mg once daily for patients with a body weight [BW] 20 kg or 0.25 mg/kg for patients with a BW 20 kg) or placebo. Randomization was stratified by age group (25 years, 611 years, 1217 years, and 1825 years at randomization). No more than 30 patients were to be randomized into the 1825 years age group. A minimum of 45 patients were to be randomized into each of the other three age groups. Patients from Part 1 were not included in Part 2.
Baseline characteristics	Patient characteristics at baseline of Risdiplam in patients with Type 2 or Type 3 SMA (SUNFISH Part 1) compared with a Natural History Cohort:

	SUNFISH (Part 1)	Natural history cohort (NatHis SMA)
Characteristic	**Risdiplam (N = 51)**	**(N = 81)**
Female sex, number (%)	27 (52.9)	44 (54.3)
Age at screening, years, median (range)	7 (2–24)	7.1 (2.1–29.8)
SMA Type, number (%)		
Type 2	37 (72.5)	53 (65)
Type 3	14 (27.5)	28 (35)
SMN2 copy number, number (%)		
1	–	
2	1 (2.0)	–
3	46 (90.2)	–
4	4 (7.8)	–
Unknown	–	–
Motor function at baseline n (%)		
Walkers	7 (13.7)	19 (23.5)
Sitters	33 (64.7)	Type 2 only
Non-sitters	11 (21.6)	19 (23.5)
Scoliosis, number (%)	29 (57)	45 (55.6)
HFMSE score, mean (SD)	17.45 (16.82)	–
MFM-32 total score, mean (SD)	42.85 (14.99)	52.0 (22.3) (N = 48)
RULM score, mean (SD)	18.47 (8.24)	–

Patient characteristics at baseline in a Study of Risdiplam in patients with Type 2 or Type 3 SMA (SUNFISH Part 2):

Baseline characteristic	Risdiplam (n = 120)	Placebo (n = 60)	Total (n = 180)

Age at screening, median (IQR), years	9.0 (5–14)	9.0 (5–14)	9.0 (5–14)
Age group at screening, n (%)			
2–5 years	37 (30.8%)	18 (30.0%)	55 (30.6%)
6–11 years	37 (32.5%)	18 (30.0%)	57 (31.7%)
12–17 years	30 (25.0%)	16 (26.7%)	46 (25.6%)
18–25 years	14 (11.7%)	8 (13.3%)	22 (12.2%)
Gender, n (%)			
Male	59 (49.2%)	30 (50.0%)	89 (49.4%)
Female	61 (50.8%)	30 (50.0%)	91 (50.6%)
SMA type, n (%)			
Type 2	84 (70.0%)	44 (73.3%)	128 (71.1%)
Type 3	36 (30.0%)	16 (26.7%)	52 (28.9%)
SMN2 copy number			
2	3 (2.5%)	1 (1.7%)	4 (2.2%)
3	107 (89.2%)	50 (83.3%)	157 (87.2%)
4	10 (8.3%)	8 (13.3%)	18 (10.0%)
Unknown	0 (0%)	1 (1.7%)	1 (0.6%)
Age at onset of symptoms, mean (SD), months	14.1 (8.4)	18.5 (21.1)	15.5 (14.1)
Number (%) of patients with scoliosis	76 (63.3%)	44 (73.3%)	120 (66.7%)
Number (%) of patients who had surgery for scoliosis before screening	29 (24.2%)	17 (28.3%)	46 (25.6%)
MFM-32 Total Score, median (min, max)	46.88 (16.7, 71.9)	47.92 (17.7, 71.9)	–
RULM Total Score, median (min, max)	19.00 (3.0, 36.0)	20.00 (9.0, 38.0)	–
HFMSE Total Score, median (min, max)	14.00 (0.0, 48.0)	13.00 (2.0, 43.0)	–

Primary and secondary endpoints

<u>The primary objectives of the study are as follows:</u>

Part 1:
To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA, and to select the dose for Part 2 of the study.

Part 2:
To evaluate the efficacy of risdiplam compared with placebo in terms of motor function in patients with Type 2 SMA and non-ambulant Type 3 SMA, as assessed by the change from baseline in the total score of the Motor Function Measure (MFM) at 12 months.

<u>Secondary objectives for Part 2 are as follows:</u>

- To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD to include SMN2 mRNA and SMN protein).
- To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by the Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), and responder analyses of the MFM.

	• To investigate the efficacy of 12-month treatment with risdiplam in terms of respiratory function as assessed by Sniff Nasal Inspiratory Pressure (SNIP) and, in patients aged 6 years and older, by maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and peak cough flow (PCF). • To investigate the proportion of patients who experience a pre-specified disease-related adverse event by Month 12. • To investigate the efficacy of 12-month treatment with risdiplam in terms of global health status as assessed by the Clinical Global Impression of Change (CGI-C). • To investigate the efficacy of 12-month treatment with risdiplam in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS). • To investigate the safety and tolerability of risdiplam treatment.
Method of analysis	For **Part 1 of SUNFISH**, the intention-to-treat population (defined as all patients randomized regardless of whether they received treatment or not) is the primary analysis population for all efficacy analyses. Efficacy analyses are presented descriptively at each time point by age group (2–11 and 12–25 years). For **Part 2 of SUNFISH**, the intention-to-treat population is the primary analysis population for all efficacy analyses.
Subgroup analyses	Subgroup analyses were explored for the following groups: • Age group (2–5, 6–11, 12–17, and 18–25 years at randomization) • Disease severity (Patient with MFM32 baseline total score below and equal to the first quartile ≤ Q1 (i.e., ≤ 25th percentile), above the first quartile and below or equal to the third quartile > Q1 to ≤ Q3 (i.e., > 25th percentile and ≤ 75th percentile) and above the third quartile >Q3 (i.e., > 75th percentile) • SMA type (Type 2, Type 3) • Region (North America, Europe, China, Japan, rest of the world) • SMN2 Copy number (< 2, 2, 3, ≥ 4 copies, unknown) from genotype analysis

Table A2c Main study characteristics

Trial name	ENDEAR
NCT number	NCT02193074
Objective	Assess the clinical efficacy and safety of nusinersen in infants who had received a genetic diagnosis of spinal muscular atrophy, had two copies of SMN2, and had had onset of symptoms at 6 months of age or younger
Publications – title, author, journal, year	Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy, Finkel et al., NEJM, 2017
Study type and design	Randomized, double-blind, sham-controlled, phase 3 efficacy and safety trial of nusinersen in infants with spinal muscular atrophy. Eligible infants were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen (nusinersen group) or a sham procedure (control group). To maintain blinding, nusinersen was administered or the sham procedure was performed by trial personnel who were aware of the group assignments, whereas the infant's parents and key trial personnel who were responsible for assessments were unaware of the group assignments
Follow-up time	The ENDEAR trial was terminated early because of the results of the interim analysis and ethical consideration for the infants in the control group. Not all the patients underwent the assigned procedure for 13 months; for many end points, data obtained on day 183, 302, or 394 were used for the final analysis

Population (inclusion and exclusion criteria)	Age eligible: up to 210 days Criteria Key Inclusion Criteria: ● 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 Key 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
Intervention	Intrathecal administration of nusinersen (nusinersen group) or a sham procedure (control group). The nusinersen dose was adjusted according to the estimated volume of cerebrospinal fluid for the infant's age on the day of dosing, such that the infant received a dose that was equivalent to a 12-mg dose in a person 2 years of age or older; thus, younger infants were injected with smaller volumes that contained lower doses of the drug. 81 were assigned to the nusinersen group, and 41 to the control group.

Baseline characteristics

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]

Primary and secondary endpoints	**Table 2. Primary and Secondary End Points.*** **End Point** / **Nusinersen Group** / **Control Group** / **Hazard Ratio (95% CI)** / **P Value** *no./total no. (%)* **Primary end points** Motor-milestone response† Interim analysis: 21/51 (41) / 0/27 / — / <0.001 Final analysis: 37/73 (51) / 0/37 / — / — No death or use of permanent assisted ventilation‡: 49/80 (61) / 13/41 (32) / 0.53 (0.32–0.89) / 0.005 **Secondary end points§** CHOP INTEND response¶: 52/73 (71) / 1/37 (3) / — / <0.001 No death: 67/80 (84) / 25/41 (61) / 0.37 (0.18–0.77) / 0.004 No use of permanent assisted ventilation‡: 62/80 (78) / 28/41 (68) / 0.66 (0.32–1.37) / 0.13 CMAP response‖: 26/73 (36) / 2/37 (5) / — / — No death or use of permanent assisted ventilation among those with disease duration ≤13.1 wk at screening‡: 30/39 (77) / 7/21 (33) / 0.24 (0.10–0.58) / — No death or use of permanent assisted ventilation among those with disease duration >13.1 wk at screening‡: 19/41 (46) / 6/20 (30) / 0.84 (0.43–1.67) / —
Method of analysis	The difference between the nusinersen group and the control group in the proportion of infants who had a motor-milestone response was analyzed with the use of Fisher's exact test. Event-free survival and overall survival were assessed with the use of a log-rank test that was stratified according to disease duration at screening (≤12 weeks or >12 weeks). The median time to death or the use of permanent assisted ventilation in each group and associated 95% confidence intervals were estimated with the use of the Kaplan–Meier product-limit method; probability of survival was estimated with the use of the Kaplan–Meier method. A hazard ratio for death or the use of permanent assisted ventilation and a hazard ratio for death were calculated with the use of a Cox proportional-hazards model that was adjusted for disease duration at screening in each infant.
Subgroup analyses	1. Time to Death or Permanent Ventilation in the Subgroup of Participants Below the Study Median Disease Duration [Time Frame: Day 91, Day 182, Day 273, Day 364, Day 394] Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) among participants below the study median disease duration (13.1 weeks), by given duration thresholds, based on the Kaplan-Meier product-limit method. 2. Time to Death or Permanent Ventilation in the Subgroup of Participants Above the Study Median Disease Duration [Time Frame: Day 91, Day 182, Day 273, Day 364, Day 394] Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) among participants above the study median disease duration (13.1 weeks), by given duration thresholds, based on the Kaplan-Meier product-limit method.

Table A2d Main study characteristics	
Trial name	CHERISH
NCT number	NCT02292537
Objective	Evaluate the efficacy and safety of nusinersen administered intrathecally in children with later- onset SMA.
Publications – title, author, journal, year	Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy, Mercuri et al., NEJM, 2018
Study type and design	Multicenter, randomized, double-blind, sham-controlled, phase 3 trial. Investigators collected the data, which were held and analyzed by Biogen. The authors had access to the complete data set after unblinding, participated in data analysis and interpretation and in manuscript development, and vouch for the accuracy and completeness of the data.
Follow-up time	15 months

Population (inclusion and exclusion criteria)	Age Eligible: 2- 12 years Criteria Key Inclusion Criteria: ● 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 Key Exclusion Criteria: ● 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 OBS: More in - and exclusion criteria exist and can be found at https://clinicaltrials.gov/ct2/show/NCT02292537?term=nusinersen&draw=3&rank=14
Intervention	126 children with SMA who had symptom onset after 6 months of age. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274.

Baseline characteristics

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]

Primary and secondary endpoints	**Table 2. Primary and Secondary End Points Assessed at Month 15.***

End Point	Nusinersen (N=84)	Control (N=42)	Difference	P Value
Interim analysis†				
Primary end point: change from baseline in HFMSE score — least-squares mean (95% CI)‡	4.0 (2.9 to 5.1)	−1.9 (−3.8 to 0)	5.9 (3.7 to 8.1)	<0.001
Final analysis§				
Primary end point: change from baseline in HFMSE score — least-squares mean (95% CI)‡	3.9 (3.0 to 4.9)	−1.0 (−2.5 to 0.5)	4.9 (3.1 to 6.7)	—
Secondary end points				
Children with change in HFMSE score of ≥3 points				
% (95% CI)¶	57 (46 to 68)	26 (12 to 40)	30.5 (12.7 to 48.3)	
Odds ratio (95% CI)	—	—	6 (2 to 15)‖	<0.001
Children who achieved ≥1 new WHO motor milestone				
No.	13	2	—	—
% (95% CI)**	20 (11 to 31)	6 (1 to 20)	14 (−7 to 34)	0.08
Change from baseline in number of WHO motor milestones achieved — least-squares mean (95% CI)‡	0.2 (0.1 to 0.3)	−0.2 (−0.4 to 0)	0.4 (0.2 to 0.7)	—
Change from baseline in RULM score — least-squares mean (95% CI)‡	4.2 (3.4 to 5.0)	0.5 (−0.6 to 1.6)	3.7 (2.3 to 5.0)	—
Children who achieved ability to stand alone				
No.	1	1	—	—
% (95% CI)**	2 (0 to 8)	3 (0 to 15)	−1 (−22 to 19)	—
Children who achieved ability to walk with assistance				
No.	1	0	—	—
% (95% CI)**	2 (0 to 8)	0 (0 to 10)	2 (−19 to 22)	—

Method of analysis	The prespecified interim analysis of the primary endpoint was performed in the intention to-treat population, which included patients who were randomly assigned to a group and underwent at least one assigned procedure; this analysis was conducted when all the children had been enrolled for at least 6 months and at least 39 children had completed their 15-month assessment. Because some children would not have completed the 15-month assessment by the time of the interim analysis, the analysis was performed with the use of a multiple-imputation method to account for missing data on HFMSE scores obtained after baseline. Least-squares mean values are reported. In the final analysis, the least squares mean changes in the total HFMSE score, the number of WHO motor milestones achieved per child, and the RULM score and least-squares mean differences in change between groups were based on an analysis of covariance, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline.
Subgroup analyses	Age subgroups < 6 years and ≥6 years as well as disease duration < 25 months, ≥25 months and < 44 months and ≥44 months. Provided by waterfall plots in supplementary appendices.

8.3 Results per study

Table A3a Results of study FIREFISH											
Trial name:	FIREFISH Part 2										
NCT number:	NCT02913482										
				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	Risdiplam	41	92.7% (82.12-97.1%)	NA	NA	NA	NA	NA	NA	Summaries of time to death (median, percentiles) are Kaplan-Meier estimates of 12 months.	CCOD: 14 Nov 2019 EPAR [20]
Ventilation-free survival	Risdiplam	41	85.4% (73.4-92.2%)	NA	NA	NA	NA	NA	NA	Summaries of time to death or permanent ventilation (median, percentiles) are Kaplan-Meier estimates of 12 months.	CCOD: 14 Nov 2019 EPAR [20]

Permanent ventilation	Risdiplam	41	[redacted]	NA	NA	NA	NA	NA	NA	Summaries of time to permanent ventilation (median, percentiles) are Kaplan-Meier estimates.	CCOD: 14 Nov 2019 Data on file
CHOP-INTEND responders (increase of >= 4 points)	Risdiplam	41	90.2% (79.1-96.6%)	NA	NA	NA	NA	NA	NA	Patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at month 12	CCOD: 14 Nov 2019 EPAR [20]
Ability to sit without support	Risdiplam	41	[redacted]	NA	NA	NA	NA	NA	NA	Patients who achieve stable sit assessed by HINE-2 at month 12	CCOD: 14 Nov 2019 Data on file
Ability to stand or walk without support	Risdiplam	41	[redacted]	NA	NA	NA	NA	NA	NA	Patients who achieve standing unaided or walking independently assessed by HINE-2 at month 12	CCOD: 14 Nov 2019 Data on file
Serious adverse events	Risdiplam	41	58.5%	NA	NA	NA	NA	NA	NA	Multiple occurrences of the same AE in one individual are counted only once. 12-months data.	CCOD: 14 Nov 2019 Data on file
Discontinuation due to adverse event	Risdiplam	41	[redacted]	NA	NA	NA	NA	NA	NA	12-months data.	CCOD: 14 Nov 2019 Data on file

Table A3b Results of study ENDEAR											
Trial name:	ENDEAR										
NCT number:	NCT02193074										
				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	Nusinersen	80	67 (83.8%)	22.8%	NA	NA	HR: 0.37	0.18-0.77	0.004	Survival rates of 13 months were estimated from the Kaplan Meier curve for time to death based on the ITT set as determined by the EAC. Treatment groups were compared using the log-rank test stratified by the disease duration at screening. Median follow-up time 280 days (6 - 422) for nusinersen and 187 days.	CCOD: Dec 16 2016 Finkel et al. 2017 [10]
	Control	41	25 (61.0%)								

Ventilation-free survival	Nusinersen	80	49 (61.3%))	29.6%	NA	NA	HR: 0.53	0.32-0.89	0.005	Analysis compared the time to death or permanent ventilation between groups using the log-rank test. The median time to death or permanent ventilation in each group and associated 95% CIs were estimated using the Kaplan-Meier product-limit method. The proportion of infants with an event was estimated based on the Kaplan-Meier curve at 13 months. A hazard ratio (HR) was calculated using a Cox proportional hazards model. Median follow-up time 280 days (6 - 422) for nusinersen and 187 days.	CCOD:Dec 16 2016 Finkel et al. 2017 [10]
	Control	41	13 (31.7%)								
Permanent ventilation	Nusinersen	80	18 (22.5%)	-9.2%	NA	NA	HR: 0.66	0.32-1.37	0.13	The proportion of infants not requiring permanent ventilation at month 13 was estimated from the probability of requiring permanent ventilation from the Kaplan-Meier curve of the time to permanent ventilation, i.e., the Kaplan-Meier product-limit estimator. Treatment groups were compared using the log-rank	CCOD: Dec 16 2016 Finkel et al. 2017 [10]
	Control	41	13 (31.7%)								

									test stratified by disease duration at screening	
CHOP-INTEND responders (increase of >= 4 points)	Nusinersen	73	52 (71.2%)	68.5	7.56-491.9	NA	RR: 26.36	3.80-183.2	<0.001	A CHOP-INTEND response was defined as an increase of at least 4 points from baseline at the end-of-trial visit (day 183, 302, or 394). The proportion of responders was compared using logistic regression (Fisher's exact test in the situation of <5 responders in either group). RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD: Dec 16 2016 Finkel et al. 2017 [10]
	Control	37	1 (2.7%)							
Ability to sit without support	Nusinersen	73	6 (8.2%)	8.2%	NA	NA	RR: 6.68	0.39-115.40	0.19	The HINE-2 motor milestone ability to sit without support at the later of days 183, 302, and 394. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD:Dec 16 2016 Finkel et al. 2017 [10]
	Control	37	0							

Standing with support and unaided	Nusinersen Control	73 1 37 0	0	NA	NA	RR: 1.52	0.06-36.43	0.80	The HINE-2 motor milestone ability to stand or walk without support at the later of days 183, 302, and 394. RR is calculated using MedCalc's Relative risk calculator.	CCOD:Dec 16 2016 Finkel et al. 2017 [10]
Serious adverse events	Nusinersen Control	80 61 (72.3%) 41 33 (80.5%)	-4.03	-17.7-12.1	NA	RR: 0.95	0.78-1.15	0.546	RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group. Median follow-up time 280 days (6 - 422) for nusinersen and 187 days.	CCOD: Dec 16 2016 Finkel et al. 2017 [10]
Discontinuation due to adverse event	Nusinersen Control	80 13 (16.3%) 41 16 (39.0%)	-22.6%	-30.4;-8.58	NA	RR: 0.42	0.22-0.78	0.006	RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group. Median follow-up time 280 days (6 - 422) for nusinersen and 187 days.	CCOD :Dec 16 2016 Finkel et al. 2017 [10]

Table A3c Results of study SUNFISH Part 2

Trial name:	SUNFISH Part 2
NCT number:	NCT02908685

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect: Difference	95% CI	*P* value	Estimated relative difference in effect: Difference	95% CI	*P* value	Description of methods used for estimation	References
Change from baseline in HFMSE *Subgroup: age 2-11*	Risdiplam	[redacted]	[redacted]	[redacted]			NA	NA	NA	MMRM analysis of the LS Mean change from baseline in HFMSE total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file
	Placebo	[redacted]	[redacted]								
Change from	Risdiplam	[redacted]	[redacted]	[redacted]			NA	NA	NA	MMRM analysis of the LS Mean change from baseline in	CCOD: Sep. 6 2019 Data on file

baseline in HFMSE *Subgroup: age 2-5*	Placebo	[redacted]					HFMSE total score at month 12 by age subgroup.	
Change from baseline in HFMSE *Subgroup: age 6-11*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in HFMSE total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file
Change from baseline in HFMSE *Subgroup: age 12-25*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in HFMSE total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file
Change from baseline in RULM *Subgroup: age 2-11*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in RULM total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file

Change from baseline in RULM *Subgroup: age 2-5*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in RULM total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file
Change from baseline in RULM *Subgroup: age 6-11*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in RULM total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file
Change from baseline in RULM *Subgroup: age 12-25*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in RULM total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file
Change from baseline in MFM-32 *Subgroup: age 12-25*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	MMRM analysis of the LS Mean change from baseline in MFM-32 total score at month 12 by age subgroup.	CCOD: Sep. 6 2019 Data on file

Serious AEs *Population ITT*	Risdiplam Placebo		Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 18.3%.	CCOD: Sep. 6 2019 Data on file
Serious AEs *Subgroup: age 2-11*	Risdiplam Placebo		Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 22.2%.	CCOD: Sep. 6 2019 Data on file
Serious AEs *Subgroup: age 2-5*	Risdiplam Placebo		Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 22.2%.	CCOD: Sep. 6 2019 Data on file

Serious AEs *Subgroup: age 6-11*	Risdiplam Placebo	[redacted]	[redacted]				Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 22.2%.	CCOD: Sep. 6 2019 Data on file
Serious AEs *Subgroup: age 12-25*	Risdiplam Placebo	[redacted]	[redacted]				Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 12.5%.	CCOD: Sep. 6 2019 Data on file
Discontinuation due to TRAEs *Population ITT*	Risdiplam Placebo	[redacted]	[redacted]				RR is calculated using MedCalc's Relative risk calculator.	CCOD: Sep. 6 2019 Data on file
Change from	Risdiplam	[redacted]	[redacted]	NA	NA	NA	Change from baseline at Week 52 in EQ-5D-L5, LS mean (SE) (95% CI) and difference from	CCOD: Sep. 6 2019

baseline at Week 52 *Subgroup: age 2-11*	Placebo	[redacted]					placebo (SE) (95% CI).	Data on file
Change from baseline at Week 52 *Subgroup: age 2-5*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	Change from baseline at Week 52 in EQ-5D-L5, LS mean (SE) (95% CI) and difference from placebo (SE) (95% CI).	CCOD: Sep. 6 2019 Data on file
Change from baseline at Week 52 *Subgroup: age 6-11*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	Change from baseline at Week 52 in EQ-5D-L5, LS mean (SE) (95% CI) and difference from placebo (SE) (95% CI).	CCOD: Sep. 6 2019 Data on file
Change from baseline at Week 52 *Subgroup: age 12-25*	Risdiplam Placebo	[redacted]	[redacted]	NA	NA	NA	Change from baseline at Week 52 in EQ-5D-L5, LS mean (SE) (95% CI) and difference from placebo (SE) (95% CI).	CCOD: Sep. 6 2019 Data on file

Table A3d Results of study CHERISH												
Trial name:	CHERISH											
NCT number:	NCT02292537											
				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**		
Least-squares mean in HFMSE *Population ITT*	Nusinersen	84	3.9 (3.0–4.9)	4.9	3.1–6.7	NR	NA	NA	NA	The endpoint was analyzed with the use of a multiple-imputation method. The least-squares mean change and least-squares mean difference in change between groups were based on an analysis of covariance, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11]
	Sham	42	-1.0 (-2.5–0.5)								

Change from baseline in HFMSE *Subgroup: age 2-5*	Nusinersen Sham	68 35	See Waterfall plots in supplementary appendix in Mercuri et al. 2018								Analysis of the change from baseline in HFMSE total score at month 9, 12 and 15 by age subgroup. Waterfall plot was based on children with nonmissing values at 12 months.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11], supp. appendix
Change from baseline in HFMSE *Subgroup: age 6-11*	Nusinersen Sham	9 6	See Waterfall plots in supplementary appendix in Mercuri et al. 2018								Analysis of the change from baseline in HFMSE total score at month 9, 12 and 15 by age subgroup. Waterfall plot was based on children with nonmissing values at 12 months.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11], supp. appendix
Least-squares mean in RULM *Population ITT*	Nusinersen Sham	84 42	4.2 (3.4-5.0) 0.5 (-0.6-1.6)	3.7	2.3–5.0	NR	NA	NA	NA		The endpoint was analyzed with the use of a multiple-imputation method. The least-squares mean change and least-squares mean difference in change between groups were based on an analysis of covariance, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11]

RULM *Subgroup: age 2-5*	Nusinersen Sham	68 35	See Waterfall plots in supplementary appendix in Mercuri et al. 2018							Analysis of the change from baseline in RULM total score at month 12 by age subgroup. Waterfall plot was based on children with nonmissing values at 12 months.	CCOD: Aug 31 2016. Mercuri et al. 2018,[11] supp. appendix
Change from baseline in RULM *Subgroup: age 6-11*	Nusinersen Sham	9 6	See Waterfall plots in supplementary appendix in Mercuri et al. 2018							Analysis of the change from baseline in RULM total score at month 12 by age subgroup. Waterfall plot was based on children with nonmissing values at 12 months.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11], supp. appendix
Serious AEs *Population ITT*	Nusinersen Sham	84 42	14 (17%) 12 (29%)	-12.2	-20.3-4.35	NA	RR: 0.58	0.30-1.15	0.12	RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11]
	Nusinersen	84	0	0	NA	NA	RR: 1.00	1.00-1.00	NA		

Discontinuation due to AEs *Population ITT*	Sham	42	0			RR is calculated using MedCalc's Relative risk calculator.	CCOD: Aug 31 2016. Mercuri et al. 2018 [11]

8.4 Results per PICO (clinical question 1)

Table A4a Results referring to clinical question 1

Results per outcome:		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Overall survival	[redacted]							The HR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The absolute difference and 95% confidence interval were estimated by applying the resulting HR and the ACR for nusinersen of 83.8% at 13 months [10]
Ventilation-free survival	[redacted]							The HR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The absolute difference and 95% confidence interval were estimated by applying the resulting HR and the ACR for nusinersen of 61.3% at 13 months [10]

Permanent ventilation	2	Narrative comparison			
CHOP-INTEND score improvement of ≥4 points					The OR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The RR was calculated by applying the OR and the ACR. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR for nusinersen of 71% at 13 months [10].
Ability to sit without support					The OR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The RR was calculated by applying the OR and the ACR. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 8% at 13 months [10] .
Ability to stand with support and unaided					The OR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The RR was calculated by

		applying the OR and the ACR. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 1% [10].
Serious adverse events		The OR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The RR was calculated by applying the OR and the ACR. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 76% [10]
Discontinuation due to adverse event		The OR and 95% CI were synthesized using MAIC analysis. FIREFISH patients were matched to the ENDEAR population on three prognostic and/or treatment predictive factors: age at first dose, disease duration and baseline CHOP-INTEND score. The RR was calculated by applying the OR and the ACR. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 16% [10].

8.5 Results per PICO (clinical question 2)

Table A4b Results referring to clinical question 2

Results per outcome:		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	**Difference**	**CI**	***P* value**	**Difference**	**CI**	***P* value**	
Change from baseline in HFMSE *Subgroup: age 2-11*	2	Narrative comparison						
Change from baseline in HFMSE *Subgroup: age 2-5*	2							Mean difference against comparator and 95% CIs were synthesized using Bucher ITC. A subset of patients with a HFMSE score ≥10 at baseline, and without severe scoliosis from SUNFISH part 2 were included in the analysis.
Change from baseline in HFMSE *Subgroup: age 6-9*	2							Mean difference against comparator and 95% CIs were synthesized using Bucher ITC. A subset of patients aged 6-9 with a HFMSE score ≥10 at baseline, and without severe scoliosis from SUNFISH part 2 were included in the analysis.

Change from baseline in RULM *Subgroup: age 2-9*	2		Mean difference against comparator and 95% CIs were synthesized using MAIC. A subset of patients aged 2-9 with a HFMSE score ≥10 at baseline, and without severe scoliosis from SUNFISH part 2 were included in the analysis.
Change from baseline in RULM *Subgroup: age 2-5*	2		Mean difference against comparator and 95% CIs were synthesized using Bucher ITC. A subset of patients with a HFMSE score ≥10 at baseline, and without severe scoliosis from SUNFISH part 2 were included in the analysis.
Change from baseline in RULM *Subgroup: age 6-9*	2		Mean difference against comparator and 95% CIs were synthesized using Bucher ITC. A subset of patients aged 6-9 with a HFMSE score ≥10 at baseline, and without severe scoliosis from SUNFISH part 2 were included in the analysis.
Serious AEs *Subgroup: age 2-9*	2		OR against comparator and 95% CIs were synthesized using Bucher ITC. A subset of patients aged 2-9 with a HFMSE score ≥10 at baseline, and without severe scoliosis from SUNFISH part 2 were included in the analysis. The RR was calculated by applying the OR and the rate for nusinersen of 17% in CHERISH [11] (RR: 1.18 (95% CI 0.29-3.18). The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 17% [11].

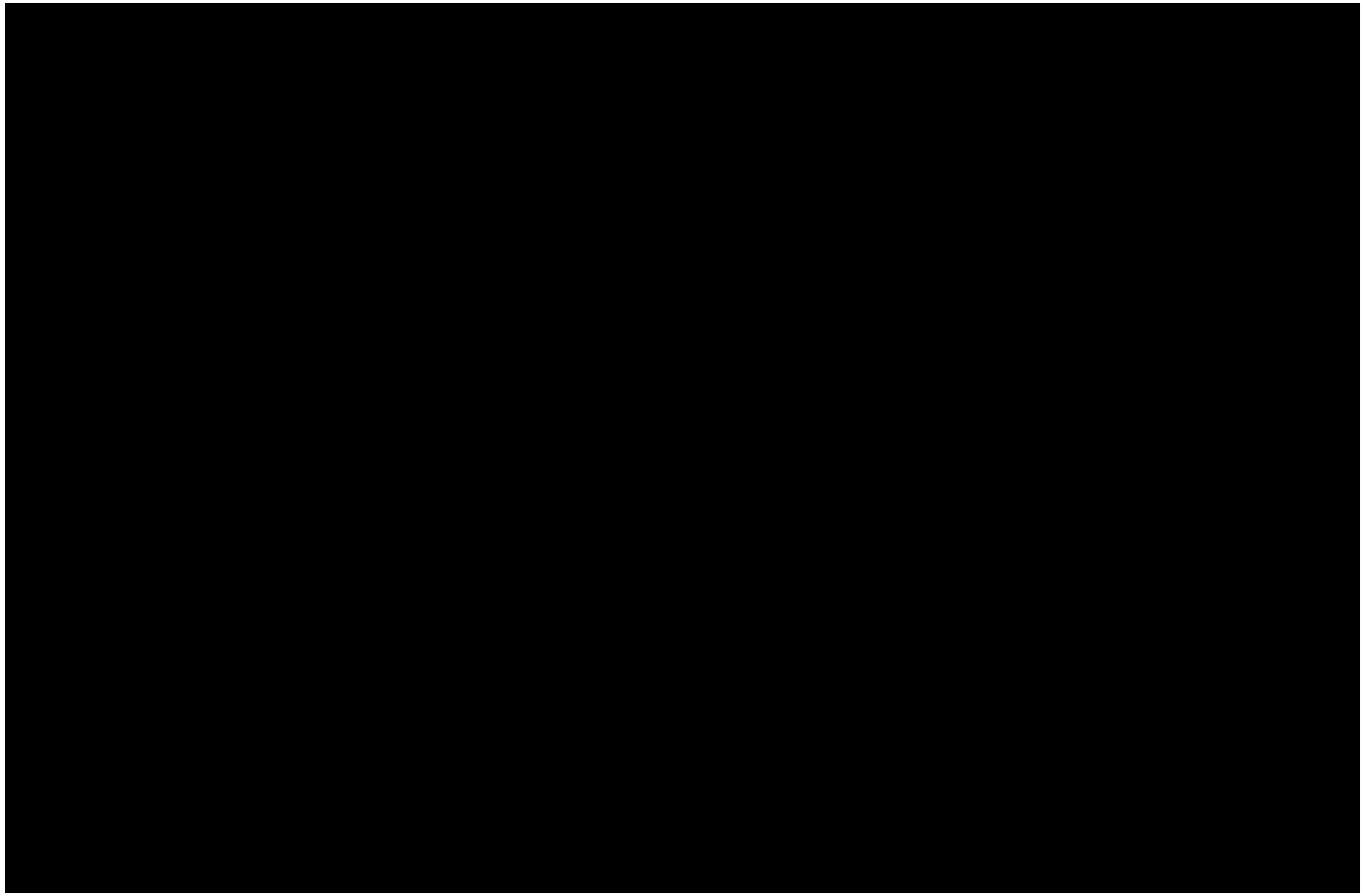
8.6 Results per PICO (clinical question 3)

Table A4c Results referring to clinical question 3								
Results per outcome:		Absolute difference in effect			Relative difference in effect			Methods used for quantitative synthesis
	Studies included in the analysis	Difference	CI	*P* value	Difference	CI	*P* value	
Change from baseline in HFMSE *Subgroup: age 12-25*	1							MMRM analysis of the LS Mean change from baseline in HFMSE total score at month 12 by age subgroup.
Change from baseline in RULM *Subgroup: age 12-25*	1							MMRM analysis of the LS Mean change from baseline in RULM total score at month 12 by age subgroup.
Change from baseline in MFM-32	1							MMRM analysis of the LS Mean change from baseline in MFM-32 total score at month 12 by age subgroup.

Subgroup: age 12-25				
Serious AEs *ITT*	1	[redacted]	[redacted]	Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR of 18.3%.
Serious AEs *Subgroup: age 12-25*	1	[redacted]	[redacted]	Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator. The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACRof 12.5%.
Discontinuation due to TRAEs *ITT*	1	[redacted]	[redacted]	Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator.
Discontinuation due to TRAEs *Subgroup: age 12-25*	1	[redacted]	[redacted]	Total number of patients who experienced ≥ 1 serious adverse event. RR is calculated using MedCalc's Relative risk calculator.

Change from baseline at Week 52 *Subgroup: age 12-25*	1	[redacted]	NA	NA	NA	Change from baseline at Week 52 in EQ-5D-L5, LS mean (SE) (95% CI) and difference from placebo (SE) (95% CI).

8.7 Additional analyses



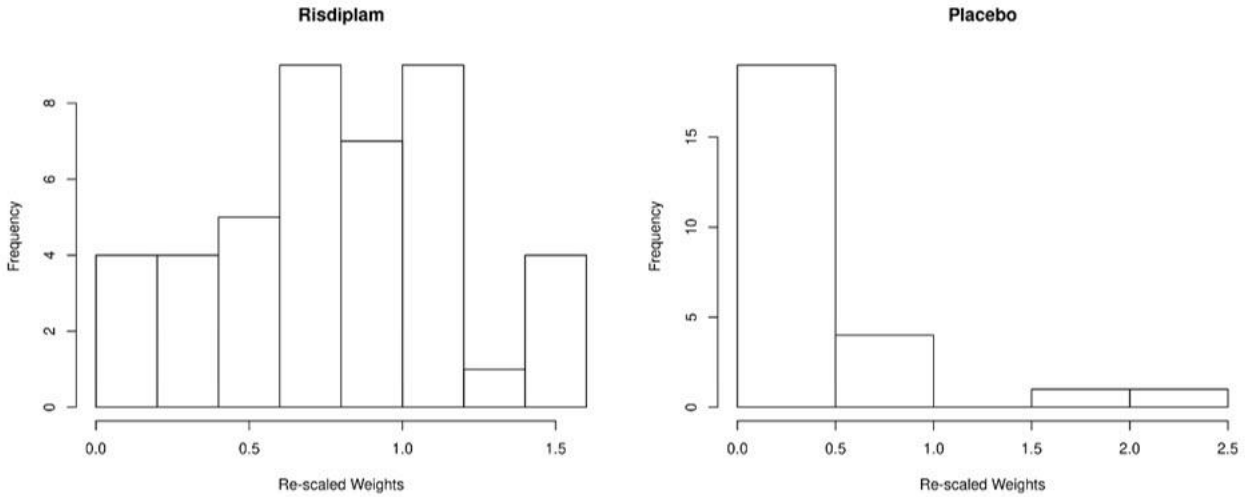
HFMSE analysis using anchored MAIC

Table S1 Baseline characteristics in the SUNFISH Part 2 subset population versus CHERISH pre- and post-matching

Baseline characteristics	SUNFISH Part 2 subset [a] Pre-matching		SUNFISH Part 2 subset [a] Post-matching		CHERISH
	Risdiplam (N = 43)	Placebo (N = 25)	Risdiplam (N = 43, ESS: 34.2)	Placebo (N = 25, ESS: 9.2)	Nusinersen and sham (N = 121)
Female gender	53%	44%	60%	46%	53%
Median age at screening in years	**5.0**	**5.3**	**4.1**	**3.7**	**3.7[b]**
Median age at symptom onset in months	13.7	16.6	12.9	13.5	10.3[b]
Median symptom duration in months	46.3	46.3	36.4	30.5	36.0[b]
Mean HFMSE baseline score	**24.21**	**23.12**	**22.41**	**21.57**	**21.57**
Mean RULM baseline score	21.65	22.28	20.02	19.71	19.07
Mean SMN2 copy number	**3.09**	**3.08**	**3.00**	**2.94**	**2.94**
% 2 copies	0%	4%	0%	8%	8%
% 3 copies	91%	84%	100%	90%	88%
% 4 copies	9%	12%	0%	2%	2%
% Unknown	0%	0%	0%	0%	2%

Overview over key baseline characteristics of SUNFISH before and after matching to the CHERISH baseline estimates (mean of both arms) of the three selected matching factors age at screening, HFMSE baseline score and SMN2 copy number. In the placebo arm, matching characteristics were perfectly matched to the means of CHERISH. However, the matching was at the expense of the ESS, which was reduced to <10 patients from 25 patients in the placebo arm of the SUNFISH subset. In the risdiplam arm, numerical differences remained between the mean characteristics of the weighted risdiplam arm and CHERISH remained post matching. The ESS after matching was 34.2 compared to 43 patients in the risdiplam arm of the SUNFISH subset. The total ESS was 43.4, a reduction of 36% from the sample size of the SUNFISH subset (N=68). [a] Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis. [b] In the absence of reported means, medians were used as a proxy for the purpose of these analyses.

Figure S1 Histograms of re-scaled weights in the CHERISH-matched restricted SUNFISH population



Distribution of the rescaled weights in the risdiplam and placebo arms. The distribution of weights was fairly even in the risdiplam arm, while in the placebo arm extreme weights of 0 or close to 0 occurred at a high frequency. This is consistent with the reduction of the ESS in the placebo arm. Results of the MAIC analyses must be interpreted with caution as very few individuals with a weight of ≥1 may dominate placebo outcomes. Statistical power to detect treatment differences will be decreased [19].

Table S2 Overview of patients with severe scoliosis, baseline HFMSE score <10, and missing data in the various age groups.

Subgroup	Total N (incl. Patients with missing data)	Baseline HFMSE score <10 only	Severe scoliosis only	Both	Data missing HFMSE	Data missing HFMSE & baseline HFMSE <10 only	Data missing RULM	Data missing RULM & baseline HFMSE <10 only	Data missing RULM & baseline HFMSE <10 & severe scoliosis
2-11 years	112	15	5	14	4	1	7	1	3
2-5 years	55	9	0	0	3	1	3	1	0
6-11 years	57	6	5	14	1	0	4	0	3
2-9 years	94	13	2	8	4	1	6	1	2
6-9 years	39	4	2	8	1	0	3	0	2
10-11 years	18	2	3	6	0	0	1	0	1

Baseline characteristics	SUNFISH Part 2 Subgroup 2-5 years		SUNFISH Part 2 Subgroup 6-11 years	
	Risdiplam (N = 37)	Placebo (N = 18)	Risdiplam (N = 39)	Placebo (N = 18)
Female gender	56.8%	44.4%	46.2%	50%
Median age at screening in years (range)	4 yrs	4 yrs	9 yrs	8 yrs
Median age at symptom onset in months (range)	12 (1–21)	12 (7–24)	13.2 (2–38)	13.2 (6–84)
Mean symptom duration in months (SD)*	40.0 (13.1)	43.7 (13.1)	96.2 (23.1)	85.1 (28.1)
Median disease duration at screening (range)	34.6 (5-53)	39.7 (14-51)	94.6 (34-130)	81.7 (0-107)
Mean HFMSE baseline score (SD)	19.1 (11.1)	23.9 (11.5)	17.9 (13.4)	16.9 (10.9)
Mean RULM baseline score (SD)	18.1 (6.9)	22.1 (6.5)	20.1 (7.4)	21.1 (6.3)
SMN2 copy number				
% 2 copies	2.7%	5.6%	2.6%	0%
% 3 copies	91.9%	83.3%	92.3%	88.9%
% 4 copies	5.4%	11.1%	5.1%	11.1%
% Unknown	0%	0%	0%	0%
SMA type				
Type 2	89.2%	77.8%	71.8%	77.8%
Type 3	10.8%	22.2%	28.2%	22.2%
Severe scoliosis (curvature >40 degrees)	0 %	0 %	33.3 %	33.3 %

Tillægsspørgsmål_ansøgning risdiplam 10082021

*Time between onset of initial SMA symptoms to first treatment (in Months)

EVRYSDI® (risdiplam) for the treatment of Spinal Muscular Atrophy (SMA) Type I, II & III

Health economic technical report for the Danish Medicines Council

Contact information	Contact persons
Roche a/s Industriholmen 59 2650 Hvidovre Denmark Marketing authorization holder in Denmark Roche Registration GmbH Emil-Barrell-Strasse1 79639 Grenzach-Wyhlen Germany	Anne Kolbye Value Demonstration Manager Mobil: +45 42 14 29 50 Mail: anne.kolbye@roche.com Pavika Jain Value Demonstration Manager Mobil: +45 42 14 29 38 Mail: pavika.jain@roche.com

EXECUTIVE SUMMARY

Introduction

Spinal muscular atrophy (SMA) is a rare, hereditary neurodegenerative disease which is the result of a survival motor neuron (SMN) protein deficiency. EVRYSDI® (risdiplam) is a novel oral treatment for the treatment for SMA. The objective of this technical report is to present the health economic analysis of EVRYSDI® (risdiplam) for the HTA submission for the Danish Medicines Council(DMC).

Methods

A Markov model (CEM), developed in MS Excel 2016 (Redmond, WA), was built to assess the cost-per-patient of EVRYSDI® (risdiplam) vs best supportive care (BSC) and vs SPINRAZA® (nusinersen) as a new treatment for patients with type II and III spinal muscular atrophy (SMA). Due to the lack of data for patients with type I, the data in the model have been assumed to act as a proxy for patients with type I. Baseline characteristics data from SUNFISH was inputted for SMA type I patients. This analysis takes a restrictive societal perspective in Denmark, and estimates outcomes related to costs over a lifetime time horizon. The model is discounted annually according to the guidelines provided by the DMC. The model was validated externally by experts, and checked by an independent third party.

The modelling of the disease is based around motor-function outcomes (according to the Motor-function Measure-32 items (MFM-32)) from the BP39055 (Sunfish) trial. Survival estimates were estimated using national life tables from the UK for type III patients, and pooled estimates for type II patients. Costs were included as per the guidelines by the DMC, and included treatment cost, administration cost, adverse event costs, monitoring costs and patient and transportation cost. The uncertainty of the results was explored in scenario analyses. Furthermore, to comply with the method guidelines by the DMC, a budget impact model have been embedded within the cost-per-patient model.

Results

Over a 5-year time horizon, for clinical question 1, the analysis estimated an incremental cost of risdiplam compared to nusinersen of DKK -4,159,010. For clinical question 2, the incremental cost of risdiplam compared to nusinersen was estimated to DKK -344,809. For clinical question 3, the incremental cost of risdiplam compared to placebo was estimated to DKK 9,122,204. For clinical question 4, the incremental cost of risdiplam compared to BSC was estimated to DKK 9,295,361.

Based on the base case assumptions, the estimated budget impact of recommending risdiplam as a possible standard treatment in Denmark for the population described in clinical question 1 was DKK -17.3 mil in year 1 and DKK -5.4 mil. in year 5. For clinical question 2, the estimated budget impact was DKK 22.2 mil. in year 5 with approx. 11 additional patients on treatment. For clinical question 3, the estimated budget impact was DKK 47.7 mil. in year 5 with approx. 26 additional patients on treatment. For clinical question 4, the estimated budget impact was DKK 29.3 mil. in year 5 with 15 additional patients on treatment. The budget impacts are driven by the additional number of patients treated for all populations.

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1 Introduction

Spinal muscular atrophy (SMA) is a rare, hereditary neurodegenerative disease that is the result of a survival motor neuron (SMN) protein deficiency. It is described as one of the most prevalent and serious genetic disorders in children, the incidence has been estimated at one in 6,000 neonates(1).

SMA is typically characterised by a weakening of the muscles, and irregular movements; however, there is considerable heterogeneity observed in SMA subtypes with regard to disease onset, rate of progression, and severity of the disease. SMA type I, also called Werdnig-Hoffmann disease, is evident in the first six months of life, and in approximately 95% of these patients life expectancy is less than 18 months(2). Due to the lack of SMN protein produced, children with SMA type I commonly require respiratory support and are unable to sit up without support (4). Type II (intermediate) SMA is evident between 7–18 months of age (3), and patients may have a reduced life expectancy but can survive into adulthood (4). In SMA types III and IV, life expectancy is not typically affected (5). Type III (mild) SMA, also called Kugelberg-Welander or juvenile SMA, is evident in children and young adults, whereas type IV (adult-onset SMA) typically presents in early adulthood without mobility, respiratory, or nutritional problems (3).

There is currently no cure for SMA, and management of patients with SMA requires a multidisciplinary approach involving the input of neurologists, respiratory specialists, gastroenterologists, geneticists, palliative care physicians, and orthopaedic surgeons (3). SMA is associated with a substantial burden, both on patients, family and caregivers, and healthcare systems (6).

Advances in the understanding of the underlying pathogenic process in SMA have led to the development of novel genetic therapies, which aim to modulate SMN protein expression and have resulted in significant clinical improvement in patients with SMA. Nusinersen (Spinraza®) is a SMN2-directed antisense oligonucleotide (ASO) drug designed to increase the production of functional SMN protein from the SMN2 gene which was approved by the European Medicines Agency in 2017(7). Nusinersen has undergone a formal Health Technology Assessment (HTA) submission process in Denmark at the Danish Medicines Council(8).

Results from clinical studies conducted to date indicate that nusinersen is associated with clinically meaningful improvement in patients with early- and later-onset SMA, although treatment does not restore age-appropriate function(9–15). However, studies examining long-term patient outcomes and safety in trials examining broader SMA populations and age categories are needed.

Roche has developed risdiplam (RG7916), an oral small molecule which function is to increase SMN protein levels to subsequently support motor neurons and muscle function(16).

EVRYSDI (risdiplam) is continuously being studied in a series of clinical trials enrolling patients with a broad range of ages and disease severity and was approved by EMA March 29, 2021 based data from the trial program:

- FIREFISH: an open-label trial in infants aged 1–7 months with type I SMA;
- SUNFISH: a placebo-controlled randomised controlled trial (RCT) in children and young adults (2–25 years) with type II and III SMA;
- JEWELFISH: an open-label study in subjects aged 12–60 years with type II or III SMA, previously treated with SMN-targeted therapy;
- RAINBOWFISH: an open-label study in pre-symptomatic patients aged 1–6 weeks.

Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (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.

The results from FIREFISH, SUNFISH and JEWELFISH studies demonstrate that risdiplam is an efficacious and safe treatment for patients with SMA over a large age range and various phenotypes of the disease.

1.1 Objective

The economic model was developed to estimate the incremental costs per patient as well as the budget impact of risdiplam as treatment for SMA patients as defined by the clinical questions in the protocol(17). The model will utilize a restricted societal perspective, thereby including patient costs and transportation costs as defined by the method guidelines of the DMC (18).

1.2 Decision problem (clinical questions)

The DMC have presented 4 clinical questions in the protocol(17):

1. What value does *risdiplam* have compared to *nusinersen* for patients with SMA type 1 who are not in permanent ventilation treatment?
2. What value does *risdiplam* have compared to *nusinersen* for non-walking patients with SMA type 2 and 3?
3. What value does *risdiplam* have compared to placebo for patients with SMA type 2 and patients with SMA type 3 who have lost gait function?
4. What value does *risdiplam* have compared to placebo for patients with SMA type 3 who have maintained gait function?

1.3 Data availability for clinical questions

1.3.1 Clinical question 1

For this clinical question, no direct comparison between risdiplam and nusinersen is available. The clinical part of the final application concludes, that using the unanchored MAIC

methodology suggests that risdiplam may be superior to nusinersen on a number of endpoints, including ventilation-free survival, overall survival, HINE-2 motor milestone response and achievement of a CHOP-INTEND score ≥40. Risdiplam was found to be superior to BSC on HINE-2, survival and safety outcomes.

Despite this, the clinical data is unfortunately not mature enough to populate a health economic model. Instead a more pragmatic health economic analysis have been conducted for this population, where we have applied the transition probabilities between the health states from SMA type 2 and type 3 patients.

Although the comparative analysis strongly suggests risdiplam might be superior to nusinersen on both a number of efficacy and safety endpoints, the inclusion of relative efficacy data between risdiplam and nusinersen based on an unanchored MAIC is expected to introduce a high degree of uncertainty to the results of the health economic analyses(19). Therefore, an assumption of equvilent effect between risdiplam and nusinersen has been applied for this clinical question to minimise the uncertainty of the model.

Furthermore, as the model is flexible and allows for the modelling of different patient populations based on patient baseline characteristics, a set of baseline characteristics have been applied for this clinical question in the model. This was done to reflect the population described in clinical question 1. Please consult section 4.6.1 for further information on the baseline characteristics modelled.

1.3.2 Clinical question 2

For this clinical question, no direct comparison between risdiplam and nusinersen is available. Risdiplam has been investigated in a placebo-controlled randomised controlled trial (RCT) on children and young adults (2–25 years) with SMA type 2 and 3 (SUNFISH part 2). Nusinersen has been investigated in two placebo-controlled RCTs (ENDEAR and CHERISH). An anchored indirect treatment comparison (ITC) was conduct on SUNFISH (risdiplam) and CHERIRSH (nusinersen) and is the evidence basis for the economic evaluation for clinical question 2. Please conduct section 4.6.3.2 for further information on the ITC conducted. Please conduct section 4.6.1 for further information on the baseline characteristics modelled.

1.3.3 Clinical question 3 and 4

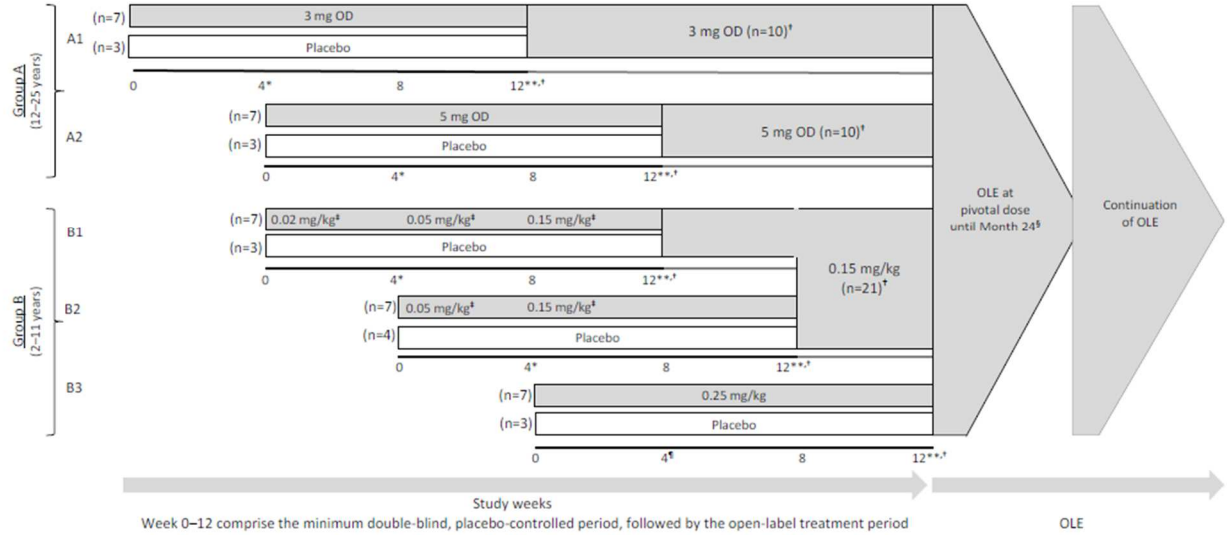
For these clinical questions, a direct comparison between risdiplam and placebo is available in the clinical trial, SUNFISH. Clinical data from SUNFISH is therefore used as the evidence basis for the economic evaluation for clinical question 3 and 4. Different patient characteristics have been deployed to model the two populations specified in the protocol for the clinical questions. Please conduct section 4.6.1 for further information on the baseline characteristics modelled.

2 Clinical trial: BP39055 (SUNFISH) STUDY (SMA type II and III)

2.1 Trial design

The BP39055(Sunfish) study is a two-part seamless, multi-center randomized, placebo controlled, double blind study to investigate the efficacy and safety of EVRYSDI® (risdiplam) against placebo (best supportive care) in patients with type II and III SMA. The design of the study is shown in Figure 1, Figure 2 and described in Table 1.

Figure 1 Design of BP39055 (Sunfish) study - Part 1 (Exploratory Dose-Finding Part)



NB. Week 0 indicates the recruitment start date for each cohort. The grey boxes comprise the all-exposure to risdiplam period, on which the main efficacy and safety analyses are based.
The grey and white cohort boxes from Week 0 to Week 12 comprise Days 1–84 (the minimum 12-week DB placebo-controlled period).
*The next cohort of patients in each age group was enrolled at a higher dose after safety and tolerability were confirmed after at least 4 weeks of treatment at the first dose level.
**Patients had to complete the minimum 12-week DB placebo-controlled period before progressing onto the open-label treatment period.

Figure 2 Design of BP39055 (Sunfish) study - Part 2

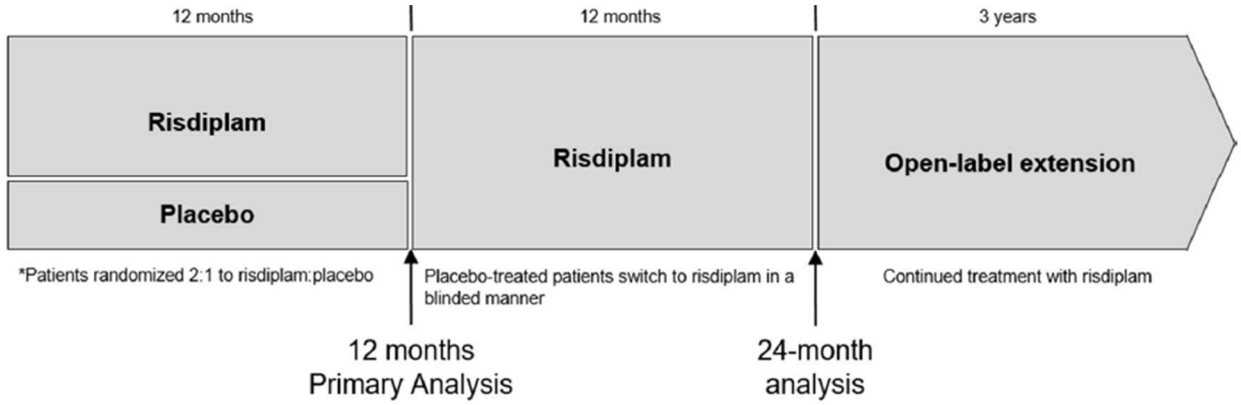


Table 1: Summary of the study design with respect to efficacy evaluation

Study no. (Phase II and III)	Clinical cut-off date: 09 Jan 2019 (part 1), 06 September 2019 (part 2), RO7034067
Study design, control type	*Prospective, two-arm randomized, multicenter, multinational, double-blind, placebo-controlled*
Population	Patients with type II/III spinal muscular atrophy (SMA)
Number of patients	Part 1: Efficacy Population (ITT): · Total: patients: 51 patients · EVRYSDI® (risdiplam): 35 patients · placebo: 16 patients Part 2: Efficacy Population (ITT): · Total: patients: 180 patients · EVRYSDI® (risdiplam): 120 patients · placebo: 60 patients
Dose and Regimen	· **Part 1:** Initial doses: · Age 12-25 years: placebo, 3 mg or 5 mg · Age 2-11 years: placebo, 0.02, 0.05, 0.15 or 0.25 mg/kg. Minimum of 12-weeks placebo-controlled treatment, after which patients on placebo switched to risdiplam at the dose tested in their cohort. After the dose selection for Part 2, all patients switched to the pivotal dose. · **Part 2:** Placebo or pivotal dose: · 0.25 mg/kg for patients with body weight (BW) <20 kg; · 5 mg for patients with BW ≥20 kg 24-month treatment period; patients on placebo switched in a blinded manner to active treatment after 12 months of treatment.
Endpoints	

Primary

- Part 2: change from baseline in the total score of the Motor Function Measure (MFM32) at 12 months.

Secondary

Motor Function

- Change from baseline in total score of the Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12.
- Change from baseline in the total score of the revised upper limb module (RULM) at Month 12.
- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline 0) on the total MFM score at Month 12.
- Proportion of patients with a change from baseline MFM32 total score of 3 or more (3) at Month 12.
- Proportion of patients who achieve an improvement of at least one standard error of measurement (SEM; calculated at baseline) on the total MFM score at Month 12
- Change from baseline in each of the MFM domain scores of D1, D2, D3, and the total combined score of (D1 + D2) and D2 + D3 at Month 12.
- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline 0) on the total HFMSE score at Month 12.
- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline 0) on the total RULM score at Month 12.
- Proportion of patients with a change from baseline HFMSE total score of 2 or more (2) at Month 12.
- Proportion of patients with a change from baseline RULM total score of 2 or more (2) at Month 12.

Respiratory

- Change from baseline in the best percentage predicted value of the Sniff Nasal Inspiratory Pressure (SNIP) at Month 12.
- For patients aged 6-25 years at screening only
  - Change from baseline in best percentage predicted value of the forced expiratory volume in 1 second (FEV1) at Month 12.
  - Change from baseline in best percentage predicted value of the forced vital capacity(FVC) at Month 12.
  - Change from baseline in the best percentage predicted value of the peak cough flow (PCF) at Month 12.
  - Change from baseline in the best percentage predicted value of the maximal inspiratory pressure (MIP) at Month 12.
  - Change from baseline in the best percentage predicted value of the maximal expiratory pressure (MEP) at Month 12.

Disease-Related Adverse Events

- Proportion of patients who experience at least one disease-related AE by Month 12.
- Number of disease-related AEs adjusted for patient-year (per 100 patient years) at Month 12.
- Clinical Global Impression of Change The proportion of patients rated by clinicians as no change or improved (i.e., rated as “no change”, “minimally improved”, “much improved” or “very much improved”) in the Clinical Global Impression of Change (CGI-C) Scale at Month 12.
- The proportion of patients rated by clinicians as improved (i.e., rated as “minimally improved”, “much improved” or “very much improved”) in the CGI-C at Month 12.

	Patient- and Caregiver-Reported Outcomes ● Change from baseline in the total score of the caregiver-reported SMA independence scale (SMAIS) at Month 12. ● In patients aged 12 to 25 years only ○ Change from baseline in the total score of the patient-reported SMAIS at Month 12.
Stratification factors	Randomization was stratified by age group (2-5 years, 6-11 years, 12-17 years, and 18-25 years at randomization).

2.1.1 Study population

Details regarding the key inclusion and exclusion criteria for trial participants in SUNFISH are provided in **Table 2** below. In addition, a summary of the baseline demographics and characteristics are reported in **Table 3** below.

Table 2: Key efficacy-related inclusion and exclusion criteria

Criteria
Inclusion
· Age: Males and females aged 2 to 25 years at screening. · SMA diagnosis: Confirmed diagnosis of 5q-autosomal recessive SMA, including: a. Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the *SMN1* gene. b. Clinical symptoms attributable to Type 2 or Type 3 SMA. · Ambulatory status: For Part 1: Type 2 or 3 SMA patients (ambulant or non-ambulant). For Part 2: Type 2 and non-ambulant Type 3 SMA patients
Exclusion
· Previous SMA treatment: Concomitant or previous administration of a *SMN2*-targeting ASO, *SMN2* splicing modifier or gene therapy. · Respiratory status: Invasive ventilation or tracheostomy. · Surgery: Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months.

Table 3: Baseline demographics and characteristics, SUNFISH Part 2

	risdiplam (N=120)	**placebo (BSC) (N=60)**	**Overall**
Age (median)	9	9	9
SMN2 copy number 2	2.5%	1.7%	2.2%
SMN2 copy number 3	89.2%	83.3%	87.2%

SMN2 copy number 4	8.3%	13.3%	10%
Weight (median)	27.1	27.15	27.1
Sex (Female)	50.8%	50%	50.6%

2.1.2 End points and assessments

The primary objective of the BP39055(Sunfish) study was to evaluate the efficacy of EVRYSDI® (risdiplam) against placebo in patients with type II and III SMA. **Table 4** lists the endpoints evaluated in the clinical trial.

Table 4: Key endpoints

Endpoint	Definition
Primary	
MFM	Change from (original) baseline in the total motor function measure 32 (MFM32) score at Month 12. The MFM total score was calculated according to the user manual. The 32 scores were summed and then transformed onto a 0100 scale (i.e., sum of 32 items scores divided by 96 and multiplied by 100) to yield the MFM total score expressed as a percentage of the maximum score possible for the scale (the one obtained with no physical impairment). The lower the total score, the more severe the impairment.
Secondary	
Motor Function	change from baseline in Total score of HFMSE, RULM and in the MFM domain scores of D1, D2, D3 and the total combined score of (D1 D2), and the proportion of patients who achieve stabilization or improvement on the total MFM score at Month 12.
Respiratory	Change from baseline in the best SNIP (expressed as a percentage of the predicted value) at Month 12. Additionally, in patients aged 6 to 25 years only: the change from baseline in MIP, MEP, FEV1, FVC and in PCF at Month 12.
Disease-Related Adverse Events	Proportion of patients who experience at least one disease-related adverse event by Month 12 and the number of disease-related adverse events per patient-year at Month 12.
Clinical Global Impression of Change Scale (CGI-C)	Proportion of patients rated by clinicians as no change or improved, and the proportion of patients rated by clinicians as improved at Month 12.
MFM improvement	Proportion of patients who achieve an improvement of at least one standard error of measurement (SEM; calculated at baseline) on the total MFM score at Month 12

Patient- and Caregiver-reported Outcomes	Change from baseline in the Total score of the caregiver-reported SMAIS and the change from baseline in the Total score of the patient-reported SMAIS (in patients aged 12 to 25 years only) at Month 12.
Exploratory	
Consistency Primary and Secondary Endpoints	The consistency of the treatment effect for the primary endpoint will be explored for the following baseline subgroups: Age group (2 to 5, 6 to 11, 12 to 17, and 18 to 25 years at randomization) Age group 2 (2 to 11 and 12 to 25 years at randomization) History of scoliosis or hip surgery (yes, no) SMA type (2, 3 non-ambulatory) Region (US, Rest of World) In patients with no major scoliosis or contractures at baseline: Age group 2 (2 to 11 and 12 to 25-years at randomization) Subgroup analysis of the secondary endpoint, the change from baseline in the Total score of the HFMSE at Month 12, will be performed on all subgroups as specified for the primary endpoint.
Motor Function	Change from baseline in the Total MFM score and its domain scores of D1, D2, D3 and the total combined score of (D1+D2), Total HFMSE and the Total score of RULM, at Month 18 and 24.

2.2 BP39055 (Sunfish) study results

2.2.1 Efficacy outcomes

The results from part 2 of the SUNFISH study (Table 5) demonstrate overall improvements with risdiplam, in comparison to placebo, for all observed endpoints. Table 5 Summary of key efficacy endpoints from BP39055 (Sunfish) (ITT Population)

Table 5: Sunfish Part 2 12-months results

	EVRYSDI® (risdiplam) (N=120)	**Placebo (N=60)**	**Difference from Placebo**
Median follow-up, months			
MFM (SE)	1.36 (0.38)	-0.19 (0.52)	1.55 (0.64)
RULM (SE)	1.61 (0.31)	0.02 (0.43)	1.59 (0.52)
HFMSE (SE)	0.95 (0.33)	0.37 (0.46)	0.58 (0.56)
SMAIS (SE)	1.65 (0.50)	-0.91 (0.67)	2.55 (0.82)

2.2.2 Subgroups

The consistency of the primary efficacy endpoint and key efficacy endpoints (all secondary endpoints up to Family 4 in the hierarchical testing) were explored for the following subgroups:

- Age group (2-5, 6-11, 12-17, and 18-25 years at randomization).
- Disease severity (Patient with MFM32 baseline total score below and equal to the first quartile ≤Q1 (i.e., ≤25th percentile), above the first quartile and below or equal to the third quartile >Q1 to ≤Q3 (i.e., >25th percentile and ≤75th percentile) and above the third quartile >Q3 (i.e., >75th percentile).
- SMA type (Type 2, Type 3).
- Region (North America, Europe, China, Japan, rest of the world).
- SMN2 Copy number (<2, 2, 3, ≥4 copies, unknown) from genotype analysis.

Subgroup analyses were broadly consistent with the overall results, although some subgroups were small and have to be interpreted with caution. It should be noted that patient numbers are small in some subgroups, and that the study was not powered to demonstrate efficacy within subgroups.

Consistent positive results were observed across Europe and North America, representing 81% of the ITT population. The results for the MFM32 total score in these regions were consistent with those from the Study BP39055 Part 1 comparison with external control data, which was conducted in Europe. Results were less consistent in Asia, however, the number of patients in this region was small (17% of the ITT population). The inconsistent results seen for China and Japan could be attributable to imbalances in the age and disease severity between treatment arms of the patients included in these regions. Notably, the PK profile of risdiplam in the Asian patient population showed no differences to that of non-Asian patients (Study BP39625), confirming that there is no pharmacokinetic reason for the inconsistencies seen in the functional assessments in Asian patients.

2.3 Safety outcomes

Risdiplam was generally well tolerated. No patient died and no patient withdrew from treatment due to an adverse event (AE). During the 12-month double-blind treatment period, the rate of both AEs and serious adverse events (SAE) was comparable in both treatment arms and was generally reflective of the underlying disease and age of patients. While the rate of AEs overall decreased over time in both treatment arms, this was more pronounced in the risdiplam arm. Generally, there was no clear age-related pattern in overall AE rates, only SAEs appeared to be reported less frequently in patients above 18 years of age in both treatment arms. In both treatment arms, AEs were mostly mild to moderate in intensity.

2.3.1 AEs/SAEs

All analyses in this section were performed on the safety population from the placebo-controlled period of SUNFISH Part 2. Multiple occurrences of the same event were counted once at the maximum severity.

2.3.1.1 Grade 3+ AEs

AEs of grade 3+ occurring in are summarized below.

Table 6: Adverse events of grade 3+ occurring in the clinical study

Grade 3+ AEs	Grades 3 and above		
	Risdiplam	Placebo	Overall
Upper respiratory tract infection	1 (0.8%)	1 (1.7%)	2 (1.1%)
Gastroenteritis	7 (5.8%)	0 (0%)	7 (3.9%)
Respiratory tract infection	1 (0.8%)	0 (0%)	1 (0.6%)
Nausea	2 (1.7%)	1 (1.7%)	3 (1.7%)

2.3.1.2 Serious AEs

During the placebo-controlled period of Part 2 of SUNFISH, the percentage of patients with at least one SAE were comparable across both treatment arms, with SAEs reported in 20.0% of patients receiving risdiplam and in 18.3% of patients receiving placebo. No SAE was considered related to study treatment.

Table 7: Serious adverse events occuring to more than 5% in any of the study arms

Any serious AE >5%	Risdiplam	Placebo (BSC)	Overall
Pneumonia	9 (7.5%)	1 (1.7%)	10 (9.2%)

2.3.1.3 AEs leading to study drug discontinuation

At the time of the CCOD, no patients had withdrawn from study treatment due to an AE.

3 Health economic model

A Markov model have been developed to simulate the progression/regression of a cohort of SMA type II/III patients through a series of motor milestones. The model was developed in Microsoft Excel 2010. (The model health states depicted in Figure 1 represent the major motor milestone achievements that are possible for the natural history of patients living with type II and III SMA: “non sitting”, “sitting”, “standing”, and “walking”. The definitions are as follows:

- non “sitting”
- The “sitting” state has been split further to highlight the clinical significance of being able to progress to sitting independently (“sitting - unsupported”) from being dependent on some form of support (“sitting - supported”).
- “standing” is the third health state with
- “walking” being the final and highest level of motor function achievable in the model. There is a possibility to further evaluate the impact of both standing and walking as either independent or with support.
- “death”

SMA is a long-term debilitating disease with various comorbidities over time. These and disease related events (scoliosis, respiratory support, feeding support, sleep apnoea, orthopaedic surgery) are considered at each state in the model proportionally with costs being applied in each model cycle for patients that remain alive. We also took into consideration the costs associated with disease morbidity and treatment related impacts.

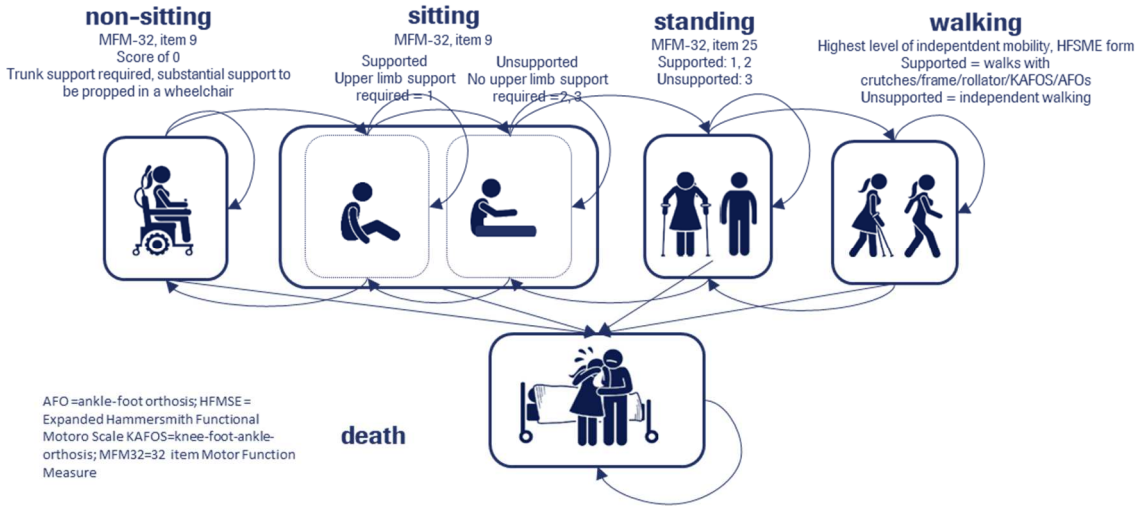


Figure 3: Spinal muscular atrophy (SMA) Type II/III (late-onset)

4 Model input

4.1 Decision problem (clinical questions)

For this health economic model, the DMC have presented 4 clinical questions in the protocol(17):

1. What value does *risdiplam* have compared to *nusinersen* for patients with SMA type 1 who are not in permanent ventilation treatment?
2. What value does *risdiplam* have compared to *nusinersen* for non-walking patients with SMA type 2 and 3?
3. What value does *risdiplam* have compared to placebo for patients with SMA type 2 and patients with SMA type 3 who have lost gait function?
4. What value does *risdiplam* have compared to placebo for patients with SMA type 3 who have maintained gait function?

4.1.1 Comparators

Therefore, based on the protocol the following comparators have been included in the model for the clinical questions:

Clinical question 1: risdiplam and nusinersen
Clinical question 2: risdiplam and nusinersen
Clinical question 3: risdiplam and placebo
Clinical question 4: risdiplam and best supportive care

4.2 Perspective

The perspective of the economic model is a restricted societal perspective, which includes costs related to drug acquisition, drug administration, monitoring, adverse events, routine care, patient time, and transportation. Indirect costs are not included as per the DMC's guidelines (18).

4.3 Time horizon

For the base case a time horizon of 5 years have been chosen.-

A scenario analysis will be conducted for a 80 years time horizon (life-time). Furthermore, additional scenario analyses will be conducted on alternate time horizons.

4.4 Discounting

In the base-case, the annual discount rate for future costs was 3,5% for model year ≤35, 2,5% for model year 35 to 70 and 1,5% from model year 70 and beyond in alignment with DMC's guidelines (18,20). Discounting in the model is performed after the first year on a yearly basis.

4.5 Outcomes

The model calculates on a monthly basis results related to costs, and life years. In addition, the time spent in each health, by comparator, has been recorded and reported per year. This allows for the possibility of a cost-consequence analysis related to motor-milestone achievements.

4.6 Model parameterisation

4.6.1 Baseline characteristics

The model is designed so that the user may define various baseline characteristics of the patient population that populates the models. These baseline characteristics include age, gender (% female), weight, SMA Type (Type II vs III), % requiring respiratory support, % with severe scoliosis (defined as curvature >40°) and the initial distribution of patients between motor function states (non-sitting, sitting supported, sitting unsupported, standing and walking).

Age at baseline allows the calculation of appropriate mortality rates for patients with SMA Types II and III at different time points. As the cohort ages, the mortality rate increases.

Gender is used in the calculation for mortality of patients with Type III SMA, as life tables provide different mortality rates based on gender. In addition, gender is used for the calculation of body weight, which is relevant for the dosing of risdiplam in patients at lower weights (refer to section). The input for body weight is only included as an informative field in the model, but does not impact any calculations. The distribution of patients across SMA Types impacts mortality, as different sources were used to estimate mortality for Type II versus Type III (refer to section **4.6.5**).

Therefore, in order to be able to model the populations of each clinical questions, patient baseline characteristic sets have have been included to allow for the modelling of each patient population described in the protocol presented by the DMC(17). This allows the user to change between the clinical questions in the model using the control-element on the "Summary"-sheet. The distribution of patients in the model is done to match the clinical questions from DMC(17). This exact distribution of patients is not presented in the published studies as they were not predefined subgroup analyses. Data-on-file from Roche suggests the distribution in Table 8 regarding type (II or III) in each age group for clinical question 2 and 3. Because type III patients often are diagnosed later than type II patients, the share of type II patients are larger ind the younger age groups (clinical question 2) than in the older (clinical question 3). Scenario analyses have been conducted to investigate the uncertainty to the distribution of baseline characteristics. The included patient baseline characteristics included in the model is presented in Table 8.

Table 8: Patient baseline characteristics applied for the patient populations of the 4 clinical questions

Baseline characteristic	Clinical question 1	Clinical question 2	Clinical question 3	Clinical question 4
Age (years)	0.45	6.13	16.41	7.71
Female (%)	57%	50%	51%	29%
Body weight (Kg)	4.9	22.4	51.0	27.7

Type II	100%	79%	57%	0%
Type III	0%	21%	43%	100%
Proportion Not sitting at baseline (MFM 9=0)	100%	0%	0%	0%
Proportion Sitting w support at baseline (MFM 9=1)	0%	8%	21%	0%
Proportion Sitting wo support at baseline (MFM 9=2,3)	0%	77%	71%	0%
Proportion Standing at baseline (MFM 25)	0%	8%	1%	0%

4.6.2 Health state transition probabilities

The motor-function health states (not sitting, sitting supported, sitting unsupported, standing, walking) were identified as previously described (refer to Figure 3) and validated with external experts, literature and real-world data.

Data from the placebo-controlled period of Sunfish Part 2 was used to analyse health states and calculate transition probabilities for risdiplam and placebo. SUNFISH Part 1 data was not used, as patients were only placebo controlled for 12 weeks. The ITT population was used in these analyses. Transition probabilities were calculated for risdiplam (EVRYSDI) and placebo (BSC).

For the base case, efficacy of BSC is based on the transition probabilities from the placebo arm (Table 10). Efficacy of risdiplam is based on the transition probabilities from the risdiplam arm (Table 9) for the duration of treatment with risdiplam. Upon discontinuation of risdiplam treatment, transition probabilities from BSC are applied in the model.

In the absence of long-term data, transition probabilities were assumed to be constant for the entire time horizon of the model.

Table 9: Risdiplam transition probabilities (SUNFISH Part 2)

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	0.8515	0.145	0.0036	0	0
Sitting supported	0.0635	0.8922	0.0442	0.0001	0
Sitting unsupported	0.0003	0.0079	0.9863	0.0054	0.0001
Standing	0	0.0003	0.0684	0.9087	0.0226

Walking	0	0	0.0025	0.0687	0.9288

Table 10: Placebo (BSC) transition probabilities (SUNFISH Part 2)

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	0.9069	0.0917	0.0014	0	0
Sitting supported	0.0628	0.91	0.0271	0	0
Sitting unsupported	0.0003	0.0076	0.9921	0	0
Standing	0	0.0003	0.0741	0.9256	0
Walking	0	0	0.0029	0.074	0.9231

4.6.3 Nusinersen treatment effect – Implication of the Indirect Treatment Comparison

4.6.3.1 Clinical question 1

The clinical part of the final application concludes, that using the unanchored MAIC methodology suggests that risdiplam may be superior to nusinersen on a number of endpoints, including ventilation-free survival, overall survival, HINE-2 motor milestone response and achievement of a CHOP-INTEND score ≥40. However as described in section 1.3.1, a conservative assumption of equal effect was applied to minimise the uncertainty of the economic analysis, therefore no description of an ITC have been included in this report for clinical question 1.

4.6.3.2 Clinical question 2

In Type 2/3 SMA, ten clinical trials were included for review and two were finally included in the evidence network: SUNFISH (risdiplam) and CHERISH (nusinersen). Outcomes considered of interest and feasible for the ITC included motor function endpoints (RULM, HFMSE) and safety endpoints (any serious AE).

In regard to Type 2/3 SMA, SUNFISH enrolled a much broader patient population compared to CHERISH, including adolescents and adults, patients with severe scoliosis and contractures, and patients with lower motor function scores. To reduce heterogeneity in the evidence network, a 'CHERISH-like' subset of the SUNFISH population was used for the analyses. This subset consisted of patients aged 2-9 years, without severe scoliosis, and with a HFMSE baseline score of at least 10.

Analyses in Type 2/3 SMA were limited by high uncertainty and wide confidence intervals for relative effect estimates. The analyses did not provide evidence of a statistically significant difference between risdiplam and nusinersen on the RULM endpoints. Robust conclusions on relative efficacy on HFMSE endpoints could not be drawn due to large differences in placebo response between CHERISH and SUNFISH. There was also no evidence of a statistically significant difference in treatment effect for safety in the base case analysis. Sensitivity analyses suggested that risdiplam may be associated with a higher reporting of serious AEs. Overall, the relative efficacy of risdiplam and other DMTs is uncertain for Type 2/3 SMA.

The base case uses RULM response to estimate the treatment effect of nusinersen treatment for the following reasons:

- The HFMSE was found to exhibit floor effects in weaker subjects, while no floor or ceiling effects were observed with the RULM (nor with the MFM) (Wijngaarde et al, 2020)
- The RULM was a secondary endpoint in both SUNFISH and CHERISH, while the HFMSE was a primary endpoint in CHERISH and a secondary endpoint in SUNFISH
- A stronger correlation was found in the change from baseline of RULM vs MFM-32 (Spearman's rho 0.506) compared to HFMSE vs MFM-32 (Spearman's rho 0.319)

It must be noted that the relative effect estimates of risdiplam versus nusinersen in Type 2/3 SMA do not allow any inference of relative efficacy in non-"CHERISH-like" patients, such as adolescents and adults, weaker patients (HFMSE score ≤10) and patients with severe scoliosis or contractures.

Incorporation of relative effects in the model to estimate the nusinersen treatment effect

The ITC presents results of RULM and HFMSE response at the 12-months timepoint. For the incorporation into the model, these had to be adjusted to the cycle length of 1 month. Proportions at 12 months for risdiplam, placebo, nusinersen and sham were converted to 1-month probabilities using the following formula:

$$P_{1m} = 1 - EXP(\frac{LN(1 - P_{12m})}{12})$$

Using the 1-month probabilities, risk ratios were calculated for nusinersen versus risdiplam were calculated as follows:

$$RR_{1m\ (Nusi\ vs\ Risdi)} = \frac{\frac{P_{1m\ (Nusi)}}{P_{1m\ (Sham)}}}{\frac{P_{1m\ (Risdi)}}{P_{1m\ (Plcb)}}}$$

The resulting risk ratio was then applied to the risdiplam transition probabilities to derive nusinersen transition probabilities. The same risk ratio was applied to all forward transitions

in the transition matrix. For backward transitions, a risk ratio of 1 had to be assumed, as no data was available on the loss of motor function for nusinersen.

The risk ratio for RULM response (change from baseline ≥2 points) based on the MAIC analysis (Table 11) is used in the base case. Alternative results using RULM responders proportions from the Bucher ITC, HFMSE or equal effect may be used in scenarios analyses and can be selected in a drop-down menu on the "Inputs" worksheet (see section 9.3.1.4). Alternatively, the user may directly enter their own risk ratios in the "Inputs" worksheet.

Table 11: Risk Ratio for RULM response (MAIC analysis)

RULM response (MAIC)	Proportion responders at 12 months	1-month probability	Risk Ratio
Nusinersen	66%	8.60%	-
Sham	56%	6.61%	-
Risdiplam	88%	16.20%	-
Placebo	64%	8.16%	-
Risk Ratio	**-**	**-**	**0.66**

4.6.4 Treatment duration, effect waning and discontinuation

In the 1-year data from SUNFISH Part 2, only four patients discontinued from the study. 1.7% of patients discontinued in the placebo arm and 2.5% in the risdiplam arm. The reason for discontinuation was initiation of another treatment (nusinersen specifically stated in 3/4 patients) for all four patients and is likely a result of nusinersen becoming available in countries during the duration of the SUNFISH study. As only very few patients discontinued from risdiplam, duration of treatment and the probability of discontinuation could not be informed by trial data. Similarly, there is only little evidence available of the treatment duration and probability of discontinuation for nusinersen, as no patients discontinued nusinersen in CHERISH.

Therefore, for all clinical questions, the probability of treatment discontinuation for both the risdiplam and nusinersen arm has been set to 0.

In the model, it is currently assumed that patients stay on risdiplam and nusinersen treatment for the entirety of the time horizon and the monthly probability of discontinuation was set to zero for both treatments. The model further allows to define a period of treatment effect

waning after discontinuation. However, since the duration of treatment was set to the time horizon, this is currently set to 0.

The user may enter alternative estimates for treatment duration, treatment effect waning (after discontinuation) and monthly probability of discontinuation in the “Inputs” sheet.

4.6.5 Overall survival

SMA type I patients

For SMA type 1 patients, the data for type 2 patients have been applied as a proxy. Although, we acknowledge the differences between SMA type 1 and type 2, we have applied this as a conservative assumption of the survival of SMA type 1 patients. However, with this assumption, no differences are therefore assumed between the two comparators for clinical question 1. Therefore, the health economic analysis on this clinical question will purely be a comparison on costs, as efficacy in other parameters than survival are assumed to be equal as well.

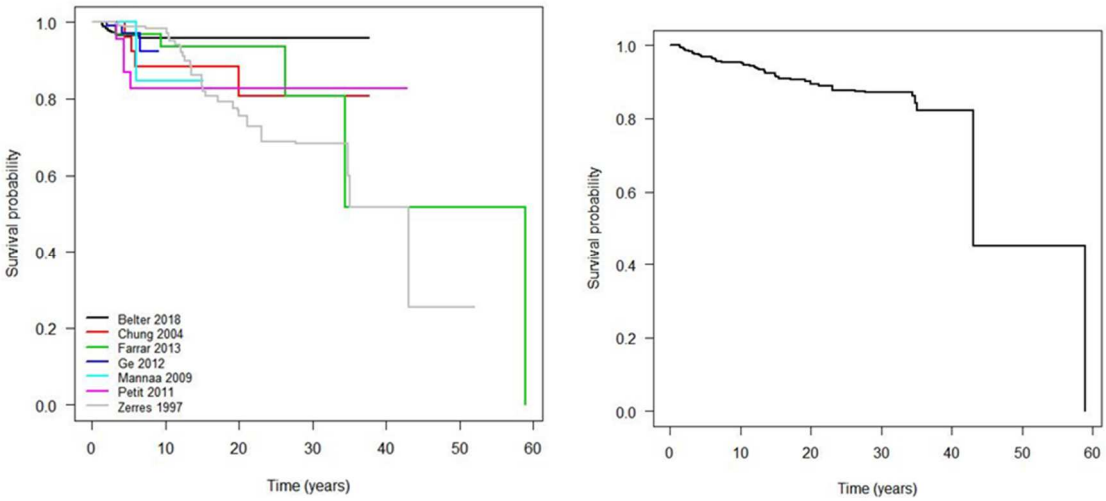
SMA type II patients

No deaths were recorded in the one-year data of the SUNFISH study and therefore, survival have been informed using external sources. Details on the sources used for Type 2 and Type 3 patients are provided in the following sections.

Feedback from internal and external clinical experts indicated that mortality in SMA is associated with lung function rather than motor function. At present, there is little evidence whether and how lung function and motor function may correlate. Further, no statistically significant or clinically relevant difference was observed in respiratory assessments in SUNFISH Part 2. Hence, the model does not consider any treatment-effect on survival, i.e, life-years gained will be equal for all comparators.

As described previously, we conducted several SLRs to inform the CEM parameters. In particular, an SLR considering the natural history of survival for type II patients was undertaken. From the seven studies identified (Belter 2018, Chung 2004, Farrar 2013, Ge 2012, Mannaa 2009, Petit 2011, Zerres 1997(21–28)), pseudo individual patient data (IPD) was created and pooled to a single survival Kaplan-Meier (KM) curve (Figure 4).

Figure 4: Individual and pooled Kaplan-Meier curve from the Type II survival SLR



Upon inspection of the individual and pooled KM curves, it was observed that the study from Belter 2018 reported a higher survival compared to the other studies. The Belter 2018 study used data from the Cure SMA database, a patient-reported data repository on SMA patients. As noted by the authors, limitations of the study include enrollment bias (e.g, Cure SMA membership may represent a more engaged population) and that data was patient reported, which is prone to reporting inaccuracies, incomplete information and errors in memory. Data from all other studies was derived from clinical settings (neuromuscular clinics, pediatric institutes, hospitals).

Two pooling scenarios were conducted in order to assess the impact of study differences on the survival estimation:

- Pooling of all identified studies
- Pooling of all studies except Belter 2018

The pooled KM curves were then fitted to several parametric functions and assessed for best fit.

Internal validity and goodness of fit

During the global development of the mode a focus group of three external experts were consulted to provide an estimate of the proportion of patients with SMA Type 2 surviving on best supportive care at years 15, 30 and 50. Table 12 provides a comparison of the experts' estimation to the Kaplan-Meier estimates of the two scenarios of the pooled survival curves including and excluding the study from Belter 2018. Based on this comparison, it was decided that the pooling scenario excluding the Belter 2018 study provided the best estimation of natural history for SMA. Results from the Pooling scenario including Belter 2018 are available in the section 9.3.1.3, Appendix A.

Table 12: Comparison of survival probabilities in Type 2 SMA elicited from external experts vs SLR pooling scenarios

Year	Expert focus group	Pooling scenario including all studies	Pooling scenario excluding Belter 2018
15	~85%	92%	84%
30	~60%	87%	71%
50	<30%, >10%	45%	31%

Table 13 provides the AIC and Bayesian Information Criterion (BIC) goodness of fit results for the functions used to model OS in Type 2 SMA (Pooling scenario excluding Belter 2018). The lower the AIC or BIC values the better the fit of the model. Based on the AIC and BIC statistics, the best fit overall would be obtained with a Generalized Gamma, followed by the Gompertz distribution. It should be noted that these statistical measures only consider model fit to the existing data and does not allow any conclusion to be drawn around the appropriateness of tail of the distribution.

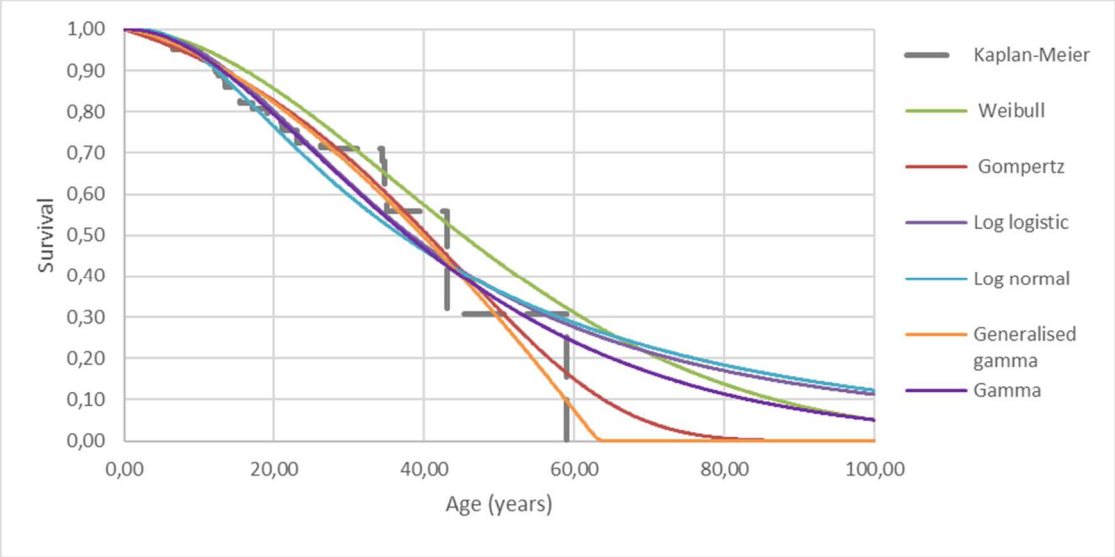
Figure 5 shows that Generalized Gamma and Gompertz are the only distributions that result in reasonable extrapolations, while all others predict survival of patients over the age of 100. The Gompertz distribution is to be used for the base case, as the tail provides a smoother transition to 0.

Table 13: AIC and BIC goodness of fit results for Type 2 survival (Pooling scenario excluding Belter 2018)

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	3434.1 (7)	3438.2 (7)
Weibull	3338.0 (3)	3346.1 (3)
Log-normal	3376.9 (6)	3385.1 (6)
Generalised Gamma	3314.2 (1)	3326.5 (1)
Log-logistic	3363.9 (5)	3372.1 (5)
Gompertz	3328.0 (2)	3336.1 (2)
Gamma	3348.3 (4)	3356.4 (4)

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 5: Comparison of Kaplan-Meier with parametric extrapolations.



SMA Type III patients

Type III patients are expected achieve a normal life expectancy(17).

National life tables from Denmark based on data for the years 2019:2020 were used to inform survival of patients with type III SMA(29).

4.6.6 Populations/Clinical questions

For this health economic analysis, the patient populations of the 4 clinical questions have been included. The patient baseline characteristics of these 4 populations are described in section 4.6.1. A deterministic result, scenario analyses and budget impact results will be presented for each clinical question included in the DMC protocol(17), e.g. modelled with the patient baseline characteristics of relevant population and relevant budget impact model settings.

4.6.7 Adverse Event Incidences

Adverse events of grade 3+ and serious adverse events of any grade reported in ≥5% of either arm in SUNFISH Part 2 or in the nusinersen arm in CHERISH have been included in the model. Adverse events that were included in the model are summarized in Table 14. Annual AE incidences were then converted to a monthly rate for incorporation in the model.

Data for risdiplam and BSC were informed by the risdiplam and placebo arms of SUNFISH Part 2. Data for nusinersen have been extracted from the CHERISH trial(30).

Table 14: List of adverse events included in the model

	Risdiplam (EVRYSDI)	Placebo (BSC)	Nusinersen (SPINRAZA)	
Source	SUNFISH Part 2		CHERISH (30)	
Gastroenteritis	7 (5.8%)	0 (0.0%)	N/A	N/A
Pneumonia (SAE)	9 (7.5%)	1 (1.7%)	2 (2.0%)	Table 3

4.7 Health resource use and costs

Our approach to understanding the costs associated with SMA patients on treatment with either risdiplam, nusinersen or BSC involved consulting a Danish clinical expert in treatment of SMA patients. The clinical expert gave input to the resource use associated with SMA patients.

The direct treatment related costs for risdiplam were based internal Roche data, while costs related to nusinersen are based on SmPC(7).

All costs reported here are in Danish kroner (DKK).

4.7.1 Treatment and administration costs

4.7.1.1 Risdiplam

The treatment dosing of EVRYSDI® (risdiplam) are presented in Table 15. Risdiplam is administered using an oral solution, allowing for accurate weight-based dosing. A bottle of risdiplam contains 60 mg of risdiplam. The unit cost per bottle is reported in Table 16. Based on KOL input, the mixing of the risdiplam solution will occur at the hospital and be preformed by a nurse. It will approximately take 15 minutes to mix upto 5 bottles of risdiplam, therefore 15 min of nurse time have been applied for the administration cost of risdiplam (see Table 17).

Table 15: Summary of daily dosing per weight category for risdiplam

Patient weight	Dose
up to 11kg	0.2mg/kg
11-20 kg	0.25mg/kg
20kg and greater	5mg

Table 16: Unit cost of risdiplam

Treatment	Package size	Composition	Cost per pack (DKK)	Source
EVRYSDI® (risdiplam)	60 mg	Powder for oral solution	DKK 64,110	Internal Roche price

Table 17: Administration cost associated with risdiplam

Activity	Unit cost (DKK)	Source
Preparation of risdiplam	136	15 min, nurse time: unit cost from the DMC's unit cost list(32)

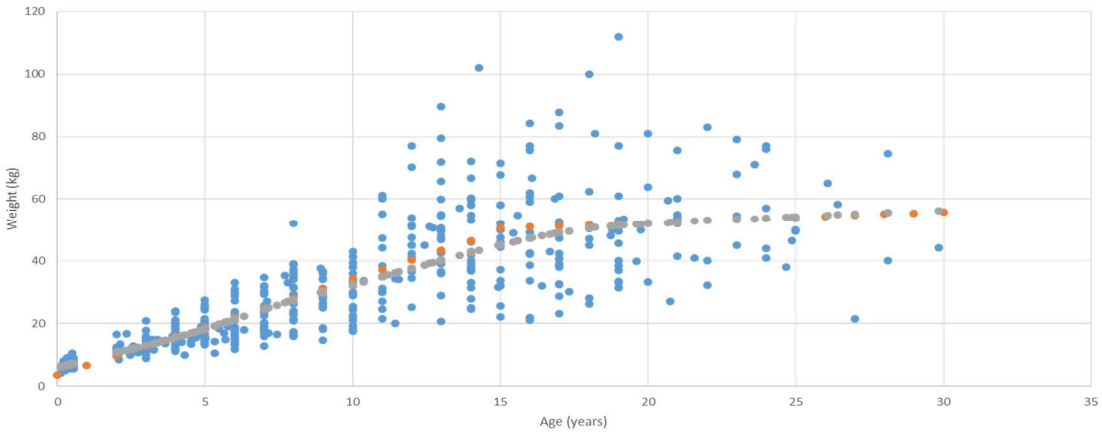
For this reason, it is important that the model is able to estimate the potential weight of a patient to ensure that a suitable monthly price is calculated in the health economic model. In order to determine this, data from patients related to weight, height and age were pooled from the TRO19622 study, OLEOS study, BP39055 (Sunfish), BP39056 (Firefish) and NatHis-SMA.

The results depicted in Figure 6 demonstrate that weight increases most rapidly in the early years, and then plateaus in early adulthood, with gender contributing to the changes. This resulted in two formulas to describe the weight estimation related to age and gender as follows:

$$\textit{Weight of patient 14 years old or less} = d\_Cons14+(d\_BAge14*age+(d\_Bfemale14*propFemale)$$

$$\textit{Weight of patient 15 years old or older} = d\_Cons15+(d\_BAge15*age)+(d\_Bfemale15*propFemale))$$

Figure 6: Weight algorithm for SMA patients



As the treatment is oral, no drug administration cost for risdiplam is expected.

4.7.1.2 Nusinersen

Nusinersen is an intrathecal treatment for SMA patients. The treatment is administered intrathecally at the hospital, either under general anesthesia or local anesthesia. Based on input from a Danish clinical expert(31), approx. 1/3 of the administration are done under general anesthesia, while the remaining patients are administered under local anesthesia. Nusinersen is administered at day 0, 14, 28 and 63, followed by a maintenance dose every 4th month, as per the SmPC (see Table 18). The unit cost per vial is reported in Table 19. The administration cost have been estimated using a DRG tariff and applied in the model at each administration of nusinersen (see Table 20).

Table 18: Dosing of nusinersen

Treatment	Dosing
Spinraza (nusinersen)	12 mg, initially at day 0, 14, 28 and 63, followed by a maintenance dose of 12 mg every 4th month

Table 19: Unit cost of nusinersen

Treatment	Package size	Composition	Cost per pack (DKK)	Source
Spinraza (nusinersen)	5 ml	2,4 mg/ml	557,926.97	Medicinpriser.dk – AIP Spinraza – 2.4 mg/ml, 5 ml, injection fluid

Table 20: Administration cost associated with nusinersen

Activity	Unit cost (DKK)	Source
Intrathecal administration	4,781	DRG 2021, 09PR04: Biopsi og væskeudsugning, overfladisk Diagnosis: DG129, Spinal muskelatrofi UNS Procedure: KTAB00, Lumbalpunktur & BWAA70, Medicingivning ved intrathekal injektion

4.7.2 Hospital cost (Outpatient costs)

The resource use and frequency of outpatient visits have been estimated in collaboration with a Danish clinical expert with SMA (31). A micro-costing approach was applied for specialist and physiotherapist resource use based on the feedback from the Danish clinical expert. A micro-costing approach was chosen for estimating the costs as this would allow us to reflect the costs as precisely as possible and to avoid double counting of resource use. The hourly wages for the oncologist and nurses used for the micro-costing approach have been derived from the DMC's unit cost list(32). The clinical expert estimates allowed for a detailed estimation of the expected resource use associated with SMA patients. The clinical expert expected no difference in outpatient visits between SMA type 1, 2 and 3, therefore

the same outpatient cost estimated has been applied across all health states and clinical questions. Please see Table 21 for a detailed breakdown of the outpatient cost included in the model.

Table 21: Estimation of outpatient cost associated with SMA type 1, 2 and 3 for all health states included in the model based on input from Danish clinical expert within SMA(31) **and unit cost from the DMC's unit cost list**(32)

Activity	Hourly wage (DKK)	Hours per visit	Cost per visit (DKK)	Annual number of visits	Total annual cost (DKK)
Neurologist consultation	1,316	0.75 hours	987	2	1,974
Orthopedic surgeon consultation	1,316	0.75 hours	987	1	987
Physiotherapist consultation	512	1 hour	512	2	1,024
				Total annual cost (DKK)	**3,985**
			Total cycle cost applied in the model (DKK)		**332**

4.7.3 AEs/SAEs

For this analysis, grade or higher AEs and SAEs with an incidence of ≥5% in at least one treatment arm were considered.

A consultation at the hospital was assumed as management for all adverse event, a DRG tariff related to the adverse event diagnosis was identified for each adverse event. Costs per adverse event are drawn from the relevant DRG tariff and are shown in Table 22. The cost of adverse events is applied using the monthly rates described in section 4.6.7.

Table 22: Cost related to adverse event management

Adverse event	Unit cost for Adverse management (DKK)	Source
Gastroenteritis	DKK 4,246	DRG 2021 - 06MA13, Betændelse i spsiserør, mave og tarm i øvrigt, pat. 0-17 år, diagnosis: DK529, Anden ikke-infektiøs gastroenteritis eller colitis UNS
Pneumonia (SAE)	DKK 2,183	DRG 2021 - 04MA99, MDC04 1-dagsgruppe, pat. 0-6 år, diagnosis: DJ189, Pneumoni UNS

4.7.4 Patient and transportation cost

Patient costs are included in the model in line with the DMC method guidelines (18). The unit cost per hour is assumed to be DKK 179 in line with the DMC guidelines (32). Risdiplam is administered as an oral solution, and can be administered either as a solution or using a feeding tube. From the internal Roche data from the compassionate use program, any administration of risdiplam would be approx. take 5 mins., regardless of it being administered

using a feeding tube or administered as a solution in the mouth. Therefore, cost related to 5 min. time usage Furthermore, the patients need to have risdiplam dispensed at the hospital. 8 dispenings would be required throughout a year, however, 2 dispensing would be in conjunction with a neurologist consultation. Therefore to avoid double counting of patient and transportation cost, 6 annual dispensing visits have been applied in the model. The estimated patient cost associated with administration of risdiplam is reported in Table 23.

Table 23: Patient costs associated with administration and dispening of risdiplam

Activity	Hours per visit	Monthly frequency	Monthly cost (DKK)
Dispensing + transport cost	0.5 hours	0.5	95
Administration of risdiplam	0.08 hours	30.44	454
		Total cost per cycle (DKK)	**549**

With nusinersen, the Danish clinical expert, reported that 1/3 of the patients would be administered under general anaesthesia, while the remaining 2/3 of the patients would be administered under local anaesthesia(31). The clinical expert estimated the patient time usage of administration under general anaesthesia to be 6 hours and 45 mins, while patient time usage of administration under local anaesthesia to be 3 hours and 45 mins. Furthermore, the clinical expert mentioned that at 50% of the administrations, one relative was present, while at the remaining 50% administration, two relatives were present, therefore the time usage for these have been included as well. The estimated patient cost associated with administration of nusinersen is reported in Table 24. A scenario analysis have been conducted to test the impact of only one caregiver being present.

Table 24: Patient costs associated with administration of nusinersen

Element	Patient cost per administration (DKK)
Administration of nusinersen	2,226

Patient cost associated with monitoring was estimated based on the time usage estimates provided by the Danish clinical expert for monitoring(31). As monitoring did not differ between the different health states, this cost have been applied to all health states in the model. The estimated patient cost associated with monitoring is reported in Table 25.

Table 25: Patient cost associated with monitoring of SMA patients

Activity	Hours per visit	Annual number of visits	Total annual cost (DKK)
Neurologist consultation	0.75 hours	2	671
Orthopedic surgeon consultation	0.75 hours	1	336
Physiotherapist consultation	1 hour	2	995
		Total annual cost (DKK)	**1,902**
		Total cycle cost applied in the model (DKK)	**159**

Transportation costs are included in the model in line with DMC guidelines(18) and was applied together with the patient cost in the model. An average rate of DKK 100 per visit was applied in the model. As nusinersen is administered at the hospital, transportation cost was applied at every nusinersen administration occurrence. See Table 26 for the applied transportation cost of the administration of nusinersen.

Table 26: Transportation costs associated with administration of nusinersen

Element	Transportation cost per administration (DKK)
Administration of nusinersen	100

Transportation cost associated with monitoring was estimated based on input from a Danish clinical expert(31). The estimated transportation cost associated with monitoring is reported in Table 27.

Table 27: Transportation cost associated with monitoring of SMA patients

Activity	Annual number of visits	Total annual cost (DKK)
Neurologist consultation	2	200
Orthopedic surgeon consultation	1	100
Physiotherapist consultation	2	200
	Total annual cost (DKK)	**500**
	Total cycle cost applied in the model (DKK)	**42**

4.8 Model uncertainty

4.8.1 Scenario analysis

Scenario analyses are undertaken to assess the impact of varying structural and methodological assumptions in the model. As all scenario analyses are run for all 4 clinical questions,

the complete results of the scenario analysis will be presented in the appendix. Please find the scenario analyses undertaken in Table 28.

Table 28: Scenario analyses undertaken

Number	Parameter	Value	Reasoning
1	Source, BSC	SUNFISH Part 2 placebo (1-year data; ITT)	Test impact of alternative BSC, transition probabilities
2	Source, BSC	SUNFISH Part 2 placebo (1-year data; Excl. Asia)	Test impact of alternative BSC, transition probabilities
3	Source, BSC	Natural history (NatHis-SMA)	Test impact of alternative BSC, transition probabilities
4	Source, BSC	SUNFISH Part 2 placebo (2-year data; ITT)	Test impact of alternative BSC, transition probabilities
5	Source, BSC	SUNFISH Part 2 placebo (2-year data; Excl. Asia)	Test impact of alternative BSC, transition probabilities
6	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; ITT)	Test impact of alternative risdiplam, transition probabilities
7	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; Excl. Asia)	Test impact of alternative risdiplam, transition probabilities
8	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; ITT)	Test impact of alternative risdiplam, transition probabilities
9	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; Excl. Asia)	Test impact of alternative risdiplam, transition probabilities
10	Source, nusinersen	RR MAIC - RULM	Test impact of alternative ITC source for nusinersen
11	Source, nusinersen	RR Bucher - RULM	Test impact of alternative ITC source for nusinersen
12	Source, nusinersen	RR MAIC - HFMSE	Test impact of alternative ITC source for nusinersen
13	Source, nusinersen	RR Bucher - HFMSE	Test impact of alternative ITC source for nusinersen
14	Source, nusinersen	Equal effect	Test impact of alternative ITC source for nusinersen
15	Pooling scenarios – OS SMA type 2	Excluding Belter 2018	Test impact of excluding/including Belter 2018 in OS for SMA type 2
16	Pooling scenarios – OS SMA type 2	Including Belter 2018	Test impact of excluding/including Belter 2018 in OS for SMA type 2
17	Parametric fct survival	Weibull	Test impact of alternative parametric function, OS SMA type 2
18	Parametric fct survival	Gompertz	Test impact of alternative parametric function, OS SMA type 2
19	Parametric fct survival	Exponential	Test impact of alternative parametric function, OS SMA type 2
20	Parametric fct survival	Log-logistic	Test impact of alternative parametric function, OS SMA type 2
21	Parametric fct survival	Log-normal	Test impact of alternative parametric function, OS SMA type 2
22	Parametric fct survival	Generalised gamma	Test impact of alternative parametric function, OS SMA type 2
23	Parametric fct survival	Gamma	Test impact of alternative parametric function, OS SMA type 2
24	Time horizon	30	Test impact of alternative time horizon
25	Time horizon	50	Test impact of alternative time horizon
26	Time horizon	70	Test impact of alternative time horizon
27	Number of caregivers at visits	0	Test impact of inclusion and number of caregivers
28	Number of caregivers at visits	1	Test impact of inclusion and number of caregivers
29	Number of caregivers at visits	2	Test impact of inclusion and number of caregivers

5 Results

5.1 Base case results

Results of the base case analyses are presented below in table 28 - 31. For clinical question 1, the analysis estimated an incremental cost of risdiplam compared to nusinersen of DKK -4,159,010 over a 5-year time horizon. For clinical question 2, the analysis estimated an incremental cost of risdiplam compared to nusinersen of DKK -344,809 over a 5-year time horizon. For clinical question 3, the analysis estimated an incremental cost of risdiplam compared to best supportive care of DKK 9,122,204. For clinical question 4, the analysis estimated an incremental cost of risdiplam compared to best supportive care of DKK 9,295,361.

Table 29: Base case analysis, clinical question 1

	Risdiplam	Nusinersen	Risdiplam vs. Nusinersen
Mean treatment duration	4.67 years	4.67 years	*0 years*
Cost			
Treatment costs	DKK 5,296,311	DKK 9,377,602	*DKK -4,081,291*
Treatment administration cost	DKK 7,620	DKK 80,359	*DKK -72,739*
AE/SAE cost	DKK 1,882	DKK 203	*DKK 1,679*
Outpatient cost	DKK 18,607	DKK 18,607	*DKK 0*
Patient and transportation cost	DKK 41,963	DKK 48,623	*DKK -6,660*
Total	**DKK 5,366,384**	**DKK 9,525,394**	***DKK -4,159,010***

Table 30: Base case analysis, clinical question 2

	Risdiplam	Nusinersen	Risdiplam vs. Nusinersen
Mean treatment duration	4.67 years	4.67 years	*0.0 years*
Cost			
Treatment costs	DKK 9,106,674	DKK 9,373,790	*DKK -267,116*
Treatment administration cost	DKK 7,616	DKK 80,326	*DKK -72,710*
AE/SAE cost	DKK 1,880	DKK 203	*DKK 1,677*
Outpatient cost	DKK 18,597	DKK 18,597	*DKK 0*
Patient and transportation cost	DKK 41,942	DKK 48,602	*DKK -6,660*
Total	**DKK 9,176,710**	**DKK 9,521,518**	***DKK -344,809***

Table 31: Base case analysis, clinical question 3

	Risdiplam	BSC	Risdiplam vs. BSC
Mean treatment duration	4.65 years	4.65 years	*0.0 years*
Cost			
Treatment costs	DKK 9,082,260	DKK 0	*DKK 9,082,260*
Treatment administration cost	DKK 7,596	DKK 0	*DKK 7,596*

AE/SAE cost	DKK 1,871	DKK 173	*DKK 1,698*
Outpatient cost	DKK 18,547	DKK 18,547	*DKK 0*
Patient and transportation cost	DKK 41,829	DKK 11,179	*DKK 30,650*
Total	**DKK 9,152,104**	**DKK 29,899**	***DKK 9,122,204***

Table 32: Base case analysis, clinical question 4

	Risdiplam	BSC	Risdiplam vs. BSC
Mean treatment duration	4.74 years	4.74 years	*0.0 years*
Cost			
Treatment costs	DKK 9,254,625	DKK 0	*DKK 9,254,625*
Treatment administration cost	DKK 7,740	DKK 0	*DKK 7,740*
AE/SAE cost	DKK 1,939	DKK 176	*DKK 1,763*
Outpatient cost	DKK 18,900	DKK 18,900	*DKK 0*
Patient and transportation cost	DKK 42,623	DKK 11,391	*DKK 31,232*
Total	**DKK 9,325,827**	**DKK 30,467**	***DKK 9,295,361***

5.2 Life-time time horizon results

Results of the life-time time horizon analyses are presented below in table 28 - 31. For clinical question 1, the analysis estimated an incremental cost of risdiplam compared to nusinersen of DKK -119,927 over a life-time time horizon. For clinical question 2, the analysis estimated an incremental cost of risdiplam compared to nusinersen of DKK 3,847,920. For clinical question 3, the analysis estimated an incremental cost of risdiplam compared to best supportive care of DKK 41,290,416. For clinical question 4, the analysis estimated an incremental cost of risdiplam compared to best supportive care of DKK 54,678,610.

Table 33: Base case analysis, clinical question 1

	Risdiplam	Nusinersen	Risdiplam vs. Nusinersen
Mean treatment duration	20.42 years	20.42 years	*0.0 years*
Cost			
Treatment costs	DKK 36,038,526	DKK 35,881,861	*DKK 156,665*
Treatment administration cost	DKK 33,331	DKK 307,480	*DKK -274,148*
AE/SAE cost	DKK 7,066	DKK 868	*DKK 6,197*
Outpatient cost	DKK 81,388	DKK 81,388	*DKK -0*
Patient and transportation cost	DKK 183,551	DKK 192,191	*DKK -8,641*
Total	**DKK 36,343,862**	**DKK 36,463,789**	***DKK -119,927***

Table 34: Base case analysis, clinical question 2

	Risdiplam	Nusinersen	Risdiplam vs. Nusinersen
Mean treatment duration	20.99 years	20.99 years	*0.0 years*
Cost			
Treatment costs	DKK 40,958,986	DKK 36,827,344	*DKK 4,131,643*
Treatment administration cost	DKK 34,256	DKK 315,582	*DKK -281,326*
AE/SAE cost	DKK 7,176	DKK 891	*DKK 6,285*
Outpatient cost	DKK 83,645	DKK 83,645	*DKK 0*
Patient and transportation cost	DKK 188,642	DKK 197,323	*DKK -8,682*
Total	**DKK 41,272,706**	**DKK 37,424,785**	***DKK 3,847,920***

Table 35: Base case analysis, clinical question 3

	Risdiplam	BSC	Risdiplam vs. BSC
Mean treatment duration	21.07 years	21.07 years	*0.0 years*
Cost			
Treatment costs	DKK 41,110,939	DKK 0	*DKK 41,110,939*
Treatment administration cost	DKK 34,383	DKK 0	*DKK 34,383*
AE/SAE cost	DKK 7,136	DKK 781	*DKK 6,355*
Outpatient cost	DKK 83,956	DKK 83,956	*DKK 0*
Patient and transportation cost	DKK 189,342	DKK 50,603	*DKK 138,739*
Total	**DKK 41,425,756**	**DKK 135,340**	***DKK 41,290,416***

Table 36: Base case analysis, clinical question 4

	Risdiplam	BSC	Risdiplam vs. BSC
Mean treatment duration	27.90 years	27.90 years	*0.0 years*
Cost			
Treatment costs	DKK 54,439,300	DKK 0	*DKK 54,439,300*
Treatment administration cost	DKK 45,530	DKK 0	*DKK 45,530*
AE/SAE cost	DKK 11,096	DKK 1,035	*DKK 10,061*
Outpatient cost	DKK 111,175	DKK 111,175	*DKK -0*
Patient and transportation cost	DKK 250,727	DKK 67,008	*DKK 183,719*
Total	**DKK 54,857,827**	**DKK 179,218**	***DKK 54,678,610***

5.3 Scenario analysis

Scenario analyses were undertaken to assess the impact of varying structural and methodological assumptions implemented in the model. The results of the scenario analyses are presented in appendix B, section 9.4.

6 Budget impact analysis

6.1 Methods

The budget impact model was developed to estimate the expected budget impact of recommending risdiplam as a possible standard treatment in Denmark for each clinical question presented in the DMC protocol(17). The budget impact was estimated per year for the first 5 years after the introduction of risdiplam in Denmark.

The cost per patient model was partially nested within the budget impact model, and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the population in the cost per patient model.

The analysis was developed by comparing the costs for the Danish regions per year over five years in the scenario where risdiplam is recommended as standard treatment and the scenario where risdiplam is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios.

6.1.1 Incidence of patients each year

For each of the clinical questions, there is an annual incidence of two new patients each year. This is based on epidemiological expectations. In addition, for each clinical question there is a pool of prevalent patients. Based on the clinical question, some of these patients are treated with Nusinersen and are potential candidates for switch. Others are treatment naïve and currently treated with best supportive care. Further details on total patient numbers can be seen in table 36-39.

Table 37: Total patients applied in the budget impact model for clinical question 1

Year 1	Year 2	Year 3	Year 4	Year 5
12	14	16	18	20

Table 38: Total patients applied in the budget impact model for clinical question 2

Year 1	Year 2	Year 3	Year 4	Year 5
36	38	40	42	44

Table 39: Total patients applied in the budget impact model for clinical question 3

Year 1	Year 2	Year 3	Year 4	Year 5
44	46	48	50	52

Table 40: Total patients applied in the budget impact model for clinical question 4

Year 1	Year 2	Year 3	Year 4	Year 5
22	24	26	28	30

6.1.2 Market Share

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. Regardless, the estimates will be associated with uncertainty, and therefore different scenarios were tested in the model.

The expected market shares and patient uptake were estimated for each population based on the DMC protocol (17), the current use of SMA treatment in Denmark and other Nordic countries and expected projections based on discussions with treating physicians. It is not expected, that all patients will be eligible for treatment which is why the estimations of the number of patients are lower than the total number of patients in Denmark.

For clinical question 1 and 2, the scenario of no recommendation from DMC, it is assumed that nusinersen is continued to be used for all eligible patients. This is not the market share is not higher, as there is a significant proportion of patients who are not eligible due to disease related complications or natural disease progression for example scoliosis. In the case of recommendation from DMC, new patients are started on risdiplam and there is a gradual shift from Nusinersen. In this case, as all incident SMA 1 patients would be eligible for risdiplam – the market share is assumed to continue increasing over time.

The market shares and the key assumptions driving the budget impact analysis can be seen in table 37 - 40.

Table 41: Market shares for clinical question 1

	No recommendation for risdiplam					Recommendation for risdiplam				
Treat-ment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Risdiplam	0%	0%	0%	0%	0%	50%	57%	63%	67%	70%
BSC	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Nusinersen	100%	100%	100%	100%	100%	50%	43%	37%	33%	30%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

For clinical question 1, the key assumptions driving market share are:

- Without recommendation, the two new incident patients start on Nusinersen every year. With recommendation, the 2 new incident patients start on Risdiplam every year
- The budget impact analysis assumes there is a pool of 12 SMA type 1 patients in Denmark in year 1. Without recommendation, all patients will be treated with Nusinersen. With recommendation, 50% of currently Nusinersen treated patients will switch to Risdiplam due to simplified administration and lack of effect on current treatment. It is assumed all the switches will occur in year 1.

Table 42: Market shares for clinical question 2

	No recommendation for risdiplam					Recommendation for risdiplam				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Risdiplam	0%	0%	0%	0%	0%	50%	53%	55%	57%	60%
BSC	50%	47%	45%	43%	41%	25%	24%	23%	21.5%	20%
Nusinersen	50%	53%	55%	57%	59%	25%	24%	23%	21.5%	20%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

For clinical question 2, the key assumptions driving market share are:

- Without recommendation, the two new incident patients start on Nusinersen every year. With recommendation, the 2 new incident patients start on Risdiplam every year
- The budget impact analysis assumes there is a pool of 36 non-walking SMA type 2 and 3 patients in Denmark in year 1. Without recommendation, 50% of these patients will be treated with Nusinersen. With recommendation, 50% of currently Nusinersen treated patients will switch to Risdiplam due to simplified administration and lack of effect on current treatment. In addition, 50% of currently untreated patients will be treated with Risdiplam due to ease of administration. It is assumed all the switches will occur in year 1.

Table 43: Market shares for clinical question 3

	No recommendation for risdiplam					Recommendation for risdiplam				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Risdiplam	0%	0%	0%	0%	0%	50%	50%	50%	50%	50%
BSC	100%	100%	100%	100%	100%	50%	50%	50%	50%	50%
Nusinersen	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

For clinical question 3, the key assumptions driving market share are:

- Without recommendation, the two new incident patients are treated with best supportive care. With recommendation, the 2 new incident patients start on Risdiplam every year

- The budget impact analysis assumes there is a pool of 44 SMA type 2 and patients with SMA type 3 who have lost gait function in Denmark in year 1. Without recommendation, 100% of these patients will be treated with best supportive care. With recommendation, 50% of of patients will be treated with Risdiplam.

Table 44: Market shares for clinical question 4

	No recommendation for risdiplam					Recommendation for risdiplam				
Treatment	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Risdiplam	0%	0%	0%	0%	0%	50%	50%	50%	50%	50%
BSC	100%	100%	100%	100%	100%	50%	50%	50%	50%	50%
Nusinersen	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

The market share is based on best available data on uptake and input from Danish experts. For clinical question 4, the key assumptions driving market share are:

- Without recommendation, the two new incident patients are treated with best supportive care. With recommendation, the 2 new incident patients start on Risdiplam every year
- The budget impact analysis assumes there is a pool of 22 SMA type 3 patients who have maintained gait function year 1. Without recommendation, 100% of these patients will be treated with best supportive care. With recommendation, 50% of of patients will be treated with Risdiplam.

6.1.3 Costs

Included costs in the budget impact model were drug acquisition costs, administration costs, supportive care costs, adverse event costs, and end-of-life care costs. Patient- and transportation costs were not included as these are not part of the regional budgets. Discounting was not used in the budget impact model in line with DMC's methods guidelines (18). The undiscounted cost output of the cost per patient model was used directly to inform the cost per year per patient in the budget impact model for risdiplam, placebo, and nusinersen.

6.2 Results

6.2.1 Base case results

Based on the base case assumptions, the estimated budget impact of recommending risdiplam as a possible standard treatment in Denmark for the population described in clinical question 1 was DKK 1.7 mil. with 4 additional patients being on treatment in year 5 as shown in Table 45. The estimated budget impact of recommending risdiplam as possible standard treatment in Denmark for the population described in clinical question 2 was DKK 6.8 mil. with 4 additional patients being on treatment at year 5 in year 5 as shown in Table 46. The

estimated budget impact of recommending risdiplam as possible standard treatment in Denmark for the population described in clinical question 3 was DKK 15.3 mil. in year 5 with 8 additional patients on treatment, as reported in Table 47. The estimated budget impact of recommending risdiplam as possible standard treatment in Denmark for the population described in clinical question 4 was DKK 9.8 mil. in year 5 with 5 additional patients on treatment as shown in Table 48.

Table 45: Budget impact for clinical question 1

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	**DKK 40,507,662**	**DKK 26,876,889**	**DKK 30,101,483**	**DKK 33,299,196**	**DKK 36,468,981**
- Number of patients on treatment (risdiplam or nusinersen)	12.0	14.0	16.0	18.0	20.0
Recommended	**DKK 23,228,402**	**DKK 17,907,640**	**DKK 22,585,127**	**DKK 26,676,327**	**DKK 31,091,386**
- Number of patients on treatment (risdiplam or nusinersen)	12.0	14.0	16.0	18.0	20.0
Total budget impact	**DKK -17,279,260**	**DKK -8,969,248**	**DKK -7,516,356**	**DKK -6,622,870**	**DKK -5,377,595**

Table 46: Budget impact for clinical question 2

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	**DKK 60,830,719**	**DKK 33,832,515**	**DKK 35,547,177**	**DKK 37,309,334**	**DKK 39,117,591**
- Number of patients on treatment (risdiplam or nusinersen)	18.0	19.1	20.2	21.3	22.5
Recommended	**DKK 65,539,719**	**DKK 53,715,576**	**DKK 56,221,030**	**DKK 58,755,818**	**DKK 61,306,459**
- Number of patients on treatment (risdiplam or nusinersen)	27.0	28.5	30.1	31.7	33.3
Total budget impact	**DKK 4,709,000**	**DKK 19,883,061**	**DKK 20,673,853**	**DKK 21,446,484**	**DKK 22,188,868**

Table 47: Budget impact for clinical question 3

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	**DKK 176,330**	**DKK 183,035**	**DKK 526,697**	**DKK 1,037,253**	**DKK 1,713,410**
- Number of patients on treatment (risdiplam or nusinersen)	0.0	0.0	0.1	0.3	0.6
Recommended	**DKK 42,995,252**	**DKK 44,629,087**	**DKK 46,237,641**	**DKK 47,819,344**	**DKK 49,374,236**
- Number of patients on treatment (risdiplam or nusinersen)	22.0	23.0	24.0	25.0	26.0
Total budget impact	**DKK 42,818,922**	**DKK 44,446,052**	**DKK 45,710,945**	**DKK 46,782,092**	**DKK 47,660,827**

Table 48: Budget impact for clinical question 4

	Year 1	Year 2	Year 3	Year 4	Year 5
Not recommended	**DKK 88,483**	**DKK 96,523**	**DKK 104,564**	**DKK 112,603**	**DKK 120,639**
- Number of patients on treatment (risdiplam or nusinersen)	0.0	0.0	0.0	0.0	0.0
Recommended	**DKK 21,574,673**	**DKK 23,535,080**	**DKK 25,495,733**	**DKK 27,455,826**	**DKK 29,415,211**

- Number of patients on treatment (risdiplam or nusinersen)	11.0	12.0	13.0	14.0	15.0
Total budget impact	**DKK 21,486,190**	**DKK 23,438,557**	**DKK 25,391,168**	**DKK 27,343,223**	**DKK 29,294,572**

7 Discussion

A number of limitations are associated with this health economic analysis, one being the absence of data in the model for clinical question 1. As the clinical data is not mature enough to populate this health economic model, the transition probabilities between the health states from SMA type 2 and type 3 have been applied to answer this clinical question. Although the clinical comparative analysis suggests risdiplam is superior to nusinersen on both a number of efficacy and safety endpoints, the inclusion of relative efficacy data between risdiplam and nusinersen based on an unanchored MAIC is expected to introduce a high degree of uncertainty to the result of the health economic analyses(19). Therefore, to avoid this uncertainty, the conservative assumption of equal efficacy between risdiplam and nusinersen and the assumption that the application of the SMA type 2 and type 3 data would apply to the SMA type 1 patients. This may underestimate the efficacy of risdiplam in the model, however, this was done to allow the estimation of a deterministic analysis result with as few uncertainties as possible. Furthermore, for us to best reflect the treatment dosing and characteristics of SMA type 1 patients, patient baseline characteristics from SUNFISH have been applied for the modelling of clinical question.

The assumption of the transition probabilities remaining constant throughout the time horizon was applied due to limitations in long-term data. Clinically, this assumption may not hold true due to the nature of the disease, however, with the current data it is not possible to predict how the transition probabilities will behave over time and whether the treatment effect will be sustained over time. Therefore, to avoid applying a larger assumption to the transition probabilities, they have been assumed to remain constant instead. This assumption is, however, not expected to have an impact on the incremental cost results, as it was observed that using alternative transition probability sets did not alter the incremental cost results in this model adaption (see section 9.4 – Appendix B). This is the case, as there is no difference in the monitoring cost between the health states in this model, as described by a Danish clinical expert(31).

The deterministic results from the model over a 5-year time horizon suggests that risdiplam is a cost-saving option for the patient population in clinical question 1 and 2, while risdiplam was observed to be associated with increased cost for the patient populations in clinical question 3 and 4.

The budget impact analysis suggested that the recommendation of risdiplam would be result in a negative budget impact at year 5 for the population in clinical question 1, while for the remaining clinical question (2, 3 and 4) an increased budget impact was suggested at year 5, but also an increased number of patients treated in all three patient populations described in the DMC protocol(17).

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9 APPENDICES

9.1 Appendix A: Health economic model

9.2 Model structure

9.2.1 State transition models

State transition models also known as Markov and Semi-Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once. Representing such clinical settings with conventional decision trees is difficult and may require unrealistic simplifying assumptions.

Structural assumption

Markov models assume that a patient is always in one of a finite number of discrete health states, called Markov states. All events are represented as transitions from one state to another.

Benefits and limitations with state transition models

Benefits

1. As a result, the use of state transition models can improve transparency around the mechanisms and processes underpinning results generated using extrapolation, and facilitate meaningful sensitivity analyses
2. Markov models allow for multiple sources (e.g. disease specific and death due to other causes)
3. The ability of the Markov model to represent repetitive events and the time dependence of both probabilities and utilities allows for more accurate representation of clinical settings that involve these issues
4. Homogenous transition probabilities

Limitations

1. Lack of memory
2. Discrete time
3. Data requirements need post-progression survival data. This has often not been published
4. Average patient, the results reflect the average patient

Model choice justification

As described above, the choice of a Markov model was deemed appropriate, albeit its limitations, to show how a cohort of patients with a rare disease can progress, regress or stabilise over time.

A Markov model have been developed to simulate the progression/regression of a cohort of SMA type II/III patients through a series of motor milestones. The model was developed in Microsoft Excel 2010. (The model health states depicted in Figure 1 represent the major motor milestone achievements that are possible for the natural history of patients living with type II and III SMA: “non sitting”, “sitting”, “standing”, and “walking”. The definitions are as follows:

- non “sitting”
- The “sitting” state has been split further to highlight the clinical significance of being able to progress to sitting independently (“sitting - unsupported”) from being dependent on some form of support (“sitting - supported”).
- “standing” is the third health state with
- “walking” being the final and highest level of motor function achievable in the model. There is a possibility to further evaluate the impact of both standing and walking as either independent or with support.
- “death”

SMA is a long-term debilitating disease with various comorbidities over time. These and disease related events (scoliosis, respiratory support, feeding support, sleep apnoea, orthopaedic surgery) are considered at each state in the model proportionally with costs being applied in each model cycle for patients that remain alive. We also took into consideration the costs associated with disease morbidity and treatment related impacts.

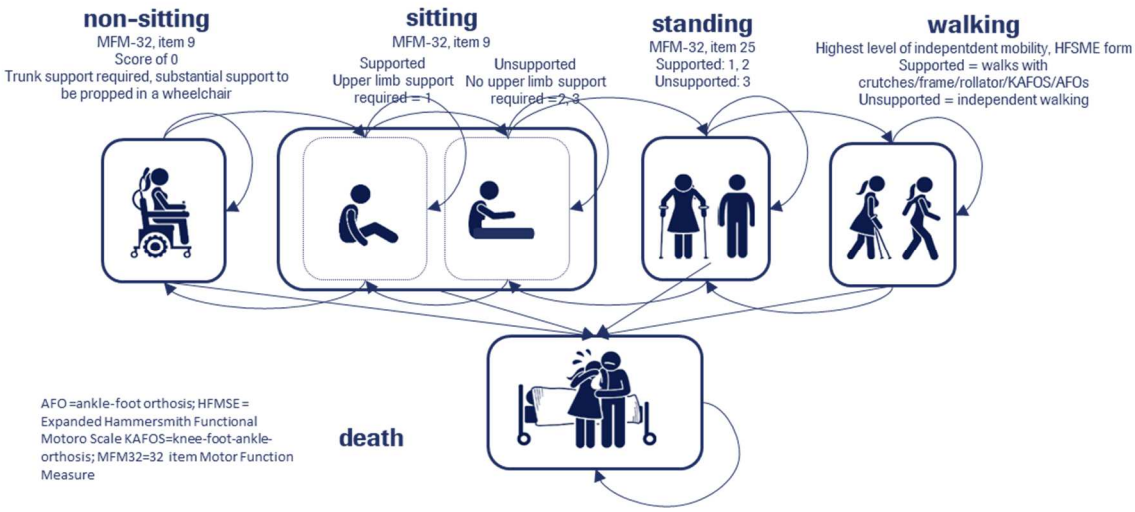


Figure 7: Spinal muscular atrophy (SMA) Type II/III (late-onset)

9.2.2 Disease process and endpoints

The clinical endpoints in the model health states align with the primary endpoint (Motor Function Measure 32 Scale (MFM-32)) that was reported in in the BP39055 (Sunfish) study. The MFM-32 was deemed appropriate to demonstrate motor-function milestones and capabilities for type II and III patients that are reflected in the BP39055 (Sunfish) study population. Therefore, with the exception of the "walking" health state "death" (tunnel state), all the model states were defined by the MFM-32.

State membership for the motor function health states (not sitting, sitting, standing, walking) were based on the MFM-32 score, the primary endpoint of the SUNFISH study. As neither the MFM-32 nor the HFMSE scale contain items that appropriately capture the 'Walking' state, information on the motor milestone achieved (HFMSE level of independent mobility: highest current level of independent mobility) as recorded in the eCRFs were used to define walking instead. Motor function health states are defined as follows:

- **Walking with or without support:** Highest current level of independent mobility, collected as an additional question with the HFMSE (variable HFMS01): "Walks with Crutches/Frame/Rollator" or "Walks with KAFOs/AFOs" or "Independent Walking"
    - Values missing at baseline (n=1) were informed by the SMA History question 'Patient's current level of function' (variable MOTCURR) in the eCRF, which includes the same responses as the HFMS01 variable.
    - Missing values in subsequent visits (n=3) were imputed using a set of rules as described below.
- **Standing with or without support:** Score of 1, 2 or 3 on the MFM item 25 and not walking (as defined above)
    - Missing values (n=4) were informed by using a definition of a score of >1 on the HFMSE items 18 (with support) or 19 (without support)
    - If HFMSE items 18 or 19 were unavailable (n=1), missing values were imputed using a set of rules as described below.
- **Sitting without support**: Score of 2, or 3 on the MFM item 9 and not standing or walking (as defined above)
- **Sitting with support**: Score of 1, on the MFM item 9 and not sitting without support, standing or walking (as defined above)
- **Not sitting**: Score of 0 on the MFM item 9

The following imputation rules were applied to inform missing values:

- If the motor milestone achieved in the next assessment was equal to or better than the previous assessment, the imputation was based on the last observation carried forward (LOCF).

- If the motor milestone achieved in the next assessment was worse than the previous assessment, the imputation was based on the next observation carried backwards (NOCB).

No imputation was conducted for missing assessments due to study discontinuation.

9.2.3 Time dependency

Transition probabilities related to the model health states (i.e. non-sitting, sitting supported, sitting unsupported, standing and walking) are assumed to be constant over the time duration due to the lack of long-term data. In the BSC arm, this is applied for the full time horizon of the model, while the treatment effects have a limited duration. Mortality for patients with Type III is assumed to change with age as represented in National Life tables, while the survival associated with Type II SMA is time dependent as observed in the literature (refer to section 4.6.5).

9.2.4 Cycle length and half-cycle correction

The model cycle length is selected to be one month. The rationale is that it is assumed that transitions from one health state to another occur at the beginning of each cycle. In reality, however, patient transition is a continuous process, which may occur any time during the cycle. By applying a relatively short cycle length of one month, the difference between the actual transition time and the model predicted time is reduced. This allows for more accurate estimation of the length of time patients remain in the health states. This allows also flexibility and accuracy in costing and dosing calculations, since the administration cycles of the different treatments assessed in the model vary between them. Half-cycle correction is applied to the model in order to account for mid-cycle transitions. This assumes that state transitions occur, on average, half-way through the cycle.

9.2.5 Model validation

During the global development of the model, several exercises have been conducted to ensure the robustness of the model:

- External review of the model by clinical experts and physiotherapists
- External review of the model for error checking, sense checking and extreme values – a complete MSExcel log of these activities can be made unavailable upon request.
- Comparison to other economic models for SMA type II/III – this is currently an ongoing activity at GA and involves comparing the model outcomes to previously published models for SMA
- Comparison of model outcomes to natural history data - this is also an ongoing activity at GA and involves comparing the model outcomes to what is seen in natural history of SMA. These estimates are already expected to be comparable, as the model uses natural history data from the literature to estimate survival for Type II SMA.

Additional external validation of the model related to survival estimates is described in the section 4.6.5.

9.2.6 Model assumptions

- We assume that patients progress from one motor milestone to the next sequentially, there is no ability for patients to "skip" a health state to progress/regress
- We assume that the MFM scores we have included are representative of daily motor function
- Proportion of AEs, SAEs and disease/treatment related impacts were assumed to be constant proportions across the health states (motor function)
- Need Treatment effect duration of risdiplam will last until death
- Adherence is 100% over a lifetime

9.2.7 Health state transition probabilities

The motor-function health states (not sitting, sitting supported, sitting unsupported, standing, walking) were identified as previously described (refer to Figure 3) and validated with external experts, literature and real-world data.

Data from the placebo-controlled period of Sunfish Part 2 was used to analyse health states and calculate transition probabilities for risdiplam and placebo. SUNFISH Part 1 data was not used, as patients were only placebo controlled for 12 weeks. The ITT population was used in these analyses. Transition probabilities were calculated for risdiplam (EVRYSDI) and placebo (BSC).

In order to estimate the probability of transition between health states, a continuous time multi-state model was fitted to the data. A multi-state model describes how an individual moves between a series of states in continuous time. Continuous time models are a natural way of modelling chronic diseases and assume that movements between health states can occur outside of the observation time points. As acquisition or loss of motor milestones is considered to be a continuous process and deemed potentially feasible in a shorter time interval than 4 months (assessment of the MFM-32 was conducted every 4 months), a continuous time model was considered to be appropriate in this setting. The continuous time Markov model was fitted using the R package 'msm 1.6.7'.

The multistate models were fitted only on the transitions between motor milestones, transitions A to F in Error! Reference source not found.. Transitions to "Death" (G1 to G5) were estimated separately. Refer to "Overall Survival" section.

A patient's improvement in motor milestone achievement was assumed to be sequential. Therefore, the multi-state model was specified so that movements between non-adjacent health states were not allowed. I.e., if a patient was observed at a worse motor function (e.g., not sitting) during one visit and at a better motor function (e.g., standing) during the next visit, it was assumed that the patient was capable of the intermediate motor function (e.g.,

sitting), even if it was not explicitly observed. This applied to both improvement and deterioration of motor function. Transitions highlighted in yellow in **Error! Reference source not found.** were specified to be feasible instantaneously in the multi-state model.

Note that while the model was specified to only allow transitions to adjacent health states *instantaneously*, the monthly transition probability matrices may still provide probabilities for non-adjacent health states, since mathematically the fitted model may predict transitions to occur within *a month*. However, since we again made the assumption that progression was always sequential, non-sequential transitions were ignored when incorporated into the cost-effectiveness model.

Table 49: Allowed instantaneous transitions in the multistate model

		To				
		Not Sitting	**Sitting supported**	**Sitting unsupported**	**Standing**	**Walking**
From	**Not Sitting**					
	Sitting supported					
	Sitting unsupported					
	Standing					
	Walking					

Treatment with risdiplam was included as a covariate on the transitions A to F (Error! Reference source not found.) in the multistate model so that transition probabilities could be estimated for risdiplam and placebo. As only few transitions were observed, constraints were applied to the treatment effect covariate and in order to reduce the risk of overfitting the data. The treatment effect was constrained to be the same for the following transitions:

- "Not Sitting" to "Sitting supported" (A) and "Sitting supported" to "Sitting unsupported" (A1) (light blue in **Error! Reference source not found.**)
- "Sitting unsupported" to "Standing" (B) and "Standing" to "Walking" (C) (light red in **Error! Reference source not found.**)
- "Walking" to "Standing" (D) and "Standing" to "Sitting unsupported" (E) (light purple in **Error! Reference source not found.**)
- "Sitting unsupported" to "Sitting supported" (E1) and "Sitting supported" to "Not Sitting" (F) (light green in **Error! Reference source not found.**)

Error! Reference source not found. provides a frequency table of the number of times each pair of health states were observed in successive observation times. Grey transitions were not considered in the multistate model.

Table 50: Frequency table of observed pairs of consecutive health states

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	8	3	1	0	0
Sitting supported	8	45	8	0	0
Sitting unsupported	4	7	378	5	0
Standing	0	0	6	27	2
Walking	0	1	3	4	24

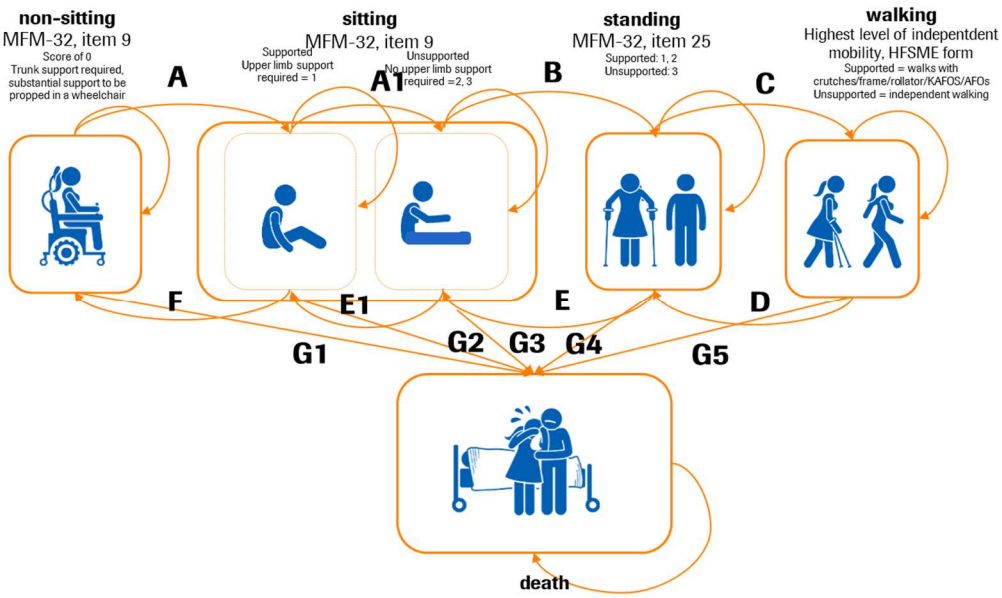


Figure 8: Spinal muscular atrophy (SMA) Type II/III (late-onset), transition probabilities

The monthly transition probabilities including confidence intervals for risdiplam and placebo are presented in Table 9 and Table 10, respectively. Confidence intervals of transition probabilities were estimated using bootstrapping.

For scenario analysis, transition probabilities were also calculated based on non-imputed health states data (missing values for walking and standing were not imputed, and data points excluded), available in section 9.3.1.1.

For the base case, efficacy of BSC is based on the transition probabilities from the placebo arm (Table 10). Efficacy of risdiplam is based on the transition probabilities from the risdiplam arm (Table 9) for the duration of treatment with risdiplam. Upon discontinuation of risdiplam treatment, transition probabilities from BSC are applied in the model.

An alternative source of transition probabilities for BSC is available from the NatHis-SMA study, which may be selected in the drop-down menu for BSC transition probabilities on the "Inputs" sheet. NatHis-SMA a prospective study of the natural history of patients with Type 2 and 3 SMA conducted in Europe. Since the NatHis-SMA study only provided data from natural history, when selecting this option, the risdiplam transition probabilities are derived by applying a hazard ratio calculated from the SUNFISH transition probabilities to the natural history transition probabilities. Refer to the section 9.3.1.2for details and input values.

In the absence of long-term data, transition probabilities were assumed to be constant for the entire time horizon of the model.

Table 51: Risdiplam transition probabilities (SUNFISH Part 2)

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	0.8515	0.145	0.0036	0	0
Sitting supported	0.0635	0.8922	0.0442	0.0001	0
Sitting unsupported	0.0003	0.0079	0.9863	0.0054	0.0001
Standing	0	0.0003	0.0684	0.9087	0.0226
Walking	0	0	0.0025	0.0687	0.9288

Table 52: Placebo (BSC) transition probabilities (SUNFISH Part 2)

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	0.9069	0.0917	0.0014	0	0
Sitting supported	0.0628	0.91	0.0271	0	0
Sitting unsupported	0.0003	0.0076	0.9921	0	0
Standing	0	0.0003	0.0741	0.9256	0

Walking	0	0	0.0029	0.074	0.9231

9.3 A. Scenario analyses, additional inputs

9.3.1.1 SUNFISH model inputs based on non-imputed health state data

As described in Section **Error! Reference source not found.**, in the base case, ability of motor function (Not Sitting, Sitting supported, Sitting unsupported, Standing, Walking) was imputed when value for *one* of the motor functions were missing at a specific time point. No imputation was conducted when values of more than one of the motor functions was missing at a specific time point, e.g. if assessments were missing due to study discontinuation.

Analyses were also conducted with a dataset where missing values were not imputed, i.e, no health state membership was defined at the time point and observations were excluded. Estimates from these analyses are described in the following tables. The user is advised to avoid "mix and matching" analyses of imputed and non-imputed data. For consistency, if the user wishes to assess the non-imputed data analyses, all inputs below should be entered at the same time into the model.

Transition probabilities
Transition probabilities using non-imputed health state data were calculated using the same approach as described in the Section Health state transition probabilities. Mean estimates and confidence intervals are presented for risdiplam in Table 53 and for placebo (BSC) in Table 54.
Note that these transition probabilities will need to be entered into the model manually on the "Treatment Efficacy" worksheet.

Table 53: Risdiplam transition probabilities (SUNFISH Part 2) – no imputation

From\To	Not Sitting	Sitting sup-ported	Sitting unsup-ported	Standing	Walking
Not Sitting	0.8517	0.1447	0.0036	0	0
Sitting sup-ported	0.0634	0.8922	0.0443	0.0001	0
Sitting unsup-ported	0.0003	0.0079	0.9863	0.0054	0.0001
Standing	0	0.0003	0.0685	0.9086	0.0226

Walking	0	0	0.0025	0.0687	0.9288

Table 54: Placebo (BSC) transition probabilities (SUNFISH Part 2) – no imputation

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	0.9068	0.0918	0.0014	0	0
Sitting supported	0.0628	0.91	0.0273	0	0
Sitting unsupported	0.0003	0.0076	0.9921	0	0
Standing	0	0.0003	0.0742	0.9255	0
Walking	0	0	0.0029	0.0739	0.9231

9.3.1.2 NatHis-SMA model inputs

In the base case, model inputs such as transition probabilities are based on analyses from data of the SUNFISH study. The NatHis-SMA study is a prospective study of the natural history of patients with Type 2 and 3 SMA conducted in Europe and is an alternative data source for model inputs. 2-year data from the NatHis-SMA study was analysed to provide alternative model inputs that may be evaluated in scenario analyses in the model.

Motor function health states were defined as follows:

- Walker: Defined as having scores larger than 0 in the MFM items 9 and 25 and being ambulant. To be defined as “ambulant” the patient must be able to walk 10 meters without human assistance or use of an ambulation device such as a cane or a walker.
- Stander without support: Defined as having a score of 1, 2 or 3 in the MFM item 9, a score of 3 in the MFM item 25 and being non-ambulant
- Stander with support: Defined as having a score of 1, 2 or 3 in the MFM item 9, a score of 1 or 2 in the MFM item 25 and being non-ambulant
- Sitter without support: Defined as having a score of 2 or 3 in the MFM item 9, a score of 0 in the MFM item 25 and being non-ambulant

- Sitter with support: Defined as having a score of 1 in the MFM item 9, a score of 0 in the MFM item 25 and being non-ambulant
- Non-Sitter: Defined as having a score of 0 in the MFM item 9, a score of score of 0 in the MFM item 25 and being non-ambulant
- Dead: Death reported in the study

Since there were some differences between NatHis-SMA and SUNFISH, including baseline characteristics, definition of respiratory support, and definition of "Walkers", the user is advised to use all data below together.

Baseline characteristics

Baseline characteristics from the NatHis-SMA study are presented in Table 55. Note that these characteristics will need to be entered into the model manually.

Table 55: Patient baseline characteristics – NatHis-SMA

Baseline characteristic	Value
Age (years)	10
Female (%)	54.32%
Body weight (Kg)	30.18
Type II	65.43%
Type III	34.57%
Respiratory support (Non-invasive BiPAP) %	25.93%
Severe scoliosis (scoliosis degree >45) %	4.94%
Proportion Not sitting at baseline (MFM 9=0)	23.08%
Proportion Sitting w support at baseline (MFM 9=1)	3.85%
Proportion Sitting wo support at baseline (MFM 9=2,3)	34.59%
Proportion Standing at baseline (MFM 25)	5.13%
Proportion Walking at baseline (ambulant)	24.36%
Standing (%) with support (MFM 25=3)	100%
Standing (%) without support (MFM 25=1,2)	*0%*
Walking (%) with support (NA)	0%
Walking (%) without support (ambulant)	*100%*

Transition probabilities

Since the NatHis-SMA study only provided data from natural history, transition probabilities could only be calculated for BSC (assuming that natural history is equivalent to BSC). The same method was applied as described in the Section Health state transition probabilities, except that no covariates were included in the model. Transition probabilities for natural history (BSC) are presented in Table 56.

When selecting this option in the model, risdiplam transition probabilities are derived by applying a hazard ratio calculated from the SUNFISH transition probabilities to the natural history transition probabilities. This approach assumes that the relative efficacy of risdiplam compared to BSC would be the same in a "NatHis-like" population as in the SUNFISH Part 2 population.

The option of using NatHis-SMA transition probabilities can be selected via a dropdown menu on the "Inputs" worksheet.

Table 56: NatHis-SMA transition probabilities

From\To	Not Sitting	Sitting supported	Sitting unsupported	Standing	Walking
Not Sitting	0.9734	0.0259	0.0007	0	0
Sitting supported	0.1037	0.8500	0.0462	0.0001	0
Sitting unsupported	0.0004	0.0066	0.9888	0.0043	0
Standing	0	0.0004	0.1141	0.8855	0
Walking	0	0	0.0002	0.0024	0.9974

9.3.1.3 Overall survival – Pooling scenario including Belter 2018

Results from the pooling scenario including all identified studies in the SLR (including Belter 2018) are provided below. This survival scenario may be selected via a dropdown menu on the "Inputs" worksheet.

Table 13 provides the AIC and Bayesian Information Criterion (BIC) goodness of fit results for the functions used to model OS in Type 2 SMA, using the pooling scenario of all studies identified in the SLR (including Belter 2018). The lower the AIC or BIC values the better the fit of the model. Based on the AIC and BIC statistics, the best fit overall would be obtained with a Gompertz, followed by the Generalised Gamma distribution. It should be noted that these statistical measures only consider model fit to the existing data and does not allow any conclusion to be drawn around the appropriateness of tail of the distribution.

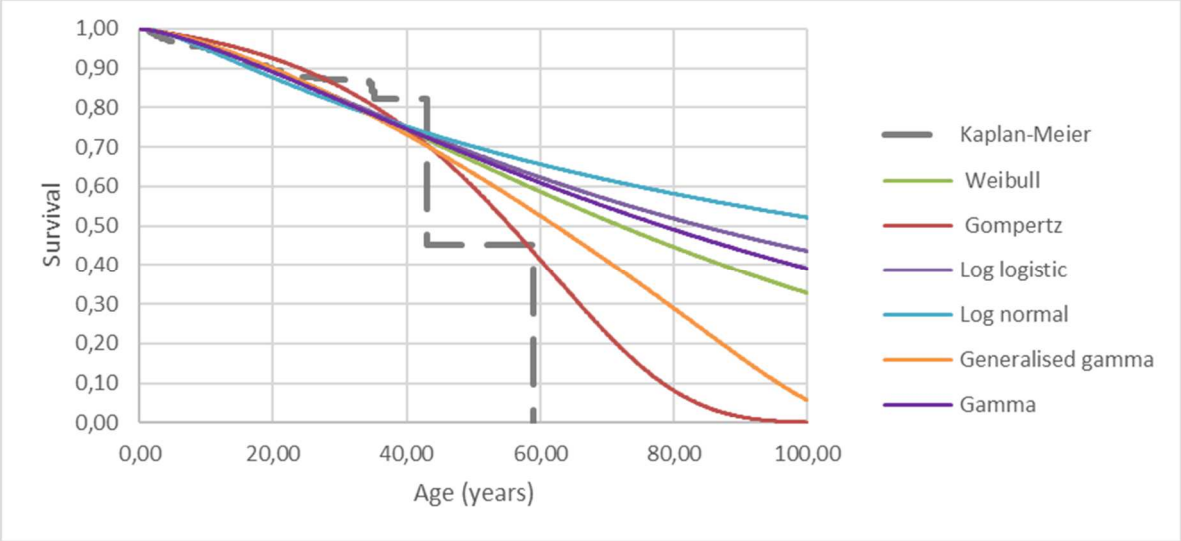
Figure 9 shows that Gompertz is the only distributions that results in a reasonable extrapolation in this pooling scenario, while all others predict survival of patients over the age of 100. Still, a visual inspection shows that the fit is not great and that survival is overestimated up until approximately 30 years of age.

Table 57: AIC and BIC goodness of fit results for Type 2 survival (Pooling scenario including Belter 2018)

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	4312.9 (6)	4317.9 (6)
Weibull	4279.5 (3)	4289.4 (3)
Log-normal	4334 (7)	4344 (7)
Generalised Gamma	4257 (2)	4271.9 (2)
Log-logistic	4299.6 (5)	4309.6 (5)
Gompertz	4213.3 (1)	4223.3 (1)
Gamma	4288.7 (4)	4298.7 (4)

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Figure 9: Comparison of Kaplan-Meier with parametric extraplations (Pooling scenario including Belter 2018)



9.3.1.4 ITC-MAIC RULM and HFMSE relative effects alternative scenarios

Table 58, Table 59 and Table 60 provide alternative risk ratios for nusinersen versus risdiplam that may be used as a proxy for motor function improvement. These have been built-in as options in the economic model and may be selected via a drop-down menu on the "Inputs" worksheet.

Table 58: Risk Ratio for RULM response (Bucher ITC)

RULM response (Bucher ITC)	Proportion responders at 12 months	1-month probability	Risk Ratio
Nusinersen	66%	8.60%	-
Sham	56%	6.61%	-
Risdiplam	79%	12.20%	-
Placebo	48%	5.30%	-
Risk Ratio	**-**	**-**	**0.57**

Table 59: Risk Ratio for HFMSE response (MAIC analysis)

HFMSE response (MAIC)	Proportion responders at 12 months	1-month probability	Risk Ratio
Nusinersen	51%	5.77%	-
Sham	24%	2.26%	-
Risdiplam	66%	8.60%	-
Placebo	49%	5.46%	-
Risk Ratio	**-**	**-**	**1.62**

Table 60: Risk Ratio for HFMSE response (Bucher ITC)

HFMSE response (Bucher ITC)	Proportion responders at 12 months	1-month probability	Risk Ratio
Nusinersen	51%	5.77%	-
Sham	24%	2.26%	-
Risdiplam	58%	7.23%	-
Placebo	48%	5.45%	-
Risk Ratio	**-**	**-**	**1.94**

9.4 B. Scenario analyses, results

9.4.1 Scenario analyses, clinical question 1

Number	Parameter	Value	Inc cost, Risdiplam vs. nusinersen
Base case			**DKK -4,189,759**
1	Source, BSC	SUNFISH Part 2 placebo (1-year data; ITT)	DKK -4,189,759
2	Source, BSC	SUNFISH Part 2 placebo (1-year data; Excl, Asia)	DKK -4,189,759
3	Source, BSC	Natural history (NatHis-SMA)	DKK -4,189,759
4	Source, BSC	SUNFISH Part 2 placebo (2-year data; ITT)	DKK -4,189,759
5	Source, BSC	SUNFISH Part 2 placebo (2-year data; Excl, Asia)	DKK -4,189,759
6	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; ITT)	DKK -4,189,759
7	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; Excl, Asia)	DKK -4,189,759
8	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; ITT)	DKK -4,189,759
9	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; Excl, Asia)	DKK -4,189,759
10	Source, nusinersen	RR MAIC - RULM	DKK -4,189,759
11	Source, nusinersen	RR Bucher - RULM	DKK -4,189,759
12	Source, nusinersen	RR MAIC - HFMSE	DKK -4,189,759
13	Source, nusinersen	RR Bucher - HFMSE	DKK -4,189,759
14	Source, nusinersen	Equal effect	DKK -4,189,759
15	Pooling scenarios – OS SMA type 2	Excluding Belter 2018	DKK -4,189,759
16	Pooling scenarios – OS SMA type 2	Including Belter 2018	DKK -4,197,338
17	Parametric fct survival	Weibull	DKK -4,200,357
18	Parametric fct survival	Gompertz	DKK -4,189,759
19	Parametric fct survival	Exponential	DKK -4,163,795
20	Parametric fct survival	Log-logistic	DKK -4,201,887
21	Parametric fct survival	Log-normal	DKK -4,204,185
22	Parametric fct survival	Generalised gamma	DKK -4,197,172
23	Parametric fct survival	Gamma	DKK -4,201,847
24	Time horizon	30	DKK -1,089,837
25	Time horizon	50	DKK -390,666
26	Time horizon	70	DKK -259,767
27	Number of caregivers at visits	0	DKK -4,168,322
28	Number of caregivers at visits	1	DKK -4,182,613
29	Number of caregivers at visits	2	DKK -4,196,904

9.4.2 Scenario analyses, clinical question 2

Number	Parameter	Value	Inc cost, Risdiplam vs. nusinersen
Base case			**DKK -375,541**

1	Source, BSC	SUNFISH Part 2 placebo (1-year data; ITT)	DKK -375,541
2	Source, BSC	SUNFISH Part 2 placebo (1-year data; Excl, Asia)	DKK -375,541
3	Source, BSC	Natural history (NatHis-SMA)	DKK -375,541
4	Source, BSC	SUNFISH Part 2 placebo (2-year data; ITT)	DKK -375,541
5	Source, BSC	SUNFISH Part 2 placebo (2-year data; Excl, Asia)	DKK -375,541
6	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; ITT)	DKK -375,541
7	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; Excl, Asia)	DKK -375,541
8	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; ITT)	DKK -375,541
9	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; Excl, Asia)	DKK -375,541
10	Source, nusinersen	RR MAIC - RULM	DKK -375,541
11	Source, nusinersen	RR Bucher - RULM	DKK -375,541
12	Source, nusinersen	RR MAIC - HFMSE	DKK -375,541
13	Source, nusinersen	RR Bucher - HFMSE	DKK -375,541
14	Source, nusinersen	Equal effect	DKK -375,541
15	Pooling scenarios – OS SMA type 2	Excluding Belter 2018	DKK -375,541
16	Pooling scenarios – OS SMA type 2	Including Belter 2018	DKK -360,117
17	Parametric fct survival	Weibull	DKK -376,946
18	Parametric fct survival	Gompertz	DKK -375,541
19	Parametric fct survival	Exponential	DKK -404,755
20	Parametric fct survival	Log-logistic	DKK -377,104
21	Parametric fct survival	Log-normal	DKK -386,413
22	Parametric fct survival	Generalised gamma	DKK -376,825
23	Parametric fct survival	Gamma	DKK -380,254
24	Time horizon	30	DKK 2,721,134
25	Time horizon	50	DKK 3,458,055
26	Time horizon	70	DKK 3,672,569
27	Number of caregivers at visits	0	DKK -354,114
28	Number of caregivers at visits	1	DKK -368,399
29	Number of caregivers at visits	2	DKK -382,684

9.4.3 Scenario analyses, clinical question 3

Num-ber	Parameter	Value	Inc cost, Risdiplam vs. BSC
Base case			**DKK 9,091,554**
1	Source, BSC	SUNFISH Part 2 placebo (1-year data; ITT)	DKK 9,091,554
2	Source, BSC	SUNFISH Part 2 placebo (1-year data; Excl, Asia)	DKK 9,091,554
3	Source, BSC	Natural history (NatHis-SMA)	DKK 9,091,554

4	Source, BSC	SUNFISH Part 2 placebo (2-year data; ITT)	DKK 9,091,554
5	Source, BSC	SUNFISH Part 2 placebo (2-year data; Excl, Asia)	DKK 9,091,554
6	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; ITT)	DKK 9,091,554
7	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; Excl, Asia)	DKK 9,091,554
8	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; ITT)	DKK 9,091,554
9	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; Excl, Asia)	DKK 9,091,554
10	Source, nusinersen	RR MAIC - RULM	DKK 9,091,554
11	Source, nusinersen	RR Bucher - RULM	DKK 9,091,554
12	Source, nusinersen	RR MAIC - HFMSE	DKK 9,091,554
13	Source, nusinersen	RR Bucher - HFMSE	DKK 9,091,554
14	Source, nusinersen	Equal effect	DKK 9,091,554
15	Pooling scenarios – OS SMA type 2	Excluding Belter 2018	DKK 9,091,554
16	Pooling scenarios – OS SMA type 2	Including Belter 2018	DKK 9,190,278
17	Parametric fct survival	Weibull	DKK 9,039,719
18	Parametric fct survival	Gompertz	DKK 9,091,554
19	Parametric fct survival	Exponential	DKK 9,031,990
20	Parametric fct survival	Log-logistic	DKK 9,013,424
21	Parametric fct survival	Log-normal	DKK 8,976,514
22	Parametric fct survival	Generalised gamma	DKK 9,071,588
23	Parametric fct survival	Gamma	DKK 9,015,276
24	Time horizon	30	DKK 32,830,138
25	Time horizon	50	DKK 38,816,073
26	Time horizon	70	DKK 40,933,577
27	Number of caregivers at visits	0	DKK 9,091,554
28	Number of caregivers at visits	1	DKK 9,091,554
29	Number of caregivers at visits	2	DKK 9,091,554

9.4.4 Scenario analyses, clinical question 4

Num-ber	Parameter	Value	Inc cost, Risdiplam vs. BSC
Base case			**DKK 9,264,129**
1	Source, BSC	SUNFISH Part 2 placebo (1-year data; ITT)	DKK 9,264,129
2	Source, BSC	SUNFISH Part 2 placebo (1-year data; Excl, Asia)	DKK 9,264,129
3	Source, BSC	Natural history (NatHis-SMA)	DKK 9,264,129
4	Source, BSC	SUNFISH Part 2 placebo (2-year data; ITT)	DKK 9,264,129
5	Source, BSC	SUNFISH Part 2 placebo (2-year data; Excl, Asia)	DKK 9,264,129
6	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; ITT)	DKK 9,264,129

7	Source, Risdiplam	SUNFISH Part 2 risdiplam (1-year data; Excl, Asia)	DKK 9,264,129
8	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; ITT)	DKK 9,264,129
9	Source, Risdiplam	SUNFISH Part 2 risdiplam (2-year data; Excl, Asia)	DKK 9,264,129
10	Source, nusinersen	RR MAIC - RULM	DKK 9,264,129
11	Source, nusinersen	RR Bucher - RULM	DKK 9,264,129
12	Source, nusinersen	RR MAIC - HFMSE	DKK 9,264,129
13	Source, nusinersen	RR Bucher - HFMSE	DKK 9,264,129
14	Source, nusinersen	Equal effect	DKK 9,264,129
15	Pooling scenarios – OS SMA type 2	Excluding Belter 2018	DKK 9,264,129
16	Pooling scenarios – OS SMA type 2	Including Belter 2018	DKK 9,264,129
17	Parametric fct survival	Weibull	DKK 9,264,129
18	Parametric fct survival	Gompertz	DKK 9,264,129
19	Parametric fct survival	Exponential	DKK 9,264,129
20	Parametric fct survival	Log-logistic	DKK 9,264,129
21	Parametric fct survival	Log-normal	DKK 9,264,129
22	Parametric fct survival	Generalised gamma	DKK 9,264,129
23	Parametric fct survival	Gamma	DKK 9,264,129
24	Time horizon	30	DKK 37,151,475
25	Time horizon	50	DKK 47,652,595
26	Time horizon	70	DKK 53,245,307
27	Number of caregivers at visits	0	DKK 9,264,129
28	Number of caregivers at visits	1	DKK 9,264,129
29	Number of caregivers at visits	2	DKK 9,264,129

Medicinrådet

Medicinrådets protokol for vurdering vedrørende risdiplam til behandling af spinal muskelatrofi

Version 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i sin endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel, Medicinrådet undersøger, den behandling, Medicinrådet sammenligner med, og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil den ansøgende virksomhed få besked.

Dokumentoplysninger	
Godkendelsesdato	26. marts 2021
Dokumentnummer	111928
Versionsnummer	1.0

Indholdsfortegnelse

1. Begreber og forkortelser

6MWT: Seks minutters gangtest (*Six minutes walk test)*

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

EMA: Det Europæiske Lægemiddelagentur (*European Medicines Agency*)

EPAR: *European Public Assessment Report*

EUnetHTA: *European Network for Health Technology Assessment*

FDA: *The Food and Drug Administration*

FINOSE: Finland, Norge og Sveriges samarbejde om medicinske teknologivurderinger

GRADE: System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)

HFMSE: *Hammersmith Functional Motor Scale Expanded*

HTA: Medicinsk teknologivurdering (*Health Technology Assessment)*

IQWIG: *The Institute for Quality and Efficiency in Healthcare*

ITT: *Intention to treat*

MFM: *Motor Function Measure scale*

MKRF: Mindste klinisk relevante forskel

NICE: *The National Institute for Health and Care Excellence*

PICO: Population, intervention, komparator og effektmål (*Population, Intervention, Comparison and Outcome)*

RULM: *Revised Upper Limb Module*

SD: Standardafvigelse

SMA: Spinal muskelatrofi

SMD: *Standardized Mean Difference*

Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 26. marts 2021

2. Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Roche, som ønsker, at Medicinrådet vurderer risdiplam (Evrysdi) til spinal muskelatrofi (SMA). Medicinrådet modtog den foreløbige ansøgning den 16. december 2020. Lægemidlet blev forhåndsgodkendt (positive opinion) i EMA den 25. februar 2021.

2.1 Spinal muskelatrofi

5q spinal muskelatrofi (SMA) er en sjælden genetisk sygdom, der medfører muskelsvind og deraf nedsat muskelkraft. Trods sygdommens sjældenhed er SMA den hyppigste genetisk betingede årsag til dødsfald blandt spædbørn. Incidensen i Europa er estimeret til 1 ud af 6000 fødte børn [1].

Sygdommen skyldes en gendefekt i *survival motorneuron 1* (*SMN1*), der betyder, at patienten ikke danner tilstrækkeligt af det SMN-protein, der sikrer fungerende motorneuroner i rygmarv og hjernestamme. SMN-proteinet dannes dog også via *SMN2*, som er til stede i genomet i et variabelt antal kopier, men kun ca. 10 % af det mRNA, som bliver transskriberet fra *SMN2,* bliver til funktionelt protein. Antallet af *SMN2*-kopier har derfor betydning for symptomdebut og sygdommens sværhedsgrad. Der er tale om et kontinuum af sværhedsgrader, der spænder fra få ugers overlevelse til progredierende forværring af motoriske funktioner over mange år. I praksis underinddeles sygdommen i fem stadier (SMA type 0-IV) ud fra tidspunkt for symptomdebut, motorisk udvikling og antal *SMN2*-kopier (Tabel 1) [1][2][3].

Tabel 1. Klinisk klassifikation af spinal muskelatrofi

Type	Antal pt.	Nye pt. per år	Debut alder	Udviklingstrin (ubehandlet)	Overlevelse (ubehandlet)	*SMN2* kopier
0	-	-	Medfødt	Ingen	< 6 måneder	1
1	6[1]	1-2[1,2]	0-6 mdr.	Sidder aldrig	< 2 år	2-3
2	Ca. 100[2]	Ca. 2[2]	6-18 mdr.	Går aldrig	Fra 2 år til normal levetid[4]	3-4
3	Ca. 100[3]	1-2[3]	> 18 mdr.	Står og går, men bliver permanente kørestolsbrugere inden eller i voksen-alder	Normal levetid	4
4	-	-	Voksen-alder[5]	Går i voksenårene	Normal levetid	4-5

1. Ifølge fagudvalget, marts 2021, er der 6 patienter i aktuel behandling med nusinersen.
2. Oplyst på rcfm.dk (RehabiliteringsCenter for Muskelsvind), november 2018.

3. Oplyst på rcfm.dk (RehabiliteringsCenter for Muskelsvind), april 2019.
4. Ubehandlet er ca. 70 % i live ved 25-års alderen [3].
5. Litteraturen oplyser forskellige aldersgrænser. 21 år ifølge Burr et al 2020 [3]. 30-35 år ifølge EMA 2016 [1].

De kliniske karakteristika gælder for ubehandlede patienter. Indførsel af behandling med nusinersen i 2017 har gjort, at der nu er patienter, der opnår motoriske milepæle, der ikke tidligere var mulige. F.eks. vil der være patienter med SMA type 1, der opnår evnen til at sidde. Internationalt er man derfor begyndt at klassificere patienter som 'non-sitters', 'sitters' og 'walkers'.

2.2 Risdiplam

Risdiplam (Evrysdi) er et *antisense oligonucleotid*, der øger mængden af funktionelt SMN-protein.

Den godkendte EMA-indikation er:
Behandling af 5q spinal muskelatrofi (SMA) hos patienter, der er ældre end 2 måneder, som har:

- Den kliniske diagnose SMA type 1, type 2 eller type 3 *eller*
- 1-4 *SMN2*-kopier.

Fagudvalget præciserer, at det betyder, at patienterne har en bi-allelisk deletion og/eller mutation i *SMN1*-genet.

Virkningsmekanismen svarer til virkningsmekanismen ved nusinersen (se afsnit 2.3). En vigtig forskel er, at patienten kan indtage risdiplam oralt hjemme hos sig selv. Lægemidlet administreres som et pulver, der skal blandes op på sygehusapotek eller sygehusafdeling, inden det udleveres til patienten. Blandingen kan indgives via en sonde, hvis patienten ikke kan spise og drikke selv.

Tabel 2. Dosering af lægemidlet afhænger af alder og vægt

Alder og vægt	Dosis
Alder fra 2 mdr. til < 2 år	0,20 mg/kg dagligt
Alder ≥ 2 år:	
- Vægt < 20 kg	0,25 mg/kg dagligt
- Vægt ≥ 20 kg	5 mg dagligt

Risdisplam er et *Orphan drug*, og bliver behandlet af EMA i en accelereret proces.

2.3 Nuværende behandling

Behandlingen af SMA varetages på tre centre i hhv. København, Aarhus og Odense. Målet med den aktuelle lægemiddelbehandling er at forsinke sygdomsprogressionen og derigennem øge patientens overlevelse, funktionsniveau og livskvalitet.

Ved SMA type 1 (non-sitters) er respirationssvigt den hyppigste dødsårsag [3]. Behandlingen handler derfor især om at nedsætte behovet for assisteret ventilation og derved øge muligheden for, at barnet overlever. Herudover tilstræber behandlingen, at barnet opnår de alderssvarende motoriske milepæle. Patienter med SMA type 1, som ikke er i permanent ventilationsbehandling, bliver i Danmark tilbudt nusinersen som standardbehandling iht. Medicinrådets anbefaling.

Ved SMA type 2 og 3 er målet primært at forbedre eller vedligeholde funktionsniveau og livskvalitet. Herunder både de grov- og finmotoriske funktioner. De grovmotoriske funktioner kan f.eks. betyde, at patienter med SMA type 2 (sitters) kan spise selv, kan vende sig selv, eller at patienter med SMA type 3 bevarer deres gangfunktion (walkers). De finmotoriske funktioner kan betyde, at patienten f.eks. kan anvende en computer eller styre et joystick på en elektrisk kørestol.

Patienter med SMA type 2 bliver tilbudt nusinersen som standardbehandling iht. Medicinrådets anbefaling, hvis deres symptomer er debuteret inden 2-års alderen, og sygdomsvarigheden er højst 4 år (svarende til alder < 6 år) ved tidspunkt for opstart af nusinersenbehandling. Det betyder i praksis, at alle nydiagnosticerede patienter med SMA type 2 (og enkelte tidligt debuterende patienter med SMA type 3) i dag får tilbudt nusinersen. I Danmark bliver børn og voksne over 6 år med SMA type 2 og 3 ikke aktuelt tilbudt nusinersen eller anden sygdomsmodificerende behandling som standardbehandling. Der er aktuelt ingen randomiserede studier af nusinersen med patienter over 12 år.

Indførsel af et nationalt screeningsprogram kan på sigt medføre, at præsymptomatiske spædbørn med 2-4 *SMN2*-kopier kan behandles med nusinersen, inden de udviser symptomer. Denne mulighed gælder i øjeblikket for praktiske formål kun til søskende til børn med SMA, som diagnosticeres præ- eller neonatalt.

3. Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, Medicinrådet undersøger (interventionen), af den behandling, Medicinrådet sammenligner med (komparator(er)), og af effektmålene.

Fagudvalget har defineret kliniske spørgsmål for følgende fire populationer:

1- SMA type 1 (non-sitters)
2- Ikke-gående SMA type 2 og 3 (sitters) i alderen 2-11 år

3- Ikke-gående SMA type 2 og 3 (sitters) i alderen 12-25 år
4- SMA type 3 med bevaret gangfunktion (walkers).

Risdiplam er ikke godkendt af EMA til behandling af børn under 2 måneder. Ansøger har oplyst, at data for præsymptomatiske børn tidligst vil være tilgængeligt i 2022-23. Derfor vil effekt hos præsymptomatiske børn ikke indgå i den aktuelle vurdering af risdiplam.

3.1 SMA type 1 (non-sitters)

Klinisk spørgsmål 1:

- Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 1, som ikke er i permanent ventilationsbehandling?

Population
Patienter med SMA type 1 defineret iht. den kliniske klassifikation i tabel 1, og som ikke er i permanent ventilationsbehandling (eksklusionskriterium i studierne).

Intervention
Risdiplam (dosering ift. produktresumé).

Komparator
Nusinersen (dosering ift. produktresumé).

Effektmål
De valgte effektmål fremgår af tabel 3.

Da der er tale om en indirekte sammenligning, vil der blive taget højde for evt. forskelle i patienternes baselinekarakteristika, som, fagudvalget vurderer, kan have betydning for effekten. Ansøger skal for begge lægemidler som minimum angive gennemsnit og range for:

- alder ved symptomdebut
- alder, sygdomsvarighed og ventilationsbehov ved 1. dosis
- CHOP-INTEND score ved baseline.

3.2 Ikke-gående SMA type 2 og 3 (sitters) i alderen 2-11 år

Klinisk spørgsmål 2:

- Hvilken værdi har risdiplam sammenlignet med nusinersen for ikke-gående patienter med SMA type 2 og 3?

Population
Patienter i alderen 2-11 år med SMA type 2 og patienter med SMA type 3, som har mistet gangfunktionen (non-ambulante). Patienter med SMA type 3 og bevaret gangfunktion indgik ikke i SUNFISH-studiet del 2 [4].

Fagudvalget har defineret populationen til alderen 2-11 år (n = 68), da den aldersmæssigt svarer til inklusionskriterierne i CHERISH-studiet, som er det randomiserede studie af nusinersen hos patienter med SMA type 2 (n = 80) [5].

Herudover vil fagudvalget også vurdere data for de to subgrupper med alder 2-5 år og 6-11 år. Årsagen hertil er, at der er evidens for, at tidlig indsættende behandling giver større effekt [6]. I Danmark er nusinersen kun anbefalet som standardbehandling til børn under 6 år. Fagudvalget forventer dog, at der kun vil være 30-40 patienter i hver aldersgruppe (se afsnit 5, særlige forhold for denne protokol).

Intervention
Risdiplam (dosering ift. produktresumé).

Komparator
Nusinersen (dosering ift. produktresumé).

Effektmål
De valgte effektmål fremgår af tabel 4.

3.3 Ikke-gående SMA type 2 og 3 (sitters) i alderen 12-25 år

Klinisk spørgsmål 3:

- Hvilken værdi har risdiplam sammenlignet med placebo for patienter med SMA type 2 og patienter med SMA type 3, som har mistet gangfunktionen?

Population
Patienter i alderen 12-25 år med SMA type 2 og patienter med SMA type 3, som har mistet gangfunktionen (non-ambulante). Patienter med SMA type 3 og bevaret gangfunktion indgik ikke i SUNFISH-studiet [4].

Intervention
Risdiplam (dosering ift. produktresumé).

Komparator
Placebo.

Placebo er valgt som komparator, da der ikke er randomiserede studier af nusinersen eller anden aktiv komparator, som inkluderer børn og voksne over 12 år.

Effektmål
De valgte effektmål fremgår af tabel 4.

3.4 SMA type 3 med bevaret gangfunktion (walkers)

Klinisk spørgsmål 4:
Hvilken værdi har risdiplam sammenlignet med nusinersen for patienter med SMA type 3, som har bevaret gangfunktion?

Population
Patienter med SMA type 3, som har bevaret gangfunktion. Fagudvalget forventer ud fra oplysninger i den foreløbige ansøgning, at der eventuelt vil foreligge ukontrollerede opfølgningsdata for denne patientgruppe, da SUNFISH-studiet del 1 inkluderede gående patienter.

Intervention
Risdisplam (dosering ift. produktresumé).

Komparator
Ingen sygdomsmodificerende behandling.

Ingen sygdomsmodificerende behandling er valgt som komparator, da Medicinrådet ikke har kendskab til randomiserede placebokontrollerede studier af SMA type 3-patienter med bevaret gangfunktion.

Effektmål
De valgte effektmål fremgår af tabel 4.

Risdiplam kan potentielt have større effekt hos gående patienter med SMA type 3, da effekten er positivt korreleret til funktionsniveau. Fagudvalget finder det derfor relevant at afsøge, om der findes effektdata for denne patientgruppe.

3.5 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, der er nævnt i tabel 3 og 4. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). MKRF udtrykker, hvor stor den absolutte forskel mellem risdiplam og nusinersen skal være, for at en eventuel statistisk signifikant forskel også er en klinisk relevant forskel? Hvornår er effekten af risdiplam klinisk relevant bedre eller dårligere end nusinersen (forskellen overstiger MKRF i positiv eller negativ retning)? Hvornår er effekten af de to lægemidler ligeværdig (forskellen overstiger ikke MKRF)? I det følgende afsnit argumenterer Medicinrådet for valget af effektmål og MKRF.

De mindste klinisk relevante forskelle tager udgangspunkt i hændelsesrater fra studierne af nusinersen hos hhv. børn med SMA type 1 (ENDEAR) [7] og SMA type 2 (CHERISH) [5].

Tabel 3. Effektmål for klinisk spørgsmål 1: Patienter med SMA type 1

Effektmål	Klinisk spørgsmål	Vigtighed	Effektmålsgruppe*	Måleenhed	Mindste klinisk relevante forskel efter 1 år**
Overlevelse	1	Kritisk	Dødelighed	Andel p.t i live	5 %-point
Kombineret mortalitet eller permanent ventilations-behandling	1	Kritisk	Alvorligt symptom	Andel pt., som er døde eller anvender respirator > 16 timer/døgn	15 %-point
Permanent ventilations-behandling	1	Vigtigt	Alvorligt symptom	Andel pt., som ikke anvender respirator > 16 timer/døgn	10 %-point
Motoriske milepæle	1	Kritisk	Alvorligt symptom	Andel respondere på CHOP-INTEND	20 %-point
		Vigtigt		Andel pt., der sidder uden støtte	10 %-point
		Vigtigt		Andel pt., der står eller går uden støtte	Narrativt ***
Alvorlige uønskede hændelser	1	Vigtigt	Alvorlig bivirkning	Andel pt., som oplever mindst én hændelse	10 %-point
Ophør pga. bivirkninger	1	Vigtigt	Ikke-alvorlig bivirkning	Andel pt., som ophører behandlingen pga. bivirkninger	10 %-point

* Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
** Effekten ønskes opgjort ved ca. 1 år (svarende til studiernes opfølgningstid: FIREFISH 12 mdr., ENDEAR 13 mdr.).
*** Fagudvalget ønsker yderligere at få oplyst, hvor mange patienter der går uden støtte efter min. 2 års behandling.

Tabel 4. Effektmål for klinisk spørgsmål 2-4: Patienter med SMA type 2 og 3

Effektmål	Klinisk spørgsmål	Vigtighed	Effektmålsgruppe*	Måleenhed	Mindste klinisk relevante forskel efter 1 år**
HFMSE	2, 3 4	Vigtigt Kritisk	Alvorligt symptom	Forskel i point	3 point
RULM	2 og 3	kritisk	Alvorligt symptom	Forskel i point	2 point
MFM-32	3 4	Kritisk Vigtigt	Alvorligt symptom	Forskel i point	3 point
6MWT	4	Vigtigt	Alvorligt symptom	Ændring i antal meter ift. baseline	30 meter
Alvorlige uønskede hændelser	2, 3 og 4	Vigtigt	Alvorlig bivirkning	Andel pt., som oplever mindst én hændelse	10 %-point
Ophør pga. bivirkninger	2, 3 og 4	Vigtigt	Ikke-alvorlig bivirkning	Andel pt., som ophører behandlingen pga. bivirkninger	10 %-point
Livskvalitet	2, 3 og 4	Kritisk	Livskvalitet	Point	5 point eller 0,5 SD

* Effektmålsgruppe refererer til de væsentlighedskriterier, som Medicinrådet lægger til grund for kategoriseringen af de relative forskelle i effekt, bivirkninger eller livskvalitet.
** Effekten ønskes opgjort ved 1 år (Studiernes opfølgningstid er: SUNFISH 12 mdr., CHERISH 15 mdr.).

3.5.1 Effektmål defineret for SMA type 1 (klinisk spørgsmål 1)

Overlevelse (kritisk)
SMA type 1-patienter har ubehandlet en gennemsnitlig forventet levetid under to år. Overlevelse er derfor et kritisk effektmål. I ENDEAR-studiet blev overlevelsen øget med 23 %-point ved behandling med nusinersen ift. sham-kontrol (84 % vs. 61 %) [7]. Størrelsen af den mindste klinisk relevante forskel på overlevelse skal ses i forhold til den forventede kvalitet af det liv, man evt. forlænger (funktionsniveau og trivsel).

Fagudvalget vurderer på denne baggrund, at en forskel på 5 %-point i overlevelsesrate efter ca. 1 år mellem risdiplam og nusinersen er klinisk relevant.

Det betyder, at risdiplam har mindst lige så god effekt som nusinersen, hvis forskellen ikke overstiger 5 %-point i hverken positiv eller negativ retning (ingen merværdi). Hvis effekten af risdiplam er både statistisk signifikant og mere end 5 %-point større end nusinersen, har risdiplam bedre effekt end nusinersen (positiv merværdi).

Permanent ventilationsbehandling (vigtigt)
Permanent ventilationsbehandling betyder, at patienten er afhængig af en respirator i mindst 16 timer i døgnet. Det er et udtryk for, at sygdommen er progredieret i så svær grad, at kraften i muskler, der skal sørge for, at patienten kan trække vejret, er svært nedsat. Det gør samtidig patienten mere modtagelig for lungeinfektioner. Effektmålet defineres derfor som vigtigt. Patienter, som er i permanent ventilationsbehandling inden studiestart, er ekskluderet fra studierne. I ENDEAR-studiet af børn med SMA type 1 endte 22 % i nusinersengruppen og 32 % i sham-kontrolgruppen i permanent ventilationsbehandling [7].

Fagudvalget vurderer på denne baggrund, at en forskel på 10 %-point efter ca. 1 år mellem risdiplam og nusinersen er klinisk relevant.

Kombination af mortalitet og permanent ventilationsbehandling (kritisk)
Kombination af mortalitet og permanent ventilationsbehandling (***event-free survival)*** er det primære effektmål i studiet af nusinersen. Effektmålet er defineret som andel patienter, som enten er døde eller i permanent ventilationsbehandling. Ved vurdering af relevansen af et kombineret effektmål er det centralt, at de hændelser, der kombineres, har samme grad af alvorlighed. Fagudvalget vurderer, at effektmålet er kritisk, da begge hændelser er alvorlige. I ENDEAR-studiet opnåede 39 % i nusinersengruppen og 68 % i sham-kontrolgruppen dette effektmål [7].

Fagudvalget vurderer på baggrund af hændelsesraterne, at en forskel på 15 %-point efter ca. 1 år mellem risdiplam og nusinersen er klinisk relevant.

Motoriske milepæle (kritisk/vigtigt)
Motoriske milepæle er evnen til at opnå aldersvarende funktioner såsom hovedkontrol, rulle fra ryg til side, sidde uden støtte, stå og gå med og uden støtte. Patienter med SMA type 1 er klinisk karakteriseret ved aldrig at opnå evnen til at sidde uden støtte.

<u>CHOP-INTEND respondere (kritisk)</u>
Måling af motoriske milepæle før siddestadiet måles i studierne med CHOP-INTEND (The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders), som er en skala valideret til brug for evaluering af motorisk funktion hos SMA type 1-patienter. Den er opdelt i 16 aktiviteter, som hver tildeles en score fra 0-4 point (max 64 point). En responder er defineret som patienter, der opnår min. 4 points stigning [1]. I ENDEAR var responsraten 71 % vs. 3 % ved sham-kontrol [7].

Fagudvalget vurderer på denne baggrund, at en forskel i respondere på 20 %-point efter ca. 1 år mellem risdiplam og nusinersen er klinisk relevant.

Evne til at sidde uden støtte (vigtigt)

Behandling af SMA type 1 gør, at flere børn opnår evnen til at sidde uden støtte, hvilket er en vigtig funktion i sig selv. Samtidig er det at kunne sidde selvstændigt et tegn på bedre muskelstyrke, stabilitet og balance. Af hensyn til barnets videre motoriske udvikling og i forventning om, at effekten på denne motoriske milepæl afspejler sig i et bedre funktionsniveau på sigt, vurderer fagudvalget, at effektmålet er vigtigt. I praksis anvender studierne forskellige metoder herfor.

I ENDEAR-studiet har man målt evnen til at sidde uden støtte med HINE-2 sitting scale (se fig. 1). Efter 13 måneders behandling opnåede 8 % et af de to stadier 'stable sit' eller 'pivots' ved behandling med nusinersen mod ingen i sham-kontrolgruppen [7].

Fig 1. HINE-2 sitting scale

Sitting	Cannot sit	With support at hips	Props	Stable sit	Pivots (rotates)
		 normal at 4m	 normal at 6m	 normal at 7-8m	 normal at 9m

I FIREFISH-studiet af risdiplam er det primære effektmål evnen til at sidde kortvarigt uden støtte i 5 sekunder efter 1 års behandling med *Bayley scales of Infants and Toddler Development version 3*. Denne måling er en surrogatmarkør for barnets muskelstyrke og ikke ensbetydende med, at barnet som sådan opnår evnen til at sidde selvstændigt i længere tid. Sekundære effektmål var 'sidde uden støtte i 30 sekunder efter 2 års behandling' og 'opnåelse af motoriske milepæle efter hhv. 1 og 2 års behandling målt med HINE-2.

Sammenligningen af effekten af nusinersen og risdiplam ved to forskellige opgørelsesmetoder vil skævvride resultatet. Da fagudvalget forventer, at der foreligger data for HINE-2 sitting scale for begge lægemidler, vil dette effektmål blive anvendt i sammenligningen.

Fagudvalget vurderer, at en forskel på 10 %-point mellem risdiplam og nusinersen i andel patienter, der har *opnået stable sit* eller *pivots* efter ca. 1 år, er klinisk relevant.

Måling af den motoriske milepæl - evne til at stå eller gå uden støtte (vigtigt)

Med nye behandlinger kan der potentielt være patienter, som kan opnå evnen til at stå eller gå uden støtte, hvilket er usandsynligt for en SMA type 1-patient uden sygdomsmodificerende behandling. Dette er derfor også et vigtigt effektmål. Raske børn går normalt omkring 12-15-måneders alderen, men der kan være stor variation selv i den raske population.

I ENDEAR opnåede ingen børn med SMA type 1 evnen til at stå eller gå uden støtte inden for studiets afslutning, hvor børnene i gennemsnit var 18 måneder gamle [8], men opfølgningsstudiet viser, at en enkelt patient opnåede denne funktion efter ca. 4 års behandling [8]. Fagudvalget vurderer, at effektmålet ikke er realistisk til at belyse en forskel på baggrund af studiernes relative korte opfølgningstid, og har derfor ikke

defineret en klinisk relevant forskel. Fagudvalget vil dog gerne have oplyst, om der er patienter, som står eller går uden støtte efter hhv. 1 og 2 års opfølgning.

3.5.2 Effektmål defineret for SMA type 2 og 3

Hammersmith Functional Motor Scale Expanded (HFMSE) (kritisk/vigtigt)
Den udvidede *Hammersmith Functional Motor Scale* kan bruges til både SMA type 2 og 3, da den dækker spektrummet fra patienter, der lige netop kan sidde selv, til patienter, som kan gå og stå uden støtte, og er valideret ved både høje og lave baseline-værdier. Skalaen består af 33 underkategorier, hvor patienten maksimalt kan opnå 66 point. Høj score udtrykker højt funktionsniveau [9].

HFMSE er anvendt som kontinuerligt effektmål i både SUNFISH [4] og CHERISH-studiet [5] og kan derfor bruges til at sammenligne forskellen i opnåede point mellem risdiplam og nusinersen. Hos ikke-gående patienter er skalaen dog mindre følsom for ændringer end RULM og MFM-32, da den ikke måler ændringer i arm- og håndfunktion. Derfor er effektmålet vægtet som vigtigt for ikke-gående patienter (klinisk spørgsmål 2 og 3) og kritisk for gående patienter (klinisk spørgsmål 4).

Størrelsen af den mindste klinisk relevante forskel for HFMSE er i studier af nusinersen defineret som minimum 3 point, men har været diskuteret i flere artikler. En nyere artikel af Stolte et al. fra august 2020 har givet nogle bud på den mindste klinisk relevante forskel ud fra beregninger af standardafvigelse (SEM) og standarddivisioner (0,3 eller 0,5 SD) hos 51 voksne patienter med SMA type 2 og 3. Resultaterne var forskellige afhængigt af, om patienterne var ambulante (gående) eller non-ambulante [10]. Traditionelt betragtes en SD på 0,3 som en lille effektstørrelse og en SD på 0,5 som en moderat effektstørrelse [11]. I den non-ambulante gruppe, der bedst svarer til patientgruppen i SUNFISH, blev 0,3-0,5 SD omregnet til 2,5-3,8 point. I den gående gruppe (belyses i klinisk spørgsmål 4) var resultatet 2,9-4,3 point [10]. Ved en tilsvarende beregning for totalpopulationen i SUNFISH-studiet kan 0,3-0,5 SD omregnes til 3,7-6,2 point [4].

I en artikel fra 2019 har man beregnet mindste klinisk relevante forskel for børn med SMA type 2 ud fra CHERISH-studiet af nusinersen. Der er anvendt en forankret metode med baggrund i resultaterne for den globale forbedring (CGIC) vurderet af hhv. kliniker og plejerperson. Forfatterne konkluderer her, at en forskel i HFMSE på 3-4 point er klinisk relevant [12].

Fagudvalget vurderer på denne baggrund, at den mindste klinisk relevante forskel i HFMSE mellem risdiplam og nusinersen eller mellem risdiplam og placebo er 3 point efter ca. 1 år. Resultaterne skal justeres for forskelle i studiernes opfølgningstid.

Det dikotome effektmål: patienter, der opnår $\geq$ 3 points forbedring på HFMSE ift. baseline (respondere), er kun prædefineret som effektmål i CHERISH. I SUNFISH er respondere i stedet prædefineret for skalaen MFM-32. Det er uvist, om der foreligger de samme data for HFMSE, men de vil formentlig ikke være publiceret. Resultater for denne

skala kan ikke sammenlignes med HFMSE. Bl.a. fordi MFM-32 er mere sensitiv for finmotoriske ændringer (se senere afsnit om MFM-32).

Revised Upper Limb Module (*RULM) (kritisk)*
Revised Upper Limb Module (RULM) er specifikt udviklet og valideret til at vurdere overekstremiteternes funktion hos patienter med type 2 og 3. Skalaen er mere sensitiv end HFMSE til at måle finmotoriske ændringer og evne til at klare dagligdags aktiviteter hos personer uden gangfunktion (SMA type 2 og ikke-ambulante SMA type 3). Fagudvalget har derfor vægtet effektmålet som kritisk for denne patientgruppe (klinisk spørgsmål 2 og 3). Skalaen omfatter 19 underkategorier, hvor patienten maksimalt kan opnå 37 point. Høj score udtrykker højt funktionsniveau [13].

I den tidligere omtalte undersøgelse af Stolte et al. (se under HFMSE) har man beregnet den mindste klinisk relevante forskel for non-ambulante patienter som 0,3-0,5 SD, som i den undersøgte population svarede til 2,9-4,4 point [10]. Ved tilsvarende beregninger for totalpopulationerne i SUNFISH og CHERISH svarer 0,3-0,5 SD til hhv. 2,1-3,5 point og 1,8-3,0 point.

Fagudvalget vurderer på denne baggrund, at den mindste klinisk relevante forskel i RULM er 2 point efter 1 år mellem risdiplam og nusinersen eller risdiplam og placebo. Resultaterne justeres for forskelle i studiernes opfølgningstid (er hhv. 12 og 15 måneder).

Motor Function Measure scale (MFM-32) (kritisk)
Motor Function Measure scale (MFM32) er en nyere skala, som er valideret til at måle funktionsændringer hos patienter ≥ 6 år med neuromuskulære sygdomme, herunder SMA type 2 og 3. Den omfatter tre domæner: domæne 1 måler 'forflytning i stående stilling', domæne 2 måler 'funktion i ekstremiteter tæt på kroppen' (skuldre, overarme, hofter) og domæne 3 måler 'funktion i ekstremiteter længere væk fra kroppen' (underarme, hænder, fødder). Patienten kan opnå fra 0 til 96 point, hvilket bliver omregnet til en procent (0-100) af højst opnåedelig score. Høj score udtrykker højt funktionsniveau [14].

MFM-32 er anvendt som det primære effektmål i SUNFISH-studiet af risdiplam [4]. Skalaen adskiller sig fra HFMSE ved at være mere sensitiv for ændringer i finmotorikken og dermed mere følsom for ændringer hos patienter uden gangfunktion. Resultater for de to skalaer kan derfor ikke sammenlignes. Heller ikke ved en simpel konvertering (f.eks. omregne HFMSE til en 0-100 skala).

MFM-32 vægtes som kritisk for klinisk spørgsmål 3, hvor risdiplam sammenlignes med placebo, og vigtigt for spørgsmål 4, hvor risdiplam sammenlignes med en sammenlignelig ubehandlet historisk kontrolgruppe (hvor der primært forventes at være data for HFMSE, da MFM-32 er en ny skala), men vil ikke blive anvendt til at belyse klinisk spørgsmål 2, hvor risdiplam sammenlignes med nusinersen, da skalaen ikke anvendes i CHERISH-studiet af nusinersen og dermed ikke kan danne grundlag for denne sammenligning [4].

I SUNFISH er respondere (som for HFMSE) defineret som patienter, der opnår ≥ 3 points forbedring [4]. Der er ikke fundet studier, som kan verificere, hvorvidt størrelsen af denne forbedring er klinisk relevant. Hvis man, jf. artiklen af Stolte et al., beregner den mindste klinisk relevante forskel som 0,3-0,5 SD for totalpopulationen, svarer det til 3,4-5,7 point.

Fagudvalget vurderer på denne baggrund, at den mindste klinisk relevante forskel i MFM-32 mellem risdiplam og placebo er 3 point efter ca. 1 år.

Stabilisering målt med MFM-32

I SUNFISH-studiet opgør man endvidere, hvor mange patienter, der opnår en 'stabilisering' defineret som 'ingen ændring eller forbedring i MFM-32 (≥ 0 point)'. Stabilisering er et mere realistisk effektmål hos ældre børn og voksne, der pga. længere sygdomsvarighed og deraf større tab af motorneuroner har vanskeligere ved at opnå egentlige forbedringer. Den definition af stabilisering, der er anvendt i SUNFISH-studiet, kan dog potentielt dække over forskelle helt ned til 1 point (0 point = stabilisering -1 point = ikke-stabilisering). I praksis falder funktionsniveauet i gennemsnit meget lidt i løbet af et år [15]. Derfor var der også et meget stort 'placeborespons' i SUNFISH-studiet, hvor mere end 50 % af patienterne i placebogruppen opnåede effektmålet 'stabilisering' (95 % CI 40-67 % aflæst på graf hos de ældre aldersgrupper er øvre CI ca. 78 %) [4].

Fagudvalget vil ikke lægge vægt på resultaterne for ´stabilisering' i den aktuelle vurdering, da der er behov for studier med længere opfølgningstid for at kunne vurdere den kliniske relevans af effekten. Fagudvalget betoner dog, at stabilisering i sig selv også er en positiv effekt, som det er vigtigt at få belyst i studier med en længere tidshorisont.

Livskvalitet (kritisk)

Ansøger foreslår data for EQ5D, men det er ikke oplyst, hvorvidt der er data herfor for risdiplam. EQ5D er et generisk redskab, som omfatter 5 spørgsmål, der omregnes til en index score samt en kontinuerlig skala fra 0-100. Der er ikke fundet artikler, som definerer en klinisk relevant ændring hos patienter med SMA.

I CHERISH-studiet af nusinersen er anvendt Pediatric Quality of Life Inventory (PedsQL™) til måling af livskvalitet. Den samlede score er mellem 0 og 100 point, hvor en score på 5 point er mindste klinisk relevante forskel [5].

Scoren på de to skaler kan ikke umiddelbart sammenlignes og vil derfor blive omregnet til en SD. En SD på 0,5 på samme skala har historisk vist sig at have næsten universel relevans som mindste klinisk relevante forskel i livskvalitet på tværs af adskillige sygdomme [16].

Fagudvalget definerer en forskel på 5 point eller 0,5 SD mellem risdiplam og nusinersen eller mellem risdiplam og placebo som den mindste klinisk relevante forskel.

3.5.3 Effektmål defineret specifikt SMA type 3 med gangfunktion

Seks minutters gangtest (6MWT)
6MWT er en simpel test, der belyser patienternes gangfunktion. Den anvendes i kliniske studier på tværs af adskillige sygdomme til at monitorere ændringer i patienterne pga. en høj grad af standardisering og testvaliditet (test-retest korrelationskoefficient på 0,85-0,99 hos gående patienter med SMA) [17,18]. For patienter med SMA-type 3 er det vist, at 6MWT er korreleret med andre motoriske funktionstest, herunder HFMSE.

Hos patienter med Duchennes muskeldystrofi er det vist, at en ændring på ca. 30 meter over en kort periode (< 1 år) er korreleret med sygdomsprogression, skeletmuskelstyrke, grovmotoriske færdigheder, tidspunkt for tab af gangfunktion og livskvalitet. Dette tal er baseret på patienter med en gennemsnitlig baseline på 358-370 meter, og det svarer således til en procentvis ændring på ca. 8 % [19].

Der er ikke selvstændigt etableret den samme dokumentation for, hvordan 6MWT hos patienter med SMA-type 3 er korreleret til livskvalitet eller tidspunkt for komplet tab af gangfunktion. I studiet af Stolte et al. svarede den mindste klinisk relevante forskel beregnet som 0,3-0,5 SD til 48-72 meter, men det er baseret på et studie af 16 voksne patienter med en gangdistance på 94-600 meter [10]. I et studie af 73 patienter (gennemsnitsalder 14 år, baseline 295; SD 133 meter) svarer 0,3-0,5 til 40-67 meter. For patienter med type 3a (gennemsnitsalder 8 år, baseline 257; SD 107) til 32-54 meter. For patienter med type 3b (gennemsnitsalder 27 år, baseline 390; SD 144 meter) til 43-72 meter [20].

Patienter med gangfunktion i SUNFISH del 1 var i gennemsnit 7 år (range 2-24 år). Det er ikke muligt at beregne SD, da fagudvalget ikke aktuelt har adgang til baselinedata. Den mindste klinisk relevante forskel er derfor defineret med forbehold for, at patienternes baselineværdier for 6MWT ikke adskiller sig markant fra ovennævnte niveauer (300-400 meter).

På denne baggrund vurderer fagudvalget, at den mindste klinisk relevante forskel i 6MWT er 30 meter sammenholdt med en ubehandlet sammenlignelig kontrolgruppe.

3.5.4 Effektmål defineret for alle SMA typer

Alvorlige uønskede hændelser (vigtigt)
Alvorlige uønskede hændelser (SAE) er alle alvorlige hændelser, som ikke nødvendigvis er relateret til behandlingen, og er derfor defineret som et vigtigt effektmål. I ENDEAR-studiet af patienter med SMA type 1 var SAE således højere (95 %) i sham-kontrolgruppen end i nusinersengruppen (76 %), og ingen af hændelserne i nusinersengruppen blev vurderet som relateret til behandlingen [7]. Tilsvarende forhold blev fundet i CHERISH, hvor frekvensen af SAE dog generelt var lavere (17 % vs. 29 %) pga. det mildere sygdomsforløb.

På baggrund af dette vurderer fagudvalget, at en forskel i alvorlige uønskede hændelser mellem risdiplam og nusinersen eller mellem risdiplam og placebo på 10 %-point efter

ca. 1 år er klinisk relevant. I sammenligningen med nusinersen skal der justeres for forskelle i studiernes opfølgningstid.

Fagudvalget vil supplere den kvantitative vurdering med en narrativ vurdering. Ansøger bedes derfor liste frekvensen for alle alvorlige uønskede hændelser for både risdiplam og komparatorer opdelt efter arten af hændelsen (f.eks. pneumoni, obstipation, hovedpine etc.).

Ophør med behandlingen pga. bivirkninger (vigtigt)
Patienterne i behandling med nusinersen kan opleve ikke-alvorlige men generende bivirkninger, hvor det kan blive aktuelt at ophøre eller skifte til anden behandling. F.eks. hvis patienter oplever hovedpine relateret til den intratekale administration af nusinersen eller obstipation eller diarré med risdiplam. Da arten af bivirkninger er forskellige mellem lægemidlerne, har fagudvalget fundet det relevant at vurdere 'bivirkninger, som medfører ophør med behandlingen', som et samlet kvantitativt udtryk for den oplevede 'bivirkningsbyrde' for patienten.

På baggrund af dette vurderer fagudvalget, at en forskel i 'ophør pga. bivirkninger' mellem risdiplam og nusinersen eller mellem risdiplam og placebo på 10 %-point efter ca. 1 år er klinisk relevant. I sammenligningen med nusinersen skal der justeres for forskelle i studiernes opfølgningstid.

Fagudvalget beder herudover ansøger liste frekvensen af alle bivirkninger (AE) opdelt efter arten af hændelsen (f.eks. pneumoni, obstipation, hovedpine etc.) med henblik på en narrativ vurdering af bivirkningsprofilerne

4. Litteratursøgning

Medicinrådets vurdering af lægemidlets værdi vil i udgangspunktet være baseret på data fra fuldtekstartikler publiceret i videnskabelige, fagfællebedømte (peer-reviewed) tidsskrifter og data fra Det Europæiske Lægemiddelagenturs (EMAs) European Public Assessment Reports (EPAR). Herudover kan data fra Food and Drug Administration (FDA) og internationalt anerkendte HTA-agenturer (f.eks. NICE, EUnetHTA, FINOSE og IQWiG) indgå i vurderingen. Anvendelse af upublicerede data sker ift. Medicinrådets princippapir [1]. Data skal derudover stemme overens med protokollens beskrivelser. Hvis ansøger har kendskab til upublicerede data, der kan belyse eventuelle angivne mangler, kan de indgå/indsendes, jf. Medicinrådets kriteriepapir.

Klinisk spørgsmål 1 og 2
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der ikke findes studier, hvor risdiplam er sammenlignet direkte med nusinersen. Ansøger har oplyst, at der for klinisk spørgsmål 1 findes ét ukontrolleret studie med risdiplam (FIREFISH). For

[1] For yderligere detaljer se Medicinrådets principper for anvendelse af upublicerede data

klinisk spørgsmål 2 findes der ét randomiseret placebokontrolleret studie af risdiplam (SUNFISH del 2).

Da der kun findes to randomiserede placebokontrollerede studier af nusinersen (ENDEAR og CHERISH) [7][5], som kan belyse effekten af komparator, forventer Medicinrådet, at ansøger anvender disse to studier i den indirekte sammenligning med risdiplam. Derfor skal ansøger ikke søge efter yderligere studier til at belyse klinisk spørgsmål 1 og 2.

Klinisk spørgsmål 3
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at der findes et randomiseret studie (SUNFISH del 2), hvor risdiplam er sammenlignet med placebo i den for spørgsmålet relevante population. Derfor skal ansøger ikke søge efter yderligere studier til at belyse klinisk spørgsmål 3.

Klinisk spørgsmål 4
Medicinrådet er i den foreløbige ansøgning blevet orienteret om, at SUNFISH-studiet del 1 også inkluderer en mindre gruppe patienter med SMA type 3, som har bevaret gangfunktion, hvorfor vi formoder, at der er, formentlig sparsomme, data for denne patientgruppe, som kan belyse klinisk spørgsmål 4. Da studiet ikke indeholder en prospektiv kontrolgruppe, skal ansøger søge efter litteratur for en tilsvarende gruppe af ubehandlede patienter med SMA type 3 og gangfunktion, der kan anvendes som kontrolgruppe i sammenligningen med risdiplam.

Søgestrengene fremgår af bilag 1. Derudover skal ansøger konsultere EMAs EPAR for både det aktuelle lægemiddel og dets komparator(er).

Ansøger skal ekskludere artikler med andre populationer end de, der er specificeret i protokollen, og artikler, der ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Kriterier for litteratursøgning
Ansøger skal søge relevant litteratur i databaserne PubMed og CENTRAL (via Cochrane Library). Ansøger skal dokumentere søgningen for hver af de to databaser, f.eks. i form af et skærmklip eller en downloadet søgestrategi. Eventuelle ændringer/tilføjelser til søgestrategien skal fremgå af dokumentationen.

Kriterier for udvælgelse af litteratur
Ansøger skal screene de artikler, der identificeres ved databasesøgningerne, for overensstemmelse med det/de i protokollen definerede kliniske spørgsmål samt kriterier for studie- og publikationstype(r). Det vil sige, at ansøger skal ekskludere artikler med andre populationer end de i protokollen specificerede. Dette gælder ligeledes for artikler, som ikke rapporterer mindst ét af de kritiske eller vigtige effektmål.

Den ansøgende virksomhed skal ved screening af artikler først ekskludere på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå af en eksklusionsliste, hvor eksklusionen

begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et flowdiagram, som beskrevet i PRISMA-Statement.

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal virksomheden anvende et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen skal vurderes.

5. Den endelige ansøgning

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv, hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO (population, intervention, komparator og effektmål) mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.

- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jf. appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jf. appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem 'fixed effects'-modeller og 'random effects'-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier, og vurdér, hvorvidt resultaterne er sammenlignelige.

Særlige forhold i denne protokol

- Ansøger bedes redegøre for, hvordan vurdering og scoring af de forskellige effektmål (f.eks. MFM-32 eller evne til at sidde uden støtte) blev kvalitetssikret i studiet, herunder træning af personalet.
- **Klinisk spørgsmål 2:** Der foreligger et placebo-kontrolleret studie af nusinersen (CHERISH) i en population, der svarer til klinisk spørgsmål 2. Fagudvalget forventer

derfor umiddelbart, at spørgsmålet helt eller delvist kan besvares ved brug af f.eks. Bucher's metode for justeret indirekte sammenligning. Hvis ansøger ikke vurderer, at det vil være metodisk forsvarligt, beder fagudvalget om en udførlig argumentation herfor.

- Ansøger anmodes om at oplyse baselinekarakteristika og data for de angivne effektmål for både de samlede studiepopulationer og specifikt for de aldersgrupper, som fagudvalget vil belyse i klinisk spørgsmål 2 og 3. Bemærk, at data for aldersgruppen 2-11 år skal angives både samlet og separat for aldersgrupperne 2-5 og 6-11 år. Dvs.:
    - Risdiplam: Baselinekarakteristika og data for effektmål for aldersgrupperne 2-11 år, 2-5 år, 6-11 år og 12-25 år.
    - Nusinersen: Baselinekarakteristika og data for effektmål for aldersgrupperne 2-11 år, 2-5 år og 6-11 år.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

Sundhedsøkonomiske analyser
En sundhedsøkonomisk ansøgning består af en sammenhængende, dynamisk sundhedsøkonomisk model og et teknisk dokument, hvor modellen og de antagelser, der er bygget ind i modellen, beskrives, og hvor ansøgers sundhedsøkonomiske analyse fremgår. Ved dynamisk forstås, at en variabel kun skal ændres ét sted for at være gennemgående for hele modellen. Anvend eventuelt Medicinrådets metodevejledning og tjekliste til sundhedsøkonomiske modeller til at teste modellens dynamik, og at modellen overholder formelle krav.

En sundhedsøkonomisk analyse er ikke et resultat, men er en bred analyse af modellens dynamik, hvilke parametre der har indflydelse på resultaterne, samt hvorfor og hvordan disse parametre indgår. Derfor skal det tekniske dokument som minimum indeholde følgende:

- Beskriv den valgte modelstruktur grundigt.
- Beskriv, hvis der er anvendt en indirekte analyse, hvordan den vil blive håndteret i den sundhedsøkonomiske analyse.
- Begrund og beskriv samtlige antagelser i modellen, og lad specifikke analysevalg fremgå tydeligt.
- Beskriv alle de inkluderede studier, argumentér for deres relevans, og beskriv, hvor og hvordan data anvendes i modellen.
- Begrund både de inkluderede og ekskluderede omkostninger.
- Beskriv, hvad der driver modellen, f.eks. behandlingslængde eller lægemiddelomkostninger.
- Ekstrapoleret data skal beskrives.

- Udfør følsomhedsanalyser, som belyser, hvilke parametre i modellen der har størst indflydelse på resultatet.
- Argumentér for eventuelle afvigelser fra protokollen og den kliniske ansøgning.
- Budgetkonsekvensanalysen skal være dynamisk med omkostningsanalysen, uden diskontering og patientomkostninger.

6. Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad man kan have tiltro til den evidens, Medicinrådet baserer vurderingen af lægemidlets værdi på.

7. Andre overvejelser

Fordele ved oral administration

Fagudvalget vil i vurderingen lægge vægt på, at risdiplam kan indtages oralt, da det både er mere sikkert og bekvemt for patienten, der hermed undgår mulige bivirkninger relatereret til den intratekale administration af nusinersen.

Fagudvalget vil derfor vurdere, hvorvidt patienter, der allerede er startet i behandling med nusinersen, med fordel kan skifte til risdiplam. Resultater fra et studie heraf (JEWELFISH) forventes dog tidligst ved udgangen af 2021. Den foreløbige vurdering vil derfor alene blive baseret på kendskab til de to lægemidlernes kemi, virkningsmekanisme og klinisk effekt.

Den nye administrationsform er samtidig en fordel for sygehusene, som undgår tid og omkostninger forbundet med den intratekale procedure (evt. bedøvelse af patienten mv.). I stedet vil der være lægemiddelrelaterede omkostninger forbundet med at gøre lægemidlet klar til brug og levere det til patienten.

Endelig er det vigtigt at have skærpet opmærksomhed på adhærens, da risdiplam skal indtages dagligt hjemme hos patienten, og sygehuset derfor ikke har samme kontrol over, om lægemidlet reelt bliver indtaget hver dag.

Kombination med andre behandlinger

Fagudvalget vil forholde sig fordele og ulemper ved at kombinere risdiplam med nusinersen eller onasemnogene abeparvovec, såfremt der er data herfor på vurderingstidspunktet for vurdering. Ansøger bedes fremsende eventuelle data herfor. Alternativt oplyse, hvornår data kan forventes.

STOP-kriterier

Fagudvalget vil, som for nusinersen, formulere STOP-kriterier for behandlingen med risdiplam. Ansøger bedes redegøre for mulige kriterier. Særligt for større børn, unge og voksne, hvor der primært er tale om en stabiliserende effekt af patientens funktioner.

8. Behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning.

9. Referencer

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10. Sammensætning af fagudvalg

Medicinrådets fagudvalg vedrørende spinal muskelatrofi

Forvaltningslovens § 3, stk. 2/§ 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg

Sammensætning af fagudvalg	
Formand	**Indstillet af**
Kirsten Svenstrup *Overlæge*	Lægevidenskabelige Selskaber
Medlemmer	**Udpeget af**
Lise Lotte Bjerregaard *Overlæge*	Region Nordjylland
Anette Torvin Møller *Overlæge*	Region Midtjylland
Charlotte Olesen *Overlæge*	Region Midtjylland
Niels Ove Illum *Specialeansvarlig overlæge*	Region Syddanmark
Jesper Nørregaard *Speciallæge i neurologi*	Region Sjælland
Peter Born *Overlæge*	Region Hovedstaden
Søren Bisgård Johansen *Farmaceut*	Dansk selskab for sygehusledelse
Jón Trærup Andersen *Læge, lektor*	Dansk Selskab for Klinisk Farmakologi
Ulla Werlauff *Fysioterapeut, ph.d., leder af UC*	RehabiliteringsCenter for Muskelsvind
Lisbeth Koed Doktor *Patient/patientrepræsentant*	Danske Patienter
Thomas Koed Doktor *Patient/patientrepræsentant*	Danske Patienter
Deltager ikke	Dansk Pædiatrisk Selskab

Medicinrådets sekretariat
Medicinrådet
Dampfærgevej 27-29, 3.th.
2100 København Ø
+45 70 10 36 00
medicinraadet@medicinraadet.dk

11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.0	26. marts 2021	Godkendt af Medicinrådet

12. Bilag

Bilag 1: Søgestrenge

Klinisk spørgsmål 4

Søgestreng til PubMed:

PubMed https://pubmed.ncbi.nlm.nih.gov/advanced/

Search	Query	Results
1	Spinal Muscular Atrophies of Childhood[mh] OR Muscular Atrophy, Spinal[mh:noexp]	Søgetermer for population (ambulante eller type 3)
2	spinal muscular atroph*[ti]	
3	SMA[ti]	
4	#1 OR #2 OR #3	
5	type*[tiab] AND (3[tiab] OR 3A[tiab] OR 3A[tiab] OR III[tiab] OR IIIA[tiab] OR IIIB[tiab] OR IIIs[tiab])	
6	ambula*[tiab]	
7	#4 AND (#5 OR #6)	
8	Kugelberg-Welander*[tiab]	
9	#7 OR #8	
10	Walking[mh] OR Walk Test[mh] OR Walking Speed[mh] OR Gait[mh] OR Gait Analysis[mh] OR walk*[tiab] OR gait[tiab]	Søgetermer for gangfunktion/test-instrumenter
11	6MWT[tiab] OR 6-MWT[tiab] OR 6MWD[tiab] OR 6-MWD[tiab]	
12	Hammersmith Functional Motor Scale Expanded[tiab] OR Expanded Hammersmith Functional Motor Scale[tiab] OR HFMSE[tiab]	
13	Motor Function Measure scale[tiab] OR MFM-32[tiab] OR MFM32[tiab]	
14	#9 AND (#10 OR #11 OR #12 OR #13)	
15	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR case report[ti]	Eksklusion af irrelevante pub.typer

16	#14 NOT #15	
17	english[la] AND hasabstract	Afgrænsning på sprog og publikationsår
18	("2010/01/01"[Date - Publication] : "3000"[Date - Publication])	
19	#16 AND #17 AND #18	Endelig søgning

89 hits

Søgestreng til CENTRAL:

CENTRAL https://www.cochranelibrary.com/advanced-search/search-manager

Search	Query	Results
#1	spinal muscular atrophy:kw	Søgetermer for population (ambulante eller type 3)
#2	(spinal next muscular next atroph*):ti	
#3	SMA:ti	
#4	#1 or #2 or #3	
#5	(type* near/3 (3* or III*)):ti,ab	
#6	ambula*:ti,ab	
#7	#4 and (#5 or #6)	
#8	Kugelberg Welander:ti,ab,kw	
#9	#7 or #8	
#10	(walk* or gait):ti,ab,kw	Søgetermer for gangfunktion/test-instrumenter
#11	(6MW* or 6 next MW*):ti,ab	
#12	("Hammersmith Functional Motor Scale" next Expanded or HFMSE):ti,ab	
#13	("Motor Function Measure scale" or MFM next 32 or MFM32):ti,ab	
#14	#10 or #11 or #12 or #13	
#15	#9 and #14	
#16	(clinicaltrials.gov or trialsearch):so	Eksklusion af irrelevante pub.typer
#17	nct*:au	
#18	#15 not (#16 or #17) with Publication Year from 2010 to 2021, in Trials	Endelig søgning, afgrænset til Trials fra 2010 og frem

21 hits