Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende onasemnogene abeparvovec til behandling af spinal muskelatrofi

Vers. 1.0

Bilagsoversigt

1. Medicinrådets sundhedsøkonomiske afrapportering vedr. onasemnogene abeparvovec, version 1.0
2. Forhandlingsnotat fra Amgros vedr. Zolgensma
3. Høringssvar fra ansøger, inkl. efterfølgende dialog vedr. lægemidlets værdi
4. Medicinrådets vurdering vedr. onasemnogene abeparvovec til behandling af spinal muskelatrofi, version 1.1
5. Ansøgers endelige ansøgning
6. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
7. Medicinrådets protokol for vurdering vedr. onasemnogene abeparvovec til behandling af spinal muskelatrofi, version 1.0

Medicinrådet

Medicinrådets sundheds-økonomiske afrapportering

Onasemnogene abeparvovec

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 analyse 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 analyse 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 indkøbspriser
SMA	Spinal muskelatrofi
SMN2	*Survival of motor neurons 2*
BSC	*Best supportive care*
WHO	*World Health Organization*
AAV9	*Adeno associated virus serotype 9*

2. Konklusion

Inkrementelle omkostninger og budgetkonsekvenser
Omkostningsminimeringsanalysen er baseret på Medicinrådets antagelse om, at onasemnogene abeparvovec og nusinersen har ligeværdig klinisk effekt. Derfor antager Medicinrådet, at der alene er forskel i omkostningerne til lægemidlerne og de omkostninger, der er forbundet med administration heraf. Da der er stor usikkerhed om langtidseffekten af onasemnogene abeparvovec samt behandlingslængden med nusinersen, opgør Medicinrådet kun de inkrementelle omkostninger over en årrække på 1-25 år.

Resultaterne viser, at de inkrementelle omkostninger bliver mindre og mindre over tid, da behandlingen med onasemnogene abeparvovec er en engangsomkostning, mens omkostningerne til behandling med nusinersen bliver akkumuleret over tid. Hvis de to behandlinger, som antaget, fortsætter uændret i ca. [redacted] år, da vil omkostninger pr. patient for onasemnogene abeparvovec og nusinersen være ens. Hvis effekten af onasemnogene abeparvovec holder længere end ca. [redacted] år, vil onasemnogene abeparvovec omkostningsmæssigt være et mere attraktivt valg. Når analysen er udført med AIP, vil omkostningerne pr. patient for onasemnogene abeparvovec og nusinersen være ens ved ca. 9 år.

Medicinrådet vurderer, at budgetkonsekvenserne for regionerne ved anbefaling af onasemnogene abeparvovec som mulig standardbehandling til patienter med SMA type 1 vil være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. [redacted] DKK i år 5. Ved anbefaling til præsymptomatiske patienter vil budgetkonsekvenserne være ca. [redacted] DKK i år 5. Når analysen er udført med AIP, er budgetkonsekvenserne ca. [redacted] DKK i år 5.

3. Introduktion

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

Analysen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra AveXis. Vi modtog ansøgningen den 18. december 2020.

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 onasemnogene abeparvovec på baggrund af følgende kliniske spørgsmål:

Klinisk spørgsmål 1:

Hvilken værdi har onasemnogene abeparvovec sammenlignet med nusinersen for børn med klinisk diagnosticeret SMA type 1?

Klinisk spørgsmål 2:

Hvilken værdi har onasemnogene abeparvovec sammenlignet med nusinersen for præsymptomatiske spædbørn?

4. Vurdering af den sundhedsøkonomiske analyse

På rådsmødet den 24. marts 2021 besluttede Medicinrådet, at ansøgers sundhedsøkonomiske analyse kun kan benyttes i et meget begrænset omfang. Baggrunden for beslutningen var grundlæggende en usikkerhed omkring langtidseffekten af onasemnogene abeparvovec. Det får betydning for, hvilken behandlingslængde for nusinersen der er den relevante at anvende, når omkostningerne for de to behandlinger skal sammenlignes. Ansøgers model indeholder herudover omfattende antagelser vedr. forskelle i effekt, sygdomsudvikling og dødelighed over tid, som ikke er tilstrækkeligt underbygget af data. Medicinrådet udarbejder derfor en simpel omkostningsanalyse, hvor det antages, at der alene er forskel i omkostningerne til lægemidlerne og de omkostninger, der er forbundet med administration heraf. Medicinrådet vælger denne simplificering af analysen på baggrund af det meget begrænsede data, samt at onasemnogene abeparvovec vurderes at være et ligeværdigt behandlingsalternativ til nusinersen vurderet på effekt og bivirkninger, jf. vurderingsrapporten.

Medicinrådets hovedanalyse beskrives i dette dokument. Medicinrådet vælger her at anvende dele af ansøgers hovedanalyse. En kort beskrivelse af ansøgers model kan findes i afsnit 9. Bilag. Beskrivelser af de dele af ansøgers hovedanalyse, som ikke er benyttet, kan findes i det tekniske dokument udarbejdet af ansøger.

Medicinrådet vurderer, jf. vurderingsrapporten, at onasemnogene abeparvovec er et ligeværdigt behandlingsalternativ til nusinersen vurderet på effekt og bivirkninger. Det er en fordel for patienterne, at onasemnogene abeparvovec kun skal gives én gang sammenlignet med potentiel livslang intratekal behandling med nusinersen hver 4. måned. Der er dog stor usikkerhed om langtidseffekt og langtidsbivirkninger.

Medicinrådet vurderer derfor, at der ikke er belæg for to centrale kliniske antagelser i ansøgers model:

Ansøger antager, at der er forskelle i effekt mellem onasemnogene abeparvovec og nusinersen og dermed forskelle i de omkostninger, der er forbundet med selve sygdomsforløbet.

Da Medicinrådet vurderer, at der ikke er vist forskel i effekt, vil omkostningerne til patienternes sygdomsforløb ikke adskille sig udover de omkostninger, der er forbundet med administrationen af lægemidlerne.

Ansøger antager, at effekten af onasemnogene abeparvovec og nusinersen er livslang.

Det betyder, at ansøgers model forudsætter, at patienten forbliver i den samme behandling resten af deres levetid uden at skifte eller få tillagt anden sygdomsmodificerende behandling. For onasemnogene abeparvovec betyder det, at patienten kun får lægemidlet én gang. For nusinersen betyder det, at patienten fortsætter behandlingen livslangt med administration af lægemidlet tre gange om året.

Den forventede behandlingstid for nusinersen er det springende punkt for analysens udfald, fordi behandlingen med onasemnogene abeparvovec er en engangsomkostning, mens omkostningerne til behandling med nusinersen akkumulerer over tid. Det betyder, at det er nødvendigt at estimere, hvor længe patienter bliver behandlet med nusinersen, for at kunne estimere de inkrementelle omkostninger forbundet med i stedet at behandle med onasemnogene abeparvovec. Nusinersen og onasemnogene abeparvovec blev markedsført i hhv. 2017 og 2020. Behandlingerne er potentielt livslange, men der er endnu kun få års erfaring med lægemidlerne og ingen viden om langtidseffekten.

Medicinrådet vurderer, at det ikke er sandsynliggjort, at effekten af onasemnogene abeparvovec er livslang, hvilket betyder, at der er yderligere usikkerhed omkring den faktiske tid, hvor behandlingen, og dermed omkostningerne, vil variere, alt efter om patienter bliver behandlet med det ene eller det andet lægemiddel. Det har altså hverken været muligt at estimere den gennemsnitlige behandlingstid for nusinersen eller længden på behandlingseffekten af onasemnogene abeparvovec. Medicinrådet vil derfor ikke præsentere ét estimat for de inkrementelle omkostninger, som primært resultat af Medicinrådets hovedanalyse, men i stedet et overblik over de inkrementelle omkostninger og de gennemsnitlige årlige inkrementelle omkostninger over en årrække på 1-25 år, hvor patienter, der behandles med nusinersen, antages at være i konstant

behandling. Resultaterne viser således, hvordan de inkrementelle omkostninger vil være givet forskellige antagelser om den gennemsnitlige tid i behandling med nusinersen og den gennemsnitlige tid med behandlingseffekt af onasemnogene abeparvovec.

4.1.1 Analyseperspektiv

Medicinrådets hovedanalyse baseres på de inkrementelle omkostninger og de gennemsnitlige årlige inkrementelle omkostninger over en årrække på 1-25 år, hvor patienter med nusinersen antages at være i konstant behandling. Den øvre grænse på 25 år er valgt, så det er muligt at præsentere, hvornår de inkrementelle omkostninger er 0 DKK pr. patient samt udviklingen i de inkrementelle omkostninger i årene umiddelbart efter. Medicinrådet er i den forbindelse opmærksom på, at markedssituationen inden for de næste 10 år kan ændre sig markant grundet patentudløb for nusinersen og markedsføring af nye lægemidler til sygdommen, som kan have betydning for omkostningerne. Derfor er særligt omkostningerne i analysens første år vigtige.

Omkostninger, der ligger efter det første år, er diskonteret med en rate på 3,5 %.

4.2 Omkostninger

Grundet antagelsen om ligeværdig klinisk effekt er de eneste relevante forskelle, når omkostningerne skal sammenlignes, baseret på lægemiddelomkostninger, hospitalsomkostninger og patientomkostninger i forbindelse med administration af lægemidlerne. Omkostninger, der vil være ens uanset lægemiddel, indgår således ikke i Medicinrådets hovedanalyse.

4.2.1 Lægemiddelomkostninger

De anvendte doser er hentet i de respektive produkters produktresuméer (SPC'er).

Onasemnogene abeparvovec gives som en engangsdosis 1,1 x 1014 vg/kg legemsvægt ved i.v.-infusion. Patienter skal have præmedicinering med prednisolon før og efter behandling med onasemnogene abeparvovec.

Nusinersen gives som støddoser på 12 mg på dag 0 og derefter på dag 14, 28 og 63. Herefter vedligeholdelsesdosis hver 4. måned. Dvs. 6 doser det første år og 3 doser hvert af de efterfølgende år.

På trods af at onasemnogene abeparvovec doseres vægtbaseret har patienternes gennemsnitlige vægt ingen betydning i Medicinrådets hovedanalyse, idet alle pakningsstørrelser på onasemnogene abeparvovec koster det samme, hvorfor prisen på onasemnogene abeparvovec vil være ens.

Anvendte lægemiddelpriser i sygehusapotekets indkøbspris (SAIP) kan ses i Tabel 1.

Tabel 1. Anvendte lægemiddelpriser, SAIP, (maj 2021)

Lægemiddel	Styrke	Pakningsstørrelse	Pris [DKK]	Kilde
Onasemnogene abeparvovec	8,3 ml	2 stk.	[redacted]	Amgros
Prednisolon	5 mg	100 stk.	[redacted]	Amgros
Nusinersen	2,4 mg/ml	1 stk. á 5 ml	[redacted]	Amgros

4.2.2 Hospitalsomkostninger

Omkostninger til administration af lægemidlerne

Medicinrådet inkluderer følgende omkostninger til administration af onasemnogene abeparvovec og nusinersen. Infusion med onasemnogene abeparvovec indebærer, at patienterne skal have foretaget en *anti adeno associated virus serotype 9* (anti-AAV9)-test. Behandling med onasemnogene abeparvovec kræver derfor to ambulante besøg på hospitalet. Som enhedsomkostning for et ambulant besøg anvendes 2021 DRG-taksten 01MA99 (MDC01 1-dagsgruppe, pat. 0-6 år) på 2.298 DKK. Derudover estimerer fagudvalget, at behandling med onasemnogene abeparvovec vil kræve en GMO-blandestation til at præparere onasemnogene abeparvovec, idet engangsdele bliver skiftet ud efter hver blanding. Det er ikke muligt at estimere omkostningerne forbundet til en blanding i en blandestation, fordi dette afhænger af Arbejdstilsynets klassificering af onasemnogene abeparvovec og det sikkerhedsniveau, der skal arbejdes efter. Fagudvalgets bedste bud er, at omkostningerne pr. blanding vil koste omkring 55.000 DKK, hvis onasemnogene abeparvovec kan gå ind under GMO klasse 1. Derudover vil patienten skulle indlægges og være til observation i et døgn i forbindelse med administration af onasemnogene abeparvovec. Medicinrådet inkluderer derfor 2021 DRG-taksten 01MA99 (MDC01 1-dagsgruppe, pat. 0-6) på 2.298 DKK, jf. Interaktiv DRG med diagnosekode: Spinal muskelatrofi og procedurekoden: Observation af patient efter undersøgelse/behandling.

Hver injektion med nusinersen kræver ét administrationsbesøg på hospitalet. Derudover kræver den intratekale administration, at størstedelen af patienterne skal i generel anæstesi. Medicinrådet inkluderer derfor 2021 DRG-taksten 01MA989 (MDC01 1-dagsgruppe, pat. 0-6) på 2.298 DKK til enhedsomkostningen for administration af nusinersen, jf. Interaktiv DRG med diagnosekode: Spinal muskelatrofi og procedurekoden: Generel anæstesi.

Anvendte ressourceforbrug for administration af onasemnogene abeparvovec og nusinersen samt enhedsomkostninger kan ses i Tabel 2.

Tabel 2. Medicinrådets estimering af omkostninger til lægemiddeladministration

		Antal	Enhedsomkostning [DKK]	Kilde
Administration med onasemnogene abeparvovec	Ambulant besøg	1	2.298	2021 DRG-takst: 01MA99
	Observation	1	2.298	2021 DRG-takst: 01MA99
	Blanding	1	55.000	Fagudvalget
	Anti-AAV9-test	1	1.513	Statens Serum Institut
Administration med nusinersen	Ambulant besøg	1	2.298	2021 DRG-takst: 01MA99
	Generel anæstesi	1	2.298	2021 DRG-takst: 01MA99

4.2.3 Patientomkostninger

Patientomkostninger omfatter den tid, patienten anvender til lægemiddeladministration, og inkluderer den effektive tid på hospitalet, ventetid og transporttid. Medicinrådet estimerer, at patienten i gennemsnit er 8 timer på hospitalet ved hver injektion med nusinersen. Patienter, der skal have infusion med onasemnogene abeparvovec, indlægges og vil være til observation i et døgn, svarende til 24 timer.

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

5. Resultater

5.1 Resultatet af Medicinrådets hovedanalyse

Nedenfor præsenteres et overblik over de inkrementelle omkostninger og de gennemsnitlige årlige inkrementelle omkostninger over en årrække på 1-25 år for både patienter med SMA type 1 og præsymptomatiske patienter med op til 3 *SMN2*-kopier. Patienter i behandling med nusinersen antages at være i konstant behandling, og patienter i behandling med onasemnogene abeparvovec antages ikke at modtage anden behandling i perioden. Resultaterne viser således, hvordan de inkrementelle omkostninger vil være givet forskellige antagelser om den gennemsnitlige tid i behandling med nusinersen og den gennemsnitlige tid med behandlingseffekt af onasemnogene abeparvovec.

Alle relevante omkostninger for behandling med onasemnogene abeparvovec falder i år 1 og udgør ca. [redacted] DKK. For behandling med nusinersen er der omkostninger forbundet med opstart i behandling det første år, hvormed omkostningerne udgør ca. [redacted] DKK, mens omkostningerne er ca. [redacted] DKK pr. år efterfølgende, så længe patienten er i behandling.

I Tabel 3 præsenteres omkostningerne for de første to år for at give et indblik i, hvad der driver de inkrementelle omkostninger. I beregningen af omkostningerne efter år 2 benyttes de samme omkostninger, som fremgår for nusinersen i år 2 (med årlig diskontering).

Tabel 3. Årlige omkostninger baseret på Medicinrådets hovedanalyse ved sammenligning med nusinersen for behandling i år 1 og år 2, DKK, diskonterede tal

	Onasemnogene abeparvovec		Nusinersen	
	År 1	**År 2**	**År 1**	**År 2**
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalsomkostninger	66.001	0	36.768	17.162
Patientomkostninger	4.854	0	7.660	4.290
Årlige omkostninger	[redacted]	[redacted]	[redacted]	[redacted]

I Tabel 4 præsenteres de akkumulerede omkostninger intervallet på 1-25 år jf. afsnit 4.1.1 Analyseperspektiv. Analysen præsenterer således resultater under forskellige antagelser, om hvor længe man kan antage, at 1) patienter i behandling med nusinersen antages at være i behandling, og 2) patienter i behandling med onasemnogene abeparvovec ikke modtager anden behandling.

De akkumulerede inkrementelle omkostninger bliver mindre, jo længere begge ovenstående antagelser holder. Hvis antagelserne holder i ca. [redacted] år, da vil omkostninger pr. patient for onasemnogene abeparvovec og nusinersen være ens. Hvis antagelserne holder udover de [redacted] år, vil onasemnogene abeparvovec omkostningsmæssigt være et mere attraktivt valg.

Tabel 4. Akkumulerede omkostninger for onasemnogene abeparvovec sammenlignet med nusinersen baseret på Medicinrådets hovedanalyse, diskonterede tal

Tid i behandling	Onasemnogene abeparvovec	Nusinersen	Inkrementelle omkostninger	
			SAIP (DKK)	**AIP (DKK)**
1 år	[redacted]	[redacted]	[redacted]	11.210.421
2 år	[redacted]	[redacted]	[redacted]	9.626.476
5 år	[redacted]	[redacted]	[redacted]	5.188.839

Tid i behandling	Onasemnogene abeparvovec	Nusinersen	Inkrementelle omkostninger	
10 år	[redacted]	[redacted]	[redacted]	-1.261.488
15 år	[redacted]	[redacted]	[redacted]	-6.692.489
20 år	[redacted]	[redacted]	[redacted]	-11.265.247
25 år	[redacted]	[redacted]	[redacted]	-15.115.387

I Tabel 5 præsenteres de gennemsnitlige omkostninger pr. behandlingsår for onasemnogene abeparvovec og nusinersen samt de gennemsnitlige årlige inkrementelle omkostninger pr. behandlingsår. Tallene i Tabel 5 svarer til dem, der er præsenteret i Tabel 4, men giver et billede af faldende omkostninger pr. behandlingsår, jo længere antagelserne holder. Hvis antagelserne holder i fx 10 år, da vil de årlige inkrementelle omkostninger pr. patient i gennemsnit blive ca. [redacted] DKK pr. år inden for denne 10-årige periode (i alt ca. [redacted] DKK for 10 år). I lighed med resultaterne i Tabel 4, vil omkostningsforskellen mellem onasemnogene abeparvovec og nusinersen være 0 DKK omkring år [redacted].

Tabel 5. Gennnesnitlige omkostninger pr. år for onasemnogene abeparvovec sammenlignet med nusinersen opgjort for forskellige antal år i behandling baseret på Medicinrådets hovedanalyse, diskonterede tal

Tid i behandling	Onasemnogene abeparvovec	Nusinersen	Gennemsnitlige årlige inkrementelle omkostninger pr. behandlingsår
1 år	[redacted]	[redacted]	[redacted]
2 år	[redacted]	[redacted]	[redacted]
5 år	[redacted]	[redacted]	[redacted]
10 år	[redacted]	[redacted]	[redacted]
15 år	[redacted]	[redacted]	[redacted]
20 år	[redacted]	[redacted]	[redacted]
25 år	[redacted]	[redacted]	[redacted]

6. Budgetkonsekvenser

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

- Onasemnogene abeparvovec bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- Onasemnogene abeparvovec bliver ikke anbefalet som standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

Budgetkonsekvenserne vil afhænge af tiden på behandling for patienter behandlet med nusinersen. Medicinrådet vurderer, at det ikke er muligt at give et estimat for dette på baggrund af data. For at kunne præsentere en budgetkonsekvensanalyse benyttes en antagelse om, at patienter, der behandles med nusinersen, vil blive behandlet i minimum 5 år. Da budgetkonsekvensanalysen opgøres over en 5-årig periode vil en eventuel længere gennemsnitlig behandlingslængde for patienter behandlet med nusinersen ikke ændre budgetkonsekvenserne. Hvis patienterne i gennemsnit reelt bliver behandlet kortere tid end 5 år med nusinersen, vil de præsenterede budgetkonsekvenser være underestimeret.

6.1 Medicinrådets estimat af patientantal og markedsandel

På nuværende tidspunkt behandles 6 patienter med SMA type 1 og er derfor kandidater til behandling med onasemnogene abeparvovec, mens der vil være en incidens på [redacted] nydiagnosticerede patienter årligt.

Fagudvalget vurderer, at onasemnogene abeparvovec vil have et markedsoptag på [redacted] % af de nydiagnosticerede patienter i år 1, 2, 3, 4 og 5. Derudover vurderer fagudvalget, at det vil være 50 % af patienterne på nusinersen, som vil ønske at skifte til onasemnogene abeparvovec, se Tabel 6. Dog pointerer fagudvalget, at markedsoptaget er usikkert, da det afhænger af patienternes præferencer.

Tabel 6. Medicinrådets estimat af antal nye patienter pr. år for patienter med SMA type 1

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke					
Onasemnogene abeparvovec	0	0	0	0	0
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Der er på nuværende tidspunkt kun én præsymptomatisk patient i behandling, og derudover vil incidensen være [redacted] med op til 3 *SMN2*-kopier hvert 5. år, se Tabel 7. Fagudvalget forventer dog, at patientantallet vil se anderledes ud, når der kommer en screeningsmetode, men den er endnu ikke implementeret. Derfor er det eksakte patientantal usikkert. Indførelse af et screeningsprogram vil betyde, at patienter med SMA type 1 bliver diagnosticeret, når de er præsymptomatiske, hvormed omkostningerne til de incidente patienter flytter fra gruppen med SMA type 1 til gruppen af præsymptomatiske.

Tabel 7. Medicinrådets estimat af antal nye patienter pr. år for præsymptomatiske patienter

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke					
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Markedsoptaget for onasemnogene abeparvovec er usikkert grundet patienternes præferencer. Medicinrådet vælger derfor at udarbejde en følsomhedsanalyse for budgetkonsekvenserne for både patienter med SMA type 1 og præsymptomatiske patienter, hvor markedsoptaget for onasemnogene abeparvovec øges til 100 % for både de nuværende patienter, som er i behandling med nusinersen, og de patienter, som diagnosticeres hvert år, se Tabel 8 og Tabel 9.

Tabel 8. Medicinrådets estimat af antal nye patienter pr. år for patienter med SMA type 1 med et markedsoptag på 100 % for onasemnogene abeparvovec

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	0	0	0	0	0
Anbefales ikke					
Onasemnogene abeparvovec	0	0	0	0	0

	År 1	År 2	År 3	År 4	År 5
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Tabel 9. Medicinrådets estimat af antal nye patienter pr. år for præsymptomatiske patienter med op til 3 *SMN2*-kopier med et markedsoptag på 100 % for onasemnogene abeparvovec

	År 1	År 2	År 3	År 4	År 5
Anbefales					
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	0	0	0	0	0
Anbefales ikke					
Onasemnogene abeparvovec	0	0	0	0	0
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2 Medicinrådets budgetkonsekvensanalyse

Budgetkonsekvenserne vil afhænge af tiden på behandling for patienter behandlet med nusinersen. Medicinrådet vurderer, at det ikke er muligt at give et estimat for dette på baggrund af det tilgængelige kliniske data. For at kunne præsentere en budgetkonsekvensanalyse benyttes en antagelse om, at patienter, der behandles med nusinersen, vil blive behandlet i minimum 5 år.

Patienter med SMA type 1

Medicinrådet estimerer, at anvendelse af onasemnogene abeparvovec for patienter med SMA type 1 vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 1 faldende til [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 10. Hvis analysen udføres med AIP, bliver budgetkonsekvenserne [redacted] DKK i år 1 faldende til [redacted] DKK i år 5.

Tabel 10. 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]

Præsymptomatiske patienter

Medicinrådet estimerer, at anvendelse af onasemnogene abeparvovec for præsymptomatiske patienter med op til 3 *SMN2*-kopier vil resultere i budgetkonsekvenser på ca. [redacted] DKK i år 1 faldende til [redacted] DKK i år 5. Resultatet er præsenteret i Tabel 11. Hvis analysen udføres med AIP, bliver budgetkonsekvenserne ca. [redacted] DKK i år 1 faldende til [redacted] DKK i år 5.

Tabel 11. Medicinrådets analyse af totale budgetkonsekvenser for præsymptomatiske patienter med op til 3 *SMN2*-kopier, 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]

6.2.1 Resultat af følsomhedsanalyser for budgetkonsekvensanalysen

Ved samme antagelser som i Medicinrådets hovedanalyse for budgetkonsekvenser men med 100 % markedsoptag for onasemnogene abeparvovec.

Patienter med SMA type 1

Medicinrådet estimerer, at omkostningerne vil være ca. [redacted] DKK i år 1 faldende til ca. [redacted] DKK i år 5 for anvendelse af onasemnogene abeparvovec for patienter med SMA type 1, se Tabel 12.

Tabel 12. Medicinrådets analyse af totale budgetkonsekvenser for patienter med SMA type 1 med et markedsoptag på 100 % for onasemnogene abeparvovec, 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]

Præsymptomatiske patienter

Medicinrådet estimerer, at omkostningerne vil være ca. [redacted] DKK i år 1 faldende til ca. [redacted] DKK i år 5 for anvendelse af onasemnogene abeparvovec for præsymptomatiske patienter med op til 3 *SMN2*-kopier, se Tabel 13.

Tabel 13. Medicinrådets analyse af totale budgetkonsekvenser for præsymptomatiske patienter med op til 3 SMN2-kopier med et markedsoptag på 100 % for onasemnogene abeparvovec, 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

Der er store usikkerheder forbundet med den sundhedsøkonomiske analyse, idet analysen bygger på to antagelser, som man ikke ved, hvor længe holder. En central uvished er langtidseffekt af onasemnogene abeparvovec, hvilket medfører en usikkerhed om, hvorvidt patienter vil overgå til anden behandling. En anden central uvished er, hvor længe patienterne vil blive behandlet med nusinersen. Endelig er der usikkerhed om, hvorvidt patienterne vil skifte til andre nye eller billigere behandlinger på markedet inden for en nærmere tidshorisont.

Omkostningerne til behandling med onasemnogene abeparvovec er dog sikre, da alle omkostninger til lægemidlet falder i år 1. Det betyder, at det som udgangspunkt vil være sundhedsvæsenet, der skal bære de mulige konsekvenser af den ovenfor beskrevne usikkerhed, medmindre der aftales en alternativ betalingsmodel med ansøger.

Med den nuværende pris vil omkostningerne til onasemnogene abeparvovec være lavere end for nusinersen efter [redacted] år, og omkostningsmæssigt mere attraktivt, jo længere effekten varer ved. Medicinrådet forventer, at der inden for de næste 10 år dels kan være patentudløb for nusinersen, som kan medføre billigere alternativer, dels kan der være markedsført andre mulige behandlingsalternativer. Derfor er der stor usikkerhed om, hvordan markedet ser ud på længere sigt. Konkret bliver ét lægemiddel (risdiplam) til samme sygdom aktuelt vurderet i Medicinrådet. Derfor er omkostningerne, som ligger de første år af analysen, særligt vigtige.

Medicinrådets hovedanalyse tager højde for de omkostninger, der vil være for patienterne i forbindelse med fortsat administration af nusinersen tre gange pr. år (inklusive tid og transport til hospitalsbesøg), men ikke for de gener, det medfører for patienten og evt. påvirkning af livskvalitet, der følger med. Den potentielle sundhedseffekt ved at undgå gene og ubehag, som gentagne behandlinger med nusinersen kan medføre, har ikke været mulig at kvantificere. Det er dog fortsat en mulighed, at Medicinrådet kan overveje, hvorvidt fordelen for patienterne ved at undgå gentagne behandlinger i sig selv skaber en yderligere værdi.

8. Referencer

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9. Bilag

9.1 Ansøgers antagelser og forudsætninger for model

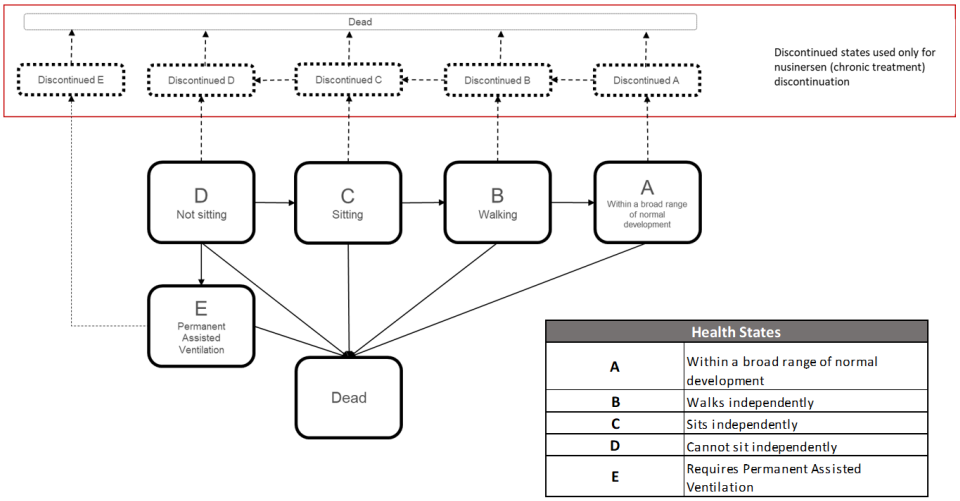
Ansøger har baseret analysen på de samme studier, som indgik i Medicinrådets vurdering af den kliniske værdi (START, STRIVE-US, ENDEAR og NURTURE [5–9]).

Analysen for SMA type 1 er baseret på data med optil 24 måneders opfølgningstid for onasemnogene abeparvovec [5-7] og 13 måneders opfølgningstid for nusinersen [8], hvilket anvendes til at modellere opnåelsen af milepæle for patienter med SMA type 1. Grundet manglende data for overlevelse udover studietiden (13-24 måneder) supplerer ansøger med data for naturhistoriske sygdomsforløb fra patienter med SMA type 1, der ikke modtager aktiv behandling. Dette inkluderer et observationelt studie for 194 SMA type 1-patienter med trakeostomi eller non-invasivventilation (NIV) offentliggjort af Gregoretti et al. 2013 [10], en 52-årig prospektiv og retrospektiv undersøgelse af 240 SMA type 2-patienter rapporteret af Zerres et al. 1997 [11] samt *data on file* for NeuroNext-databasen, som indeholder naturhistoriske data for 16 patienter med SMA type 1 [12].

Analysen for præsymptomatiske spædbørn er baseret på data med ca. 34 måneders opfølgningstid for nusinersen [9], hvilket i modellen anvendes til at modellere opnåelsen af milepæle for både præsymptomatiske patienter, der modtager nusinersen og onasemnogene abeparvovec. Ligeledes supplerer ansøger med naturhistoriske overlevelsesdata fra undersøgelsen af SMA type 2-patienter rapporteret af Zerres et al. 1997 [11] samt en generel befolkningsmortalitetsrate fra Danmarks Statistik [13].

9.1.1 Modelbeskrivelse

Ansøger har for patienter med SMA type 1 og præsymptomatiske patienter indsendt en Markov-model med ens modelstruktur for de to populationer. Derfor er følgende modelbeskrivelse gældende for begge populationer. Modellen estimerer omkostninger baseret på det sygdomsstadie, patienten befinder sig i. Hvert stadie er forbundet med bestemte sandsynligheder for sygdomsforbedring og død. Stadierne er defineret ud fra opnåelsen af motoriske milepæle. Se Figur 1 for de forskellige sygdomsstadier, og hvordan patienten kan bevæge sig mellem de forskellige stadier.



Figur 1. Beskrivelse af modelstrukturen i indsendte markovmodel, der danner grundlag for omkostningsanalysen

Ansøger har baseret modellen på tre grundliggende antagelser, som har betydning for estimering af omkostningerne forbundet med behandling med onasemnogene abeparvovec og nusinersen:

- At effekten af onasemnogene abeparvovec er livslang.
- At overlevelse forbedres i korrelation med opnåelse af motoriske milepæle, samt at overlevelsen for hvert sygdomsstadie kan estimeres ved tilsvarende sundhedstilstande. Dermed antager ansøger, at overlevelse for patienter, der kan sidde uden støtte, er lig overlevelse for patienter med SMA type 2 behandlet med BSC, samt at overlevelse for patienter, der kan gå uden støtte, er lig overlevelse for patienter med SMA type 3 behandlet med BSC.
- At omkostninger for hver motorisk milepæl ligeledes kan estimeres ved tilsvarende sundhedstilstande. Dermed antager ansøger, at omkostninger forbundet med at kunne sidde uden støtte er lig omkostninger forbundet med at have SMA type 2 behandlet med BSC, samt at omkostninger forbundet med at kunne gå uden støtte er lig omkostningerne forbundet med at have SMA type 3 behandlet med BSC.

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Forhandlingsnotat

Dato for behandling i Medicinrådet	26. maj 2021
Leverandør	Novartis Gene Therapies
Lægemiddel	Onasemnogene abeparvovec (Zolgensma)
Ansøgt indikation	Patienter med 5q spinal muskelatrofi

Forhandlingsresultat

Amgros har opnået følgende pris på Zolgensma:

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP	Forhandlet pris (SAIP)	Rabatprocent ift. AIP
Zolgensma	Alle styrker	Alle størrelser	14.531.555,00	[redacted]	[redacted]

Prisen er fortrolig. Aftalen løber frem til 31. december 2023 med mulighed for forlængelse 1x12 måneder.

Prisen er betinget af, at Medicinrådet anbefaler Zolgensma som standardbehandling.

[redacted]

[redacted]

[redacted]

Vurdering af forhandlingsresultatet

Det er Amgros' vurdering, at vi har opnået den bedst mulige pris som vi kan få på nuværende tidspunkt. Denne vurdering baserer vi på følgende punkter:

- [redacted]
- [redacted]
- [redacted]

Konklusion

Amgros vurderer, at vi har opnået den bedst mulige pris som vi kan få på nuværende tidspunkt.

[redacted]

Relation til markedet

Medicinrådet har anbefalet nusinersen (Spinraza) til behandling af patientpopulationen. Yderligere et lægemiddel, risdiplam (Evrysdi), til behandling af SMA, er under behandling i Medicinrådet. Det er Amgros' klare forventning, at den øgede konkurrence kan være med til at skubbe til det eksisterende meget høje prisniveau på behandlingerne til indikationen.

[redacted]

I tabellen herunder ses Amgros' beregninger for den inkrementelle lægemiddelomkostning over årene, og dermed, hvornår Zolgensma med den tilbudte flade rabat er omkostningsneutral ift. Spinraza (ved rene lægemiddelomkostninger).

[redacted]

År	Akkumuleret diskonteret lægemiddelomkostning for Spinraza (SAIP)	Lægemiddelomkostning for Zolgensma (SAIP)	Inkrementel lægemiddelomkostning (SAIP)
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]

Status fra andre lande

Norge

Vurderingen er fortsat i gang. Der afventes en beslutning.

[redacted]

Sverige

TLV har i marts 2021 publiceret den sundhedsøkonomiske afrapportering i Sverige[1]. NT-rådet har endnu ikke truffet beslutning om, hvorvidt Zolgensma er et omkostningseffektivt alternativ til Spinraza og derfor bør anbefales som standardbehandling. Anbefalingen er derfor foreløbigt at afvente med behandling.

UK

I marts 2021 godkendte NICE Zolgensma som mulig standardbehandling[2].

[1] https://www.tlv.se/lakemedel/kliniklakemedelsuppdraget/avslutade-halsoekonomiska-bedomningar/arkiv/2021-03-12-halsoekonomisk-bedomning-av-zolgensma-vid-spinal-muskelatrofi.html

[2] https://www.nice.org.uk/news/article/nice-approves-life-changing-gene-therapy-for-treating-spinal-muscular-atrophy

Fra: Dorte Glintborg
Sendt: 10. maj 2021 07:59
Til: Wiren, Astrid <astrid.wiren@novartis.com>
Emne: Tilbagemelding på høringssvar

Kære Astrid

Tak for jeres høringssvar vedr. Medicinrådets vurdering af Zolgensma.

Vi har gennemgået jeres kommentarer og finder ikke anledning til at ændre i vurderingen af lægemidlets værdi.

Jeres høringssvar vil blive medsendt til Rådet forud for det rådsmøde, hvor Rådet behandler anbefalingen for Zolgensma. Herefter vil det blive offentliggjort sammen med den endelige anbefaling.

Jeg noterer mig, at I ikke har fremsendt bemærkninger til udkast for Medicinrådets sundhedsøkonomiske afrapportering for Zolgensma.

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Medicinrådet

Medicinrådets behandling af personoplysninger
Når du har kontakt med Medicinrådet (f.eks. når du sender en e-mail til os), indsamler og behandler vi dine personoplysninger (f.eks. kontaktoplysninger i form af navn, e-mailadresse, titel/stilling mv.) I Medicinrådets persondatapolitik finder du mere information om Medicinrådets behandling af personoplysninger, dine rettigheder og oplysninger om, hvordan du kan kontakte os.

5. maj 2021

Svar til Medicinrådets evalueringsrapport for Zolgensma

Novartis Gene Therapies (Novartis GT) har læst Medicinrådets evaluering af Zolgensma (onasemnogene abeparvovec). Rapporten konkluderer, at Zolgensma er et ligeværdigt behandlingsalternativ til Spinraza (nusinersen) til behandling af børn med SMA-type 1.

Det er vanskeligt at forstå, hvordan Medicinrådet er nået frem til denne konklusion under hensyntagen til 1) data præsenteret i rapporten og 2) det faktum at EMA´s expertgruppe vurderer Zolgensma til at være en *"major therapeutic advantage."*[1] – dette baseret på de samme studier, som Medicinrådet har haft til rådighed.

Medicinrådets konklusion kan ikke forankres i data eller i de på forhånd fastsatte kriterier
Af Medicinrådets evaluering fremgår det p.12:
"Generelt kan værdien ikke kategoriseres for de anvendte effektmål, da vurderingen bygger på en naiv sammenligning af resultaterne for onasemnogene abeparvovec og nusinersen. De tilfælde, hvor punktestimatet overstiger den mindste klinisk relevante forskel, kan derfor ikke tolkes som, at der reelt er forskel mellem lægemidlerne."

Det vækker forundring, at metoden, dvs. den naive, indirekte sammenligning medfører, at der slet ikke kan drages konklusioner om de observerede forskelle imellem Zolgensma og Spinraza, og i stedet drages en skarp konklusion om, at behandlingerne er ligeværdige. Længe inden Medicinrådets evaluering blev igangsat, var Medicinrådet bekendt med, at det udelukkende var muligt at tilvejebringe naive, indirekte sammenligninger med tanke på, hvordan de kliniske udviklingsprogrammer for Spinraza og Zolgensma ser ud. I Medicinrådets protokol for evalueringen står der heller intet om, at der ikke kan konkluderes ud fra naive, indirekte sammenligninger. Derimod synes der at være tilstrækkeligt grundlag til at konkludere at produkterne er helt ligeværdige. Efterfølgende fremgår det af den endelige rapport, at naive, indirekte sammenligninger ikke ville blive anset for valide af Medicinrådet. Fra vores perspektiv ser det ud som om, at Medicinrådet har tilføjet et nyt kriterium for sammenligningen undervejs i evalueringsprocessen, efter det stod klart, at Zolgensma ville vise en klinisk relevant forskel i merværdi på de fleste endepunkter, herunder overlevelse, permanent ventilationsbehandling samt evnen til at sidde uden støtte.

Selvom Medicinrådet lægger til grund, at effektanalysen ikke kan danne grundlag for en konklusion om merværdi, så er det fortsat et faktum, at Zolgensma, til forskel fra Spinraza, ikke kræver rygmarvsinjektion tre gange om året på hospitalet. Sygehusindlæggelser er ofte et vigtigt endepunkt i Medicinrådets evalueringer, og en behandling, som reducerer indlæggelser, burde kunne tilskrives en merværdi for patienten. Det europæiske lægemiddelagentur, EMA, fremhævede specifikt behandlingsformen i sin vurderingsrapport ved sammenligningen mellem Zolgensma og Spinraza: "*at en engangsbehandling med Zolgensma er en fordel for patienter sammenlignet med behovet for gentagen behandling med nusinersen"*[1]

[1] Zolgensma assessment report, EMA/200482/2020, March 26th 2020

Medicinrådets konklusion adskiller sig fra andre europæiske myndigheder
Det europæiske lægemiddelagentur, EMA, nåede i sin evaluering og godkendelse af Zolgensma frem til, at effekten af Zolgensma overstiger effekten af Spinraza til behandling af patienter med SMA-type 1.
I forlængelse heraf står Medicinrådets konklusion vedr. Zolgensma i kontrast til en række andre europæiske myndigheder og evalueringsorganer for lægemidler:

Myndighed	Citat fra konklusion vedr. Zolgensma
Medicinrådet	"Zolgensma og Spinraza virker lige godt til spædbørn med spinal muskeldystrofi"
European Medicines Agency	*"major therapeutic advantage"* (EPAR)[1] "*the effect of Zolgensma is expected to have a large therapeutic effect compared to existing treatment"*[1] *"outstanding contribution to public health"* (EMAs årsrapport)[2]
National Health Service England	*"life-changing therapy"* (NHS England)[3]
The National institute for Health and Care Excellence	*"evidence of exceptional benefit to young babies"* (NICE)[4]
The Italian Medicines Agency	*"radically better life prospect for children with SMA Type 1"* (AIFA)[5]
Tandvårds- och läkemedels-förmånsverket	"Resultat från en indirekt jämförelse tyder på att patienter med SMA typ 1 (...) behandlade med Zolgensma lever längre och utvecklar fler motoriska förmågor jämfört med patienter behandlade med Spinraza." (TLV's vurderingsrapport)[6]

[2] EMAs årsrapport 2020 https://www.ema.europa.eu/en/news/human-medicines-highlights-2020
[3] https://www.england.nhs.uk/2021/03/nhs-england-strikes-deal-on-life-saving-gene-therapy-drug-that-can-help-babies-with-rare-genetic-disease-move-and-walk/
[4] https://www.nice.org.uk/news/article/nice-approves-life-changing-gene-therapy-for-treating-spinal-muscular-atrophy
[5] https://www.aifa.gov.it/en/-/aifa-approva-rimborsabilita-zolgensma-terapia-genica-per-i-bambini-con-sma1
[6] https://www.tlv.se/lakemedel/kliniklakemedelsuppdraget/avslutade-halsoekonomiska-bedomningar/arkiv/2021-03-12-halsoekonomisk-bedomning-av-zolgensma-vid-spinal-muskelatrofi.html

Medicinrådet har haft de samme studier til rådighed for deres evaluering af Zolgensma, som andre europæiske såvel som nationale myndigheder har haft. Derfor forekommer det besynderligt, at Medicinrådets læsning af data kan afvige så stærkt og entydigt nå frem til, at Zolgensma til SMA-type 1 patienter er et "*ligeværdigt behandlingsalternativ til nusinersen*" uden klinisk merværdi.

Modstridende udsagn i evalueringen
Af rapportens konklusion fremgår det:
"Begge lægemidler kan forbedre patientens funktionsniveau, men ingen af dem giver et normalt funktionsniveau."

Denne delkonklusion i rapporten er ikke i overensstemmelse med et andet udsagn om Zolgensma p. 8:
"Behandlingen ændrer sygdomsforløbet, så barnet får et mildere sygdomsforløb eller potentielt udvikler sig inden for normalområdet."

Selv om Zolgensma ikke betragtes som en kurativ behandling for SMA, er udsagnet om, at børnene kan udvikle sig inden for normalområdet i fuld overensstemmelse med, hvad EMA's expertgruppe skrev i sin rapport om udviklingen af patienter, som havde fået Zolgensma meget tidligt i den præ-symptomatiske fase (EPAR p.101).

Novartis GT ser frem til at finde en løsning sammen med de danske myndigheder
Novartis GT samarbejder intensivt med myndighederne i bestræbelsen på at gøre Zolgensma tilgængeligt for patienter i Danmark og andre europæiske lande. Det er hidtil lykkedes i flere lande, og vi er optimistiske omkring, at det med et konstruktivt samarbejde også vil lykkes i Danmark.

Fra: Wiren, Astrid <astrid.wiren@novartis.com>
Sendt: 29. april 2021 10:30
Til: Dorte Glintborg <DGL@medicinraadet.dk>
Cc: Krogh Hansen, Johnny <johnny.krogh_hansen@novartis.com>; Grauholt, Anne-Marie <anne-marie.grauholt@novartis.com>
Emne: RE: Medicinrådets vurdering af Zolgesma er GODKENDT

Kära Dorte,

Tack för detta.

Vad gäller konklusion på sidan tre i den senaste versionen så har vi några omedelbara kommentarer från teamet:

Vi vil meget gerne opfordre til at teksten i Medicinrådets rapport om bivirkninger og trombotisk mikroangiopati ændres, så den svarer til teksten i SmPC – se også vedhæftet:
Trombotisk mikroangiopati (TMA) er en akut og livstruende tilstand – så vi anmoder om at ordet 'livstruende' anvendes i stedet for 'dødelig'.

Vi menar det är relevant att tillägga att TMA kan behandles med korrekt medicinsk intervention og det er tydeligt beskrevet i SmPC hvilke forholdsregler, der skal tages før og efter behandling med Zolgensma.

Vi arbetar på ett höringsvar och kommer att skicka detta innan fristen 5. Maj.

Med vänlig hälsning,
Astrid

Medicinrådet

Medicinrådets vurdering vedrørende onasemnogene abeparvovec 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	18. maj 2021
Dokumentnummer	115776
Versionsnummer	1.1

Indholdsfortegnelse

1. Medicinrådets konklusion

Medicinrådet vurderer, at onasemnogene abeparvovec og nusinersen er ligeværdige behandlingsalternativer, selvom værdien af onasemnogene abeparvovec ikke kan kategoriseres efter Medicinrådets metoder. Det betyder, at onasemnogene abeparvovec ikke vurderes at være bedre eller dårligere end nusinersen, som er den behandling, patienterne bliver tilbudt i dag.

Begge lægemidler kan forbedre patientens funktionsniveau. Især når behandlingen gives, inden patienten har symptomer eller meget tidligt i sygdomsforløbet, men ingen af dem helbreder sygdommen. Der er ikke dokumentation for, at patienterne opnår mere effekt ved at kombinere de to behandlinger – altså tillægge nusinersen efter onasemnogene abeparvovec eller fortsætte med nusinersen efter onasemnogene abeparvovec.

Medicinrådets vurdering omfatter spædbørn med klinisk SMA type 1, som ikke er i permanent ventilationsbehandling og starter behandling inden 6 måneders alderen, samt præsymptomatiske spædbørn med mindst to SMN2-kopier. Der er endnu ingen data for ældre børn eller patienter med SMA type 2 og 3.

Der er fordele og ulemper ved begge behandlinger. Det er en fordel, at onasemnogene abeparvovec kun skal gives én gang. Til gengæld er det ikke muligt at stoppe behandlingen igen, hvis der senere skulle opstå bivirkninger. Nusinersen er potentielt en livslang behandling, der hver 4. måned bliver indsprøjtet i det hulrum, som omgiver rygmarven, hvilket i sig selv kan medføre gener og bivirkninger for patienten.

Ved behandling med onasemnogene abeparvovec er der set sjældne, men alvorlige og livstruende bivirkninger i form af trombotisk mikroangiopati.

Medicinrådet lægger i vurderingen vægt på, at der er stor usikkerhed om langtidseffekt og langtidsbivirkninger. Vurderingen er baseret på et yderst begrænset datagrundlag. Medicinrådet opfordrer derfor firmaet til at levere nye substantielle data for både effekt og bivirkninger.

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Publikationen kan frit refereres
med tydelig kildeangivelse.

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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

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*)
IQWIG:	*The Institute for Quality and Efficiency in Healthcare*
NICE:	*The National Institute for Health and Care Excellence*
PICO:	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
SMA:	Spinal muskelatrofi

3. Introduktion

Formålet med Medicinrådets vurdering af onasemnogene abeparvovec 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 Novartis. Medicinrådet modtog ansøgningen den 18. december 2020.

De kliniske spørgsmål er:

1. *Hvilken værdi har onasemnogene abeparvovec sammenlignet med nusinersen for børn med klinisk diagnosticeret SMA type 1?*

2. *Hvilken værdi har onasemnogene abeparvovec sammenlignet med nusinersen for præsymptomatiske spædbørn?*

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][2][3].

Ved SMA type 1 har barnet symptomer, før han/hun er seks måneder. Der er ofte symptomer allerede fra fødslen. Uden medicinsk behandling kommer barnet aldrig til at sidde selv og bliver sjældent mere end et par år. Levealderen er afhængig af, hvor intensiv vejrtrækningshjælp, der bliver iværksat.

Tabel 1. Klinisk klassifikation af spinal muskelatrofi

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

1. Ifølge fagudvalget, februar 2020: 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.

3.2 Onasemnogene abeparvovec

Onasemnogene abeparvovec er en genterapi, som erstatter det defekte *SMN1*, så patienten selv kan danne SMN-protein, som er afgørende for funktionen af motorneuronerne. Lægemidlet gives intravenøst som vægtbaseret engangsdosis iht. produktresumé. Behandlingen ændrer sygdomsforløbet, så barnet får et mildere sygdomsforløb eller potentielt udvikler sig inden for normalområdet.

Onasemnogene abeparvovec fik positiv opinion i EMA den 26. marts 2020 og blev godkendt den 18. maj til indikationen:

Patienter med 5q SMA med bi-allelic mutation i *SMN1*-genet og

- klinisk diagnosticeret SMA type 1, eller
- op til 3 kopier af *SMN2*-genet.

Indikationsteksten rummer således ikke en afgrænsning på alder eller sværhedsgrad af sygdommen. Ifølge det godkendte produktresumé er virkning og sikkerhed på godkendelsestidspunktet ikke klarlagt hos patienter over 2 år eller hos patienter, som vejer over 13,5 kg. Ved fremskreden SMA, hvor der formodes at være sket irreversibel skade af motorneuroner, afhænger effekten af graden af muskelsvækkelse på behandlingstidspunktet. Af produktresumét fremgår også, at effekten formodes markant reduceret hos patienter med udtalt muskelsvækkelse og respirationssvigt, patienter i permanent ventilation samt patienter, der ikke kan synke. Benefit/risk-profil hos patienter med fremskreden SMA, der behandles med permanent ventilation, og som ikke tager på, er ikke klarlagt.

I produktresuméet fremgår også, at studieopfølgningstiden for patienter med 3 *SMN2*-kopier er for kort til at drage nogen definitive konklusioner om fordelene i denne patientpopulation i øjeblikket.

3.3 Nuværende behandling

Nye patienter med SMA type 1, som ikke er i permanent ventilationsbehandling samt præsymptomatiske børn, bliver i dag tilbudt behandling med nusinersen iht. Medicinrådets anbefaling fra 2017. Målet med behandlingen er at nedsætte sygdomsprogressionen og derigennem øge barnets overlevelse, funktionsniveau og livskvalitet.

Behandlingen varetages på tre centre i hhv. København, Aarhus og Odense. I Danmark tilbydes patienter med SMA type 1 almindeligvis ikke invasiv ventilationsbehandling, men der er enkelte SMA type 1-patienter, der efter forældrenes ønske får invasiv respiration.

4. Metode

Medicinrådets protokol for vurdering af onasemnogene abeparvovec (version 1.0) beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan vi vil vurdere lægemidlets værdi for patienterne.

5. Resultater

5.1 Klinisk diagnosticeret SMA type 1

Hvilken værdi har *onasemnogene abeparvovec* sammenlignet med nusinersen for børn med klinisk diagnosticeret SMA type 1?

5.1.1 Litteratur

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

Ansøger har søgt litteratur med søgestrengen fra protokollen og udvalgt to fuldtekstartikler [7][8]. Herudover har ansøger anvendt data for onasemnogene abeparvovec fra EPAR'en [9] samt upublicerede og fortrolige data-on-file. Medicinrådet kan inddrage upublicerede og fortrolige data i vurderingen under hensyn til faglighed og åbenhed. Fagudvalget har derfor, i det omfang det var muligt, erstattet ansøgers fortrolige data-on-file med offentligt tilgængelige data fra FDA´s kliniske rapport [10]. Tilbage er få upublicerede fortrolige data vedr. baselinekarakteristika, der senest vil blive offentliggjort et år fra dato for anbefaling.

For komparator (nusinersen) har ansøger anvendt supplerende data fra NICE [11] og IQWIG [12] til brug for en subgruppeanalyse, som Medicinrådet har anmodet om i protokollen. Herudover har fagudvalget anvendt supplerende oplysninger vedr. baselinekarakteristika for ENDEAR-studiet fra en publiceret artikel af Dabbous et al. 2019 [13].

Tabel 2 viser en oversigt over de referencer for de tre studier, som fagudvalget har anvendt som datagrundlag.

Tabel 2. Oversigt over studier af patienter med SMA type 1

Reference	Studie (NCT-nummer)	Lægemiddel
Zolgensma EPAR 2020 [9]	STR1VE-US (NCT03306277)	onasemnogene abeparvovec
Mendell 2017 [7] FDA clinical review [10]	START (NCT02122952)	onasemnogene abeparvovec
Finkel 2017 [8] NICE commitee papers 2018 [11] IQWIG-report 2020 [12] Dabbous 2019 [13]	ENDEAR (NCT02193074)	nusinersen

Studie- og baselinekarakteristika

STR1VE-US er et enkeltarmet fase 3-studie af intravenøs administration af onasemnogene abeparvovec til 22 patienter med SMA type 1 og to SMN2-kopier. Patienterne blev fulgt indtil alder 18 måneder [9].

START er et fase 1-studie med dosiseskalering af intravenøs administration af onasemnogene abeparvovec til i alt 15 patienter med SMA type 1. Tre patienter i kohorte 1 blev behandlet med en lavere dosis og indgår ikke i Medicinrådets vurdering. De 12 patienter i kohorte 2 blev fulgt i 2 år [7].

ENDEAR er et randomiseret dobbeltblindet studie med intratekal administration af nusinersen overfor sham-kontrol. Der indgik i alt 120 patienter med SMA type 1, hvoraf 80 patienter var i den aktive behandlingsarm. Opfølgningstiden var 13 måneder [8].

I tabel 3 ses baselinekarakteristika for de tre studier. Ansøger har poolet data fra START (kohorte 2) og STR1VE-US, da der er få patienter i hvert af de to studier. Baselinekarakteristika fra ENDEAR-studiet er angivet for både totalpopulationen og den præspecificerede subgruppe af patienter med ≤ 12 ugers sygdomsvarighed (ved screening), som Medicinrådet specifikt har bedt om i protokollen. En oversigt over definition af effektmål i studierne kan ses i bilag 1.

Tabel 3. Baselinekarakteristika. OBS! De markerede data er fortrolige

	Population onasemnogene abeparvovec			Population nusinersen	
	STR1VE-US [9] [10]	START (kohorte 2) [9] [10]	POOLED (oplyst i ansøgningen)	ENDEAR subgruppe [8] [12]	ENDEAR totalpopulation [8] [13]
Opfølgning	Alder 18 mdr. (ca. 14 mdrs. opfølgningstid)	24 mdrs. opfølgningstid	Alder 18 mdr. (ca. 14 mdrs. opfølgningstid)	13 mdrs. opfølgningstid	13 mdrs. opfølgningstid
N	22	12	34	34	80
SMN2-kopi antal	2	2	2	2	2
Sygdomsvarighed ved 1. dosis, mdr. mean (range)	[redacted] (1,9 (1,1-3,7))[1]	ca. 2 (0,6-5,9)[1]	[redacted]	2,4[2]	3,5[2]
Sygdomsvarighed ved screening (n)					
≤ 12 uger	22	[redacted]	[redacted]	34	34
>12 uger	0	[redacted]	[redacted]	0	46
Alder ved symptomdebut, mdr. mean (range)	[redacted] (2,1 (0,5-4))[1]	1,4 (0-3)	[redacted]	1,3 (0,7-4,2)	1,8 (0,5-4,1)
Alder ved 1. dosis, mdr. mean (range)	3,7 (0,5-5,9) (4,0 (1,9-5,9))[1]	3,4 (0,9-7,9)	3,6 (0,5-7,9)	3,7 (1,7-7,9)	5,3 (1,7-8,0).
Vægt i kg, mean (range)	5,8 (3,9-7,5)	5,7 (3,6-8,4)	5,8 (3,6-8,4)	Ikke oplyst	Ikke oplyst[3]
CHOP-INTEND mean (range)	32,0 (17-52)	28,2 (12-50)	30,8 (12-52)	Ikke oplyst	26,6 (SD 8.1)
Ventilationsstøtte n (%)	0 (0)	2 (17)	[redacted]	Ikke oplyst	21 (26)

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
1. Beregnet ud fra FDA-data. START: 12 patienter. STRIVE-US: kun opgivet for 20 patienter (tabel 15 s. 45) [10], da oplysninger fra ansøger er fortrolige. En patient indgår ikke pga. ukendt alder for symptomdebut (startet behandling ved 0,5 mdr.). En patient blev klassificeret som præsymptomatisk. Den gennemsnitlige alder og sygdomsvarighed for alle 22 patienter er derfor lavere.
2. Beregnet af Medicinrådet som alder ved 1. dosis minus alder ved symptomdebut.
3. Patienterne er ikke undervægtige, da det var eksklusionskriterium.

Der er i gennemsnit ca. 2 måneders forskel i alder og sygdomsvarighed ved 1. dosis mellem studierne af hhv. onasemnogene abeparvovec og nusinersen (ENDEAR-totalpopulationen). For ENDEAR-subgruppen var alder ved 1. dosis sammenlignelig med gennemsnitsalderen i den poolede analyse af START og STRIVE-US, mens

sygdomsvarigheden i gennemsnit var minimum en halv måned længere. De angivne minimumsværdier tyder dog på, at der var flere yngre patienter i studierne af onasemnogene abeparvovec, hvor den yngste patient var 0,5 måneder, mens den yngste patient i ENDEAR var 1,7 måneder.

Den gennemsnitlig CHOP-INTEND-score ved baseline var lidt lavere i ENDEAR-totalpopulationen, og flere patienter havde behov for ventilationsstøtte. Baselinedata for CHOP-INTEND-score er ikke opgjort for ENDEAR-subgruppen.

Der er stor forskel i alder og sygdomsvarighed ved 1. dosis mellem studierne af hhv. onasemnogene abeparvovec og totalpopulationen for nusinersen, men kun mindre forskelle ift. subgruppen med sygdomsvarighed < 12 uger. Det er tidligere vist, at alder og sygdomsvarighed ved 1. dosis har stor betydning for effekten [8]. Derfor vil sammenligningen mellem onasemnogene abeparvovec og nusinersen blive baseret på data fra ENDEAR-subgruppen.

5.1.2 Databehandling og analyse

Nedenunder beskriver vi ansøgers datagrundlag, databehandling og analyse.

Ansøger har leveret data for totalpopulationen og subgruppen af patienter med mindre end 12 ugers sygdomsvarighed ved tidspunktet for screening. Ansøger har ikke leveret data for subgruppen af patienter med mere end 12 ugers sygdomsvarighed, da der i studierne af onasemnogene abeparvovec er meget få patienter, som falder ind under det kriterium, og det derfor ikke er meningsfuldt at lave en subgruppeanalyse herfor.

Ansøger har beregnet relative og absolutte forskelle og konfidensintervaller baseret på en naiv indirekte sammenligning uden matching for potentielle skævheder mellem datakilderne, hvilket giver en betydelig risiko for, at punktestimater og konfidensintervallerne ikke er retvisende. Medicinrådet vil derfor ikke lade de anførte konfidensintervaller i ansøgningen danne grundlag for en formel kategorisering af lægemidlets værdi. Vurderingen vil derfor bygge på en naiv sammenligning af de rapporterede resultater for onasemnogene abeparvovec og nusinersen.

For yderligere kommentarer til data for de enkelte effektmål henvises til afsnit 5.1.4.

5.1.3 Evidensens kvalitet

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

Da vurderingen af onasemnogene abeparvovec er baseret på en naiv sammenligning med nusinersen, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Risiko for bias i de to ukontrollerede studier af onasemnogene abeparvovec kan ikke vurderes systematisk. Risiko for bias i det randomiserede studie af nusinersen er tidligere vurderet af Medicinrådet som 'lav' (se Baggrund for Medicinrådet anbefaling).

5.1.4 Effektestimater og kategorier

I tabel 4 ses en samlet oversigt over de absolutte effektforskelle og kategori for de enkelte effektmål, der anvendes til at belyse klinisk spørgsmål 1 samt kvalitet af evidensen.

Generelt kan værdien ikke kategoriseres for de anvendte effektmål, da vurderingen bygger på en naiv sammenligning af resultaterne for onasemnogene abeparvovec og nusinersen. De tilfælde, hvor punktestimatet overstiger den mindste klinisk relevante forskel, kan derfor ikke tolkes som, at der reelt er forskel mellem lægemidlerne.

Tabel 4. Resultater for onasemnogene abeparvovec vs. nusinersen ved SMA type 1

Effektmål	Måleenhed MKRF (måletidspunkt)	Vigtighed	Forskel i absolutte tal	Forskel i relative tal	Kategori for effektmålet	Klinisk vurdering
Overlevelse	Andel pt. i live **5** %-point (10-14 mdr.)	Kritisk	5,9 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger MKRF til fordel for onasemnogene abeparvovec
Kombineret mortalitet / permanent ventilations-behandling	Andel pt., som enten er døde eller anvender respirator > 16 timer/døgn **15** %-point (10-14 mdr.)	Kritisk	17,6 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger MKRF til fordel for onasemnogene abeparvovec
Permanent ventilations-behandling	Andel pt., som ikke anvender respirator > 16 timer/døgn **10** %-point (12-18 mdr.)	Vigtig	13,1 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger MKRF til fordel for onasemnogene abeparvovec
Motoriske milepæle	Respondere (andel patienter med min. 4 point bedring på CHOP-INTEND) **20** %-point (12-18 mdr)	Kritisk	5,9 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger *ikke* MKRF

	Andel pt., der opnår evnen til at: • Sidde uden støtte **10 %**-point (12-18 mdr)	Vigtig	32,2 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger MKRF til fordel for onasemnogene abeparvovec
	• Gå uden støtte **5 %**-point (12-18 mdr.)		2,9 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger *ikke* MKRF
Alvorlige bivirkninger (relateret til behandlingen)	Andel pt, som oplever mindst én alvorlig bivirkning **10 %**-point (12-18 mdr.)	Vigtig	2,9 %-point	-	Kan ikke kategoriseres	Punktestimatet overstiger *ikke* MKRF
Livskvalitet	Kun kvalitativ bedømmelse	Vigtig	-	-	Kan ikke kategoriseres	Ingen data
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres. Fagudvalget vurderer, at onasemnogene abeparvovec er et ligeværdigt behandlingsalternativ sammenlignet med nusinersen på baggrund af data for effekt og bivirkninger.				
Kvalitet af den samlede evidens		Meget lav - nye studier vil med høj sandsynlighed ændre effektestimaterne.				

Overlevelse
Effektmålet er defineret som kritisk for vurderingen af lægemidlets værdi for patienterne, fordi ubehandlede patienter med SMA type 1 i gennemsnit lever mindre end to år, og mortaliteten er stadig høj trods behandling med nusinersen.

Da studierne har forskellige opfølgningstider, har ansøger anvendt Kaplan-Meyer-estimaterne for overlevelse ved 14 mdr. som udgangspunkt for sammenligningen.

Tabel 5. Overlevelsesdata for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec (poolet) [7] [9]	Nusinersen (ENDEAR subgruppe) [11]	Absolut forskel	MKRF (%-point)
Overlevelsesrate ved 14 mdrs. opfølgning	97,1 %	91,2 %	5,9 %-point	5 %-point

Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel til fordel for onasemnogene abeparvovec, men kan ikke tolkes som en reel forskel, da vurderingen bygger på en naiv sammenligning mellem lægemidlerne.

Fagudvalget kan ikke vurdere, om der er forskel i overlevelse mellem de to lægemidler.

Permanent ventilationsbehandling
Effektmålet er defineret som vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi patienten er afhængig af en respirator min. 16 timer i døgnet, da evnen til at trække vejret er svært nedsat. Samtidig er patienten mere modtagelig for lungeinfektioner.

I START- og STRIVE-US-studierne blev permanent ventilationsbehandling defineret som ventilationsbehandling anvendt i > 16 timer/døgn i 14 dage eller mere. I ENDEAR var definitionen tracheostomi eller noninvasiv ventilation > 16 timer/døgn i mere end 21 dage.

Ansøger har estimeret effektforskellen på baggrund af data for det kombinerede effektmål (se næste punkt) ved 14 måneders opfølgningstid. Bemærk, at effektmålet er rapporteret som patienter, der *ikke* er i permanent ventilationsbehandling.

Tabel 6. Permanent ventilationsbehandling for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec (poolet) [7] [9]	Nusinersen (ENDEAR subgruppe) [11]	Absolut forskel	MKRF (%-point)
Andel patienter uden behov for permanent ventilationsbehandling	97,0 %	83,9 %	13,1 %-point	10 %-point

ved 14 mdrs. opfølgning				

Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel til fordel for onasemnogene abeparvovec, **men kan ikke tolkes som en reel forskel, da vurderingen bygger på en naiv sammenligning mellem lægemidlerne.** Der mangler oplysninger om, hvorvidt patienternes behov for ventilationsstøtte var sammenlignelige ved baseline.

Fagudvalget kan ikke vurdere, om der er forskel i behov for permanent ventilationsbehandling mellem de to lægemidler.

Kombineret mortalitet eller permanent ventilationsbehandling (eventfree survival)
Effektmålet er defineret som kritisk for vurderingen af lægemidlets værdi for patienterne, fordi fagudvalget anser begge effektmål som alvorlige hændelser.

Da studierne har forskellige opfølgningstider, har ansøger anvendt Kaplan-Meyer-estimaterne ved 14 mdr. som udgangspunkt for sammenligningen. Bemærk, at effekten er rapporteret som, hvor mange patienter der er *i live* og *ikke* er i permanent ventilationsbehandling.

Tabel 7. Kombineret mortalitet eller permanent ventilationsbehandling for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec (poolet) [7] [9]	Nusinersen (ENDEAR subgruppe) [11]	Absolut forskel	MKRF (%-point)
Overlevelse uden behov for permanent ventilationsbehandling ved 14 mdrs. opfølgning	94,1 %	76,5 %	17,6 %-point	15 %-point

Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel til fordel for onasemnogene abeparvovec, **men kan ikke tolkes som en reel forskel, da vurderingen bygger på en naiv sammenligning mellem lægemidlerne.** Der mangler oplysninger om, hvorvidt patienternes behov for ventilationsstøtte var sammenlignelige ved baseline.

Fagudvalget kan ikke vurdere, om der er forskel i det kombinerede effektmål mellem de to lægemidler.

Motoriske funktioner og milepæle
Effektmålene omfatter barnets evne til at opnå motoriske pilepæle før siddestadiet (målt som respons på CHOP-INTEND minimum 4 point) samt evne til hhv. at sidde og gå uden støtte. CHOP-INTEND er defineret som kritisk for vurderingen af lægemidlets værdi for

patienterne, fordi SMA type 1 er klinisk karakteriseret ved et naturforløb, hvor patienterne aldrig opnår evnen til at sidde uden støtte. De øvrige milepæle er defineret som vigtige.

Da ansøger har markeret data fra START-studiet ved alder 18 måneder som fortrolige i ansøgningen, har fagudvalget i stedet anvendt de data fra START-studiet, som er offentligt tilgængelige i den publicerede artikel [7] eller FDA´s kliniske rapport [10]. Disse data er efterfølgende lagt sammen (poolet) med data fra STRIVE-US. Tallene fra de to studier fremgår også af tabellen, så det er transparent, hvordan de fører frem til det sammenlagte resultat

Tabel 8. Motoriske funktioner og milepæle for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec [7] [9] [10]	**Nusinersen (ENDEAR subgroup)** [11]	**Absolut forskel**	**MKRF (%-point)**
Andel patienter med min. 4 points forbedring på CHOP-INTEND ved 14 mdrs. opfølgning	STRIVE-US 22/22 (100 %)[1] START 12/12 (100 %)[2] Sammenlagt 34/34 (100 %)	32/34 (94,1 %)	5,9 %-point	20 %-point
Sidder uden støtte i mindst 30 sekunder ved alder 18 mdr. eller 'stable sit or pivots' på HINE-2 ved ca. 14 mdrs. opfølgningstid	STRIVE-US 13/22 (59 %)[1] START 4/12 (33 %)[3] Sammenlagt 17/34 (50 %)	6/32 (18,8 %)	32,2 %-point	10 %-point
Går uden støtte ved alder 18 mdr. eller ca. 14 mdrs. opfølgningstid	STRIVE-US 1/22 (4,5 %)[1] START 0/12 (0 %)[3] Sammenlagt 1/34 (2,9 %)	0/32 (0 %)	2,9 %-point	5 %-point

1. Fra EMAs assessment report [9].
2. Fra Mendell et al. Aflæst fra fig. 2 [7].
3. Fra FDA´s kliniske rapport [10].

CHOP-INTEND
Punktestimatet for den absolutte effektforskel (5,9 %-point) overstiger ikke den mindste klinisk relevante forskel (20 %-point).

Forskellen på 20 %-point blev oprindeligt valgt på baggrund af data for den fulde population i ENDEAR-studiet, hvor 71 % i nusinersengruppen, og kun 3 % i shamkontrolgruppen opnåede dette effektmål. Da resultatet i ENDEAR-subgruppen er væsentligt højere, (94,1 %) er det dog reelt ikke muligt at opnå en effektforskel, som overstiger den mindste klinisk relevante forskel på 20 %-point. Der er uvist, om patienterne er sammenlignelige, da der ikke er baselinedata for CHOP-INTEND fra ENDEAR-subgruppen.

Fagudvalget kan ikke vurdere, om der er forskel mellem de to lægemidler for dette effektmål.

Evne til at sidde uden støtte
Effektmålet for onasemnogene abeparvovec og nusinersen er opgjort med to forskellige metoder og kan derfor ikke direkte sammenlignes.

For onasemnogene abeparvovec er effektmålet opgjort på *Bayley Scales Gross Motor subset* #26 som 'evne til at sidde uden støtte i 30 sekunder' ved alder 18 måneder. Resultaterne i tabel 8 viser, at 50 % af børnene kunne sidde uden støtte efter denne definition.

For nusinersen er effektmålet opgjort med HINE-2 sitting scale som antallet af børn, der har opnået 'stable sit' eller 'pivots' (se figur 1.). Heri indgår ikke en tidsangivelse. Efter denne definition sidder 18,8 % uden støtte ved studiets afslutning.

Da effektmålene ikke er direkte sammenlignelige, har ansøger foreslået en alternativ definition for nusinersen, som medtager alle børn, der opnår min. ét points stigning på HINE-2 sitting scale, hvilket ifølge data fra IQWIG var 50 % [12] . Denne definition medtager dog også børn, som kan sidde med støtte (se figur 1). Fagudvalget vurderer derfor, at denne alternative opgørelse ikke er relevant for sammenligningen.

Figur 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

Source: (De Sanctis 2016)

Punktestimatet for den absolutte effektforskel afspejler en klinisk relevant effektforskel til fordel for onasemnogene abeparvovec, men usikkerheden kan ikke kvantificeres pga. manglende retvisende konfidensintervaller.

Fagudvalget bemærker, at punktestimatet (32,2 %-point) langt overstiger den mindste klinisk relevante forskel (10 %). Forskellen kan dog til dels skyldes, at studierne har anvendt forskellige definitioner af effektmålet og/eller, at der er flere yngre børn i studierne af onasemnogene abeparvovec end i ENDEAR-subgruppen for nusinersen.

Evne til at gå uden støtte
Data fra tabel 8 viser, at en patient fra STRIVE US-studiet og 0 patienter fra START og ENDEAR-studiet kunne gå uden støtte i en alder af 18 måneder.

Punktestimatet for den absolutte effektforskel (2,9 %) afspejler ikke en klinisk relevant effektforskel. Tallene er desuden så små, at blot én ekstra patient kan ændre konklusionen.

Ifølge oplysninger fra FDA´s rapport var der yderligere to patienter i START-studiet, der gik uden støtte i en alder af ca. 20 måneder [10]. De to patienter var hhv. 0,9 og 1,9 måneder på tidspunktet, hvor de startede behandling [9], hvilket tyder på, at muligheden for at komme til at gå er størst ved tidlig behandling. Til sammenligning var den yngste patient i ENDEAR-studiet 1,7 måneder gammel ved 1. dosis af nusinersen.

Fagudvalget kan ikke vurdere, om der er forskel mellem de to lægemidler for dette effektmål.

Alvorlige hændelser
Effektmålet er defineret som vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi effekten altid skal ses ift. alvorlige behandlingsrelaterede hændelser (bivirkninger).

Tabel 9. Alvorlige hændelser for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec (poolet) [7] [9] [10]	Nusinersen (ENDEAR Totalpopulation) [8]	Absolut forskel	MKRF (%-point)
Alle alvorlige hændelser (SAE)	20/34 (58,8%)	61/80 (76,3%)	17,5 %-point	-
Alvorlige behandlingsrelaterede hændelser (bivirkninger)	Min. 1 /34 (2,9 %)	0/80 (0 %)	2,9 %-point	10 %-point

Ansøger har angivet poolede data for onasemnogene abeparvovec for alle SAE, hvoraf 10 blev rapporteret i START-studiet [7], og 10 blev rapporteret i STRIVE-US [9]. Data for nusinersen er kun angivet for den fulde population [8], da der ikke findes tilgængelige bivirkningsdata for subgruppen.

I START-studiet (kohorte 2) var der ét alvorligt tilfælde af forhøjede aminotransferaser (35 gange højere end den øvre grænse), som, investigator vurderede, var definitivt relateret til behandlingen. Patienten fik derfor yderligere behandling med prednisolon [7] [10]. Der er ikke oplysninger om, hvorvidt at SAE rapporteret i STRIVE-US-studiet er relateret til behandlingen [9].

I ENDEAR-studiet af nusinersen blev ingen SAE vurderet som relateret til behandlingen [8]. Forekomsten af alle SAE i totalpopulationen var lavere end i sham-kontrolgruppen (SAE 76 vs. 95 %). Herunder også fatale SAE (16 vs. 39 %). Da SAE således afspejler mortalitet pga. sygdommen og andre alvorlige sygdomsrelaterede hændelser, som forventes at være højere i totalpopulationen end i subpopulationen, kan SAE for totalpopulation ikke anvendes i sammenligningen.

Fagudvalget vurderer, på baggrund af de kliniske studier, at der ikke er klinisk relevante forskelle i behandlingsrelaterede SAE mellem lægemidlerne.

Livskvalitet
Effektmålet er defineret som vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi muligheden for en forbedret overlevelse også må ses i lyset af den livskvalitet, der følger med hos et barn med en alvorlig invaliderende sygdom.

Ansøger har ikke leveret data for livskvalitet, og fagudvalget kan derfor ikke vurdere dette effektmål.

5.1.5 Fagudvalgets konklusion for SMA type 1

Fagudvalget vurderer, at den samlede værdi af onasemnogene abeparvovec sammenlignet med nusinersen til behandling af klinisk diagnosticeret SMA type 1 ikke kan kategoriseres.

Fagudvalget vurderer, at onasemnogene abeparvovec er et ligeværdigt behandlingsalternativ til nusinersen vurderet på effekt og bivirkninger hos børn med SMA type 1 med alder under 6 måneder, der ikke er i permanent ventilationsbehandling.

Fagudvalget kan ikke på det foreliggende datagrundlag vurdere, om der er forskelle i effekten på de to lægemidler. For de fleste effektmål overstiger punktestimatet den mindste klinisk relevante forskel til fordel for onasemnogene abeparvovec, hvorfor fagudvalget vurderer, at det som minimum har ligeværdig effekt med nusinersen.

Overvejelser vedr. praktiske forhold og bekymringer om langtidseffekt og langtidsbivirkninger har dog også betydning for vurderingen. Se afsnit 6 Andre overvejelser herfor.

5.2 Præsymptomatiske spædbørn

Hvilken værdi har onasemnogene abeparvovec *sammenlignet med nusinersen for præsymptomatiske spædbørn?*

5.2.1 Litteratur

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

Ansøger har identificeret to studier. Søgningen efter litteratur med søgestrengen fra protokollen resulterede i en udvalgt fuldtekstartikel. Data for det andet studie indgår i *European Public Assessment Report* (EPAR).

Tabel 10. Oversigt over studier

Publikationer	Studie (NCT mummer)	Lægemiddel
Zolgensma EPAR [9]	SPR1NT (NCT03505099)	Onasemnogene abeparvovec
De Vivo et al. 2019 [14]	NURTURE (NCT02386553)	Nusinersen

Studiekarakteristika

SPR1NT er et igangværende fase 3, enkelt-armet studie, der evaluerer sikkerheden og effekten af en enkelt i.v. infusion af onasemnogene abeparvovec i spædbørn, som er genetisk diagnosticerede og har præsymptomatisk SMA med 2 eller 3 kopier af SMN2. Onasemnogene abeparvovec administreres, før de første kliniske symptomer af SMA debuterer. Data cut-off i EPAR'en var den 31. december 2019 [9]. Fortrolige data fra SPRINT-studiet inkluderer baselinekarakteristika, data omkring alder ved interimanalysen samt en række detaljer omkring effektmålene. Det betyder, at disse data for onasemnogene abeparvovec vil være blændede ved offentliggørelsen af Medicinrådets anbefaling.

NURTURE er et igangværende fase 2, enkelt-armet studie, der evaluerer langtidssikkerhed og effekt af intratekal nusinersen i spædbørn med 2 eller 3 SMN2-kopier, som begynder behandling, inden de første kliniske symptomer på SMA debuterer. NURTURE omfatter en 5-års behandlingsperiode og en opfølgningsperiode efter endt behandling. Nusinersenbehandling består af 4 loadingdoser (hver 12 mg, administreres på dag 1, 15, 29 og 64) efterfulgt af vedligeholdelsesdosis hver 4. måned over 5 år. Interimresultater med cut-off den 29. marts 2019 er publiceret [14].

Baselinekarateristika

Nedenfor rapporteres de relevante baselinekarakteristika for patienter i SPR1NT (onasemnogene abeparvovec) og NURTURE (nusinersen) (tabel 2). Fagudvalget vurderer overordnet set, at studiepopulationen er sammenlignelig med en tilsvarende dansk patientpopulation.

Tabel 11. Baselinekarakteristika. OBS! De markerede data er fortrolige

	Population onasemnogene abeparvovec [upubliceret]		Population nusinersen [14]	
	2 SMN2-kopier N = 14	3 SMN2-kopier N = 15	2 SMN2-kopier N = 15	3 SMN2-kopier N = 10
Piger, n (%)	[redacted]	[redacted]	7 (47)	6 (60)
Alder ved 1. dosis, dage, gennemsnit (SD)	[redacted]	[redacted]	19,5 (9,29)	22,3 (12,45)
CHOP INTEND total score, gennemsnit (SD)	[redacted]	Ikke angivet	47,0 (10,04)	51,9 (6,10)
HINE total motor milepæle, gennemsnit (SD)	Ikke angivet	Ikke angivet	2,7 (1,59)	3,2 (1,87)
Vægt, gennemsnit, kg (SD)	[redacted]	[redacted]	--	--

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
HINE, Hammersmith Infant Neurologic Examination.

5.2.2 Databehandling og analyse

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

Ansøger har udført en indirekte sammenligning af interimdata fra det igangværende SPR1NT-studie (delvist data fra EPAR [9] og upublicerede data) og interimdata fra NURTURE-studiet [14]. Data er opgjort i forhold til antallet af SMN2-kopier (henholdsvis 2 og 3) men ikke samlet for alle præsymptomatiske børn, som efterspurgt i protokollen. Beregningen for hele populationen af præsymptomatiske børn er udført af Medicinrådets sekretariat, hvor det er muligt ved simpel addition.

Protokollen omfatter præsymptomatiske spædbørn med optil tre *SMN2*-kopier". Der er dog ingen børn med kun én SMN2-kopi inkluderet i de kliniske studier med onasemnogene abeparvovec eller nusinersen. Effekten vil derfor ikke blive vurderet i denne population.

Ansøger har ikke beregnet relative og absolutte forskelle og konfidensintervaller for de ønskede effektmål. Medicinrådet kan derfor ikke foretage en formel kategorisering af lægemidlets værdi. Vurderingen vil bygge på en naiv sammenligning af de rapporterede resultater for onasemnogene abeparvovec og nusinersen. Medicinrådets sekretariat har beregnet de absolutte forskelle, hvor dette er muligt.

Ansøger har ikke opgjort data ved 24 måneder, som efterspurgt i protokollen, idet data ikke er tilgængelige. Data er opgjort ved de respektive tidspunkter for interimanalyserne af de to studier (henholdsvis ca. 10 og ca. 34 måneder) (se tabel 3). Børnene behandlet med nusinersen i NURTURE-studiet er dermed væsentligt ældre på opgørelsestidspunktet end børnene behandlet med onasemnogene abeparvovec. Resultaterne er derfor ikke sammenlignelige. Med hensyn til de motoriske milepæle betyder det endvidere, at en del af børnene behandlet med onasemnogene abeparvovec endnu ikke har en alder, hvor børn med normal motorisk funktion ville have opnået de motoriske milepæle, som indgår i vurderingen.

Tabel 12. Alder ved interimanalysen. OBS! De markerede data er fortrolige

	Population onasemnogene abeparvovec [upubliceret]		Population nusinersen [14]	
	2 SMN2-kopier N = 14	3 SMN2-kopier N = 15	2 SMN2-kopier N = 15	3 SMN2-kopier N = 10
Alder ved interim data-cut, måneder, median (range)	[redacted]	[redacted]	34,8 (25,7-45,4)	
Tid i studiet ved interim data-cut måneder, median (range)	10,5 (5,1-18)	8,74 (2-13,9)	33,9 (25,3-45,1)	

Der er tale om en indirekte sammenligning af data fra to studier med et meget lille antal patienter med meget store forskelle i opfølgningstid og deraf børnenes alder på tidspunktet, hvor data opgøres. Dette betyder, at lægemidlernes effekt på børnenes evne til at opnå aldersvarende motoriske milepæle har et meget begrænset sammenligningsgrundlag med det nuværende datagrundlag.

5.2.3 Evidensens kvalitet

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

Da vurderingen af onasemnogene abeparvovec er baseret på en naiv sammenligning med nusinersen, kan Medicinrådet ikke anvende GRADE til at vurdere kvaliteten af evidensen.

Risiko for bias i de to studier med henholdsvis onasemnogene abeparvovec (SPR1NT) og nusinersen (NURTURE) kan ikke vurderes systematisk med Cochrane Risk of Bias Tool, da de ikke er randomiserede og ikke indeholder en kontrolgruppe.

5.2.4 Effektestimater og kategorier

I tabel 13 ses en samlet oversigt over de absolutte effektforskelle og kategori for de enkelte effektmål, der anvendes til at belyse klinisk spørgsmål 1 samt kvaliteten af evidensen.

Generelt kan værdien ikke kategoriseres for de anvendte effektmål, fordi usikkerheden ikke kvantificeres pga. manglende retvisende konfidensintervaller. De tilfælde, hvor punktestimatet overstiger den mindste klinisk relevante forskel, kan derfor ikke tolkes som et udtryk for, at der reelt er forskel mellem lægemidlerne.

Tabel 13. Resultater for klinisk spørgsmål 2

Effektmål	Måleenhed MKRF (måletidspunkt)	Vigtighed	Forskel i absolutte tal	Forskel i relative tal	Kategori for effektmålet	Klinisk vurdering
Overlevelse	Andel pt. i live **5 %**-point (24 mdr.)	Kritisk	0*	-	Kan ikke kategoriseres	Punktestimatet overstiger *ikke* MKRF
Kombineret mortalitet / permanent ventilations-behandling	Andel pt., som enten er døde eller anvender respirator > 16 timer/døgn **15 %**-point (24 mdr.)	Kritisk	0*	-	Kan ikke kategoriseres	Punktestimatet overstiger *ikke* MKRF
Permanent ventilations-behandling	Andel pt., som ikke anvender respirator > 16 timer/døgn **10 %**-point (24 mdr.)	Vigtig	0*	-	Kan ikke kategoriseres	Punktestimatet overstiger *ikke* MKRF
Motoriske milepæle	Andel pt., der opnår evnen til at sidde uden støtte **5 %**-point (24 mdr.)	Vigtig	Kan ikke beregnes ved samme opfølgningstidspunkt	-	Kan ikke kategoriseres	
	Andel pt., der går uden støtte ved **10 %**-point (24 mdr.)	Vigtig	Kan ikke beregnes ved samme opfølgningstidspunkt	-	Kan ikke kategoriseres	
Alvorlige bivirkninger (relateret til behandlingen)	Andel pt., som oplever mindst én alvorlig bivirkning	Vigtig	Kan ikke beregnes ved samme opfølgningstidspunkt	-	Kan ikke kategoriseres	

	10 %-point (24 mdr.)						
Livskvalitet	Kun kvalitativ bedømmelse	Vigtig	Ingen data	-	Kan ikke kategoriseres	Ingen data	
Samlet kategori for lægemidlets værdi		Kan ikke kategoriseres. Fagudvalget vurderer, at onasemnogene abeparvovec er et ligeværdigt behandlingsalternativ sammenlignet med nusinersen på baggrund af data for effekt og bivirkninger.					
Kvalitet af den samlede evidens		Meget lav - nye studier vil med høj sandsynlighed ændre effektestimaterne.					

*Effektmålet er opgjort ved følgende mediantidspunkter i studiet: onasemnogene abeparvovec ca. 10 måneder og nusinersen ca. 34 måneder, og kan derfor ikke umiddelbart sammenlignes

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.

Der var ingen tilfælde af død ved interimanalysen for hverken onasemnogene abeparvovec eller nusinersen og dermed ingen påviste forskelle i dette effektmål ved de forskellige opfølgningstider. Mindste klinisk relevante forskel er dermed ikke opnået. Data er opsummeret i tabel 14.

Tabel 14. Overlevelsesdata for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec n/N (%)	Nusinersen n/N (%)	Absolut forskel (% point)	MKRF (% point)
Andel pt. i live	29/29 (100 %) (ved ca. 10 mdrs. opfølgning)	25/25 (100 %) (ved ca. 34 mdrs. opfølgning)	0	5 %-point (ved 24 mdrs. opfølgning)

Fagudvalget vurderer, at onasemnogene abeparvovec og nusinersen er sammenlignelige for dette effektmål ved 10 måneders median opfølgning/behandling.

Kombineret mortalitet eller permanent ventilationsbehandling
Effektmålet er defineret som kritisk for vurderingen af lægemidlets værdi for patienterne, fordi fagudvalget anser begge effektmål som alvorlige hændelser.

Der var ingen tilfælde af død eller permanent ventilationsbehandling (anvender respirator > 16 timer/døgn) ved interimanalysen for hverken onasemnogene abeparvovec eller nusinersen og dermed ingen påviste forskelle i dette effektmål ved de forskellige opfølgningstider. Mindste klinisk relevante forskel er dermed ikke opnået. Data er opsummeret i tabel 15.

Tabel 15. Kombineret mortalitet eller permanent ventilations- behandling for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec n/N (%)	Nusinersen n/N (%)	Absolut forskel (% point)	MKRF (% point)
Andel pt., som er i live og ikke anvender respirator > 16 timer/døgn	29/29 (100 %) (ved ca. 10 mdrs. opfølgning)	25/25 (100 %) (ved ca. 34 mdrs. opfølgning)	0	15 (ved 24 mdr.)

Fagudvalget vurderer, at onasemnogene abeparvovec og nusinersen er sammenlignelige for dette effektmål ved 10 måneders median opfølgning/behandling.

Permanent ventilationsbehandling
Effektmålet er defineret som vigtigt for vurderingen af lægemidlets værdi for patienterne, da evnen til at trække vejret er så nedsat, at patienten er afhængig af en respirator mindst 16 timer i døgnet. Samtidig er patienten mere modtagelig for lungeinfektioner.

Der var ingen tilfælde af permanent ventilationsbehandling (anvender respirator > 16 timer/døgn) ved interimanalysen for hverken onasemnogene abeparvovec eller nusinersen og dermed ingen påviste forskelle i dette effektmål ved de forskellige opfølgningstider. Mindste klinisk relevante forskel er dermed ikke opnået. Data er opsummeret i tabel 16.

Tabel 16. Permanent ventilationsbehandling for onasemnogene abeparvovec og nusinersen

	Onasemnogene abeparvovec n/N (%)	Nusinersen n/N (%)	Absolut forskel (% point)	MKRF (% point)
Andel pt., som ikke anvender respirator > 16 timer/døgn	29/29 (100 %) (ved ca. 10 mdrs. opfølgning)	25/25 (100 %) (ved ca. 34 mdrs. opfølgning)	0	10 % (ved 24 mdr.)

Fagudvalget vurderer, at onasemnogene abeparvovec og nusinersen er sammenlignelige for dette effektmål ved 10 måneders median opfølgning/behandling.

Motoriske milepæle
Med nye behandlinger kan der potentielt være flere præsymptomatiske børn, som 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. Endvidere kan der med nye behandlinger potentielt være flere præsymptomatiske børn, der kan gå uden støtte, hvilket vil være helt usandsynligt uden behandling. Disse motoriske milepæle er derfor også vigtige effektmål.

Opnår evnen til at sidde uden støtte
For dette effektmål er der brugt forskellige definitioner i de to studier, og resultaterne er derfor ikke fuldstændig sammenlignelige. I SPR1NT er brugt Bayley Scales Gross Motor subset #26 (barnet sidder uden støtte ≥ 30 sekunder), mens NURTURE har brugt WHO's definition (Barnet sidder op med hovedet oprejst ≥ 10 sekunder, barnet bruger ikke hænder eller arme til at holde balancen eller støtte). Det medfører potentielt en overestimering af effekten af nusinersen i forhold til onasemnogene abeparvovec

Ved interimanalysen havde i alt 18/29 (62,0 %) behandlet med onasemnogene abeparvovec opnået evnen til at sidde selv uden støtte; for gruppen med 3 SMN2-kopier var det 10/15 (66,7 %). Alle børn (25/25 (100 %)) behandlet med nusinersen kunne sidde uden støtte ved interimanalysen. Data for effektmålet er opsummeret i tabel 8.

Tabel 8. Motorisk milepæl "sidde uden støtte" for onasemnogene abeparvovec og nusinersen. OBS! De markerede data er fortrolige

	Onasemnogene abeparvovec 2 SMN2-kopier n/N (%)	Onasemnogene abeparvovec 3 SMN2-kopier n/N (%)	Nusinersen 2 SMN2-kopier	Nusinersen 3 SMN2-kopier n/N (%)
Andel pt., der opnår evnen til at sidde uden støtte	8/29 (57,1 %)[1] (ved ca. 10 mdrs. opfølgning)	10/15 (66,7 %)[1] (ved ca. 9 mdrs. opfølgning)	15/15 (100 %)[2] (ved ca. 34 mdrs. opfølgning)	10/10 (100 %)[2] (ved ca. 34 mdrs. opfølgning)
Andel, der sidder uden støtte, og som er ældre end WHO's alders-range for normal udvikling (9,2 måneder [15]) ved interimanalysen, n/N (%)	[redacted]	[redacted]	15/15 (100)	10/10 (100 %)
Alder, hvor "sidde uden støtte" blev rapporteret, måneder, median (range)	[redacted]	[redacted]	7,9 (5,9-9,2)	6,4 (5,1-7,9)

[1]Bayley Scales Gross Motor subset item #26: Barnet sidder uden støtte i ≥30 sekunder. [2] WHO definition af at side selv (barnet sidder op med hovedet oprejst i ≥ 10 sekunder; barnet bruger ikke hænder eller arme som støtte eller til at holde balancen).

Andelen af børn, der sidder uden støtte, kan dog ikke sammenlignes pga. den store forskel i opfølgningstid. En del af børnene behandlet med onasemnogene abeparvovec havde ved interimanalysen endnu ikke nået den alder, hvor raske børn lærer at sidde uden støtte (99 percentilen er 9,2 måneder ifølge WHO [15]). Tabel 8 angiver også, hvor mange børn behandlet med henholdsvis onasemnogene abeparvovec og nusinersen, der kunne sidde uden støtte, og som var ældre end den alder, hvor 99 percentilen af raske børn kan sidde ved interimanalyserne. Dette afspejler ikke den alder, hvor børnene opnåede milepælen. Det fremgår, at alle børn behandlet med nusinersen, og som havde passeret denne alder kunne sidde (25/25), mens det var tilfældet for 15/17 børn (88,2 %) behandlet med onasemnogene abeparvovec.

Opnår evnen til at gå uden støtte
Ved interimanalysen havde i alt 7/29 (24,1 %) behandlet med onasemnogene abeparvovec opnået evnen til at gå uden støtte; for gruppen med 3 SMN2-kopier var det 3/15 (20,0 %).

I gruppen behandlet med nusinersen kunne 22/25 (88,0 %) gå uden støtte ved interimanalysen. I gruppen med 3 SMN2-kopier var det alle (10/10 (100 %)).

Data for effektmålet er opsummeret i tabel 9.

Tabel 9. Motorisk milepæl "gå uden støtte" for onasemnogene abeparvovec og nusinersen. OBS! De markerede data er fortrolige

	Onasemnogene abeparvovec 2 SMN2-kopier n/N (%)	Onasemnogene abeparvovec 3 SMN2-kopier n/N (%)	Nusinersen 2 SMN2-kopier	Nusinersen 3 SMN2-kopier n/N (%)
Andel pt., der opnår evnen til at gå uden støtte	4/14 (28,6 %)[1] (ved ca. 10 mdrs. opfølgning)	3/15 (20 %)[1] (ved ca. 9 mdrs. opfølgning)	12/15 (80,0)[1] (ved ca. 34 mdrs. opfølgning)	10/10 (100%)[1] (ved ca. 34 mdrs. opfølgning)
Andel, der går uden støtte, og som er ældre end WHO's alders-range for normal udvikling (17,6 måneder [15]) ved interimanalysen, n/N (%)	[redacted]	[redacted]	12/15 (80 %)	10/10 (100 %)
Alder, hvor "gå uden støtte" blev rapporteret, måneder, median (range)	[redacted]	[redacted]	20,4 (15,5-29,7[2])	12,3 (11,2-14,9[2])

[1] WHO's definition af "går uden støtte" (Barnet tager mindst 5 trin uafhængigt i oprejst position med ret ryg. Et ben bevæger sig fremad, mens det andet støtter det meste af kropsvægten. Der er ingen kontakt med en person eller et objekt.). [2]95 % konfidensinterval.

Andelene af børn, der går uden støtte kan dog ikke sammenlignes pga. den store forskel i opfølgningstid. En betydelig andel af børnene behandlet med onasemnogene abeparvovec havde ved interimanalysen endnu ikke nået den alder, hvor raske børn lærer at gå uden støtte (99 percentilen er 17,6 måneder ifølge WHO [15]).

Tabel 9 angiver også, hvor mange børn behandlet med henholdsvis onasemnogene abeparvovec og nusinersen, der kunne gå uden støtte, og som ved interimanalysen var ældre end den alder, hvor 99 percentilen af raske børn kan sidde. Dette afspejler ikke den alder, hvor børnene opnåede milepælen.

Fagudvalget vurderer, at dette effektmål ikke kan vurderes med de tilgængelige data, da kun en lille del af gruppen behandlet med onasemnogene abeparvovec har nået en alder, hvor de kan forventes at gå. Fagudvalget bemærker, at det vil være relevant at evaluere dette effektmål, når der foreligger onasemnogene abeparvovecdata med længere opfølgningstid.

Alvorlige hændelser bivirkninger
Effektmålet er defineret som vigtigt for vurderingen af lægemidlets værdi for patienterne, fordi effekten altid skal ses ift. alvorlige behandlingsrelaterede hændelser (bivirkninger).

I SPR1NT var der samlet 6 alvorlige hændelser rapporteret i 6/29 børn (20,7 %) behandlet med onasemnogene abeparvovec (ikke opgjort i forhold til antal SMN2-kopier). [redacted]

I NURTURE var der samlet 33 alvorlige hændelser rapporteret i 12/25 børn (48 %) behandlet med nusinersen (ikke opgjort i forhold til antal SMN2-kopier). Ingen blev vurderet til at være relateret til behandlingen med nusinersen [14].

Alvorlige uønskede hændelser rapporteret under behandling med onasemnogene abeparvovec inkluderede lyskebrok (1), falsk strubehoste (1), pyelonefritis (1), pharyngitis (1), udmatning (1) og hypercalcæmi (1).

Alvorlige uønskede hændelser rapporteret med nusinersen omhandlede lungebetændelser (bakterielle og virale) (10) samt forskellige infektioner i de øvre og nedre luftveje (8), i nogle tilfælde ledsaget af åndedrætsbesvær (2) og åndedrætssvigt (2), dehydrering (2), feber (1), urinvejsinfektion (1), enterovirus (1), viral gastroenteritis (1), abdominal distension (1), takykardi (1), dårlig trivsel (1) og seneskade (1).

Data for alvorlige uønskede hændelser og bivirkninger (vurderet relateret til behandlingen af den behandlende læge) er opsummeret i tabel 10.

Tabel 10. Alvorlige uønskede hændelser og bivirkninger for onasemnogene abeparvovec og nusinersen[14]. OBS! De markerede data er fortrolige

	Onasemnogene abeparvovec	Nusinersen	Absolut forskel	MKRF (%-point)
Andel pt. med alvorlige uønskede hændelser (SAE)	6/29 (20,7 %)	12/25 (48,0 %)	-27,3 % point	Ikke angivet
Andel pt. med alvorlige behandlingsrelaterede hændelser (bivirkninger)	[redacted] (ved ca. 10 mdrs. opfølgning)	0/25 (0 %) (ved ca. 34 mdrs. opfølgning)	[redacted]	10 %-point

Det er på nuværende tidspunkt ikke muligt at konkludere på baggrund af disse data, om der er forskel på behandlingerne, hvad angår alvorlige bivirkninger, på grund af studiernes forskellige opfølgningstider ved interimanalyserne.

5.2.5 Fagudvalgets konklusion for præsymptomatiske spædbørn

Fagudvalget vurderer, at den samlede værdi af onasemnogene abeparvovec sammenlignet med nusinersen til behandling af præsymptomatiske spædbørn ikke kan kategoriseres.

Fagudvalget vurderer, at onasemnogene abeparvovec er et ligeværdigt behandlingsalternativ til nusinersen vurderet på effekt og bivirkninger hos præsymptomatiske spædbørn med mindst to SMN2-kopier.

Fagudvalget vurderer, at effekten på overlevelse og permanent ventilationsbehov er sammenlignelig, men kan ikke på det foreliggende datagrundlag vurdere, om der er forskelle i effekten på de motoriske milepæle eller bivirkninger pga. den meget kortere opfølgningstid for onasemnogene abeparvovec.

Overvejelser vedr. praktiske forhold og bekymringer om langtidseffekt og langtidsbivirkninger har dog også betydning for vurderingen. Se afsnit 6 Andre overvejelser herfor.

6. Andre overvejelser

6.1.1 Patienter, som tidligere er behandlet med nusinersen

Nydiagnosticede børn med klinisk diagnosticerede SMA type 1 er under 6 mdr. gamle og vejer i praksis under 13,5 kg, når behandlingen med nusinersen eller onasemnogene abeparvovec påbegyndes. Der kan dog være ældre børn, som allerede er i behandling med nusinersen, hvor barnets læge og/eller forældre ønsker at skifte til onasemnogene abeparvovec.

Ifølge det godkendte produktresumé er effekten og sikkerheden af onasemnogene abeparvovec ikke klarlagt hos patienter over 2 år eller hos patienter, som vejer over 13,5 kg. Det fremgår ligeledes af produktresuméet, at effekten må formodes at være markant reduceret ved fremskreden SMA, hvor der er udtalt muskelsvækkelse og respirationssvigt.

Fagudvalget bemærker, at gennemsnitsvægten i de kliniske studier var 5,8 kg (range 3,6-8,4). Alle, på nær ét barn, var under 6 mdr. på infusionstidspunktet og med en sygdomsvarighed på højst 3,2 mdr. Ét barn på 7,9 mdr. og sygdomsvarighed på 5,9 mdr. havde ikke opnået hovedkontrol og havde et dagligt ventilationsbehov på 5-8 timer.

Fagudvalget vurderer på denne baggrund, at børn under 6 mdr., som allerede er i behandling med nusinersen, kan skifte til onasemnogene abeparvovec, såfremt de ikke har udtalt muskelsvækkelse eller respirationssvigt. I praksis vil disse børn typisk have modtaget mellem 1-3 doser nusinersen.

For børn, som er ældre end 6 måneder og vejer under 13,5 kg, vurderer fagudvalget, at man kan overveje at skifte fra nusinersen til onasemnogene abeparvovec, såfremt de ikke har udtalt muskelsvækkelse eller respirationssvigt.

6.1.2 Kombinationsbehandling

Den kliniske gevinst af at kombinere de to behandlinger, altså forsætte med eller tillægge nusinersen efter behandling med onasemnogene abeparvovec, er uafklaret, men vil blive belyst i igangværende studier. Fagudvalget bemærker, at der i et opfølgningsstudie, hvor man følger 10 patienter fra det tidligere START-studie, var 4 patienter som startede behandling med nusinersen. Det er uafklaret, hvorvidt en fortsat effekt er et resultat af

kombinationsbehandlingen eller onasemnogene abeparvovec alene. Fagudvalget vurderer derfor, at der ikke er evidens på nuværende tidspunkt for at anbefale kombinationsbehandling.

6.1.3 Præsymptomatiske spædbørn med én SMN2-kopi

Børn med én SMN2-kopi udvikler SMA type 0, hvor barnet har symptomer allerede ved fødslen. Der er ingen data for børn med én SMN2-kopi. Fagudvalget kan derfor ikke vurdere værdien af onasemnogene abeparvovec i denne patientgruppe.

6.1.4 Forskelle i bivirkningsprofilerne

Der foreligger ikke langtidsdata for bivirkningerne af hverken onasemnogene abeparvovec eller nusinersen. Bekymringerne for typen af mulige langtidsbivirkninger er lidt forskellige.

Onasemnogene abeparvovec
Genterapi er et forholdsvist nyt behandlingsprincip, hvor behandlingen ikke kan stoppes ved eventuelle alvorlige bivirkninger, som i stedet må håndteres symptomatisk. Selve behandlingen er mere skånsom, da den gives som en engangsinfusion, dog fuldt op af tæt monitorering de første 3 måneder.

Hyppige bivirkninger (forekommende i ≥ 1/100 til < 1/10) relateret til onasemnogene abeparvovec behandling er ifølge EMAs produktresumé: trombocytopeni, opkastning, feber, forhøjet aspartat-aminotransferase, forhøjet alanin-aminotransferase og forhøjet troponin I. Forhøjede transaminaser forekommer i ≥ 1/10 patienter.

Efter administration af onasemnogene abeparvovec fremkaldes et immunrespons pga. den virale vector, som benyttes ved genterapien. Dette immunrespons kan medføre forhøjede levertransaminaser, forhøjet troponin I eller fald i blodplader. Forhøjelsen af transaminaser kan være alvorlig, og der er set akut alvorlig leverskade. Patienter med nedsat leverfunktion eller akut viral infektion af leveren kan være i øget risiko for leverskader.

I de kliniske studier med onasemnogene abeparvovec er der observeret forbigående fald i antallet af blodplader, som i flere tilfælde opfyldte kriterierne for trombocytopeni. I de fleste tilfælde forekom den laveste blodpladeværdi i den første uge efter infusionen. Der er observeret stigninger i hjerte troponin I-niveauer efter infusion med onasemnogene abeparvovec. Forhøjede troponin I-niveauer kan i nogle patienter indikere potentiel skade på myokardiet.

For at dæmpe immunresponset anvendes immunomodulation med kortikosteroider før og efter infusion med onasemnogene abeparvovec og monitorering af leverfunktion, troponin I-niveauer og blodplader. Se detaljer for håndtering heraf i produktresuméet. Fagudvalget vurderer, at dette er håndterbart i klinisk praksis.

Efter markedsføringen er der, efter behandling af ca. 800 patienter, konstateret fem tilfælde af trombotisk mikroangiopati - en akut og livstruende tilstand, som er karakteriseret ved trombocytopeni, hæmolytisk anæmi og akut nyreskade. Èt tilfælde var fatalt. EMA har den 18. marts 2021 udsendt en 'Direkte kommunikation til sundhedspersoner' herom, og produktresuméet er efterfølgende blevet opdateret med den nye information.

Nusinersen
Ved behandling med nusinersen er der risici forbundet ved lumbalpunkturen ved hver behandling, som eventuelt foregår under sedation.

Bivirkninger relateret til nusinersen er ifølge EMAs produktresumé hovedpine, rygsmerter og opkastning, og det forventes, at ≥ 1/10 vil opleve disse kendte bivirkninger til lumbalpunktur-proceduren.

Efter markedsføring af nusinersen er der rapporteret alvorlige infektioner, herunder meningitis, i patienter behandlet med nusinersen ved lumbalpunktur. Kommunikerende hydrocephalus, aseptisk meningitis og hypersensitivitetsreaktioner (angioødem, urtikaria og udslæt) er også beskrevet. Hyppigheden af disse bivirkninger kan ikke bestemmes, da de kun er rapporteret efter markedsføring.

Endvidere er der set trombocytopeni, koagulationsforstyrrelser og nyretoksicitet i forbindelse med andre subkutane eller intravenøse antisense oligonukleotider.

6.1.5 Praktiske forhold

Der er afgørende forskelle på de to behandlingsmodaliteter, som kan have stor betydning for både patienten og omkostningerne til behandlingen. Onasemnogene abeparvovec er éngangsbehandling. Nusinersen skal administreres intratekalt seks gange det første år og tre gange om året de efterfølgende år og er i princippet livslang behandling, medmindre patienten ophører pga. manglende effekt eller bivirkninger eller skifter til en ny oral behandling med samme virkningsmekanisme.

6.1.6 Fagudvalgets konklusion for andre overvejelser

For begge lægemidler er der stor usikkerhed om langtidseffekt og langtidsbivirkninger. Fagudvalget vurderer, at nogle familier vil foretrække éngangsbehandling med onasemnogene abeparvovec frem for potentiel livslang behandling med nusinersen. Andre vil lægge vægt på bekymringer ift. mulige langtidsbivirkninger.

7. Fagudvalgets konklusion

Værdien af onasemnogene abeparvovec sammenlignet med nusinersen kan ikke kategoriseres.

Fagudvalget vurderer, at onasemnogene abeparvovec er et ligeværdigt behandlingsalternativ til nusinersen vurderet på effekt og bivirkninger. Vurderingen omfatter patienter med klinisk SMA type 1, som ikke er i permanent ventilationsbehandling, som starter behandling inden 6 måneders alderen samt præsymptomatiske spædbørn med mindst to SMN2-kopier.

Det er en fordel for patienterne, at onasemnogene abeparvovec kun skal gives én gang sammenlignet med potentiel livslang intratekal behandling med nusinersen hver 4. måned.

Der er stor usikkerhed om langtidseffekt og langtidsbivirkninger. Fagudvalget er opmærksom på ny sikkerhedsinformation, der senere kan ændre konklusionen.

Vurderingen er baseret på evidens af meget lav kvalitet.

8. Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget har derfor ikke taget stilling til en foreløbig placering af lægemidlet.

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10. 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**
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11. Versionslog

Versionslog		
Version	**Dato**	**Ændring**
1.1	18. maj 2021	Medicinrådet har justeret formuleringen af Medicinrådets konklusion (s. 3)
1.0	28. april 2021	Godkendt af Medicinrådet

12. Bilag

Bilag 1

	Onasemnogene abeparvovec (START og STRIVE-US)	**Nusinersen (ENDEAR)**
Mortalitet	Alle dødsfald	Alle dødsfald
Permanent ventilationsbehandling	Ventilationsbehandling >16 timer/døgn i 14 dage eller mere	Tracheostomi eller noninvasiv ventilation > 16 timer/døgn i mere end 21 dage
Eventfree survival	Død eller permanent ventilationsbehandling	Død eller permanent ventilationsbehandling
CHOP-INTEND	Andel patienter med > 4 point forbedring	Andel patienter med > 4 point forbedring
Motoriske milepæle	Sidder uden støtte i 30 sek jf. item22 på *Bailey Scales of Infant and Toddler Development gross motor subtest*	Patienter, som opnår *stable sit* eller pivots på *HINE2-sitting scale*

Medicinrådet

Application for the assessment of Zolgensma (onasemnogene abeparvovec) for the treatment of patients with 5q spinal muscular atrophy with a bi-allelic mutation in the *SMN1* gene and:

- a clinical diagnosis of SMA Type 1, or
- up to 3 copies of the *SMN2* gene

October 20th, 2020

Contents

1 Basic information

TABLE 1: CONTACT INFORMATION

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TABLE 2: OVERVIEW OF THE PHARMACEUTICAL

Proprietary name	Zolgensma
Generic name	Onasemnogene abeparvovec
Marketing authorization holder in Denmark	Novartis Gene Therapies, formerly AveXis, Inc.
ATC code	M09AX09
Pharmacotherapeutic group	Other drugs for disorders of the muscular-skeletal system
Active substance(s)	Onasemnogene abeparvovec

Pharmaceutical form(s)	Solution for infusion
Mechanism of action	Gene replacement therapy
Dosage regimen	Single dose of 1.1×10^{14} vg/kg
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Zolgensma is indicated for the treatment of: • patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or • patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Oral prednisolone prior to and 30 days post-administration
Packaging – types, sizes/number of units, and concentrations	Each mL contains Zolgensma with a nominal concentration of 2×10^{13} vector genomes. Vials will contain an extractable volume of not less than either 5.5 mL or 8.3 mL. The total number of vials and combination of fill volumes in each finished pack will be customised to meet dosing requirements for individual patients depending on their weight
Orphan drug designation	Yes

2 Abbreviations

TABLE 3: LIST OF ABBREVIATIONS

Abbreviation	
AAN	American Academy of Neurology
AAV9	Adeno-associated virus serotype 9
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ASO	Antisense oligonucleotide
AST	Aspartate transaminase
BiPAP	Bi-level positive airway pressure
BSC	Best supportive care
CDC	Center for Disease Control
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound motor action potential
CNS	Central nervous system
CSF	Cerebrospinal fluid
DILI	Drug-induced liver injury
DMC	Danish Medicines Council
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EFS	Event-free survival
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol-5 Dimensions
EU	European Union
GGT	gamma glutamyl- transpeptidase
HINE-2	Hammersmith Infant Neurological Examination-2
HRQoL	Health related quality of life
HR	Hazard Ratio
HTA	Health technology assessment
IMP	Investigational medicinal product
IPD	Individual patient data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Intrathecal
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan meier
LT	Long-term
MDT	Multidisciplinary team
MMDR	Modified Maintenance Dosing Regimen
MUNE	Motor unit number estimation
NA	Not applicable
NICE	The National Institute for Health and Care Excellence
NR	Not reached
OR	Odds Ratio
OS	Overall survival
PICOS	Population, Interventions, Comparisons, Outcomes, and study design

PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomoised control trial
RR	Relative Risk
RSV	Respiratory syncytial virus
RULM	Revised Upper Limb Module
SAE	Searious asdverse event
SD	Standard deviation
SLR	Structured literature review
SMA	Spinal muscular atrophy
SMD	Standardized mean difference
SMDM	Society for Medical Decision Making
SMN	Survival motor neurone
UK	United Kingdom
US	United States
WBC	White blood cell
WHO	World Health Organization
ZOL	Zolgensma

3 Summary

The European Medicines Agency (EMA) approved onasemnogene abeparvovec (Zolgensma) on May 18th2020 for the treatment of:

- patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

SMA is a rare genetic disease in which infants with the most severe phenotype, SMA type 1, never sit independently and >90% die or require permanent ventilation by the age of 2 years when managed with best supportive care (BSC). Despite the availability of Spinraza, the current standard of care for SMA in Denmark, significant unmet needs exist in terms of survival without the need for permanent ventilatory support, the achievement of developmental milestones, and the burden of chronic, life-time invasive therapy.

Zolgensma is the first one-time therapy which addresses the monogenic root cause of SMA by delivering a functional copy of the SMN gene that rapidly restores continuous SMN protein expression to prevent further motor neuron loss. In Denmark, within its licensed indication, Zolgensma is positioned for use in two patient groups: Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1, below 21 kg, or a pre-symptomatic diagnosis of SMA with up to 3 copies of *SMN2*, below 21 kg.

Clinical evidence supporting the use of intravenous Zolgensma in these patient groups comes from a comprehensive trial programme in infants with SMA type 1 (START, STR1VE-US, STR1VE-EU, LT-001, LT-002) and in pre-symptomatic infants with genetically diagnosed SMA and up to three copies of the *SMN2* gene (SPR1NT). To date, these studies have enrolled approximately 100 patients.

As a result of the single arm open-label trial design used to assess Zolgensma, unanchored indirect treatment comparisons are used to assess the relative efficacy versus the comparator Spinraza. For infants with SMA type 1, the comparisons were made vs the entire ITT population from the ENDEAR trial, and vs a pre-specified subgroup of patients from ENDEAR with a disease duration ≤12 weeks at screening. as this subgroup was considered relevant in the protocol provided by the medicine council.

In comparison with Spinraza, the unanchored ITC demonstrated that Zolgensma showed consistent benefit over Spinraza in SMA type 1 patients in several of the key outcomes analysed (event-free survival and achievement of motor milestones).

Due to the rapid loss of motor neurons in infants with SMA type 1, prompt diagnosis and early intervention are key to the optimal achievement of clinical outcomes, highlighting the importance of new-born screening. Pre-symptomatic SMA patients (up to 3 *SMN2* copies) treated with Zolgensma or Spinraza soon after birth in ongoing trials are achieving age-appropriate developmental milestones

Our data does not indicate any major differences in the safety profile between Zolgensma and Spinraza, which is supported by the following statement from EMA: “Zolgensma effectively targets the disease mechanism in 5q SMA, has improved efficacy and a more convenient method of administration when compared to those of nusinersen; and has at least a comparable safety profile to that of nusinersen.”

4 Literature search

A systematic literature review was conducted to identify relevant publications to assess the clinical added value of Zolgensma (onasemnogene abeparvovec) for the treatment of patients with 5q spinal muscular atrophy with a bi-allelic mutation in the *SMN1* gene and: a clinical diagnosis of SMA Type 1; or up to 3 copies of the *SMN2* gene.

The systematic literature review included the search string as defined in the protocol provided by the Medicines Council. The results from the systematic search performed on 14 AUG 2020 in both CENTRAL and Medline are presented in Table 4 and Table 5, respectively.

TABLE 4. SEARCH STRING AND RESULTS OF THE SYSTEMATIC SEARCH IN CENTRAL (VIA COCHRANE LIBRARY)

#	Query	Search facet	No. of hits
#1	(onasemnogene next abeparvovec or Zolgensma* or "avxs 101" or avxs101):ti,ab,kw	Search terms for medication	4
#2	((adeno next associated next vir* and "serotype 9") or scAAV9):ti,ab		2
#3	(nusinersen or nusinersen or Spinraza* or ISIS next SMN*):ti,ab,kw		39
#4	#1 or #2 or #3		45
#5	(clinicaltrials.gov or trialsearch):so	Exclusion of specific publication types	330 220
#6	"conference abstract":pt		158 466
#7	#5 or #6		488 686
#8	#4 not #7	Fine search Limited to trials	13

TABLE 5. SEARCH STRING AND RESULTS OF THE SYSTEMATIC SEARCH IN MEDLINE (VIA PUBMED)

#	Query	Search facet	No. of hits
#1	onasemnogene abeparvovec[tiab] OR Zolgensma*[tiab] OR avxs-101[tiab] OR avxs101[tiab]	Search terms for medication	44
#2	(adeno-associated vir*[tiab] AND serotype 9[tiab]) OR scAAV9[tiab]		330
#3	SMA[tiab] OR SMA1[tiab] OR SMA2[tiab] OR SMA3[tiab] OR spinal muscular atrophy[tiab] OR Spinal Muscular Atrophies of Childhood[mh] OR Muscular Atrophy, Spinal[mh]		25 927
#4	#2 AND #3		31
#5	nusinersen[nm] OR nusinersen[tiab] OR Spinraza*[tiab] OR ISIS-SMN*[tiab]		309
#6	#1 OR #4 OR #5		358
#7	Case Reports[pt] OR Comment[pt] OR Guideline[pt] OR Letter[pt] OR News[pt]	Exclusion of specific publication types	3 623 626
#8	#6 NOT #7	Fine search	318

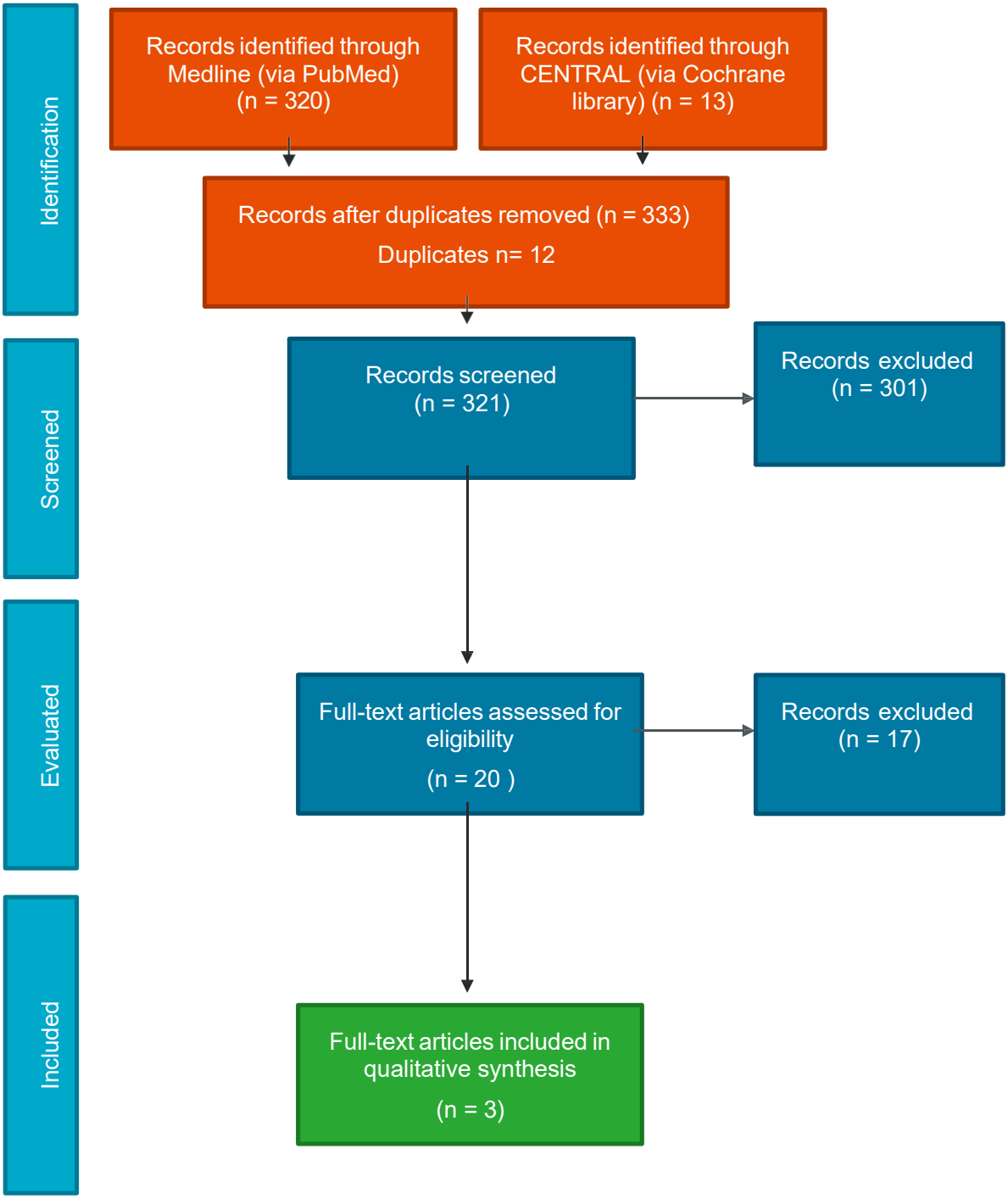
The eligibility criteria used for the systematic literature review are defined in terms of the Population, Interventions, Comparisons, Outcomes, and study design (PICOS) framework, as well as language and time frame (see Table 22 in appendix, section 7.1).

A total of 331 records were identified through CENTRAL and MEDLINE. With the addition of 2 records not captured in the database search and duplicates removed 321 records were left to be screened. Two reviewers, working independently reviewed the identified records for inclusion by title or abstract according to the PICO selection criteria, resulting in 301 excluded records. The 20 full-text publications that passed the first screening underwent a more rigorous screening to asses any data of interest according to PICO. Of these 20 publications, three publications were found relevant, where a manual desk search had also captured three additional publication—European Medicines Agency assessment report (European Medicines Agency 2020), NICE committee papers for Spinraza (National Institute for Health and Care Excellence 2018), and IQWiG report on SMA new born screening (IQWiG 2020)—resulting in a total of 6 publications corresponding to 5 clinical trials. Further details described in section 4.1 and 4.2.

The process of study identification and selection are summarized in Figure 1 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

All records excluded after the full-text review are presented with reason for exclusion in Table 23 in the Appendix section 7.1.

FIGURE 1. PRISMA FLOW DIAGRAM OF MEDLINE (VIA PUBMED) AND CENTRAL (VIA COCHRANE LIBRARY)



4.1 Relevant studies

The three publications identified in the literature search included the following five studies. In addition, three publications were captured manually (National Institute for Health and Care Excellence 2018, European Medicines Agency 2020, IQWiG 2020) (also see Table 6):

– STR1VE-US: pivotal phase 3 trial studying open-label intravenous administration of Zolgensma in SMA type 1 patients (European Medicines Agency 2020)

- START: phase 1 open-label, dose-escalation trial of Zolgensma in SMA type 1 patients (Mendell 2017)
- ENDEAR/SHINE: a randomized, double blind, sham-procedure controlled study to assess the clinical efficacy and safety of Spinraza administrated intrathecally in patients with infantile-onset SMA as well as a long-term follow up of patients which have participated in ENDEAR (called SHINE) (Finkel 2017, National Institute for Health and Care Excellence 2018, IQWiG 2020)
-
- SPR1NT: a global study of a single, one-time dose of Zolgensma delivered to infants with genetically diagnosed and pre-symptomatic SMA with multiple copies of *SMN2* (European Medicines Agency 2020)
- NURTURE: an open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of Spinraza delivered intrathecally to subjects with genetically diagnosed and pre-symptomatic Spinal Muscular Atrophy (De Vivo 2019).

TABLE 6: 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 1	Relevant for clinical question 2
European Medicines Agency assessment report (European Medicines Agency 2020)	*STR1VE-US*	*NCT03306277*	*Start October 24, 2017* *Completion November 12, 2019*	*Y*	
Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy (Mendell 2017)	*START*	*NCT02122952*	*Start May 5, 2014* *Completion December 15, 2017*	*Y*	
Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy (Finkel 2017) Single Technology Appraisal. Nusinersen for treating spinal muscular atrophy [ID1069], Committee Papers. (National Institute for Health and Care Excellence 2018)	*ENDEAR* *ENDEAR/SHINE (in practice follow-up of ENDEAR)*	*ENDEAR: NCT02193074* *SHINE: NCT02594124*	*ENDEAR: Start August 19, 2014* *Completion November 21, 2016* *SHINE: Start November 4, 2015* *Estimated completion August 2023*	*Y*	

Neugeborenenscreening auf 5q-assoziierte spinale Muskelatrophie, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG 2020)	*ENDEAR/SHINE*				
European Medicines Agency assessment report (European Medicines Agency 2020)	*SPR1NT*	NCT03505099	*Start* *April 10, 2018* *Completion* *July 26, 2021*		*Y*
Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study (De Vivo 2019)	*NURTURE*	NCT02386553	*Start* *May 20, 2015* *Completion* *February 25, 2025*		*y*

4.2 Main characteristics of included studies

The clinical trials relevant for this application differ in study design and follow-up. While the Zolgensma studies in general are open-label, the Spinraza ENDEAR study in symptomatic SMA type 1 patients used randomization where sham-procedure was used as control. Follow-up time range from 10 months (interim data cut for SPR1NT) up to 4 years in NURTURE. Primary endpoints differ between studies, however, when looking at all endpoint the overlap may be more aligned. The population, for example number of *SMN2* copies, is similar between studies, which is expected due to the set inclusion/exclusion criteria of the literature review. Additional information regarding the main characteristics of the six included trials are presented in Table 24 to Table 28 in appendix, section 7.2.

5 Clinical questions

5.1 What is the value of Zolgensma compared to Spinraza in children with clinically diagnosed SMA type 1?

Relevant studies were identified in the SLR performed in August 2020 and in AveXis clinical data on file (AveXis ITC Technical Report 2020). The SLR identified trials assessing Zolgensma and relevant competing interventions for SMA type 1.

5.1.1 Presentation of relevant studies

Studies relevant for the analysis are STR1VE-US, START (Zolgensma), ENDEAR, and SHINE (Spinraza). For the comparison, only STR1VE-US, START and ENDEAR were considered relevant. SHINE is the long-term follow-up study of ENDEAR and the time points of interest exceeded the ones requested by the Medicines Council.

5.1.1.1 STR1VE-US

STR1VE-US was a Phase III, open-label, single-arm study of a one-time intravenous infusion of Zolgensma, with the objective to determine the efficacy of Zolgensma in patients with SMA type 1 with one or two *SMN2* copies. 22 patients enrolled in STR1VE-US, all of whom had two copies of *SMN2*. During the outpatient follow-up period (Day 4 to End of Study at 18 months of age), patients returned at regularly scheduled intervals for efficacy and safety assessments (AveXis CSR STR1VE-US 2018). An overview of the study is presented in Table 24

5.1.1.2 START

START was a Phase I/II, open-label, one-time infusion, ascending-dose, single-centre study with the objective to assess the safety of Zolgensma. Fifteen patients were recruited, with cohort 1 (n=3) receiving a low dose (6.7×10^{13} vg/kg) and cohort 2 (n=12) receiving the proposed therapeutic dose (2.0×10^{14} vg/kg). When evaluated by the more advanced assay, the Cohort 2 dose showed equivalence to the approved therapeutic dose of 1.1×10^{14} vg/kg. During the first year of the 2-year follow-up period, patients returned for post-dose follow-up visits on Days 7, 14, 21, and 30, followed by monthly visits through Month 12. During the second year, patients with CHOP-INTEND scores ≥62 were assessed with the Bayley Scales and completed visits every 3 months; all other patients completed monthly visits (subsequently changed to quarterly visits). An overview of the study is presented in Table 25.

5.1.1.3 ENDEAR

ENDEAR was a phase III, randomised, double-blind, sham-procedure controlled study with the primary objective to examine the clinical efficacy of Spinraza administered intrathecally to participants with infantile-onset SMA; secondary objects were to study the safety and tolerability of the treatment. The study had recruited 122 patients, where 81 patients were assigned to the Spinraza group and 41 patients to the control. Doses were administered on days 1, 15, 29, and 64, and maintenance doses on days 183 and 302. Efficacy end points were assessed on days 64, 183, 302, and 394 (±7 days for each visit), with additional safety-monitoring visits occurring on days 16, 30, 65, 184, and 303. An overview of the study is presented in Table 26.

A pre-specified subgroup of relevance was identified in the primary publication of ENDEAR (Finkel 2017), which included patients with a disease duration at screening equal to or below twelve weeks (≤12 weeks). Disease duration was defined as the age at screening minus the age at symptom onset. Further details about the baseline characteristics and outcomes for this pre-specified subgroup—hereinafter referred to as the

'ENDEAR subgroup' dataset—were identified in the NICE committee papers for Spinraza (National Institute for Health and Care Excellence 2018) and the recent IQWiG report on SMA new born screening (IQWiG 2020).

5.1.2 Results per study

Results from the studies included in the analyses are presented in Table 29 to Table 34 in the appendix 7.2.

5.1.3 Comparative analyses

5.1.3.1 Baseline characteristics

Baseline characteristics, where available, of the cohorts enrolled in the identified clinical trials were qualitatively compared, to select appropriate evidence for inclusion in the relative effectiveness assessment. A juxtaposition of these baseline characteristics for the identified clinical trials, including the POOLED dataset (START [Cohort 2] and STR1VE-US) for Zolgensma and the ENDEAR subgroup (patients with ≤12 weeks disease duration at screening) and ENDEAR ITT population for Spinraza is presented in below in Table 7.

TABLE 7: BASELINE CHARACTERISTICS OF PATIENT COHORTS ENROLLED IN THE IDENTIFIED CLINICAL TRIALS

Characteristic	[redacted]	**Spinraza**	
		ENDEAR subgroup (≤12 weeks disease duration)	**ENDEAR ITT population**
N		34	80
Female, n (%)		18 (53)	43 (54)
Mean disease duration at dosing, weeks (range)			13.2 (0, 25.9)
Mean disease duration at screening, weeks (range)***		NR	NR
≤12 weeks disease duration at screening, n		34	34
>12 weeks disease duration at screening, n		0	46
Mean age at onset of symptoms, weeks (range)		6** (3–18)	7.9 (2–18)
Mean age at genetic diagnosis, weeks (range)		9** (0–22)	12.6 (0–29)
Mean age at first dose, weeks (range)		16 (7–34)	23.3 (7.4–34.6)
Mean weight, kg (range)		NR	NR
Mean CHOP-INTEND, n (range)		NR	26.6 (8.1*)

Nutritional support, n (%)	[redacted]	5 (41.7)	[redacted]	NR	7 (9)
Ventilatory support, n (%)	[redacted]	2 (17)	[redacted]	NR	21 (26)

Abbreviation: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ITT, intent to treat, NR, not recorded.
Note: *standard deviation, **median values, ***disease duration at screening is defined as the age at screening minus the age at symptom onset. Age at symptom onset was reported in months, then converted to weeks in the calculation. Due to the conversion, a negative mean duration of disease at screening was calculated for two patients in the Zolgensma trials.
Data for pooled STR1VE-US and START studies and for the ENDEAR study ITT population has been converted from days to weeks, to match the ENDEAR subgroup dataset (≤12 weeks disease duration duration), for consistency and to support the comparison.
Source: (National Institute for Health and Care Excellence 2018)

Mean age at symptom onset, age at treatment, and CHOP-INTEND scores were slightly lower in START (Cohort 2) compared with STR1VE-US, and the proportion of patients on nutritional support at baseline was higher. The range of age at treatment in START (Cohort 2) was also wider than in STR1VE-US. When pooling the two completed Zolgensma studies to create the POOLED dataset, these differences were balanced and closely matched the baseline characteristics of the ENDEAR subgroup.

Whilst the age at SMA symptom onset is similar across all datasets, in the ENDEAR ITT dataset the age at diagnosis (mean age of 12.6 weeks) and age at treatment initiation (mean age of 23.3 weeks) were notably higher than those reported in the other datasets. In the ENDEAR ITT dataset a considerable proportion of patients (26%) were also dependent on ventilatory support at baseline, which is a higher proportion compared with the other datasets. Mean CHOP-INTEND score was also lower in the ENDEAR ITT dataset, when compared with the Zolgensma datasets.

Some baseline parameters were not reported for the ENDEAR subgroup, including CHOP-INTEND and the proportion of patients on nutritional and ventilatory support. However, age at genetic diagnosis and age at first dose closely correspond with the Zolgensma datasets. Based on the well-known natural history and progressive nature of SMA, it is considered plausible that in the ENDEAR subgroup a smaller proportion of patients were dependent on ventilatory support and also had higher motor function at baseline, compared to the ENDEAR ITT population, given their younger age at diagnosis and at first treatment.

Considerations

The Medicines Council have asked for separate analyses for patient subgroups according to duration of disease, referring to the prespecified subgroups in the Spinraza ENDEAR study (disease duration at screening ≤ 12 weeks or > 12 weeks). A substantial part of the patient population in ENDEAR (46/80 [redacted] had a disease duration at screening >12 weeks. Due to the limited data on patients with a longer duration at screening in the Zolgensma studies, it was not considered meaningful to conduct a statistical analysis for patients with disease duration at screening >12 weeks. For this reason, the comparative analyses presented below are the following:

- POOLED Zolgensma data (STR1VE-US and START) vs ENDEAR subgroup (base case)
- POOLED Zolgensma data (STR1VE-US and START) vs ENDEAR ITT population (scenario)

For simplicity, the Zolgensma POOLED ITT population is used in both analyses, including the one patient in the Zolgensma trials with a disease duration at screening >12 weeks. As treatment outcome can be assumed to be less beneficial in later treated patients, use of the POOLED ITT population in the comparison with the ENDEAR subgroup may therefore be considered conservative.

5.1.3.2 Comparative analyses of overall survival

The Medicines Council have asked for a comparison on the proportion of patients alive at 10-14 months.

Overall survival from the POOLED dataset (START and STR1VE-US) for Zolgensma were compared with the ENDEAR subgroup and ENDEAR ITT population Spinraza. Since the exact time to event for the ENDEAR subgroup has not been published elsewhere, figures available from the NICE assessment of Spinraza (National Institute for Health and Care Excellence 2018) were digitized to obtain these data, using the method described in Appendix Section 7.4.

Results for overall survival at 14 months are presented in Table 8.

Compared to the ENDEAR subgroup, the proportion of patients alive at 14 months was 6% higher (relative) in the POOLED ZOL dataset, resulting in an absolute risk reduction of 5%, matching the minimal clinically relevant difference set by the Medicines Council (5 percent). However, this effect was not statistically significant. Compared to the ENDEAR ITT population, the relative improvement was 16% and 21% and absolute improvement was 13% and 17%, depending on calculation method, well exceeded the 5 percent minimal clinically relevant difference and was statistically significant.

TABLE 8: STATISTICAL ANALYSIS RESULTS OVERALL SURVIVAL

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR subgroup (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Survival at 14 months of follow-up – calculated from survival probabilities	33/34 (97.1%)	31/34 (91.2%)	1.06 (0.95 to 1.23)	-0.06 (-0.22 to 0.05)	-0.05 (-0.18 to 0.04)	0.05 (-0.04 to 0.21)
Survival at 14 months of follow-up – actual (at end ENDEAR follow-up)	33/34 (97.1%)	NR	N/A	N/A	N/A	N/A
			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR ITT (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Survival at 14 months of follow-up – calculated from survival probabilities	33/34 (97.1%)	64/80 (80,0%)	**1.21 (1.07 to 1.39)**	**-0.21 (-0.39 to -0.07)**	**-0.17 (-0.27 to -0.06)**	**0.17 (0.06 to 0.31)**
Survival at 14 months of follow-up – actual (at end ENDEAR follow-up)	33/34 (97.1%)	67/80 (83.8%)	**1.16 (1.04 to 1.31)**	**-0.16 (-0.31 to -0.04)**	**-0.13 (-0.23 to -0.03)**	**0.13 (0.03 to 0.26)**

Abbreviation: ZOL, Zolgensma (onasemnogene abeparvovec), ITT, intent to treat, NR, not recorded, N/A not applicable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. For overall survival, relative risk >1, Relative risk reduction and absolute risk reduction <0 and risk difference >0 indicate results in favour of onasemnogene abeparvovec vs Spinraza.

5.1.3.3 Comparative analysis of event-free survival (combined mortality or permanent assisted ventilation)

The Medicines Council have asked for a comparison on the proportion of patients alive and event-free (i.e. combined mortality or permanent assisted ventilation) at 10-14 months.

Event-free survival from the POOLED dataset (START and STR1VE-US) for Zolgensma were compared with the ENDEAR subgroup and ENDEAR ITT population for Spinraza. Since the exact time to event for the ENDEAR subgroup has not been published elsewhere, figures available from the NICE assessment of Spinraza (National Institute for Health and Care Excellence 2018) were digitized to obtain these data, using the method described in Appendix Section 7.4.

Results of the statistical comparison for event-free survival are presented in Table 9.

Zolgensma had beneficial effects on event-free survival, i.e. survival without permanent ventilation, at 14 months of follow-up both in comparison with the ENDEAR subgroup with a 23% relative improvement and 17% absolute improvement. In the ENDEAR ITT population the relative improvement was 54% and 79% and absolute improvement was 33% and 42%, depending on calculation method. The effect size exceeded the minimal clinically relevant difference set up by the Medicines Council (15 percent).

It should be noted that the definition for event-free survival differed slightly between the studies. In START and STR1VE-US the patients met the endpoint for permanent assisted ventilation after 14 consecutive days with assisted ventilation for ≥16 hours per day, whilst in ENDEAR the definition was >21 continuous days. This difference creates a potential bias to Zolgensma's disadvantage.

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TABLE 9: STATISTICAL ANALYSIS RESULTS SURVIVAL WITHOUT PERMANENT VENTILATION

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR subgroup (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Survival without permanent ventilation (number of patients alive without permanent ventilation) at 14 months of follow-up (n/N) – calculated from survival probabilities	32/34 (94.1%)	26/34 (76.5%)	**1.23 (1.02 to 1.56)**	**-0.22 (-0.56 to -0.02)**	**-0.17 (-0.34 to -0.02)**	**0.17 (0.02 to 0.43)**
Survival without permanent ventilation (number of patients alive without permanent ventilation) at 14 months of follow-up (n/N) – actual (at end ENDEAR follow-up)	32/34 (94.1%)	NR	N/A	N/A	N/A	N/A

Outcome			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR ITT (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Survival without permanent ventilation (number of patients alive without permanent ventilation) at 14 months of follow-up (n/N) – calculated from survival probabilities	32/34 (94.1%)	42/80 (52.5%)	**1.79 (1.45 to 2.29)**	**-0.79 (-1.29 to -0.45)**	**-0.42 (-0.54 to -0.27)**	**0.42 (0.24 to 0.68)**
Survival without permanent ventilation (number of patients alive without permanent ventilation) at 14 months of follow-up (n/N) – actual (at end ENDEAR follow-up)	32/34 (94.1%)	49/80 (61.3%)	**1.54 (1.27 to 1.89)**	**-0.54 (-0.89 to -0.27)**	**-0.33 (-0.46 to -0.19)**	**0.33 (0.17 to 0.55)**

Abbreviation: ZOL, Zolgensma (onasemnogene abeparvovec), ITT, intent to treat, NR, not recorded, N/A not applicable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. For survival without permanent ventilation, relative risk >1, Relative risk reduction and absolute risk reduction <0 and risk difference >0 indicate results in favour of onasemnogene abeparvovec vs Spinraza.

5.1.3.4 Comparative analysis of permanent assisted ventilation

The Medicines Council have asked for a comparison on the proportion of patients on permanent ventilation at 12-18 months. Our interpretation is that the parameter of interest is proportion of live patients not on permanent ventilation.

Results on permanent ventilation are presented in Table 10. The proportion of live patients not requiring permanent ventilation at 14 months of follow-up was 15% (relative) higher in the POOLED ZOL dataset compared to the ENDEAR subgroup with an absolute risk reduction of 12% exceeding the minimal clinically significant difference set by the Medicines Council (10 percent). However, the effect was of borderline statistical significance.

Compared with the ENDEAR ITT population, the relative improvement of 50% and absolute improvement of 32% was statistically significant and exceeded the minimal clinically significant difference.

It should be noted that the definition for permanent assisted ventilation differed slightly between the studies. In START and STR1VE-US the patients met the endpoint for permanent assisted ventilation after 14 consecutive days with assisted ventilation for ≥16 hours per day, whilst in ENDEAR the definition was >21 continuous days. This difference creates a potential bias to Zolgensma's disadvantage.

TABLE 10: STATISTICAL ANALYSIS RESULTS LACK OF PERMANENT VENTILATION

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR subgroup (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Lack of permanent ventilation (number of live patients not requiring assisted ventilation > 16 h/d) at 14 months of follow-up or last patient visit if prior to 14 months (n/N)	32/33 (97,0%)	26/31 (83.9%)	1.15 (1.00 to 1.41)	-0.15 (-0.41 to -0.00)	-0.13 (-0.28 to -0.00)	0.12 (0.00 to 0.34)
			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR ITT (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Lack of permanent ventilation (number of live patients not requiring assisted ventilation > 16 h/d) at 14 months of follow-up or last patient visit if prior to 14 months (n/N)	32/33 (97,0%)	42/65 (64.6%)	**1.50 (1.26 to 1.85)**	**-0.50 (-0.85 to -0.26)**	**-0.32 (-0.45 to -0.19)**	**0.32 (0.17 to 0.55)**

Abbreviation: ZOL, Zolgensma, ITT, intent to treat, NR, not recorded, N/A not applicable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. Numbers are showing alive patients without need of permanent ventilation. For lack of permanent ventilation, relative risk >1, Relative risk reduction and absolute risk reduction <0 and risk difference >0 indicate results in favour of Zolgensma vs Spinraza.

5.1.3.5 Comparative analysis of CHOP-INTEND responders

The Medicines Council have asked for a comparison of the proportion of patients responding, defined by ≥ 4 point improvement on CHOP-INTEND, at 12-18 months. [redacted]

In the comparison vs the ENDEAR ITT population' [redacted]

TABLE 11: STATISTICAL ANALYSIS RESULTS CHOP-INTEND RESPONDERS

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	ENDEAR subgroup (Spinraza arm) n/N (%)	Relative risk (95% CrI)	Relative risk reduction (95% CrI)	Absolute risk reduction (95% CrI)	Risk difference (95% CrI)
CHOP-INTEND responders (number of patients with at least 4 p improvement on CHOP-INTEND) at 14 months of follow-up or last patient visit if prior to 14 months (n/N)	[redacted]	32/34 (94.1%)	[redacted]	[redacted]	[redacted]	[redacted]
			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	ENDEAR ITT (Spinraza arm) n/N (%)	Relative risk (95% CrI)	Relative risk reduction (95% CrI)	Absolute risk reduction (95% CrI)	Risk difference (95% CrI)
CHOP-INTEND responders (number of patients with at least 4 p improvement on CHOP-INTEND) at 14 months of follow-up or last patient visit if prior to 14 months (n/N)	[redacted]	52/73 (71.2%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: ZOL, Zolgensma , ITT, intent to treat, NR, not recorded, N/A not applicable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. For CHOP-INTEND responders, relative risk >1, Relative risk reduction and absolute risk reduction <0 and risk difference >0 indicate results in favour of Zolgensma vs Spinraza

5.1.3.6 Comparative analysis of sitting without support

The Medicines Council have asked for a comparison on the proportion of patients sitting without support at 12-18 months. The 99th percentile of the window of milestone achievement for sitting without support is 9.2 months for healthy children according to WHO (WHO Multicentre Growth Reference Study Group 2006).

It should be noted that the analysis of patients sitting without support is complicated by different definitions used in the different studies. The following definitions were applied to allow for a comparison

- STR1VE-US measured independent sitting as both sitting alone for ≥30 seconds as per Bayley Scales item #26 and sitting alone for ≥5 seconds as per Bayley Scales item #22, however, only item #26 was video-confirmed, so this was taken as the primary measure of independent sitting for STR1VE-US patients in the pooled data set.
- START assessed independent sitting using both Bayley Scales item #26 and item #22, both of which were video-confirmed. However, for independent sitting ≥30 seconds as per Bayley Scales item #26, the dataset in START is unfortunately incomplete when it comes to date of attainment. For two patients with video confirmed sitting ≥30 seconds, the dates of attainment are lacking.
- When selecting motor milestone data for the POOLED dataset, we used the ≥30 second threshold (item #26) for STR1VE-US and the ≥5 second threshold for START (item #22) to define 'sitting without support'. In addition, we present scenarios using the ≥30 second threshold (item #26) for both STR1VE-US and START.
- Data for independent sitters ≥30 seconds in the POOLED dataset is available for patients meeting the endpoint ≤18 months of age and by end of follow-up.

- Two different definitions of sitting was used for the ENDEAR subgroup. It should be noted that the HINE-2 scale was used in both definitions, and that this instrument does not include any time threshold that needs to be exceeded in order for the baby to be qualified as a sitter:
    - Definition 1: In the IQWiG report on SMA newborn screening (IQWiG 2020), number of patients sitting is reported for the ENDEAR subgroup. However, in the IQWiG report a different definition of sitting is used: "improvement by ≥ 1 point on a HINE-2 sitting scale of 3 to 5 development stages; late children and dropouts were rated as non-responders" (See Figure 2: HINE-2 sitting scale for reference). This definition should be regarded as overly inclusive, as a 1 point improvement on this scale may include improvements from the lower stages of this scale, e.g. from "cannot sit" to "sit with support at hips" which is not synonymous with independent sitting. Hence it is considered conservative to compare this proportion of sitters with the proportion of independent sitters in START and STR1VE. Finally, as it is not stated in the IQWIG-report what the timepoint was for this measurement, it is assumed that it was measured at the end-of-study follow-up.
    - Definition 2: In the second analysis, it is assumed that the patients sitting at the end of follow-up in the ENDEAR ITT population (Finkel 2017) all belong to the ENDEAR subgroup. In this definition the patients are regarded as independent sitters only if they had reached 'stable sit' or 'pivots' on the HINE-2 sitting scale by end of ENDEAR follow-up. The number of sitters was taken from Finkel 2017 online supplement Figure S3 page 34.

FIGURE 2: 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

Source: (De Sanctis 2016)

Results of the statistical analysis of achievement of independent sitting are presented in Table 12.

When using definition 1 for Spinraza sitters in the ENDEAR subgroup, Zolgensma is numerically superior to Spinraza when using the ≥30 second definition for Zolgensma for STR1VE-US and ≥5 second definition for START. However, the difference was not statistically significant, and the effect size did not reach the minimal clinically relevant difference set by the Medicines Council (10 percent). When using the ≥30 second definition for Zolgensma for both STR1VE-US and START, [redacted]

When applying definition 2 for Spinraza sitters in the ENDEAR subgroup, Zolgensma is numerically superior to Spinraza regardless of definition of sitting in the Zolgensma trials, exceeding the minimal clinically relevant difference set by the Medicines Council (10 percent).

Compared to the ENDEAR ITT population, Zolgensma was numerically superior with regards to sitting without support regardless of the definition of sitting in the Zolgensma and Spinaza trials.

TABLE 12: STATISTICAL ANALYSIS RESULTS ACHIEVEMENT OF SITTING WITHOUT SUPPORT

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	ENDEAR subgroup (Spinraza arm) n/N (%)	Relative risk (95% CrI)	Relative risk reduction (95% CrI)	Absolute risk reduction (95% CrI)	Risk difference (95% CrI)
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 1 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	16/32 (50%)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US and START) • Definition 1 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	16/32 (50%)				
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 2 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	6/32 (18.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US and START)	[redacted]	6/32 (18.8%)				

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR subgroup (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
• Definition 2 for Spinraza, assumed end of ENDEAR follow-up						
Sitting without support (number of patients sitting) at end of follow-up (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 1 for Spinraza, assumed end of ENDEAR follow-up	25/34 (73.5%)	16/32 (50.0%)	**1.47 (1.01 to 2.30)**	**-0.47 (-1.30 to -0.01)**	**-0.24 (-0.45 to -0.01)**	**0.24 (0.00 to 0.65)**
Sitting without support (number of patients sitting) at end of follow-up (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 2 for Spinraza, assumed end of ENDEAR follow-up	25/34 (73.5%)	6/32 (18.8%)	**4.05 (2.09 to 10.08)**	**-3.05 (-9.08 to -1.09)**	**-0.55 (-0.73 to -0.34)**	**0.57 (0.20 to 1.70)**

Outcome			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	ENDEAR ITT (Spinraza arm) n/N (%)	Relative risk (95% CrI)	Relative risk reduction (95% CrI)	Absolute risk reduction (95% CrI)	Risk difference (95% CrI)
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 1 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	21/73 (28.8%)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US and START) • Definition 1 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	21/73 (28.8%)				
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 2 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	6/73 (8.2%)	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support (number of patients sitting without support) at 18 months of age (n/N), • ≥30 seconds for Zolgensma (STR1VE-US and START) • Definition 2 for Spinraza, assumed end of ENDEAR follow-up	[redacted]	6/73 (8.2%)				

Sitting without support (number of patients sitting) at end of follow-up (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 1 for Spinraza, end of ENDEAR follow-up	25/34 (73.5%)	21/73 (28.8%)	**2.57** **(1.72 to 4.01)**	**-1.57** **(-3.01 to -0.72)**	**-0.45** **(-0.62 to -0.26)**	**0.45** **(0.21 to 0.87)**
Sitting without support (number of patients sitting) at end of follow-up (n/N), • ≥30 seconds for Zolgensma (STR1VE-US), ≥5 seconds (START) • Definition 2 for Spinraza, end of ENDEAR follow-up	25/34 (73.5%)	6/73 (8.2%)	**9.32** **(4.57 to 24.04)**	**-8.32** **(-23.04 to -3.57)**	**-0.66** **(-0.80 to -0.48)**	**0.68** **(0.29 to 1.89)**

Abbreviation: ZOL, Zolgensma, ITT, intent to treat, NR, not recorded, N/A not applicable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. For achievement of sitting without support, relative risk >1, Relative risk reduction and absolute risk reduction <0 and risk difference >0 indicate results in favour of Zolgensma vs Spinraza. In the Zolgensma studies, sitting was defined by sitting for ≥30 sec according to Bayleys item #26. In the Spinraza ENDEAR trial, sitting was defined (1) by improvement by ≥1 point on a HINE-2 sitting scale of 3-5 development stages (IQWiG 2020), or (2) by HINE-2 categories "stable sit" and "pivots (rotates" without information regarding time sitting) (Finkel 2017), assumes that all patients sitting in the ENDEAR ITT population belongs to the ENDEAR subgroup.

5.1.3.7 Comparative analysis of walking without support

The Medicines Council have asked for a comparison of the proportion of patients that achieved the milestone of walking without support at 18 months of age. The 99th percentile of the window of milestone achievement for walking without support according to the WHO criteria is at 17.6 months for healthy children (WHO Multicentre Growth Reference Study Group 2006). For children with a clinical diagnosis of SMA, who are already experiencing symptoms when they are treated, a delay in achieving the milestone of walking may be expected, despite being treated with Zolgensma or Spinraza. [redacted]

In a recent conference presentation of the SHINE 27 August 2019 data cut (Castro 2020), the long-term follow up of ENDEAR, it is reported that 1 patient is walking independently at Modified Maintenance Dosing Regimen (MMDR) day 480. Details on the more exact age that this patient achieved the milestone of walking are currently not available. This patient was not walking on MMDR day 1 (median time on study from first Spinraza dose to MMDR day 1 = 2.08 year), neither was any patient reported to be walking in the previously reported SHINE data cut from June 30 2017 (Castro 2018). Consequently, it is unlikely that the patient achieved walking at a timepoint close to age 18 months that was specified in the Medicines Council protocol.

Results are presented in Table 13.

TABLE 13: STATISTICAL ANALYSIS RESULTS ACHIEVEMENT OF WALKING WITHOUT SUPPORT

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR subgroup (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Walking without support at 18 months of age		0/32 (0%)				
Walking without support at end follow-up	3/34 (8.8%)	0/32 (0%)	12.39 (0.84 to 5095.10)	-11.39 (-5094.10 to 0.16)	-0.08 (-0.21 to 0.01)	0.00 (0.00 to 0.00)
			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	**ENDEAR ITT (Spinraza arm) n/N (%)**	**Relative risk (95% CrI)**	**Relative risk reduction (95% CrI)**	**Absolute risk reduction (95% CrI)**	**Risk difference (95% CrI)**
Walking without support at 18 months of age		0/73 (0%)				
Walking without support at end follow-up	3/34 (8.8%)	0/73 (0%)	**27.77 (1.88 to 10700.00)**	**-26.77 (-10700.00 to -0.88)**	**-0.09 (-0.21 to -0.02)**	**0.00 (0.00 to 0.00)**

Abbreviation: ZOL, Zolgensma, ITT, intent to treat, NR, not recorded, N/A not applicable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. For achievement of walking without support, relative risk >1, Relative risk reduction and absolute risk reduction <0 and risk difference >0 indicate results in favour of Zolgensma vs Spinraza. Due to 0 events in some data sets continuity correction was used, adding 0.5 to the numerator and 1 to the denominator to both groups in order to avoid an infinite RR.

5.1.3.8 Comparative analysis of serious adverse events (related to treatment)

In the Zolgensma clinical programme, events were reported as treatment-emergent adverse events: treatment-emergent adverse event, serious treatment-emergent adverse event, treatment-emergent adverse event leading to discontinuation, treatment-emergent adverse event related to treatment, and treatment-emergent adverse event leading to death. For both STR1VE-US and START, the number of patients with SAEs and serious treatment-related AEs was the same.

It should be noted that the figure for serious adverse events in the ENDEAR publication does not specify explicitly that the events were treatment related. Events are reported as any adverse event, adverse event leading to discontinuation, severe adverse event, serious adverse event and serious adverse event with fatal outcome. Adverse event data is unfortunately not available for the ENDEAR subgroup.

Data could only be extracted as end of study, not specifically at the time points requested by the Medicines Council. Results of the comparison are shown in Table 14. In the comparison with the ENDEAR ITT population, the rate of serious adverse events was 23% relative and 17% absolute lower in the POOLED Zolgensma dataset than ENDEAR. The effect size exceeded the minimal clinically relevant difference set up by the Medicines Council (10 percent), however it did not reach the level of statistical significance.

As the infants enrolled in the clinical trial programmes are nonverbal, some adverse events may not have been captured.

In ENDEAR, the frequency of serious adverse events with fatal outcome was 13 out of 80 (16 percent), in most cases as a result of respiratory disorder (7 out of 13). In the sham control group of the ENDEAR study, for comparison, there were 16/41 (39 percent) serious adverse events with fatal outcome, most of respiratory nature. Deaths were thus consistent with the typical causes of death in SMA type 1 and none were considered related to study treatment. In the POOLED Zolgensma dataset, there was 1 event out of 34 (3 percent) leading to death [redacted]

These analyses do not take into consideration the overall treatment burden with respective drug. Spinraza is administered intrathecally every 4 months, adverse events may occur at every administration. The post-lumbar puncture syndrome, described by headache, back pain and transient or persistent cerebrospinal fluid leakage, is frequently reported in children, and in rare cases more severe symptoms have been reported, such as intracranial hypotension, epidural hematoma and cauda equina syndrome (Haché 2016). It is stated in the ENDEAR publication that adverse events associated with the post-lumbar puncture syndrome increase in frequency with increasing age. Higher incidence of adverse events observed in older children are likely related to use of larger gauge spinal needles but may also be due to technical difficulties resulting from increased body weight and the presence of scoliosis or excessive lumbar lordosis (Haché 2016). In the Zolgensma EPAR it is stated that “nusinersen treatment is associated with significant burden for the patient since it requires lifelong intrathecal injection, which is associated with safety risks”. By contrast, Zolgensma “has improved efficacy and a more convenient method of administration when compared to nusinersen, and has at least a comparable safety profile to that of nusinersen” (European Medicines Agency 2020).

[redacted] (AveXis CSR STR1VE-US 2018).

[redacted] (Avexis CSR START 2018).

TABLE 14: STATISTICAL ANALYSIS RESULTS SERIOUS SIDE EFFECTS

Outcome			POOLED ZOL vs ENDEAR subgroup (base case)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	ENDEAR subgroup (Spinraza arm) n/N (%)	Relative risk (95% CrI)	Relative risk reduction (95% CrI)	Absolute risk reduction (95% CrI)	Risk difference (95% CrI)
Serious treatment related side effects	20/34 (58.8%)	NR	NC	NC	NC	NC
			POOLED ZOL vs ENDEAR ITT (scenario)			
	POOLED ZOL (START cohort 2 and STR1VE-US) n/N (%)	ENDEAR ITT (Spinraza arm) n/N (%)	Relative risk (95% CrI)	Relative risk reduction (95% CrI)	Absolute risk reduction (95% CrI)	Risk difference (95% CrI)
Serious treatment related side effects	20/34 (58.8%)	61/80 (76.3%)	0.77 (0.54 to 1.01)	0.23 (-0.02 to 0.46)	0.17 (-0.01 to 0.36)	-0.17 (-0.35 to 0.01)

Abbreviation: ZOL, Zolgensma, ITT, intent to treat, NR, not recorded, NC not calculable, CrI, credible interval.

Note: A Bayesian method was used for the statistical analyses, therefore the uncertainty is expressed in credible intervals. For serious adverse events, relative risk <1, Relative risk reduction and absolute risk reduction >0 and risk difference <0 indicate results in favour of Zolgensma vs Spinraza.

5.1.3.9 Switching from Spinraza to Zolgensma

The Medicines Council has requested information on whether patients that already received one or several doses of Spinraza also may be candidates for treatment with Zolgensma.

Zolgensma has the potential to mark a step change in the treatment of patients with SMA type 1, 2, and 3.

Zolgensma is expected to primarily be used in incident and newly diagnosed prevalent SMA patients. It is anticipated that Zolgensma will be administered as soon as practically possible after a diagnosis of SMA is made. However, it is likely that some of the prevalent SMA patients currently treated with Spinraza at the time of Zolgensma market entry—and who still qualify for treatment under the indication for Zolgensma—will benefit from treatment with Zolgensma [redacted]

Since Zolgensma restores the production of necessary SMN protein, there is no biological justification to initiate or continue treatment with Spinraza following the one-time IV administration of Zolgensma.

5.1.4 Discussion

The indirect comparison shows that, compared with the Spinraza ENDEAR ITT population Zolgensma is superior on many of the outcomes of interest, including overall and event free survival, proportion of live patients not dependent on permanent assisted ventilation, CHOP-INTEND responders and proportion of patients sitting without support. At end-of-study, a few patients with SMA type 1 treated with Zolgensma were walking without support. Compared with the Spinraza ENDEAR subgroup, the differences are smaller. However, despite the greater similarities between the patient populations, treatment with Zolgensma was associated with statistically and clinically significant improvements in e.g. event-free survival and proportion of patients sitting without support. Regarding safety, there were no differences as to number of patients affected with serious adverse events.

These findings are in general agreement with the following statement in the Zolgensma EPAR (p. 13):

”Zolgensma effectively targets the disease mechanism in 5q SMA, has improved efficacy and a more convenient method of administration when compared to those of nusinersen; and has at least a comparable safety profile to that of nusinersen.” (European Medicines Agency 2020)

5.2 What is the value of onasemnogene abeparvovec compared to Spinraza in pre-symptomatic infants?

5.2.1 Presentation of relevant studies

Two trials were identified for the comparison of Zolgensma and Spinraza in pre-symptomatic SMA patients; SPR1NT (Zolgensma) (AveXis 2020b) and NURTURE (Spinraza) (De Vivo 2019). See tables with main characteristics of SPR1NT and NURTURE below.

SPR1NT is an ongoing, Phase III, open-label, single-arm trial in infants with genetically diagnosed and pre-symptomatic SMA with multiple copies of *SMN2* (2 × *SMN2*; n=14; 3 × *SMN2*; n=15) who receive Zolgensma treatment prior to the onset of clinical symptoms of SMA.

NURTURE is an ongoing, Phase II, open-label, single-arm trial to evaluate the long-term safety and efficacy of intrathecal Spinraza in infants (2 × *SMN2*; n=15; 3 × *SMN2*; n=10) who initiate treatment prior to the onset of clinical symptoms of SMA. Interim results from the 29 March 2019 NURTURE data cut were recently published (De Vivo 2019).

See section 7, Study characteristics for more details

5.2.2 Results per study

The results per study is presented in Table 29 to Table 34.

5.2.3 Comparative analyses

For infants with pre-symptomatic SMA with 2–3 copies of *SMN2*, interim data from the ongoing Zolgensma SPR1NT trial (De Vivo 2019, AveXis 2020b) were compared with interim data from the Spinraza NURTURE trial (De Vivo 2019) in an unanchored ITC.

As the two trials are very different with respect to the maturity of the trial data and the endpoint definitions (see section 0) it was not feasible to carry out a statistical comparison of SPR1NT and NURTURE, as requested by the Medicines Council. Instead the results of the two ongoing trials have simply been tabulated side by side. Results of the narrative comparison are presented below by outcome in Section 5.2.3.2 – Section 5.2.3.7.

5.2.3.1 Baseline characteristics

As shown in Table 15, age at first dose was similar between the two studies, as were the CHOP-INTEND total scores for children with 2 copies of *SMN2*. CHOP-INTEND is not measured as part of the SPR1NT trial protocol for infants with 3 copies of *SMN2*.

TABLE 15: BASELINE CHARACTERISTICS FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA)

Characteristic	Zolgensma		Spinraza	
	SPR1NT (ongoing study)		NURTURE (ongoing study)	
	2 *SMN2* copies	**3 *SMN2* copies**	**2 *SMN2* copies**	**3 *SMN2* copies**
N	14	15	15	10
Female, n (%)	[redacted]	[redacted]	7 (47)	6 (60)
Age at first dose, days, mean (SD)	[redacted]	[redacted]	19.5 (9.29)	22.3 (12.45)
CHOP INTEND total score, mean (SD)	[redacted]	[redacted]	47.0 (10.04)	51.9 (6.10)
HINE total motor milestones, mean (SD)	[redacted]	[redacted]	2.7 (1.59)	3.2 (1.87)

Mean weight, kg (SD)	[redacted]	[redacted]	--	--

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurologic Examination; NA, not applicable; SD, standard deviation; *SMN2*, survival motor neuron 2.

Note: *range

Source: (De Vivo 2019, AveXis ITC Technical Report 2020)

Considerations

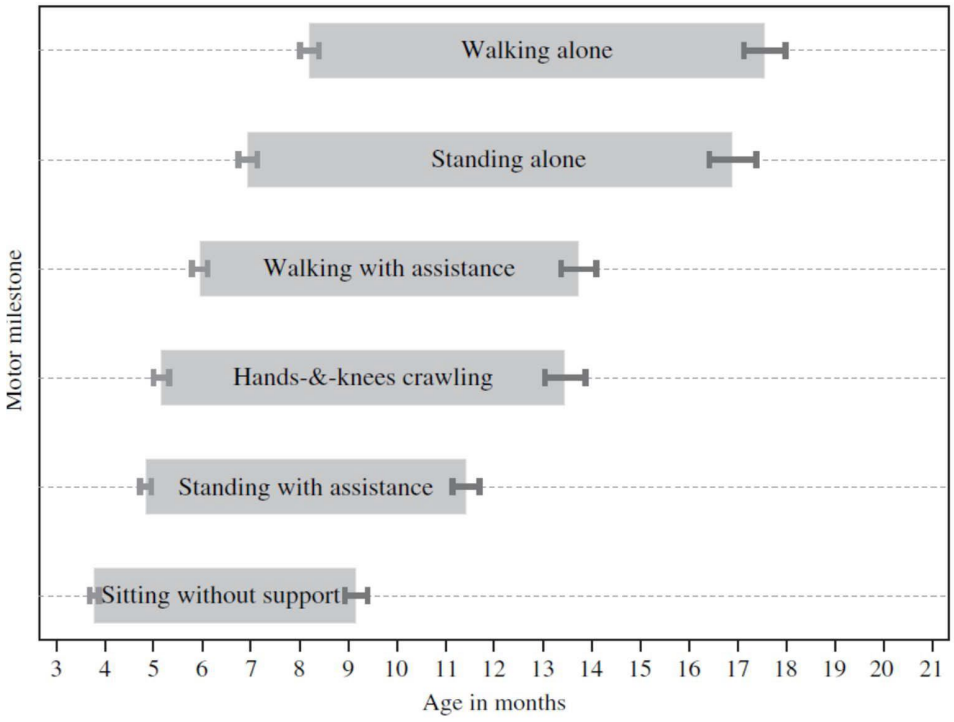
Different degree in maturity of trial data

The interim NURTURE data is more mature than the interim data from SPR1NT, with a median age at last visit of approximately 35 months in NURTURE compared with a median age at last visit of approximately 10 months for SPR1NT. This difference in maturity of the trial data limits the interpretation of any indirect comparison of effectiveness

With regard to milestone achievement, it is critical to consider the ages for normal development in healthy children. This has been thoroughly examined in the WHO Motor Development Study (WHO Multicentre Growth Reference Study Group 2006). The estimated 1st and 99th percentiles in months are: 3.8, 9.2 (sitting without support) and 8.2, 17.6 (walking alone). In Figure 3, the windows of achievement for six different milestones are expressed graphically.

[redacted] in SPR1NT were younger than the age at which they would have been expected to achieve the milestone of sitting without support. In contrast, all NURTURE patients were aged above the upper limit for normal development for all WHO motor milestones, including independent walking, at the time of the most recent data cut available.

FIGURE 3: WINDOWS OF MILESTONE ACHIEMENT EXPRESSED IN MONTHS



Source: (WHO Multicentre Growth Reference Study Group 2006)

Difference in endpoint definitions

Different definitions of sitting independently were used in the two trials. In SPR1NT, the Bayley Scales Gross Motor subset item #26 was used (Child sits alone without support for ≥30 seconds), whereas in NURTURE, the WHO definition was used (Child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position). Moreover, in SPR1NT, motor milestone attainment is documented by video and centrally reviewed for confirmation. In NURTURE there is no video-confirmation of motor milestones by a central reviewer.

Difference in reported time points for milestone achievement

In SPR1NT videos of scheduled study-visits (e.g. at month 6, 9, and 12) and videos submitted by caregivers are centrally reviewed in order to confirm the attainment, and age at attainment, of motor milestones. In contrast, in NURTURE, only site- or caregiver-reported age at first WHO motor milestone achievement are used, with no video-confirmation of motor milestones by a central reviewer. This means that in SPR1NT, a child achieving the milestone of independent sitting between two study visits may be recorded as a sitter at an older age compared to NURTURE. Thus, in considering time to achievement of a milestone, the methodology employed is likely to introduce bias in favour of Spinraza.

5.2.3.2 Narrative comparison of overall survival

As of the efficacy data cut of 31 December 2019 (AveXis 2020b), 14 patients had enrolled in Cohort 1 of SPR1NT (2 copies of *SMN2*) and 15 patients in Cohort 2 (3 copies of *SMN2*) and all had survived without permanent ventilation and were continuing in the study (Table 16, Table 17 and Table 18). The patients in Cohort 1 ranged in age [redacted] months and were [redacted] months post Zolgensma administration at last visit. The patients in Cohort 2 ranged in age [redacted] as of the 31 December 2019 data cut and were 2.0 to 13.9 (median: 9.0) months post-dose at last visit (AveXis 2020b).

At the time of the NURTURE interim analysis, all 25 participants (15 with 2 copies and 10 with 3 copies of *SMN2*) were alive and none required permanent ventilation (De Vivo 2019). At the time of the interim analysis, median (range) age at last visit was 34.8 (25.7–45.4) months and time on study was 33.9 (25.3–45.1) months.

For both SPR1NT and NURTURE, median time to death could not be estimated as there were no such events.

Results of the analysis of overall survival are shown in Table 16.

TABLE 16: OVERALL SURVIVAL FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA)

Characteristic	Zolgensma		Spinraza	
	SPR1NT (ongoing study)		NURTURE (ongoing study)	
	2 *SMN2* copies	*3 SMN2* copies	2 *SMN2* copies	3 *SMN2* copies

N	14	15	15	10
Age at interim data-cut, months, median (range)	[redacted]	[redacted]	34.8 (25.7–45.4)	
Overall survival, n/N (%)	14/14 (100)	15/15 (100)	15/15 (100)	10/10 (100)

Abbreviations: *SMN2*, survival motor neuron 2.
Source: (AveXis 2020b, De Vivo 2019)

5.2.3.3 Narrative comparison of event-free survival (combined mortality or permanent assisted ventilation)

For both SPR1NT and NURTURE, no patients have met the endpoint of death or permanent assisted ventilation. See section 5.2.3.2 for details. In NURTURE, the primary endpoint was time to death or *respiratory intervention*. The latter was defined as "invasive or non-invasive for ≥6 h per day continuously for ≥7 days or tracheostomy". This differs from the permanent ventilation, used in SPR1NT and defined as "tracheostomy or requirement of ≥16 h of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation". In the NURTURE 2 *SMN2* copy cohort, there were four (16%) infants that initiated respiratory intervention during an acute reversible illness.

Results of the analysis of event-free survival are shown in Table 17.

TABLE 17: EVENT-FREE SURVIVAL (COMBINED MORTALITY OR PERMANENT ASSISTED VENTILATION) FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA)

Characteristic	**Zolgensma**		**Spinraza**	
	SPR1NT (ongoing study)		**NURTURE (ongoing study)**	
	2 *SMN2* copies	***3 SMN2* copies**	**2 *SMN2* copies**	**3 *SMN2* copies**
N	14	15	15	10
Age at interim data-cut, months, median (range)	[redacted]	[redacted]	34.8 (25.7–45.4)	
Event-free survival, n/N (%)	14/14 (100)	15/15 (100)	15/15 (100)	10/10 (100)

Abbreviations: *SMN2*, survival motor neuron 2.
Source: (AveXis 2020b, De Vivo 2019)
Note: In SPR1NT, permanent ventilation is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via noninvasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. In NURTURE, the term respiratory intervention was used, defined as (invasive or non-invasive for ≥6 h per day continuously for ≥7 days or tracheostomy)

5.2.3.4 Narrative comparison of permanent assisted ventilation

For both SPR1NT and NURTURE, no patients have met the endpoint of permanent assisted ventilation. See section 5.2.3.2 for details.

Results of the analysis of permanent assisted ventilation are shown in Table 18.

TABLE 18: PERMANENT ASSISTED VENTILATION FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA)

Characteristic	Zolgensma		Spinraza	
	SPR1NT (ongoing study)		NURTURE (ongoing study)	
	2 *SMN2* copies	*3 SMN2* copies	2 *SMN2* copies	3 *SMN2* copies
N	14	15	15	10
Age at interim data-cut, months, median (range)	[redacted]	) [redacted]	34.8 (25.7–45.4)	
Permanent ventilation, n/N (%)	0/14 (100)	0/15 (100)	0/15 (100)	0/10 (100)

Abbreviations: *SMN2*, survival motor neuron 2.
Source: (AveXis 2020b, De Vivo 2019)
Note: In SPR1NT, permanent ventilation is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via noninvasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. In NURTURE, the term respiratory intervention was used, defined as (invasive or non-invasive for ≥6 h per day continuously for ≥7 days or tracheostomy)

5.2.3.5 Narrative comparison of sitting without support

At the time of the SPR1NT 31 December 2019 data cut, 8/14 (57.1%) of the patients with 2 *SMN2* copies had achieved the milestone of sitting without support (defined by Bayley Scales Gross Motor subset item #26: child sits alone without support for ≥30 seconds) at a median age [redacted] which is the upper limit of the WHO 99th percentile window for healthy children were able to sit without support. Six infants with 2 copies of *SMN2* had not yet achieved sitting without support at the last study visit prior to the data cut. All of these were younger than [redacted]

Of the infants in SPR1NT with 3 copies of *SMN2*, 10/15 (66.7%) were sitting without support (according to Bayley Scales Item #26 and WHO criteria) and did so at a median age of [redacted]

At the time of the data cut, all (25/25; 100%) infants in NURTURE with 2 (15/15; 100%) or 3 copies of *SMN2* (10/10; 100%) had achieved the WHO motor milestone criteria for sitting without support (Child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position). Age at sitting without support was 7.9 months (range 5.9-9.2) in those with 2 copies, and 6.4 months (range 5.1-7.9) in those with 3 copies of *SMN2*.

Results of the analysis of sitting without support are shown in Table 19.

TABLE 19: MOTOR MILESTONE ACHIEVEMENT FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA): SITTING WITHOUT SUPPORT

Characteristic	Zolgensma		Spinraza	
	SPR1NT (ongoing study)		NURTURE (ongoing study)	
	2 *SMN2* copies	3 *SMN2* copies	2 *SMN2* copies	3 *SMN2* copies
N	14	15	15	10
Age at interim data-cut, months, median (range)	[redacted]	[redacted]	34.8 (25.7–45.4)	
Sitting without support, n/N (%)	8/14 (57.1)[§]	10/15 (66.7)[§]	15/15 (100)[†]	10/10 (100)[†]
Sitting without support in patients exceeding WHO age-range for normal development at the time of the data cut (9,2 months), n/N (%)	[redacted]	[redacted]	15/15 (100)	10/10 (100)
Age at study visit when sitting without support was reported, months, median (range)	[redacted]	[redacted]	NR	NR
Caregiver reported age at achievement of sitting without support, months, median (range)	NR	NR	7.9 (5.9–9.2)	6.4 (5.1–7.9)

Abbreviations: *SMN2*, survival motor neuron 2.
[§] Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds. [†] WHO definition of sitting alone (Child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position).
Source: (AveXis 2020b, De Vivo 2019)

Difference in degree of maturity of trial data

At the SPR1NT 31st December 2019 data cut, the median age of the patients was [redacted] in those with 2 copies of *SMN2* [redacted] in those with 3 copies [redacted] A significant proportion of the patients were thus below the 99th percentile for normal development according to WHO (Figure 3) and cannot be expected to sit independently. When taking into account only those patients that were above the age of WHO estimated normal development (9.2 months), [redacted]

Endpoint definition of sitting independently

Different definitions of sitting independently were used in the two trials. In SPR1NT, the Bayley Scales Gross Motor subset item #26 was used (Child sits alone without support for ≥30 seconds), whereas in NURTURE, the WHO definition was used (Child sits up straight with head erect for ≥10 seconds; child does not use hands

or arms to balance body or support position). This means that a child sitting unsupported for less than 30 seconds, but more than 10 seconds, will be counted as a sitter in NURTURE but not in SPR1NT.

Measurement of age at motor milestone attainment

A stricter measurement of the age at motor milestone attainment is used in SPR1NT than in NURTURE; in SPR1NT videos of scheduled study-visits and videos submitted by caregivers are centrally reviewed in order to confirm the attainment, and age at attainment, of motor milestones. In contrast, in NURTURE, only site- or caregiver-reported age at first WHO motor milestone achievement are used, with no video-confirmation of motor milestones by a central reviewer. This means that in SPR1NT, a child achieving the milestone of independent sitting between two study visits may be recorded as a sitter at an older age compared to NURTURE.

Summary

Differences in trial maturity, endpoint definition and method of measurement of age at motor milestone attainment introduces bias in favour of Spinraza in the comparison of SPR1NT and NURTURE data. The comparison should therefore be considered conservative. Despite these apparent sources of bias, patients in the SPR1NT study that did achieve the motor milestones of sitting independently did so within or slightly above the WHO window of normal development, as was the case for patients in NURTURE.

5.2.3.6 Narrative comparison of walking without support

For SPR1NT, at the time of the 31 December 2019 data cut, 4/14 infants with 2 copies of *SMN2* (28.6%) had achieved the milestone of walking alone according to the WHO criteria.[1] For those that did walk alone, the this milestone achievement was recoded at a median age of [redacted] Of the infants in SPR1NT with 3 copies of *SMN2*, 3/15 (20%) were walking without support at a median [redacted] whereas the remaining infants would not be expected to do so as they had not yet passed through the typical window of achievement to develop this milestone according to WHO.

For NURTURE, at the time of the data cut, 12/15 (80%) of those with two *SMN2* copies and 10/10 (100%) of those with three *SMN2* copies achieved the milestone walking independently, also using the WHO criteria. Most participants achieved these milestones within the 99th percentile age of achievement window established for WHO for healthy children. The median (95% CI) age for first achievement of walking alone in children with two *SMN2* copies was 20.4 months (15.5–29.7). In those with three *SMN2* copies, the corresponding age was 12.3 (11.2–14.9) months.

Results of the analysis of walking without support are shown in Table 20.

[1] WHO motor milestone criteria: Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object

TABLE 20: MOTOR MILESTONE ACHIEVEMENT FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA): WALKING WITHOUT SUPPORT

Characteristic	Zolgensma		Spinraza	
	SPR1NT (ongoing study)		NURTURE (ongoing study)	
	2 *SMN2* copies	*3 SMN2* copies	2 *SMN2* copies	3 *SMN2* copies
N	14	15	15	10
Age at interim data-cut, months, median (range)	[redacted]	[redacted]	34.8 (25.7–45.4)	
Walking without support, n/N (%)	4/14 (28.6)‡	3/15 (20)‡	12/15 (80.0)‡	10/10 (100)‡
Walking without support in subgroup exceeding WHO range for normal development at the time of the data cut (17.6 months), n/N (%)	[redacted]	[redacted]	12/15 (80)	10/10 (100)
Age at walking without support, months, median (range)	) [redacted]	) [redacted]	20.4 (15.5–29.7§)	12.3 (11.2–14.9§)

Abbreviations: NR, not reported; N/A, not applicable; *SMN2*, survival motor neuron 2.
§95% CI ‡ WHO definition of walking alone (Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object).
Source: (AveXis 2020b, De Vivo 2019)

Summary

Differences in trial maturity and method of measurement of age at motor milestone attainment introduces bias in favour of Spinraza in the comparison of SPR1NT and NURTURE data. The comparison should therefore be considered conservative. Despite these apparent sources of bias, patients in the SPR1NT study with 2 copies of *SMN2* that did achieve the motor milestones of sitting and walking independently did so within or slightly above the WHO window of normal development, as was the case for patients in NURTURE.

5.2.3.7 Narrative comparison of severe adverse events (related to treatment)

[redacted]

In NURTURE, a total of 33 serious adverse events were reported in 12 participants (48 percent). Treatment emergent SAEs in those 12 participants included tendon disorder and dehydration (n=1), bronchitis, choking, pneumonia (n=1), pneumonia (n=1), mycoplasma pneumonia (n=1), viral upper respiratory tract infection

(n=1), abdominal distention, respiratory distress, dehydration, enterovirus infection, corona virus infection, respiratory syncytial virus bronchiolitis, bacterial pneumonia, acute respiratory failure, respiratory failure, tachycardia, viral gastroenteritis, pneumonia (n=1), respiratory distress, respiratory syncytial virus bronchiolitis, aspiration pneumonia, pneumonia (n=1), failure to thrive (n=1), urinary tract infection (n=1), respiratory syncytial virus infection (n=1), upper respiratory tract infection (n=1). None of the SAEs were related to study drug according to investigators (De Vivo 2019).

Results of the analysis of serious adverse events are shown in Table 21.

TABLE 21: SERIOUS ADVERSE EVENTS (RELATED TO TREATMENT) FOR SPR1NT (ZOLGENSMA) AND NURTURE (SPINRAZA)

Characteristic	Zolgensma		Spinraza	
	SPR1NT (ongoing study)		NURTURE (ongoing study)	
	2 *SMN2* copies	*3 SMN2* copies	2 *SMN2* copies	3 *SMN2* copies
N	14	15	15	10
Patients with any serious treatment emergent adverse event, n (%)	[redacted]	[redacted]	12 (48)	
Patients with any serious adverse event related to treatment, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: NR, not reported; *SMN2*, survival motor neuron 2.
Source: (AveXis 2020b, De Vivo 2019)

5.2.4 Discussion

Based on the above observations, there was no evidence to support one of the treatments being superior to the other in pre-symptomatic infants lacking a functional *SMN1* gene and with 2 or 3 copies of the *SMN2* gene. Based on the positive interim results to date, it is expected that motor milestones will continue to be achieved in SPR1NT, with most patients expected to achieve independent sitting and walking within the range of normal development. Therefore, Zolgensma and Spinraza were assumed to have a similar efficacy in this population. This assumption is supported by the EPAR for Zolgensma, in which the EMA concludes that the gross and fine motor development in pre-symptomatic patients with 2 copies of *SMN2* is largely developmentally appropriate and similar to neurologically normal peers (European Medicines Agency EPAR 2020).

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7 Appendices

7.1 Literature review

Below tables present the inclusion/exclusion criteria as well as a list of excluded articles.

TABLE 22: INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	**Population:** Patients with clinically diagnosed SMA type 1 Pre-symptomatic infants with verified 5q SMA gene defect and up to 3 *SMN2* copies **Intervention(s):** Zolgensma (onasemnogene abeparvovec) Spinraza (nusinersen) **Comparator(s):** Any **Outcomes:** Overall survival • Survival • Combined mortality or permanent assisted ventilation • Permanent assisted ventilation Motor milestones achieved • CHOP-INTEND score • Sitting and walking without support Adverse events • Adverse events • Serious adverse events (related to treatment) Quality of life • Using validated tool **Settings (if applicable):** n/a **Study design:** Randomised control trials Single-arm trials **Language restrictions:** English, Norwegian, Swedish, Danish **Other search limits or restrictions applied:** Patient population needs to be comparable to START/STR1VE for the SMA type 1 indication and to SPR1NT for the pre-symptomatic population Outcomes data needs to be extractable at the time points set by the DMC

Exclusion criteria	**Population:** Patient population not comparable to START/STR1VE for the SMA type 1 indication and to SPR1NT for the pre-symptomatic population **Intervention(s):** Not Zolgensma (onasemnogene abeparvovec) or Spinraza (nusinersen) **Comparator(s):** n/a **Outcomes:** Data that is not extractable at the time points set by the Danish Medicines Council in the protocol **Settings (if applicable):** n/a **Study design:** Non RCTs, animal studies, case reports, editorials & opinion pieces, reviews, conference abstract poster **Language restrictions:** Not English, Norwegian, Danish or Swedish **Other search limits or restrictions applied:** n/a

TABLE 23: ALL EXCLUDED ARTICLES AFTER FULL TEXT REVIEW WITH REASON FOR EXCLUSION ACCORDING TO PICO

#	Reference	Reason for exclusion
1	Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy Al-Zaidy (2019)	Population Too old at time of treatment, data non extractable
2	AVXS-101 (Onasemnogene Abeparvovec) for SMA1: Comparative Study with a Prospective Natural History Cohort; Al-Zaidy (2019)	Study design Not RCT
3	Nusinersen in patients older than 7 months with spinal muscular atrophy type 1; Aragon-Gawinska (2018)	Population Age too old at treatment
4	Sitting in patients with spinal muscular atrophy type 1 treated with nusinersen Aragon-Gawinska (2019)	Population Age too old at time of treatment, data non extractable
5	Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy Chiriboga (2016)	Population
6	Nusinersen treatment and cerebrospinal fluid neurofilaments: An explorative study on Spinal Muscular Atrophy type 3 patients Faravelli (2019)	Population Sma type 3
7	Nusinersen for SMA: expanded access programme Farrar (2018)	Study design Not RCT
8	Intrathecal Injections in Children With Spinal Muscular Atrophy: Nusinersen Clinical Trial Experience Hache (2016)	Population Age non-comparable to Zolgensma clinical trials: SMA types, outcomes

9	Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies Darras (2019)	Population SMA type 2/3
10	Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function Pane (2018)	Study design Only 6 month follow-up
11	Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany Pechmann (2018)	Study design Only 6 month follow-up
12	Respiratory Needs in Patients with Type 1 Spinal Muscular Atrophy Treated with Nusinersen Sansone (2020)	Population Age too old at time of treatment, data non extractable
13	Feeding and Swallowing Problems in Infants with Spinal Muscular Atrophy Type 1: an Observational Study Van der Heul (2020)	Data non-extractable
14	An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials Darras (2019)	Data not relevant for analysis
15	Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy Lowes (2019)	Data not relevant for analysis
16	Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study Finkel (2016)	Data not relevant for analysis
17	Longer-term assessment of safety and efficacy of nusinersen for the treatment of spinal muscle atrophy (SMA) an interim analysis of the SHINE study Castro 2018	Data not relevant for analysis

7.2 Main characteristics of included studies

TABLE 24: MAIN STUDY CHARACTERISTICS STR1VE-US

Trial name	STR1VE-US
NCT number	NCT03306277
Objective	To determine the efficacy by demonstrating achievement of developmental milestone of functional independent sitting for >30 seconds at the 18 months of age study visit; to determine the efficacy based on survival at 14 months of age, where survival is defined by the avoidance of either death or permanent ventilation
Publications – title, author, journal, year	Protocol (AveXis 2018), Clinical overview (8 Mar 2019 data cut) (AveXis 2019), 180-Day efficacy and safety update (31 December 2019) (AveXis 2020b); European Medicines Agency assessment report (European Medicines Agency 2020); Clinical study report (AveXis 2018)
Study type and design	Completed, phase III, open-label, non-randomised, single arm, single group assignment trial
Follow-up time	18 months of age
Population (inclusion and exclusion criteria)	**Population** Patients in the US with SMA type 1 with 1 or 2 copies of *SMN2*, aged <6 months at the time of gene replacement therapy (N=22[§]) **Inclusion criteria** A. SMA Type 1 as determined by a gene mutation analysis with bi-allelic *SMN1* mutations and 1 or 2 copies of *SMN2* B. <6 months (<180 days) of age at the time of gene replacement therapy C. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy D. Up to date on childhood vaccinations **Exclusion criteria** Please note the below criteria are references for other studies throughout this document A. Previous, planned, or expected scoliosis repair surgery/procedure during the study assessment period B. Pulse oximetry <96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes >1000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support 1. Pulse oximetry saturation may decrease to <96% after screening provided that the saturation does not decrease by ≥4 percentage points C. Tracheostomy or requirement of non-invasive ventilatory support averaging ≥6 hours daily over the 7 days prior to the screening visit; or ≥6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing D. Signs of aspiration/inability to tolerate non-thickened liquids 1. Patients with a gastrostomy tube who pass the swallowing test are allowed to enrol in study

<table>
<tr><td></td><td>E. Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards
F. Active viral infection
G. Serious non-respiratory tract illness requiring treatment and/or hospitalisation within 2 weeks prior to screening; respiratory infection requiring medical attention or increase in supportive care within 4 weeks prior to dosing; or severe non-pulmonary/respiratory tract infection within 4 weeks before administration of gene replacement therapy or concomitant illness that creates unnecessary risks for gene replacement therapy
H. Allergy or hypersensitivity to prednisolone, other glucocorticosteroids, or their excipients
I. Concomitant use of drugs for treatment of myopathy, neuropathy, or diabetes mellitus, or ongoing immunomodulators treatment or immunosuppressive therapy within 3 months prior to gene replacement therapy
J. Anti-AAV9 antibody titer >1:50
K. Clinically significant abnormal laboratory values prior to gene replacement therapy
L. Participation in recent SMA treatment clinical study (with the exception of observational Cohort studies or non-interventional studies) or receipt of a therapy administered with the intent to treat SMA at any time prior to screening for this study.
M. Expectation of major surgical procedures during the study assessment period
N. Gestational age at birth <35 weeks (245 days)</td></tr>
<tr><td>Intervention</td><td>Zolgensma (one-time IV administration) (1.1 × 10^{14} vg/kg)</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics of STR1VE-US
<table>
<tr><th>Characteristic</th><th>N=22</th></tr>
<tr><td>SMN2 copy number</td><td>2</td></tr>
<tr><td>Age at treatment†, months</td><td></td></tr>
<tr><td>Mean (SD)</td><td>3.7 (1.6)</td></tr>
<tr><td>Median (Min, Max)</td><td>3.5 (0.5, 5.9)</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Weight at baseline, kg
Mean (SD)
Median (Min, Max)</td><td>
5.8 (1.1)
5.8 (3.9, 7.5)</td></tr>
<tr><td>[redacted]</td><td></td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Sex, n (%)</td><td></td></tr>
<tr><td>Female</td><td>12 (54.5)</td></tr>
<tr><td>Male</td><td>10 (45.5)</td></tr>
<tr><td>Race, n (%)</td><td></td></tr>
<tr><td>White</td><td>11 (50.0)</td></tr>
<tr><td>Other</td><td>6 (27.3)</td></tr>
<tr><td>Black or African American</td><td>3 (13.6)</td></tr>
<tr><td>Asian</td><td>2 (9.1)</td></tr>
<tr><td>Ethnicity, n (%)</td><td></td></tr>
<tr><td>Not Hispanic or Latino</td><td>18 (81.8)</td></tr>
<tr><td>Hispanic or Latino</td><td>4 (18.2)</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>[redacted]</td><td>0</td></tr>
<tr><td>[redacted]</td><td>0</td></tr>
<tr><td>Score on CHOP-INTEND scale‡</td><td></td></tr>
<tr><td>Mean (SD)</td><td>32.0 (9.69)</td></tr>
<tr><td>Median (Min, Max)</td><td>33.5 (18, 52)</td></tr>
</table></td></tr>
</table>

	[redacted]
	Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. † Age = (dose date - date of birth + 1). ‡ Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function. Note: 1/22 infants was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018. Source: 31 December 2019 efficacy data cut (data on file) (AveXis. 2019).
Primary and secondary endpoints	**Primary endpoint** • Achievement of independent sitting for >30 seconds at 18 months of age visit • Event-free survival at 14 months of age visit **Other endpoints** • Ability to thrive, defined as not receiving nutrition through mechanical support or other non-oral method, at 18 months of age visit • Ventilatory support independence, through 18 months of age visit
Method of analysis	[redacted]
Subgroup analyses	N/A

Abbreviations: AAV9, adeno-associated virus serotype 9; ALT, alanine aminotransferase; AST, Aspartate transaminase; ELISA, Enzyme-linked Immunosorbent Assay; GGT, gamma glutamyl-transpeptidase; Hgb, haemoglobin; RSV, respiratory syncytial virus; SMA = spinal muscular atrophy; SMN = survival motor neuron; WBC, white blood cell; WHO = World Health Organization.
Notes: § 1/22 patient was initially enrolled as a pre-symptomatic SMA patient; however this patient was reclassified as symptomatic by the Investigator after 31 Dec 2018.
Sources: Zolgensma EPAR Tables 3 and 4, and pages 67 – 68, Protocol (AveXis 2018), Clinical overview (8 Mar 2019 data cut) (AveXis 2019), 180-day efficacy and safety update (31 December 2019)(AveXis 2020b)

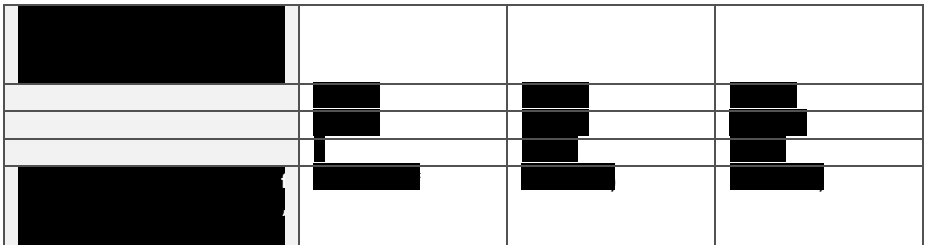
TABLE 25: MAIN STUDY CHARACTERISTICS START

Trial name	START
NCT number	NCT02122952
Objective	The primary objective of the study was safety. Efficacy objectives were secondary objectives, with a primary efficacy endpoint of time from birth to either: requirement of ≥16-hour respiratory assistance per day (BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation; or death
Publications – title, author, journal, year	Mendell et al. 2017 (Mendell 2017); Al-Zaidy et al. 2019 (Al-Zaidy 2019); European Medicines Agency assessment report (European Medicines Agency 2020); Clinical study report (Avexis CSR START 2018)
Study type and design	Completed, phase I/II, open-label, non-randomised, single group assignment trial
Follow-up time	2 years follow-up
Population (inclusion and exclusion criteria)	**Population** SMA type 1 possessing 2 copies of *SMN2* without c.859G>c modification in exon 7; aged ≤6 months; symptom onset at ≤6 months (N=15)

<table>
<tr><td></td><td>Inclusion criteria
Bi-allelic SMN1 gene mutations with 2 copies of SMN2; patients age 6 months and younger with disease onset up to age 6 months; and hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture, and hypermobility of joints

Exclusion criteria
The study included the following same exclusion criteria as seen in STR1VE-US (letters refer to the description of STR1VE-US criteria presented above):
D (not including criteria D1), F, I–L

Additional exclusion criteria include:
Use of invasive ventilatory support or pulse oximetry <95% saturation at the screening visit, or non-invasive ventilator support for >16 hours/day; and c.859G>C modification in exon 7, based on predicted mild phenotype</td></tr>
<tr><td>Intervention</td><td>Zolgensma (one-time IV administration)
(Cohort 1 6.7 × 10^{13} vg/kg, n=3; Cohort 2 2.0 × 10^{14} vg/kg*, n=12)</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics of START
<table>
<tr><th>Characteristic</th><th>Cohort 1
6.7×10¹³ vg/kg
(N=3)</th><th>Cohort 2
2.0×10¹⁴ vg/kg
(N=12)</th><th>All infants
(N=15)</th></tr>
<tr><td>SMN2 copy number</td><td>2</td><td>2</td><td>2</td></tr>
<tr><td>Age at treatment†, months
Mean (SD)
Median (Min, Max)</td><td>
6.3 (0.75)
5.9 (5.9, 7.2)</td><td>
3.4 (2.06)
3.1 (0.9, 7.9)</td><td>
4.0 (2.21)
4.1 (0.9–7.9)</td></tr>
<tr><td>Sex</td><td></td><td></td><td></td></tr>
<tr><td>Female, %</td><td>66.7</td><td>58.3</td><td>60.0</td></tr>
<tr><td>Male, %</td><td>33.3</td><td>41.7</td><td>40.0</td></tr>
<tr><td>Race, %</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>100</td><td>91.7</td><td>93.3</td></tr>
<tr><td>Other</td><td>0</td><td>8.3</td><td>6.7</td></tr>
<tr><td>Ethnicity, %</td><td></td><td></td><td></td></tr>
<tr><td>Not Hispanic or Latino</td><td>100</td><td>83.3</td><td>86.7</td></tr>
<tr><td>Hispanic or Latino</td><td>0</td><td>16.7</td><td>13.3</td></tr>
<tr><td>Weight, mean (SD), kg</td><td>6.6 (0.56)</td><td>5.7 (1.34)</td><td>5.9 (1.27)</td></tr>
<tr><td>Gestational age at birth, weeks</td><td></td><td></td><td></td></tr>
<tr><td>n</td><td>2</td><td>10</td><td>12</td></tr>
<tr><td>Mean (SD)</td><td>39.0 (1.41)</td><td>38.5 (1.43)</td><td>38.6 (1.38)</td></tr>
<tr><td>Mean age at symptom onset, (months)</td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>1.7 (1.15)</td><td>1.4 (1.0)</td><td>1.5 (0.99)</td></tr>
<tr><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean CHOP-INTEND score (SD)¶</td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>16.3 (10.5)</td><td>28.2 (12.3)</td><td>-</td></tr>
<tr><td>Median (Min, Max)</td><td>16.0 (6, 27)</td><td>29.0 (12, 50)</td><td>-</td></tr>
<tr><td>Swallowing thin liquid, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>0 (0.0)</td><td>4 (33.3)</td><td>4 (26.7)</td></tr>
<tr><td>No</td><td>3 (100)</td><td>8 (66.7)</td><td>11 (73.3)</td></tr>
<tr><td>Non-oral feeding support, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>3 (100)</td><td>5 (41.7)</td><td>8 (53.3)</td></tr>
<tr><td>No</td><td>0</td><td>7 (58.3)</td><td>7 (46.7)</td></tr>
<tr><td>Ventilatory support (invasive/non-invasive), n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>3 (100)</td><td>1 (8.3)‡</td><td>4 (26.7)‡</td></tr>
<tr><td>No</td><td>0</td><td>11 (91.7)</td><td>11 (73.3)</td></tr>
</table></td></tr>
</table>

	
Primary and secondary endpoints	**Primary endpoint** **Safety** • AEs, [redacted] **Efficacy** • Survival (birth to either requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation, or death) Efficacy analyses were conducted at the following time points: • The date at which all patients had completed a study visit after reaching 13.6 months of age • When last enrolled patient had a study visit after reaching 20 months of age • When all patients completed 24 months of post-dose follow-up **Other endpoints** • Change in CHOP-INTEND from baseline score • Demonstration of improvement of motor function and muscle strength as determined by achievement of significant development milestones, including the ability to sit alone and roll over unassisted
Method of analysis	Safety analyses were performed in all the patients, who were also included in the primary analysis of survival (as defined above and in the protocol) and in analyses of changes on the CHOP INTEND scale from baseline to 1 month and 3 months. Such changes from baseline to each study visit were analyzed with the use of a mixed-effects model for repeated measurements. The mixed model included the fixed effects of cohort and visit and a covariate of baseline score. Milestone achievements and nutritional and ventilatory support were analyzed in cohort 2. All comparisons with historical cohorts were solely descriptive.
Subgroup analyses	N/A

Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potential; [redacted] GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; IV, intravenous; SD, standard deviation; SMA, spinal muscular atrophy; *SMN*, survival motor neurone.
Sources: Al-Zaidy (2019), Mendell (2017) (Table 9, page 1715), Zolgensma EPAR (Table 3 and 4, pages 79-9).
Note: * Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has assigned a value of 1.1×10^{14} vg/kg to the actual dose received by Cohort 2. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials. † On day of Zolgensma administration. ‡ Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site. § Age = (Visit Date - Date of Birth + 1) / 365.25. ¶ Scores on the CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function. †† Data for 'All infants' were calculated using CHOP-INTEND data for all infants (Listing 16.2.6.4-24). ‡ [redacted]

TABLE 26: MAIN STUDY CHARACTERISTICS ENDEAR/SHINE

Trial name	ENDEAR (SHINE)
NCT number	NCT02193074 (*NCT01494701)*
Objective	The primary objective of the study is to examine the clinical efficacy of Spinraza (ISIS 396443) administered intrathecally (IT) to participants with infantile-onset with infantile-onset spinal muscular atrophy (SMA). The secondary objective of the study is to examine the safety and tolerability of Spinraza administered intrathecally to participants with infantile-onset SMA. (The primary objective is to evaluate the long-term safety and tolerability of Spinraza (ISIS 396443) administered by intrathecal (IT) injection to participants with Spinal Muscular Atrophy (SMA) who previously participated in investigational studies of Spinraza. The secondary objective is to examine the long-term efficacy of Spinraza administered by IT injection to participants with SMA who previously participated in investigational studies of Spinraza.)
Publications – title, author, journal, year	(Finkel 2017, National Institute for Health and Care Excellence 2018, IQWiG 2020)
Study type and design	Phase III, randomised, double-blind, sham-procedure controlled study *(Open-label extension study for patients with spinal muscle atrophy who previously participated in investigational studies of Spinraza)*
Follow-up time	13 months (up to 5 years)
Population (inclusion and exclusion criteria)	**Population** • SMA type 1 with homozygous deletion or mutation in the SMN1 gene and 2 copies of *SMN2* • Aged ≤7 months at screening • Symptom onset at ≤6 months **Inclusion criteria** • Be born (gestational age) between 37 and 42 weeks • Be medically diagnosed with SMA • Have two copies of *SMN2* • 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 centre, for the duration of the study **Exclusion criteria** • Hypoxemia (O_2 saturation awake less than 96% or O_2 saturation asleep less than 96%, without ventilation support) during screening evaluation • Clinically significant abnormalities in haematology or clinical chemistry parameters or ECG • 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

SHINE:

Population:

- SMA type 1 with homozygous deletion or mutation in the SMN1 gene and 2 copies of *SMN2*

Inclusion criteria:

- Signed informed consent of parent or guardian and signed informed assent of participant, if indicated per participant's age and institutional guidelines.
- Completion of the index study in accordance with the study protocol or as a result of Sponsor decision (e.g., early termination of the index study) within the preceding 16 weeks

Exclusion criteria:

- Have any condition or worsening condition which in the opinion of the Investigator would make the participant unsuitable for enrollment, or could interfere with the participant participating in or completing the study
- Clinically significant abnormalities in haematology 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 or able to meet standard of care guidelines (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study
- Treatment with another investigational agent, biological agent, or device within one month of Screening, or 5 half-lives of study agent, whichever is longer)

Intervention

Spinraza via intrathecal administration;
12 mg for patients 2 years and older (dose adjusted for younger patients)

Baseline characteristics

Baseline characteristics of ENDEAR

Characteristic	Spinraza group (N=80)	Control group (N=41)
Female sex, n (%)	43 (54)	24 (59)
Age at first dose, days		
Mean	163	181
Range	52–242	30–262
Age at symptom onset, weeks		
Mean	7.9	9.6
Range	2–18	1–20
Age at diagnosis of SMA, weeks		
Mean	12.6	17.5
Range	0–29	2–30
Disease duration at screening, weeks		
Mean	13.2	13.9
Range	0–25.9	0–23.1
Symptoms of SMA, n (%)		
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, n (%)	21 (26)	6 (15)
Use of gastrointestinal tube, n (%)	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

	<table><tr><td>CMAP amplitude</td><td></td><td></td></tr><tr><td>Peroneal</td><td>0.371±0.31</td><td>0.317±0.29</td></tr><tr><td>Ulnar</td><td>0.226±0.19</td><td>0.225±0.12</td></tr></table> Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination; SD, standard deviation; SMA, spinal muscular atrophy. * 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. Baseline characteristics of SHINE <table><tr><th>Characteristic</th><th>Control in ENDEAR N=41</th><th>Control in ENDEAR and Spinraza treated in SHINE N= 24</th><th>Spinraza treated in ENDEAR and SHINE N=81 [a]</th></tr><tr><td>Female sex, n (%)</td><td>24 (59)</td><td>15 (63)</td><td>4 (54)</td></tr><tr><td>Median (range) age at first dose, months</td><td>6.7 (1-9)</td><td>17.8 (10-23)[b]</td><td>5.4 (2-15)</td></tr><tr><td>Median (range) age at symptom onset, months</td><td>1.8 (0-5)</td><td>2.1 (1-5)[c]</td><td>1.6 (0-4)</td></tr><tr><td>SMN2 gene copies, n(%)</td><td></td><td></td><td></td></tr><tr><td>2</td><td>40 (98)</td><td>23 (96)</td><td>81 (100)</td></tr><tr><td>3</td><td>1 (2)</td><td>1 (4)</td><td>0 (0)</td></tr><tr><td>Mean (SD) total HINE-2 motor milestone score</td><td>1.4 (1.29)</td><td>1.4 (1.28)</td><td>1.3 (1.08)</td></tr><tr><td>Mean (SD) CHOP-INTEND score</td><td>28.4 (7.56)</td><td>17.3 (9.71)</td><td>26.7 (8.13)</td></tr></table> Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination; SD, standard deviation; SMA, spinal muscular atrophy. Notes: a) one infant randomized to receive Spinraza in ENDEAR was not dosed, but was dosed in SHINE. b) Median in the 12 participants who were alive and without permanent ventilation at baseline in SHINE was 16.8 (range 10-23) months. c) Median in the 12 participants who were alive and without permanent ventilation at baseline in SHINE was 2.2 (range 1-5) months

Primary and secondary endpoints	**<u>Primary endpoint</u>**
	Efficacy
	Motor milestones responders, based on improvement in HINE (with the exclusion of voluntary grasp), as follows:
	• ≥ 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category, or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking
	• More categories where there is improvement than worsening; for the category of ability to kick, worsening is defined as ≥ 2-point decrease or decrease to the lowest possible score of no kicking; for the other categories, worsening is defined as ≥ 1-point decrease
	Time to Death or Permanent Ventilation, on the Kaplan-Meier product-limit method, as follows:
	• Tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event
	<u>Other endpoints</u>
	Efficacy
	• CHOP-INTEND responders
	  ○ Change from baseline in CHOP-INTEND total score is ≥ 4 points
	• Time to death
	  ○ Estimated proportion of participants who died by given duration thresholds, based on the Kaplan-Meier product-limit method
	• Participants not requiring permanent ventilation
	• CMAP responders

	○ CMAP amplitude at the peroneal nerve increasing to or maintained at ≥ 1 mV (comparing to the baseline) Time to death or permanent ventilation in the two subgroups of participants who are (i) below or (iii) above the study median disease duration ○ Estimated proportion of participants who died or required permanent ventilation (EAC-adjudicated events) given duration thresholds, based on the Kaplan-Meier product-limit method **Safety** AEs, SAEs, discontinuations due to AEs, changes in haematology values, changes in blood chemistry values, vital signs, ECG, changes in urinalysis values (**SHINE:** **Primary endpoint** **Safety** • AEs and SEAs • Clinically significant abnormalities of: vital signs, weight, neurological examination, laboratory assessment, coagulation parameters, 12-lead electrocardiograms • Change in concomitant medications **Other endpoints** • % participants attained motor milestones as assessed by WHO criteria • % participants attained motor milestones as assessed by section 2 in HINE • Time to death or permanent ventilation • % participants not requiring permanent ventilation • Change from baseline in CHOP-INTEND motor function scale • Change from baseline in HINE • Change from baseline in RULM • Change from baseline in 6-min walking test • Change from baseline in compound muscular action potential (CMAP) • Change from baseline in body length and/or height • Change from baseline in head circumference • Change from baseline in chest circumference • Change from baseline in arm circumference • Proportion of CMAP responders • Number of participants with motor milestones achieved • Proportion of participants who achieved standing alone • Proportion of participants who achieved walking with assistance • Number of participants with serious respiratory events • Number of participants hospitalized • Duration of hospitalizations

	• Change from baseline in cobb-Angle on X-Ray of the thoracolumbar spine • Change from baseline in QoL questionnaires • Number of disease-related hospitalizations and AEs Overall survival rate)
Method of analysis	First primary efficacy end point was statistically assessed in the interim analysis. Because the P value for the first primary end point was significant in the interim analysis, this end point was not tested for significance in the final analysis. The second primary efficacy end point and all secondary efficacy end points were assessed in the final analysis. A hierarchical testing strategy was used to control the overall type I error rate at 0.05; in the final analysis, end points were ranked and tested for statistical significance in a hierarchical order. The difference between the Spinraza 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	Disease duration: ≤12 weeks disease duration vs. >12 weeks disease duration

Abbreviations: AE, adverse event; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, Compound Muscular Action Potential; EAC, Event Adjudication Committee; ECG, electrocardiogram; HINE, Hammersmith Infant Neurological Examination; SAE, serious adverse event; SMA, spinal muscular atrophy; SMN, Survival Motor Neuron.
Reference:(ClinicalTrials.gov 2017, Finkel 2017)

TABLE 27: MAIN STUDY CHARACTERISTICS SPR1NT

Trial name	SPR1NT
NCT number	NCT03505099
Objective	To evaluate the safety through incidence of AE and/or SAE; to assess the safety based on the change from baseline in clinical laboratory parameters; and to assess the efficacy by demonstrating functional independent sitting for >30 seconds at any visit up to 18 months of age
Publications – title, author, journal, year	Protocol (AveXis 2018), Clinical overview (8 Mar 2019 data cut) (AveXis 2019), 180-day efficacy and safety update (31 December 2019) (AveXis 2020b); European Medicines Agency assessment report (European Medicines Agency 2020)
Study type and design	This is a phase III, open-label, non-randomised, single arm, single group assignment trial. The study is on-going
Follow-up time	Cohort 1: 18 months of age Cohort 2: 24 months of age
Population (inclusion and exclusion criteria)	**Population**

Pre-symptomatic patients with SMA type 1 or 2 with 2 or 3 copies of *SMN2*; ≤6 weeks of age at the time of gene replacement therapy (N=30*: 2 × *SMN2* n=14, 3 × *SMN2* n=15, 4 × *SMN2* n=1)

Inclusion criteria

Age ≤6 weeks (≤42 days) at dose, with a gestational age of 35 to 42 weeks; CMAP ≥2 mV at baseline; centralized review of CMAP data will be conducted; Pre-symptomatic SMA Type 1 as determined by 2 copies of *SMN2*, or pre-symptomatic SMA Type 2 as determined by 3 copies of *SMN2*

Exclusion criteria

The study included the following same exclusion criteria as seen in STR1VE-US (letters refer to the description of STR1VE-US criteria presented above): A, B (not including criteria B1), D (not including criteria D1) G–K

Additional exclusion criteria include:
Weight at screening visit <2 kg, and/or weight-for-age is <3rd percentile based on WHO Child Growth Standards; any clinical signs at prior to dosing that are strongly suggestive of SMA; tracheostomy or requirement of non-invasive ventilatory support prior or during the screening period; treatment with an investigational or commercial product given for the treatment of SMA; biological mother with active viral infection; and previous or expected major surgical procedure during the study period

Intervention

Zolgensma (one-time IV administration) (1.1 × 10^{14} vg/kg)

Baseline characteristics

Primary and secondary endpoints

Primary endpoint

	Safety • Incidence of AEs and/or serious AEs • Change from baseline in clinical laboratory parameters **Efficacy** • 2 copies of *SMN2*: Proportion of patients achieving the ability of functional independent sitting for >30 seconds up to 18 months of age • 3 copies of *SMN2*: Proportion of patients achieving the ability to stand without support for >3 seconds up to 24 months of age **Other endpoints** **2 copies of *SMN2*** • Proportion of patients that have survived and have not required permanent ventilation in the absence of acute illness and perioperatively, assessed at 14 months of age. Permanent ventilation is defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation • Proportion of patients that have achieved the ability to maintain weight ≥3rd percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age **3 copies of *SMN2*** • Proportion of patients demonstrating the ability to walk alone defined as the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age
Method of analysis	[redacted]
Subgroup analyses	N/A

Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; CMAP, compound muscle action potential; IV, intravenous; MUNE, motor unit number estimation; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; WHO, World Health Organization.
* The protocol was modified post-study initiation in October 2018, where enrolment of 4 copy *SMN2* pre-symptomatic patients was suspended. No such patients with 4 copies of *SMN2* had been enrolled in the study at the time that this amendment was implemented. Subsequent to the amendment, a single patient who was initially enrolled in Cohort 2 was later discovered to have 4 copies of *SMN2*. This patient is neither accounted as a participant of Cohort 2 nor part of the ITT population, but this patient remains in the safety population.
Sources: Zolgensma EPAR, Table 3 and 4, pages 91-92, Clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03505099), Protocol (AveXis 2018), Clinical overview (8 Mar 2019 data cut) (AveXis 2019), 180-Day efficacy and safety update (31 December 2019)(AveXis 2020b)

TABLE 28: MAIN STUDY CHARACTERISTICS NURTURE

Trial name	NURTURE
NCT number	NCT02386553

<table>
<tr><td>Objective</td><td>The primary objective of the study is to examine the efficacy of multiple doses of Spinraza administered intrathecally in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA. Secondary objectives of this study are to examine the effects of Spinraza in infants with genetically diagnosed and presymptomatic SMA.</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>(De Vivo 2019)</td></tr>
<tr><td>Study type and design</td><td>Phase II, open-label, multiple-dose study</td></tr>
<tr><td>Follow-up time</td><td>4 years</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Population
Pre-symptomatic SMA
Inclusion criteria
• Age ≤ 6 weeks at first dose
• Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation
• Genetic documentation of 2 or 3 copies of SMN2
• Ulnar CMAP ≥ 1 mV at baseline
• Gestational age of 37 to 42 weeks for singleton births; gestational age of 34 to 42 weeks for twins
Exclusion criteria
• Hypoxemia (O2 saturation <96% awake or asleep without any supplemental oxygen or respiratory support)
• Any clinical signs or symptoms at screening or immediately prior to the first dosing (Day 1) that are strongly suggestive of SMA
• Clinically significant abnormalities in haematology or clinical chemistry parameters
• Treatment with an investigational drug given for the treatment of SMA biological agent, or device; any history of gene therapy, prior ASO treatment, or cell transplantation</td></tr>
<tr><td>Intervention</td><td>Spinraza via intrathecal administration;</td></tr>
<tr><td>Baseline characteristics</td><td>Baseline characteristics of NURTURE
<table>
<tr><th>Characteristic</th><th>2 SMN2 copies (n=15)</th><th>3 SMN2 copies (n=10)</th><th>Total (n=25)</th></tr>
<tr><td>Sex, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Female</td><td>7 (47)</td><td>6 (60)</td><td>13 (52)</td></tr>
<tr><td>Male</td><td>8 (53)</td><td>4 (40)</td><td>12 (48))</td></tr>
<tr><td>Age at first dose, days, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>≤14</td><td>6 (40)</td><td>3 (30)</td><td>9 (36)</td></tr>
<tr><td>>14 and ≤28</td><td>7 (47)</td><td>5 (50)</td><td>12 (48)</td></tr>
<tr><td>Median (range)</td><td>19.0 (8-41)</td><td>23.0 (3-42)</td><td>22.0 (3-42)</td></tr>
<tr><td>Mean (SD)</td><td>19.5 (9.29)</td><td>22.3 (12.45)</td><td>20.6 (10.51)</td></tr>
<tr><td>CHOP-INTEND total score</td><td></td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>45.0 (25.0-60.0)</td><td>53.5 (40.0-60-0)</td><td>50.0 (25.0-60-0)</td></tr>
<tr><td>Mean (SD)</td><td>47.0 (10.04)</td><td>51.9 (6.10)</td><td>49.0 (8.87)</td></tr>
<tr><td>HINE total motor milestones</td><td></td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>3.0 (0-5)</td><td>3.0 (0-7)</td><td>3.0 (0-7)</td></tr>
<tr><td>Mean (SD)</td><td>2.7 (1.59)</td><td>3.2 (1.87)</td><td>2.9 (1.69)</td></tr>
</table>
Data are n (%), median (range) or mean (SD), unless otherwise stated.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Exam—Part 2; SMN2, Survival Motor Neuron 2.</td></tr>
</table>

Primary and secondary endpoints	**Primary endpoint** **Efficacy** Time to death or respiratory intervention • The age of the participant at the first occurrence of either a respiratory intervention or death; respiratory intervention is defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for 7 or more days or tracheostomy **Other endpoints** **Efficacy** • Developing clinically manifested SMA • Participants alive • Attaining motor milestones as assessed by WHO criteria and HINE • Change from baseline in: CHOP-INTEND; Hammersmith Functional Motor Scale - Extended; weight for age/length; head circumference; chest, head to chest, and arm circumference ratios **Safety** AEs, SAEs, clinical laboratory parameters, laboratory tests, ECGs, vital signs, neurological examinations, CSF and plasma Spinraza concentrations
Method of analysis	Time to death or respiratory intervention, proportion of participants alive, proportion of participants achieving WHO motor milestones, proportion of participants developing clinically manifested SMA, and safety analyses were analyzed in all study participants who received ≥1 dose of nusinersen (intent-to-treat population). All other efficacy analyses were performed on interim efficacy sets that comprised all dosed participants who attended or had the opportunity to attend the targeted visit of the analysis (efficacy set). All secondary endpoints were assessed at ages 13 and 24 months. Proportion of participants alive and proportion who achieved WHO motor milestones at ages 13 and 24 months were estimated using the Kaplan-Meier method. CHOP INTEND total score, HINE-2 total motor milestone score, change in growth parameters, ulnar and peroneal CMAP amplitude, and pNF-H concentrations were summarized using descriptive statistics.
Subgroup analyses	N/A

Abbreviations: AE, adverse event; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF, cerebrospinal fluid, ECG, electrocardiogram; HINE, Hammersmith Infant Neurological Examination; SAE, serious adverse event; SMA, spinal muscular atrophy; WHO, World Health Organization.
Reference: (De Vivo 2019) (ClinicalTrials.gov 2018)

7.3 Results per study

TABLE 29: RESULTS OF STUDY STR1VE-US

Trial name: STR1VE-US						
NCT number: *NCT03306277*						
Outcome	Time point	Result n/N (%)	n (number of patients affected)	n (total number of patients	Comments	References
Survival (number of patients alive)	14 months of follow-up	21/22 (95.5)	21	22	Extracted from IPD	Zolgensma EPAR page 69
Survival without permanent ventilation	14 months of follow-up	20/22 (90.9)	20	22	Number of patients alive without permanent ventilation Extracted from IPD	Zolgensma EPAR page 71
Lack of permanent ventilation	14 months of follow-up or last patient visit if prior to 14 months	20/21 (90.9)	20	22	Number of patients not requiring assisted ventilation Extracted from IPD Permanent ventilation defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation	Derived from survival and survival without permanent ventilation
CHOP-INTEND responders	At 14 months of follow-up or last patient visit if prior to 14 months	22/22 (100)	22	22	Number of patients with at least 4 point improvement on CHOP-INTEND	Zolgensma EPAR page 73 Table 6
[redacted]						

Sitting without support (30 seconds)	At 18 months of age	18 months age: 13/22 (59)	13	22	Number of patients sitting without support Sitting without support defined by sitting for 30 seconds according to Bayleys items #26.	Zolgensma EPAR page 72
Sitting without support (30 seconds)	End of follow-up	End of follow-up: 14/22 (63.6)	14	22	Number of patients sitting without support Sitting without support defined by sitting for 30 seconds according to Bayleys items #26.	Zolgensma EPAR page 72 Table 5
Walking without support	18 months of age	1/22 (4.5)	1	22	Number of patients walking without support WHO definition of walking alone: Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object	Zolgensma EPAR page 72 table 5
Walking without support	End of follow-up	1/22 (4.5)	1	22	Number of patients walking without support WHO definition of walking alone: Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object	Zolgensma EPAR page 72 table 5
Serious treatment related side effects	14 months of follow-up	10/22 (45.5)	10	22	Number of patients experiencing at least one serious adverse event	Zolgensma EPAR page 105 table 19

TABLE 30: RESULTS OF STUDY START

Trial name: START						
NCT number: *NCT02122952*						
Outcome	Time point	Result n/N (%)	n (number of patients affected)	n (total number of patients	Comments	References
Survival (number of patients alive)	14 months of follow-up	12/12 (100)	12	12	Number of patients alive,	Clinical study report (Avexis CSR START 2018) Mendell 2017, Fig 1
Survival without permanent ventilation	at 14 months of follow-up	12/12 (100)	12	12	Number of patients alive without permanent ventilation,	Clinical study report (Avexis CSR START 2018) Mendell 2017, Fig 1
Lack of permanent ventilation	at 14 months of follow-up or last patient visit if prior to 14 months	12/12 (100)	12	12	Number of patients not requiring assisted ventilation, permanent ventilation defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation	Clinical study report (Avexis CSR START 2018) Mendell 2017, Fig 1
[redacted]						Clinical study report (Avexis CSR START 2018)
[redacted]						Clinical study report (Avexis CSR START 2018)

		[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Number of patients sitting without support Sitting without support defined by sitting for 30 seconds according to Bayleys items #26	Clinical study report (Avexis CSR START 2018)
Sitting without support (30 seconds)	At end of follow-up	End of follow-up: 9/12 (75)	9	12	Number of patients sitting without support Sitting without support defined by sitting for 30 seconds according to Bayleys items #26.	Clinical study report (Avexis CSR START 2018) EPAR page 84, Table 11
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Clinical study report (Avexis CSR START 2018)
Walking without support	End of follow-up	2/12 (16.67%)	2	12	Number of patients walking without support WHO definition of walking alone: Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object	Clinical study report (Avexis CSR START 2018) EPAR page 84 Table 11

Serious treatment related side effects	at 14 months of follow-up	10/12 (83.3)	10	12	Number of patients experiencing at least one serious adverse event	Clinical study report (Avexis CSR START 2018) Mendell 2017 table 3

TABLE 31: RESULTS OF STUDY: ENDEAR ITT

Trial name: ENDEAR						
NCT number: *NCT02193074*						
Outcome	Time point	Result n/N (%)	n (number of patients affected)	n (total number of patients	Comments	References
Survival, calculated	14 months of follow-up	64/80 (80)	64	80	Number of patients alive, calculated from survival probabilities	Finkel 2017, Figure 2
Survival, actual	End of of follow-up	67/80 (83.8)	67	80	Number of patients alive, at end ENDEAR follow-up, actual	Finkel 2017, Table 2
Survival without permanent ventilation, calculated	14 months of follow-up	42/80 (52.5)	42	80	Number of patients alive without permanent ventilation, calculated from survival probabilities	Finkel 2017, Figure 2
Survival without permanent ventilation - actual	End of follow-up	49/80 (61.3)	49	80	Number of patients alive without permanent ventilation at end ENDEAR follow-up, actual	Finkel 2017, Table 2
Lack of permanent ventilation	14 months of follow-up or last patient visit if prior to 14 months	42/65 (64.6)	42	80	Number of patients not requiring assisted ventilation > 16 h/d Calculated from OS and EFS numbers (number off ventilation / number alive)	Finkel 2017, Figure 2
CHOP-INTEND responders	14 months of follow-up or last patient visit if prior to 14 months	52/73 (71.2)	52	73	Number of patients with at least 4 point improvement on CHOP-INTEND	NICE committee papers pg 565

Sitting without support	End of follow-up	Definition 1: 21/73 (28.8) Definition 2: 6/73 (8.2)	21 6	73 73	Number of patients sitting without support Definition 1: improvement by ≥ 1 point on a HINE-2 sitting scale of 3 to 5 development stages; late children and dropouts were rated as non-responders. Definition 2: HINE-2 categories "stable sit" and "pivots (rotates)"	Definition 1: IQWiG report, table 26 Definition 2: Finkel 2017
Walking without support	End of follow-up	0/73 (0)	0	73	Number of patients walking without support	IQWiG report, table 26
Serious treatment related side effects	End of follow-up	61/80 (76.3)	61	80	Number of patients experiencing at least one serious adverse event	Finkel 2017

TABLE 32: RESULTS OF STUDY: ENDEAR SUBGROUP

Trial name: ENDEAR						
NCT number: *NCT02193074*						
Outcome	Time point	Result n/N (%)	n (number of patients affected)	n (total number of patients	Comments	References
Survival (number of patients)	14 months of follow-up	31/34 (91.2)	31	34	calculated from survival probabilities	NICE nusinersen committee papers pg 676-7
Survival without permanent ventilation (number of patients alive without permanent ventilation)	14 months of follow-up	26/34 (76.5)	26	34	calculated from survival probabilities	NICE nusinersen committee papers pg 676-7
Lack of permanent ventilation (number of patients not	14 months of follow-up or last patient visit if prior to 14 months	26/31 (83.9)	26	31	Calculated from OS and EFS numbers (number off ventilation / number alive)	NICE nusinersen committee papers pg 676-7

requiring assisted ventilation > 16 h/d)						
CHOP-INTEND responders (number of patients with at least 4 p improvement on CHOP-INTEND)	14 months of follow-up or last patient visit if prior to 14 months	32/34 (94.1)	32	34	Number of patients with at least 4 point improvement on CHOP-INTEND	NICE nusinersen committee papers pg 565
Sitting without support* (number of patients sitting without support)	End of follow-up	Definition 1: 16/32 (50) Definition 2: 6/32 (18.8)	16 6	32	Definition 1: improvement by ≥ 1 point on a HINE-2 sitting scale of 3 to 5 development stages; late children and dropouts were rated as non-responders. Definition 2: HINE-2 categories "stable sit" and "pivots (rotates)". Assumes all sitters in the ITT population belongs to the ENDEAR subgroup	Definition 1: IQWiG report, table 26 Definition 2: Finkel 2017
Walking without support (number of patients walking without support)	18 months of age End of follow-up	0/34 (0)	0	34	No walkers reported either in the ENDEAR ITT population or in IQWiG 2020	Finkel 2017 IQWiG 2020, table 26
Serious treatment related side effects (number of patients experiencing at least one serious adverse event)	14 months of follow-up	NR	NR	NR	Adverse event data not available for the ENDEAR subgroup	-

TABLE 33: RESULTS FROM STUDY: SPR1NT

Trial name: SPR1NT
NCT number:

Outcome	Time point	Result n/N (%)	n (number of patients affected)	n (total number of patients	Comments	References
Overall survival	10 months (31 December 2019 data cut)	2 *SMN2* copies: 14/14 (100) 3 *SMN2* copies: 15/15 (100)	14 15	14 15	Number of patients alive Extracted from IPD	(AveXis 2020b) Zolgensma EPAR page 94
Event-free survival (combined mortality or permanent assisted ventilation)	10 months (31 December 2019 data cut)	2 *SMN2* copies: 14/14 (100) 3 *SMN2* copies: 15/15 (100)	14 15	14 15	Number of patients alive without permanent ventilation Extracted from IPD	Zolgensma EPAR page 94
Permanent assisted ventilation	10 months (31 December 2019 data cut)	0/29 (0)	0	29	Number of live patients with permanent assisted ventilation	Zolgensma EPAR page 94
Sitting without support	10 months (31 December 2019 data cut)	2 *SMN2* copies: 8/14 (57.1) 3 *SMN2* copies: 10/15 (66.7)	18	29	Sitting defined by Bayley Scales Gross Motor subset item #26: child sits alone without support for ≥30 seconds	Zolgensma EPAR Tables 16 and 17
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(AveXis 2020b)
Walking without support	10 months (31 December 2019 data cut)	2 *SMN2* copies: 4/14 (28.6) 3 *SMN2* copies: 3/15 (20.0)	7	29	WHO definition of walking alone: Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object	(AveXis 2020b) Zolgensma EPAR Tables 16 and 17
[redacted]						(AveXis 2020b)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(AveXis 2020b)

TABLE 34: RESULTS FROM STUDY: NURTURE

Trial name: NURTURE						
NCT number: NCT02386553						
Outcome	Time point	Result n/N (%)	n (number of patients affected)	n (total number of patients	Comments	References
Overall survival	35 months	2 *SMN2* copies: 15/15 (100) 3 *SMN2* copies: 10/10 (100)	15 10	15 10		(De Vivo 2019)
Event-free survival (combined mortality or permanent assistend ventilation)	35 months	2 *SMN2* copies: 15/15 (100) 3 *SMN2* copies: 10/10 (100)	15 10	15 10		
Lack of permanent assisted ventilation	35 months	2 *SMN2* copies: 15/15 (100) 3 *SMN2* copies: 10/10 (100)	0 0	15 10		
Sitting without support	35 months	2 *SMN2* copies: 15/15 (100) 3 *SMN2* copies: 10/10 (100)	15 10	15 10	Defined by WHO motor milestone criteria for sitting without support (Child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position	
Walking without support	35 months	2 *SMN2* copies: 12/15(80%) 3 *SMN2* copies: 10/10 (100%)	12 10	15 10	WHO definition of walking alone: Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object	
Treatment-related adverse events	35 months	2 or 3 *SMN2* copies: 12/25 (48)	12	25		

7.4 Extraction of survival data for the ENDEAR subgroup

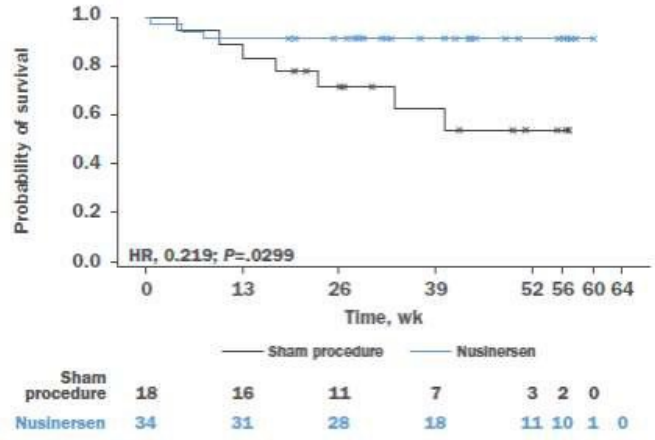
In the ENDEAR publication (Finkel 2017), the exact overall and event-free survival for the subgroup with a disease duration at screening ≤12 weeks was not available. However, a graphical representation of these had been made available as part of the NICE committee papers for the HTA appraisal of Spinraza in the UK (National Institute for Health and Care Excellence 2018), p. 676-7. In order to utilise the subgroup OS and EFS data, the Kaplan Meier graphs (

Figure 4 and Figure 5) were imported using the method explained below.

Figure 4 and Figure 5 were loaded as images within a web-based digitisation software. After tracing over the graphs, the software produced co-ordinates for both OS and EFS data which were then imported into RStudio to finalise the digitisation process. RStudio code was run and produced two separate CSV files containing the digitised data. However, as there was a lack of empirical data for OS/EFS for the period of ~20 months age (14 months ENDEAR follow-up) to 36 months of age for the subgroup, extrapolation had to be made for the remaining time. A parametric distribution was fitted based upon the recorded data, however, given the short time for which data was available it was eventually determined that the preferred approach would be to just utilize the Kaplan-Maier data and assumed that the last observation could be carried forward to month 36.

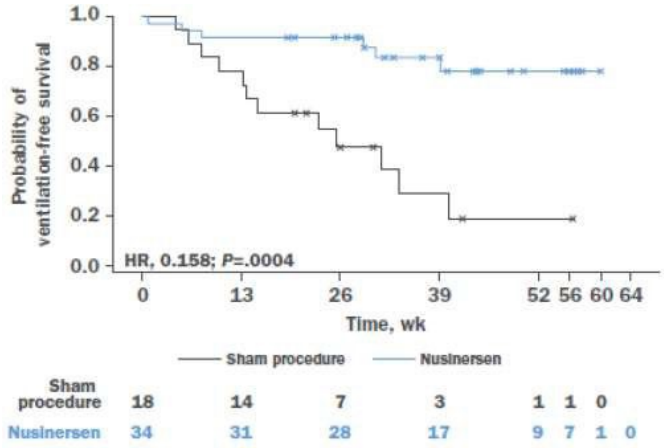
Note that since START and STR1VE-US were single-arm trials, direct comparisons made to Spinraza in the model are unanchored, naïve comparisons and no adjustment has been made for differences (known or unknown) in trial populations or settings. Therefore, caution is required in any interpretation of results.

FIGURE 4: OVERALL SURVIVAL OF PATIENTS WITH DISEASE DURATION ≤12 WEEKS AT SCREENING IN ENDEAR



Source: NICE committee papers (National Institute for Health and Care Excellence 2018)

FIGURE 5: EVENT-FREE SURVIVAL FOR PATIENTS WITH DISEASE DURATION ≤12 WEEKS AT SCREENING IN ENDEAR



Source: NICE committee papers (National Institute for Health and Care Excellence 2018)

Tabelle 16: Charakterisierung der Studienpopulationen (Vergleich früh- vs. spätsymptomatischen Therapiebeginn)

Studie Charakteristika	Krankheitsdauer ≤ 12 Wochen (frühsymptomatischer Therapiebeginn)		Krankheitsdauer > 12 Wochen (spätsymptomatischer Therapiebeginn)	
	Nusinersen	Scheinbehandlung	Nusinersen	Scheinbehandlung
ENDEAR				
N	34	18	46	23
Geschlecht [w], n (%)	18 (53)	7 (39)	25 (54)	17 (74)
Alter bei Symptombeginn [Wochen], Median (Spannweite)	6 (3–18)	8 (1–20)	8 (2–16)	8 (4–16)
Alter bei Diagnose [Wochen], Median (Spannweite)	9 (0–22)	10 (2–25)	12 (2–29)	20 (12–30)
Erkrankungsdauer [Wochen], Median (Spannweite)[a]	8 (0–12)	9 (0–12)	16 (12–26)	18 (13–23)
Alter bei 1. Dosis [Wochen], Median (Spannweite)[b]	16 (7–34)	19 (4–33)	28 (18–35)	30 (20–37)

a: Differenz zwischen Alter bei Studieneinschluss und Alter bei Symptombeginn
b: In den Herstellerunterlagen finden sich Angaben in unterschiedlichen Zeiteinheiten. Zur Vereinheitlichung wurden alle in Wochen ausgedrückt.
MW: Mittelwert; N: Anzahl eingeschlossener Kinder; n: Anzahl Kinder in Kategorie; w: weiblich

Source: IQWiG report S18-02, p. 63

Tabelle 26: Ergebnisse – Responder Erreichen motorischer Meilensteine HINE-2 (Vergleich früh- vs. spätsymptomatischen Therapiebeginn)

Subgruppe	Erkrankungsdauer ≤ 12 Wochen (frühsymptomatischer Therapiebeginn)							Erkrankungsdauer > 12 Wochen (spätsymptomatischer Therapiebeginn)							Inter-aktionstest
	Nusinersen		Schein-behandlung		Scheinbehandlung vs. Nusinersen			Nusinersen		Schein-behandlung		Scheinbehandlung vs. Nusinersen			
	N	n (%)	N	n (%)	RD[a]	[95 %-KI][b]	p-Wert[c]	N	n (%)	N	n (%)	RD[a]	[95 %-KI][b]	p-Wert[c]	p-Wert
ENDEAR															
HINE-2 gesamt	34	24 (71)	18	0 (0)	0,71	[0,55; 0,86]	< 0,001	46	17 (37)	23	0 (0)	0,37	[0,23; 0,51]	< 0,001	0,003
Strampeln[d]	32[e]	10 (31)	16[e]	0 (0)	–	–	–	41[e]	2 (5)	21[e]	0 (0)	–	–	–	–
Kopfkontrolle[f]	32[e]	21 (66)	16[e]	0 (0)	–	–	–	41[e]	12 (29)	21[e]	0 (0)	–	–	–	–
Drehen[f]	32[e]	18 (56)	16[e]	0 (0)	–	–	–	41[e]	7 (17)	21[e]	1 (5)	–	–	–	–
Sitzen[f]	32[e]	16 (50)	16[e]	0 (0)	–	–	–	41[e]	5 (12)	21[e]	0 (0)	–	–	–	–
Krabbeln[f]	32[e]	6 (19)	16[e]	0 (0)	–	–	–	41[e]	2 (5)	21[e]	0 (0)	–	–	–	–
Stehen[f]	32[e]	5 (16)	16[e]	0 (0)	–	–	–	41[e]	2 (5)	21[e]	0 (0)	–	–	–	–
Gehen[f]	32[e]	0 (0)	16[e]	0 (0)	–	–	–	41[e]	0 (0)	21[e]	0 (0)	–	–	–	–

a: Da keine Ereignisse in der Kontrollgruppe auftraten, wurde auf eine Berechnung eines relativen Effektmaßes (OR) verzichtet und stattdessen die Risikodifferenz (RD) herangezogen; eigene Berechnung.
b: eigene Berechnung, asymptotisch
c: eigene Berechnung (unbedingter exakter Test [CSZ-Methode nach [93])
d: Responder: Verbesserung um ≥ 2 Punkte auf der Skala von insgesamt 5 Entwicklungsstufen; verstorbene Kinder sowie Studienabbrecher wurden als Non-Responder bewertet
e: Anzahl ausgewerteter Kinder im Efficacy Set mit mindestens 6-monatiger (Studientag 183) Nachbeobachtung
f: Responder: Verbesserung um ≥ 1 Punkt auf der Skala von insgesamt 3 bis 5 Entwicklungsstufen; verstorbene Kinder sowie Studienabbrecher wurden als Non-Responder bewertet
HINE-2: Hammersmith Infant Neurological Examination – Subscale 2; KI: Konfidenzintervall; n: Anzahl Kinder mit Ereignis; N: Anzahl ausgewerteter Kinder; RD: Risikodifferenz; vs.: versus

Source: IQWiG report S18-02, page 75

Health economic evidence for the assessment of Zolgensma (onasemnogene abeparvovec) for the treatment of patients with 5q spinal muscular atrophy with a bi-allelic mutation in the *SMN1* gene and:

- a clinical diagnosis of SMA Type 1, or up to 3 copies of the *SMN2* gene, or
- pre- symptomatic patients with up to 2 copies of the *SMN2* gene

Contents

1 Basic information

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Table 2 Overview of the pharmaceutical

Proprietary name	Zolgensma
Generic name	Onasemnogene abeparvovec
Marketing authorization holder in Denmark	Novartis Gene Therapies, formerly AveXis, Inc.
ATC code	M09AX09
Pharmacotherapeutic group	Other drugs for disorders of the musculo-skeletal system
Active substance(s)	Onasemnogene abeparvovec
Pharmaceutical form(s)	Solution for infusion
Mechanism of action	Gene replacement therapy
Dosage regimen	Single dose of 1.1×10^{14} vg/kg
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Zolgensma is indicated for the treatment of: • patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or • patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes

Combination therapy and/or co-medication	Oral prednisolone prior to and 30 days post-administration
Packaging – types, sizes/number of units, and concentrations	Each mL contains Zolgensma with a nominal concentration of 2×10^{13} vector genomes. Vials will contain an extractable volume of not less than either 5.5 mL or 8.3 mL. The total number of vials and combination of fill volumes in each finished pack will be customised to meet dosing requirements for individual patients depending on their weight
Orphan drug designation	Yes

2 Abbreviations

Abbreviation	Description of abbreviation
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ATMP	Advanced therapy medicinal products
BIC	Bayesian information criterion
BiPAP	Bi-level positive airway pressure
BSC	Best supportive care
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound motor action potential
CPI	Consumer Price Index
CSF	Cerebrospinal fluid
DKK	Danish krone
DMC	Danish Medicine Council
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
EFS	Event-free survival
EMA	European Medicines Agency

EQ-5D	EuroQol-5 Dimensions
ERG	Evidence review group
EU	European Union
FDA	Food and Drug Administration
GP	General practitioner
HCP	Health care professional
HCRU	Health care resource utilization
HE	Health Economics
HINE-2	Hammersmith Infant Neurological Examination-2
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITU	Intensive care unit
IV	Intravenous
KM	Kaplan meier
KOL	Key opinion leader
LY	Life-years
MUNE	Motor unit number estimation
NICE	The National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NRA	Non-invasive respiratory muscle aid
OS	Overall survival
PAV	Permanent assisted ventilation
PNCR	The Paediatric Neuromuscular Research Network
PPP	Pharmacy purchase prices
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
SD	Standard deviation
SE	Standard error
SMA	Spinal muscular atrophy

SMN	Survival motor neurone
SMPC	Summary of product characteristics
UK	United Kingdom
US	United States
WHO	World Health Organization

3 Summary

Spinal muscular atrophy (SMA) is a rare genetic disease in which infants with the most severe phenotype, SMA type 1, never sit independently and >90% die or require permanent ventilation by the age of 2 years when managed with best supportive care (BSC) (Finkel 2014, Kolb 2017). Despite the availability of nusinersen (Spinraza), the current standard of care for SMA in Denmark, significant unmet needs exist in terms of survival without the need for permanent ventilatory support, speed of onset of treatment effect, the achievement of developmental milestones, and the burden of chronic, life-time invasive therapy.

Onasemnogene abeparvovec (Zolgensma) is the first one-time therapy which addresses the monogenic root cause of SMA by delivering a functional copy of the SMN gene that rapidly restores continuous SMN protein expression to prevent further motor neuron loss (European Medicines Agency 2020).

The DMC protocol has defined two patient segments of interest for treatment with Zolgensma: Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and

- a clinical diagnosis of SMA type 1
- a pre-symptomatic diagnosis of SMA with up to 3 copies of SMN2

There is product specification for patients with up to 21 kg bodyweight. Clinical evidence supporting the use of intravenous Zolgensma in the segments described above comes from a comprehensive trial programme in infants with symptomatic SMA type 1 (START, STR1VE-US, STR1VE-EU, LT-001, LT-002) and in pre-symptomatic infants with genetically diagnosed SMA and up to three copies of the SMN2 gene (SPR1NT)

Within the indication of patients with 2 or 3 copies of the SMN2 gene, a broader population of patients may be covered, including prevalent type 2 and 3 patients under 21 kg. Many of these patients are currently treated with Spinraza and some could be considered also eligible for treatment with Zolgensma.

As a result of the single arm open-label trial design used to assess Zolgensma, unanchored indirect treatment comparisons are used to assess the relative efficacy versus Spinraza, as Spinraza is the standard of care in Denmark for the treatment of SMA.

Across Phase I–III trials, infants with SMA type 1 treated with Zolgensma experienced significantly improved survival and freedom from permanent ventilatory support and showed improved motor milestone achievement compared with the natural history.

In comparison with Spinraza, the unanchored indirect treatment comparison (ITC) demonstrated that Zolgensma showed consistent benefit over Spinraza in SMA type 1 patients in the key outcomes analysed (overall survival, event-free survival and achievement

of motor milestones), for more details see the submitted Clinical Evidence Report for Zolgensma (v1.0) 16-SEP-2020 (AveXis 2020c).

Due to the rapid loss of motor neurons in infants with SMA type 1, prompt diagnosis and early intervention are key to the optimal achievement of clinical outcomes, highlighting the importance of new-born screening. Pre-symptomatic SMA patients (up to 3 SMN2 copies) treated with Zolgensma or Spinraza soon after birth in ongoing trials are achieving age-appropriate motor milestones.

The objective of this report is to estimate the total cost over time and the budget impact of the introduction of Zolgensma in Denmark for the treatment of patients with SMA type 1 and for pre-symptomatic patients with up to 3 copies of SMN2. The cost-analysis for patients with SMA type 1 is based on a cohort Markov state-transition model, with transition probabilities based upon clinical study data for Zolgensma and Spinraza, augmented with long-term extrapolation of observational data. This report presents total costs, and cost per patient but also the gains in quality adjusted life years to further demonstrate the value of Zolgensma vs Spinraza.

The cost-analysis for SMA type 1 shows that compared to treatment with Spinraza, Zolgensma is associated with a cost increase (2 975 768 DKK per patient over a lifetime). In part, this increase stem from the higher survival (18.40 undiscounted life years gained, and 7.50 discounted life years gained) achieved through treatment with Zolgensma.

The cost-analysis for pre-symptomatic patients assumes that Zolgensma is clinically non inferior to Spinraza with regards to survival and the achievement of milestones. This assumption is supported by the descriptive comparison of results from trials including pre-symptomatic patients (see submitted “Clinical Evidence Report for Zolgensma (v1.0) 16-SEP-2020” (AveXis 2020c)). To model this effect, Zolgensma was given the same survival and transitional probabilities as Spinraza and the analysis focuses on two separate patient populations: those with 2 SMN2 copies (assuming 80% of surviving patients would achieve independent walking) and those with 3 SMN2 copies (assuming 100% of surviving patients would achieve independent walking). The cost-analysis shows that over a lifetime, introducing Zolgensma would save a total of 29 565 291 DKK per patient with 2 copies of SMN2, assuming a discount rate of 4.0% (3.0% beyond year 35). For patients with 3 SMN2 copies, a total of 32 864 746 DKK would be saved per patient.

The budget impact analysis for SMA type 1 patients and for pre-symptomatic patients where all costs and health outcomes data are drawn from the cost-effectiveness models for SMA type 1 and pre-symptomatic patients, shows that the additional costs would be the highest in the first year (where also two treatment switches from Spinraza to Zolgensma is assumed)

and then drop significantly already in the second year and thereafter decrease annually during the first 10 years.

4 Background

Spinal muscular atrophy (SMA) is a rare, genetic, neuromuscular disease associated with progressive, irreversible motor neuron loss that results in muscle atrophy (wasting or loss of muscle tissue) leading to progressive muscle weakness and paralysis, and impairment of swallowing and breathing, and premature death in its more severe forms (Kolb 2011, Kolb 2015). People with 5q SMA have two faulty copies of the survival motor neuron 1 gene (SMN1), which in the majority of cases (95%) is due to a homozygous biallelic deletion of SMN1, resulting in a lack of survival motor neuron (SMN) protein (Kolb 2011, Kolb 2015). The SMN protein is also encoded by the SMN2 back-up gene that is closely homologous to SMN1, however, only 10–15% of the protein produced by SMN2 is full-length, functional SMN protein (Gennarelli 1995, Lefebvre 1995, Darbar 2011, Anderton 2015).

SMA exists on a spectrum of five types (0 through 4), which are classified based on the age at onset and motor milestone achievement (Kolb 2011).

Infants with SMA type 1 are never able to sit or walk, the maximum motor milestones achieved for SMA type 2 and type 3, respectively (Kolb 2011). SMN2 copy number is inversely associated with disease severity and is prognostic of SMA type; infants with two SMN2 copies have a 97% chance of developing SMA type 1, and infants with three copies of SMN2 have a 7% chance of developing SMA type 1 and 83% chance of developing SMA type 2 (Feldkotter 2002, Calucho 2018, Wirth 2020). More than 90% of infants with SMA type 1 die or require permanent ventilation by the age of 2 years if managed with best supportive care (BSC) only (Finkel 2014). While infants with a later onset of clinical symptoms can attain initial motor milestones, their condition deteriorates over time and often results in loss of motor milestones and severe disability when managed with BSC only, regardless of SMA type.

The annual incidence of SMA (all types) is approximately 9.4:100,000 live births (Lally 2017). SMA type 1 accounts for the majority of SMA cases, approximately 60%, with SMA type 2 and type 3 accounting for the remaining 40% (Verhaart 2017). Due to the high mortality rate of infants with SMA type 1 prior to the introduction of active treatments, there is a wide range in historically reported prevalence rates for SMA type 1 in the literature (0.04 to 0.28 per 100,000 population) (Verhaart 2017). The estimated combined prevalence of SMA type 2 and type 3 is 1.5 per 100,000 (Verhaart 2017). In Scandinavia, the estimated incidence of SMA (all types) is to 1/6000 (Danish Medicines Council 2020a). In Denmark, the estimate annual prevalence for SMA type 1 is approximately 6 per year and the annual incidence is 1-2 (Danish Medicines Council 2020a).

Patients with SMA require care and support from multidisciplinary teams of healthcare professionals, including rehabilitation, nutritional, and respiratory care. From 2017 and onwards, nusinersen (Spinraza) is widely used as part of the established clinical practice in Denmark, as an active treatment for 5q SMA type 1 and pre-symptomatic patients (Danish Medicines Council 2017). The patients are treated in three centres of excellences; in Copenhagen, in Arhus and in Odense.

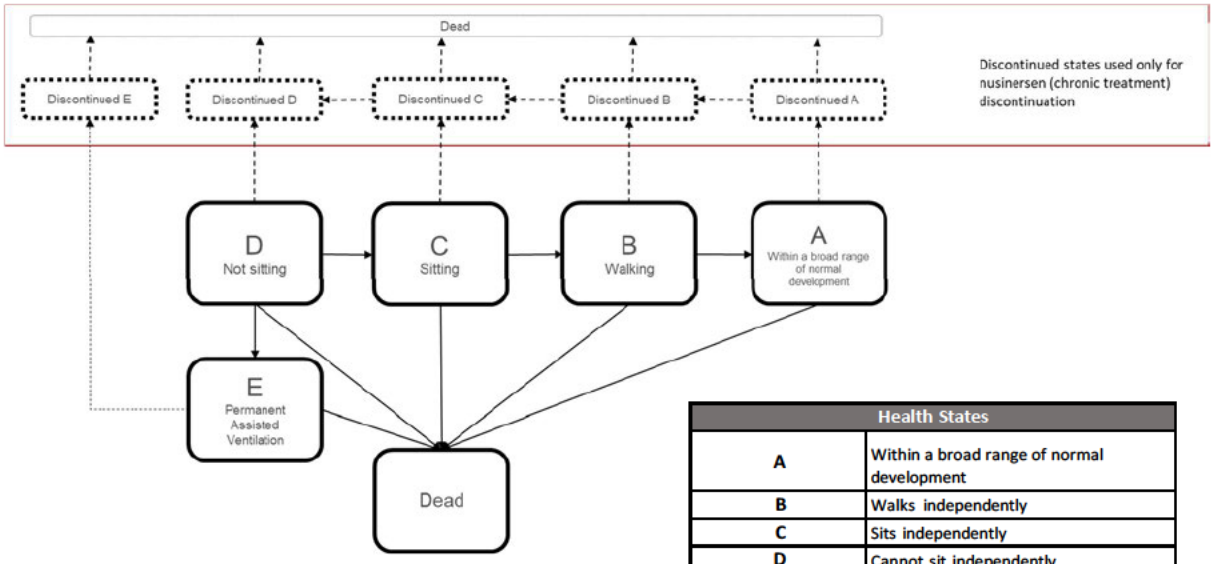
5 Cost- analysis SMA type 1

5.1 Model approach

A cost analysis model and a budget impact model were developed for the evaluation of the cost of introducing Zolgensma for the management of 5q SMA infants with either 2 or 3 SMN2 copies, or a clinical diagnosis of type 1 SMA, from a Danish perspective.

The cost-analysis is based on a cohort Markov state-transition model, with transition probabilities based upon clinical study data for Zolgensma and nusinersen (Spinraza), augmented with long-term extrapolation of observational data. Five health states (plus death) were chosen to capture the clinically relevant motor milestones for patients regarding treatment costs and quality of life, ranging from needing permanent ventilation, to broadly in line with normal development. The analyses were carried out in line with the Danish Medicine's Council's (DMC) guidelines (AMGROS 2018), using a restricted societal perspective and a life-time horizon with a four percent discount rate applied from the start of the first year (beyond 35 years, the discount rate is three percent). The cost analysis estimates the total cost per patient based on published unit costs and resource usage and on the time spent in the different health states. An overview of the model structure is presented in Figure 1 and see Section 5 for a complete description of the analysis.

FIGURE 1: MODEL SCHEMATIC



Health States	
A	Within a broad range of normal development
B	Walks independently
C	Sits independently
D	Cannot sit independently
E	Requires Permanent Assisted Ventilation

For patients with pre-symptomatic SMA, the clinical evidence and current treatment practice is different from patients described above. For this reason, a separate cost-analysis model was developed, relying on the assumption that Zolgensma is not clinically inferior to Spinraza. A detailed description of the cost-analysis for pre-symptomatic patients can be found in section 9.

5.2 Patient population

The patient group included in this cost analysis is infants with 5q spinal SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1 based on the enrolled cohorts of the available completed clinical trials (START and STR1VE-US). The modelled population includes those:

- with two copies of the SMN2 gene
- with the onset of symptoms at age ≤6 months
- who are symptomatic at baseline

Data has been derived from the two completed trials – START (AVXS-101-CL-101) and STR1VE-US (AVXS-101-CL-303) – and pooled into one dataset (hereinafter referred to as the 'POOLED' dataset). The POOLED dataset has been estimated by summing up the number of patients attaining a milestone in the same cycle from each trial. This increased the total patient number used for the pooled dataset to 34 patients (START, Cohort 2: 12 patients; STR1VE-US:

22 patients). Data from the trials were pooled to facilitate comparison to nusinersen. It also supports health economic modelling, where only 4 outcomes were important: overall survival (OS), event-free survival (EFS), and the shares of patients achieving the "sitting independently" and "walking independently" milestones.

5.3 Intervention- Zolgensma

Zolgensma is a one-time gene replacement therapy that addresses the genetic root cause of SMA, by delivering a stable, functional human SMN gene that rapidly restores continuous SMN protein expression, thus preventing motor neuron loss in symptomatic infants with SMA and pre-symptomatic infants genetically predicted to have SMA (European Medicines Agency 2020, AveXis 2019). It is suggested that treatment with Zolgensma early in the course of the disease is key to maximising the efficacy outcomes (Alfano 2018).

Zolgensma is an Advanced Therapy Medicinal Product (ATMP) and is the first ever gene therapy approved for a neuromuscular condition. The treatment is administered as a single, IV infusion over approximately 60 minutes at a dose of 1.1x1014 vg/kg (European Medicines Agency 2020). There is a product carton configuration with dosing for patients up to 21 kg of bodyweight (European Medicines Agency 2020).

A positive opinion from the Committee for Medicinal Products for Human Use opinion was granted in March 2020, with conditional marketing authorisation granted in May 2020. The indication statement reads (European Medicines Agency 2020):

Zolgensma is indicated for the treatment of:

- patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene

Administration of Zolgensma does not require any changes in hospital practice or requirements for additional machines. The duration of the Zolgensma infusion is through single-dose intravenous infusion with a slow infusion of approximately 60 minutes (European Medicines Agency 2020, AveXis 2019). Before administration of Zolgensma, baseline laboratory testing is required, including AAV9 antibody testing using an appropriately validated assay (provided free of charge from Novartis Gene Therapies), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, platelet count, and troponin-I.

5.4 Comparator- Spinraza

Spinraza is an SMN2-directed antisense oligonucleotide for the treatment of SMA and has demonstrated an improvement in some clinical outcomes versus BSC, but only temporarily increases SMN protein expression and therefore requires repeated and chronic intrathecal administration, indicated for treatment of patients with 5q SMA (European Medicines Agency 2017, Finkel 2017).

In 2017, DMC issued recommendations for Spinraza for an SMA diagnosis genetically verified with a SMN1 mutation and at least 2 copies of the SMN2 gene in patients with SMA type 1 and type 2, and type 3; for type 3, the onset of symptoms must be before the age of 3 years (Danish Medicines Council 2017). There are currently 206 patients with SMA being treated with Spinraza in Denmark (6 SMA type 1, 100 SMA type 2, and 100 SMA type 3 patients) (Danish Medicines Council 2020a). In 2020 the DMC issued a restricted reimbursement to avoid treating patients with SMA type 2 or 3 above the age of 6 (Danish Medicines Council 2020b).

Treatment with Spinraza is given in addition to best supportive care and is administered through intrathecal use by lumbar puncture. The recommended dosage is 12 mg per administration in 4 loading doses (on Days 0, 14, 28 and 63), followed by a maintenance dose administered once every 4 months thereafter (Electronic Medicines Compendium (eMC) 2019). Patients receive six injections in the first year and three injections in subsequent years.

5.5 Perspective

The model adopts a restricted societal perspective in line with the DMC's guidelines (Danish Medicines Council 2020c).

5.5.1 Time horizon

In the base-case, a lifetime horizon was considered in order to comprehensively capture the expected costs and health outcomes of patients over their remaining lifetime from the initiation of the treatment. SMA type 1 is a progressive, lifelong, life-limiting disease and patients will continue to need management and/or treatment for the whole of their lives. Considering the potentially great survival gains associated with effective treatment, anything shorter than a lifetime time horizon would underestimate the value of treatment. The cost analysis allows patients to live up to 100 years.

5.6 Discounting and model cycles

5.6.1 Discount rate

The discount rate applied in the analysis are in accordance with guidelines from the DMC and is four percent for the first 35 years (Finansministeriet 2020). Beyond this, the discount rate is three percent. No discounting is applied during the first year, in line with guidelines (AMGROS 2018).

5.6.2 Model cycle length

The Markov state model structure relies upon the events, costs and health outcomes occurring in discrete cycles. A cycle length of 6 months was used during the patients' first 3 years of life, to accurately capture milestone achievements and transitions between different health states. Beyond the first 3 years of life, a 12-month cycle length was used. The model also contain cycle 0, which is only one day long at the start of treatment. Cycle 0 is used for two reasons: 1) to ensure that the first treatment administration is not subject to discounting, and 2) to apply half cycle discontinuation (see below).

5.6.3 Half cycle correction

As a standard methodology, half-cycle correction (HCC) is used to adjust for the necessary assumptions in a Markov model that events occur at the start or end of the cycle which leads to bias (overestimation or underestimation, respectively) (Gray 2010). In this model, patient transitions occur at the end of each cycle and thus costs are estimated based on the proportion of patients in each health state at the end of the cycle. This results in a general underestimation of costs, which we address by applying half-cycle correction.

Due to the structure of the Markov model, the model does not account for treatment costs for patients that occur during a cycle, unless the patient remains in this state by the end of the cycle. Thus, a patient who dies during a cycle may have incurred costs before this occurred. Since we cannot know when during the cycle the patient died, the expected cost that is unaccounted for within this cycle is half that of a full cycle's cost. As more and more patients die, the sum of the costs unaccounted for in any cycle will hence approach half a full cycle's cost. To offset this underestimation, this model applies half cycle correction within cycle 0; i.e. the cycle when all patients are alive. This approach has been described in Section 9.2.1 in Gray (2010).

It should be noted that different cycle lengths are used within this model; cycle 0 is only one day long, cycles 1-6 are 6 months long, and cycles 7 and onwards are 12 months long. For half cycle correction, costs for a 12-month cycle are applied to cycle 0, as most model cycles are of this length.

5.7 Health states

The model health states differ based on the motor function milestones achieved by the patient, the need for permanent assisted ventilation, and time to death. The model includes two health states that reflect the natural history of SMA type 1: D state (not sitting) and E-state (permanent assisted ventilation). Three higher functioning health states are possible for patients in the pharmacotherapy-treated arms: C state (sits independently), B state (walks unassisted), and A state (within a broad range of normal development). An overview of the health states is presented in Table 1. Whilst the health states are broadly defined by the motor function milestone achieved, each health state also captures the likely associated symptoms and complications of SMA.

TABLE 1: FUNCTIONAL STATUS ACROSS HEALTH STATES

State	Motor features	Additional features
A	Within a broad range of normal development	• Within a broad range of normal development
B	Walks unassisted	• No breathing difficulties • Number and severity of chest infections similar to a typically developing child of the same age • Does not require a feeding tube – few difficulties swallowing, is able to eat and, for instance, swallow water • Talking ability similar to that of a typically developing child of the same age
C	Sits independently	• May have breathing problems and sometimes require NIV • Development of chest infections more frequently than a typically developing child of the same age • Some difficulties with eating and swallowing but able to swallow thin liquids and take some food by mouth • Risk of choking • Temporary placement of a gastric tube may be required • Requires help moving • Can talk, but ability to speak will deteriorate over time
D	Not sitting	• Experiences breathing problems and requires regular NIV for several hours every night or during the day • Development of chest infections more frequently than a typically developing child of the same age • Difficulties feeding and swallowing • High risk of choking • Only able to swallow thick fluids • Fed by a feeding tube (gastrostomy) surgically placed directly into the stomach • Requires moving regularly to prevent sores • Unable to talk, but can make sounds and cry
E	Permanent assisted ventilation	• Require 16+ hours daily of non-invasive ventilation • May require a tracheostomy if NIV is not working well • Require gastrostomy to be surgically placed directly into the stomach due to difficulty feeding and swallowing • High risk of choking • Require moving regularly to prevent sores • Develop chest infections more often than healthy children of the same age • Unable to talk, but can make sounds and cry

Abbreviations: NIV, non-invasive ventilation.

5.8 Transitions

The model consists of two parts: 1) a short-term model concordant with observed clinical trial data, and 2) a long-term extrapolation model. Observed clinical outcomes are captured in the model by moving treated patients into higher functioning health states; higher functioning health states are associated with longer survival, and lower health care costs. Patients can only be in one state at a time (mutually exclusive) and all patients must be captured in a state (collectively exhaustive).

At model baseline, all patients are in the D state (not sitting). At the end of each model cycle (every 6 months for the first 3 years, then every cycle is 1 year long), patients can transition into another health state or stay in the same health state. Patients transition to higher health states when they attain motor milestones (sits independently or walks unassisted). A 6-monthly model cycle was chosen for the first three years to allow changes in childhood development and milestone achievement to be adequately captured. After the first year of life, the model resumes a 12-month cycle length.

It is not possible to reach health state A (broadly within normal development) within the model's first 10 cycles (5 years). However, children who were observed walking unassisted (B state) before 2 years of age during START and STR1VE-US are transitioned to the A state (within a broad range of normal development) at 5 years of age. Walking independently by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children (World Health Organization 2006a).

Transition to the E state (permanent assisted ventilation) in the model was only possible for patients who did not attain any motor function milestones (i.e. those in the D state [not sitting]). For D-state patients, both overall survival and permanent ventilation-free survival (described as event-free survival) were modelled. Patients who achieved motor function milestones (sits independently, walks unassisted or within broad range of normal development) were not considered to be at risk of transitioning to permanent assisted ventilation, although transition to 'death' was possible from any health state.

In the base case analysis, it is assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e. patients stay in the same motor function milestone-based health state at the end of the short-term model until death). Backwards transitions, i.e. regression from higher functioning health states to worse functioning health states are only applicable for patients that discontinue Spinraza (discontinuation does not apply to Zolgensma as it requires a one-time, single IV administration).

A technical consideration when pooling the data from the START and STR1VE-US trials for use in the cost analysis is the difference in follow-up periods of each respective trial. START followed patients to 24 months post-dose (approximately 30 months of age), whereas STR1VE-US captured outcome data only up to 18 months of age. Due to the relatively short follow-up period of STR1VE-US (up to 18 months of age), it is possible that patients would have reached additional milestones beyond the trial follow-up. For this reason, the economic model includes the possibility for the user to add additional milestone achievements within STR1VE-US beyond 30 months of age. However, for the base case, no additional such milestone achievements have been assumed.

5.9 Justification of the model structure

The model framework was conceptualised with clinical experts, both from the UK and from the Nordics, drawing on frameworks developed for other SMA pharmacotherapies and models for similar rare genetic neuromuscular disorders, such as Duchenne's muscular dystrophy. In addition, using a five functioning health state model framework (from permanent assisted ventilation [E state] to within a broad range of normal development [A state]) that applies a short-term (observed data) and a long-term (extrapolation) modelling period, the developed model is broadly aligned to the model structure chosen by the US ICER, who recently published an assessment of SMA therapies (US Institute for Clinical and Economic Review 2019).

Prior to the development of disease-modifying therapies for SMA type 1, patients would never achieve motor milestones, such as sitting unassisted, and would experience rapid, progressive deterioration and death without permanent assisted ventilation, typically by the age of 2 years. With the development of innovative therapies, infants and children with SMA type 1 now have the potential to attain motor milestones with improved functionality and survival. The cost-analysis consequently considers these outcomes by including health states aligned with motor milestone development.

The cost-analysis model structure captures the main drivers of costs with SMA type 1 to ensure that the natural history modelled accurately. In addition, the model uses SMA type 2 and SMA type 3 populations managed with BSC alone as proxies for SMA type 1 pharmacotherapy-treated patients' resource utilisation, survival and outcomes in higher functioning health states (C state [sits independently] and B state [walks unassisted]), as under BSC, SMA type 1 patients would never reach such health states.

5.10 Foundational model assumptions

The cost-analysis is underpinned by three foundational assumptions:

Zolgensma will have a lifelong duration of effect

The missing/dysfunctional SMN1 gene is replaced and normal gene biology is restored, which results in long-term motor neuron survival for innervation and the development of functioning neuromuscular junctions and skeletal muscles.

Justification: The results of LT-001 to date indicate that a one-time IV administration of Zolgensma at the therapeutic dose provides prolonged efficacy for durations longer than 5 years (up to 61.9 months) post gene therapy administration (AveXis 2020b). In addition, the mechanism of action of Zolgensma results in the delivery of a stable, functioning SMN gene that remains in non-mitotic cells indefinitely and enables continuous and sustained SMN protein expression, eliminating the need for repeat administration of Zolgensma. Evidence

from animal models also support the prolonged duration of effect of Zolgensma (Foust 2010, Meyer 2015).

Survival is improved in correlation with motor function milestone achievement, and life expectancy can be estimated using proxies

The model uses long-term survival data (observed and extrapolated) for SMA patients treated with BSC alone who sit unassisted (SMA type 2 used as proxy) and walk unassisted (SMA type 3 used as proxy) to predict survival for pharmacotherapy treated SMA type 1 patients who achieve motor milestones.

Justification: The use of proxy long-term survival data in the model was the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of Zolgensma and Spinraza for SMA (Institute for Clinical and Economic Review 2019) and was considered appropriate by participants in the UK clinical advisory board (AveXis 2019a).

Costs for each motor milestone group can be estimated using proxies

The model base case uses HCRU costs for SMA patients receiving BSC only who sit unassisted (SMA type 2 used as proxy) and walk unassisted (SMA type 3 used as proxy) to predict the costs and utilities of pharmacotherapy treated SMA type 1 patients who achieve motor milestones.

Justification: The use of costs and utilities based upon proxies was the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of Zolgensma and Spinraza for SMA (Institute for Clinical and Economic Review 2019) and was considered appropriate by participants in the UK clinical advisory board (AveXis 2019a).

5.11 Clinical parameters and variables

5.11.1 Milestone achievements

Zolgensma

The milestone achievements for Zolgensma is based upon pooled data from START (cohort 2, 12 patients) and STR1VE-US (22 patients); hereinafter referred to as the 'POOLED' dataset. The POOLED dataset has been estimated by summing up the number of patients attaining a milestone in the same cycle from each trial. Data from the trials were pooled to facilitate comparison to Spinraza. It also supports health economic modelling, where only 4 outcomes were important: overall survival (OS), event-free survival (EFS), and the shares of patients achieving the "sitting independently" and "walking independently" milestones.

All milestones achievements have been implemented in the following model cycle, hence the data in the model is offset by one cycle. As a result of using this 'offset' approach when incorporating motor milestones from the POOLED dataset into the model, it is appropriate

for the short-term model time horizon for motor milestone attainment to be up to cycle 6 (up to 36 months of age), i.e. 6 months longer than the observed data in START (up to 30 months of age) and STR1VE-US (up to 18 months of age). This approach can be seen as conservative because milestone attainment is being modelled as occurring at a later age than was observed in both trials. Whilst an analysis with cut-off at 18 months of age is also available for START patients (see "Clinical Evidence Report for Zolgensma (v1.0) 16-SEP-2020" (AveXis 2020c)), in the economic model – which spans over a life-time – it was not found appropriate to disregard milestone attainment post 18 months of age.

The milestone achievement for Zolgensma is shown in Table 2 (START), Table 3 (STR1VE-US), and Table 4 (POOLED). The definition used for 'sitting unassisted' when incorporating milestones from STR1VE-US into the POOLED base case analysis is 'sitting unassisted for ≥30 seconds in accordance with the criteria of item 26 on the Bayley-III assessment tool gross motor subtest'. This outcome was chosen as it is the co-primary endpoint of STR1VE-US and this outcome was one of the milestones confirmed through video review by an external reviewer.

The definition used for 'sitting unassisted' when incorporating milestones from START into the POOLED base case analysis is 'sitting unassisted for ≥5 seconds in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest'. This outcome was chosen as attainment was confirmed through video review by an external reviewer(see Table 32 in the updated version of "Clinical Evidence Report for Zolgensma (v1.0) 16-SEP-2020" (AveXis 2020c)).

The base case is based upon study data only, with no additional sitters or walkers. However, since patients achieved milestones beyond 18 months of follow-up in START, it seems likely that some patients in STR1VE-US would sit and/or walk independently beyond 18 months of age if more mature data was available. For this reason, several scenarios are presented where additional patients achieve independent sitting and/or walking in STR1VE-US, beyond 18 months of age. More details about these scenarios are presented in Section 5.13.3.

Table 2: Milestone achievement, START (cohort 2, n=12)

Cycle	Age at end of cycle (mo.)	Not sitting	Sitting but not walking	Walking	Dead or PAV
1	6	12	0	0	0
2	12	12	0	0	0
3	18	10	2	0	0
4	24	6	6	0	0
5	30	3	7	2	0
6	36	1	9	2	0
7	48	1	9	2	0
8	60	1	9	2	0

Table 3: Milestone achievement, STR1VE-US (n=22)

Cycle	Age at end of cycle (mo.)	Not sitting	Sitting but not walking	Walking	Dead or PAV
1	6	22	0	0	0
2	12	20	0	0	2
3	18	14	6	0	2
4	24	7	12	1	2
5	30	6	13	1	2
6	36	6	13	1	2
7	48	6	13	1	2
8	60	6	13	1	2

Table 4: Milestone achievement, POOLED dataset (pooled data from START and STR1VE-US)

Cycle	Age at end of cycle (mo.)	Not sitting	Sitting but not walking	Walking	Dead or PAV
1	6	34	0	0	0
2	12	32	0	0	2
3	18	24	8	0	2
4	24	13	18	1	2
5	30	9	20	3	2
6	36	7	22	3	2
7	48	7	22	3	2
8	60	7	22	3	2

Spinraza

The data on proportions of Spinraza patients achieving motor function milestones at different time points were based on observed data from ENDEAR. However, this study included many patients with long duration between the detection of the disease and the start of treatment.

Since it has been noted that that the clinical efficacy differs for patients with disease duration <12 weeks compared to >12 weeks (Danish Medicines Council 2020) a pre-specified subgroup of relevance was identified in the primary publication of ENDEAR, which included patients with a disease duration at screening equal to or below twelve weeks (≤12 weeks) (Finkel 2017). The baseline characteristics of this subgroup is also more comparable to the clinical evidence available from the clinical trials of Zolgensma.

The ENDEAR subgroup comprised a total of 52 children (Spinraza n = 34 versus sham treatment n = 18). The results for this pre-specified subgroup of ENDEAR has previously been reported (IQWiG 2020). Data on relevant motor milestones (sitting and walking) was available for 32 participants. Out of these, 16 participants (50%) were sitting, but no one was walking. In the report, it is not mentioned at what timepoint the measurement of sitting was done. We have assumed that the 16/32 figure is drawn from the last study visit at the timepoint when the ENDEAR trial was terminated, i.e. when approximately 80 participants had passed the 183 day visit. Follow-up time was estimated from Figure S3A in the online supplement (Finkel 2017), in which individual patients are listed together with disease duration ≤12 weeks at baseline and last study visit. According to this graph, last study visit was the 183 day visit for three of the infants in the ENDEAR subgroup, and the 394 day visit for 12 of the infants. For the remaining infants, last study visit was in the range 197 – 350. Mean follow-up time for the ENDEAR subgroup was 307 days. Assigning the "sitting independently" milestone already by day 183 for any patients who reach it before the last study visit is a generous assumption towards Spinraza treatment. However, in the absence of exact data on the timing of this milestone achievement, this assumption was made to not underestimate the clinical effect of the comparator.

In the absence of later follow-up, it was assumed that the milestone achievements could be extrapolated until 36 months of age (the end of the 6th cycle in the model). The milestones were recorded using the HINE-2 definitions which makes exact comparisons to treatment with Zolgensma difficult. However, in the absence of more reliable data sources, this data was chosen for the milestone achievements in the model. (Castro 2020, Finkel RS 2020, Mercuri E et al 2020). More details about the different measurements and definitions of 'sitting' is found in Section 5.1.3.6 of the updated version of "Clinical Evidence Report for Zolgensma (v1.0) 16-SEP-2020" (AveXis 2020c).

The proportions of patients in each motor function milestone health state at each time point is presented in Table 5. An underlying assumption is that patients who continue Spinraza treatment do not lose milestones gained. As per the description provided for how observed milestone data from START and STR1VE-US are 'offset' by a model cycle when calculating transition probabilities, the same approach is taken when calculating transition probabilities from observed milestone data from ENDEAR subgroup in the model.

Table 5: Calculated proportions of patients achieving motor milestones on Spinraza, base case

Cycle	Visit (Day)	Approx. age at end of cycle (mo.) ‡	Not sitting	Sitting but not walking	Walking
			%	%	%
1	1	6	100%	0%	0%
2	183	12	50%	50%	0%
3	394	18	50%	50%	0%
4	548	24	50%	50%	0%
5	730	30	50%	50%§	0%
6	913	36	50%	50%§	0%

‡ Based on a mean age at first dose of 5.4 months.
§ In the absence of later follow-up for the ENDEAR subgroup treated <=12 weeks of disease duration at screening, it was assumed that the milestone achievements at day 183 could be extrapolated until 36 months of age (the end of the 6th cycle in the model).
Source: IQWiG report (IQWiG 2020)

5.11.2 Transition probabilities

Transition probabilities between health states were based on the proportion of patients sitting or walking unassisted. The probability of transitioning to a higher functional health state was calculated using the number of patients who achieved new motor milestones before the start of each cycle as the numerator and the number of patients in the outgoing state in the previous cycle as the denominator. The transitional probabilities for Zolgensma treatment are shown in Table 6 and the transitional probabilities for Spinraza in Table 7.

Table 6: Transitional probabilities for milestone achievement of alive/event free patients, Zolgensma

Cycle	Age at end of cycle (mo.)	D to C	C to B	B to A †
1	6	0,0%	0,0%	0,0%
2	12	0,0%	0,0%	0,0%
3	18	25,0%	0,0%	0,0%
4	24	45,8%	12,5%	0,0%
5	30	30,8%	11,1%	0,0%
6	36	22,2%	0,0%	0,0%
7	48	0,0%	0,0%	0,0%
8	60	0,0%	0,0%	0,0%
9	72	0,0%	0,0%	100,0% ‡

Milestones gained during a cycle is accounted for in the next full cycle, i.e. calculations are 'offset' so that patients transition in the following cycle.
† In the base case scenario, health states A and B are assumed to be identical
‡ Patients achieving independent walking are assumed to transition to health state A during cycle 9

Table 7: Transitional probabilities for milestone achievement of alive/event free patients, Spinraza

Cycle	Age at end of cycle (mo.)	D to C	C to B	B to A †
1	6	0,0%	0,0%	0,0%
2	12	0,0%	0,0%	0,0%

3	18	50,0%	0,0%	0,0%
4	24	0,0%	0,0%	0,0%
5	30	0,0%	0,0%	0,0%
6	36	0,0%	0,0%	0,0%
7	48	0,0%	0,0%	0,0%
8	60	0,0%	3,8%	0,0%

Milestones gained during a cycle is accounted for in the next full cycle, i.e. calculations are 'offset' so that patients transition in the following cycle.
† In the base case scenario, health states A and B are assumed to be identical

The model accounts for milestones gained during a cycle in the next full cycle, i.e. calculations are "offset" so that patients are transitioned in the following cycle. This is a conservative approach when assigning motor milestones to cycles. For example, if a patient achieved a motor milestone at age 19 months, that patient only appears as having achieved the milestone for the cycle beginning age 24 months.

5.11.3 Motor function milestone loss

Zolgensma

Zolgensma patients do not regress (i.e., lose milestones) in the base case, as per the observed data from START and STR1VE-US. To date, there has been no loss of previously attained milestones for patients who received the therapeutic dose of Zolgensma in START as part of LT-001 (long-term follow-up of START), in which the oldest patient is 5.6 years at the latest data cut (31 December 2019). On the contrary, two patients in LT-001 attained the new video-confirmed milestone of standing with assistance in LT-001 (European Medicines Agency EPAR 2020). Furthermore, there is no evidence of the loss of milestones in interim analysis from other ongoing Phase III trials for Zolgensma.

Spinraza

Duration of effect continues while patients remain on treatment with Spinraza and motor function milestones achieved in ENDEAR subgroup (day 183) are sustained until death. Patients only regress (i.e., lose milestones) if they discontinue Spinraza. Spinraza is a chronic therapy with a cerebrospinal fluid (CSF) half-life of around four to six months; therefore, treatment effect is no longer maintained after cessation of therapy. It is assumed the annual probability of regression through the health states is 90% for patients that discontinue Spinraza. This 90% regression rate is based on compound motor action potential amplitude (CMAP) and motor unit number estimation (MUNE) values from untreated (i.e. who have not received pharmacotherapy) SMA type 1 patients (Swoboda 2005).

All patients discontinue Spinraza in the E state (permanent assisted ventilation). For patients in the D state and C state there is an annual risk of withdrawal . The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer Spinraza by intrathecal

administration because of spinal fusion surgery or a worsening in motor function. The rate of annual risk of discontinuation in D state and C state is modelled as 3%; for the first six model cycles, where the cycle length is six instead of 12 months, the probability has been modified to keep the same rate as for the annual discontinuation. This rate is obtained from data reported in ENDEAR (Finkel 2017) (i.e., 3% of the cohort were reported as achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the Spinraza UK/Ireland EAP (National Institute for Health and Care Excellence 2019).

5.11.4 Survival

Survival in each health state is based on observed data and extrapolated survival curves from clinical trials and natural history studies. The sources for survival data for each health state and by treatment arm are described in Table 8 for the base case.

TABLE 8: SOURCES OF SURVIVAL DATA – BASE CASE ASSUMPTIONS

Transition	Zolgensma	Spinraza
D to death	**Short-term model, observed data** Ages 0–36 months: POOLED data from START and STR1VE-US (Mendell 2017, Avexis 2018, AveXis 2020) **Long-term model, extrapolated data** Ages 36+ months: projected survival using parametric curves fitted to natural history data (NeuroNext†)	**Short-term model, observed data** Ages 0–36 months: ENDEAR trial subgroup analysis (IQWiG 2019) **Long-term model, extrapolated data** Ages 36+ months: projected survival using parametric curves fitted to natural history data (NeuroNext†)
D to E	**Short-term model, observed data** Ages 0–36 months: POOLED data from START and STR1VE-US (Mendell 2017, Avexis 2018, AveXis 2020) **Long-term model, extrapolated data** Ages 36+ months: projected permanent ventilation-free survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–36 months: ENDEAR trial subgroup analysis (IQWiG 2019) **Long-term model, extrapolated data** Ages 36+ months: projected permanent ventilation-free survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)
E to death	**Short-term and long-term model:** E state patients requiring PAV are assumed to have long-term survival consistent with an observational study of SMA type 1 patients with tracheostomy or NIV (defined in the study as continuous NRA, including non-invasive ventilation and mechanically assisted cough) published by Gregoretti et al. 2013 (Gregoretti 2013).	
C to death	**Short-term and long-term model:** The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective study of SMA type 2 patients, as reported by Zerres et al. 1997 (Zerres 1997). The parametric function fitted to the observed data is used for the entire model time horizon, except in the first five model cycles (up to 30 months of age), when 100% survival has been modelled	**Short-term and long-term model:** The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective study of SMA type 2 patients, as reported by Zerres et al. 1997 (Zerres 1997). The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the study
B/A to death	In the first five model cycles (up to 30 months of age), 100% survival has been modelled based upon trial data. From cycle 6,the survival for SMA type 1 patients that can walk unassisted is modelled based on general population survival from the 2020 National Life tables for Denmark (Statistics Denmark 2020)	The survival for SMA type 1 patients that can walk unassisted is modelled based on general population survival from the 2020 National Life tables for Denmark(Statistics Denmark 2020).

Abbreviations: N/A, not applicable; NIV, non-invasive ventilation; NRA, non-invasive respiratory muscle aid; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.
† NeuroNext cohort as reported in AveXis external control database (n=16 patients with *SMN2* copy x 2) is selected as the data source for BSC in the base case (AveXis 2018)

Zolgensma

In the short-term model for patients in the Zolgensma arm, the observed post-dose data from START and STR1VE-US were used directly in the D state (modelled as up to 36 months of age). As STR1VE-US patients only provide survival data up to 18 months of age, they are censored from survival curves in the short-term model from 18 months to 36 months of age. Of the pooled N=34 patients from START and STR1VE-US, one patient died, and one patient met the

permanent assisted ventilation event endpoint. In the long-term model (i.e. cycle 6 onwards), the parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period for the Zolgensma arm in the D state. More details about survival extrapolations for each health state is provided in section 5.11.5 (and in section14.1 Appendix A).

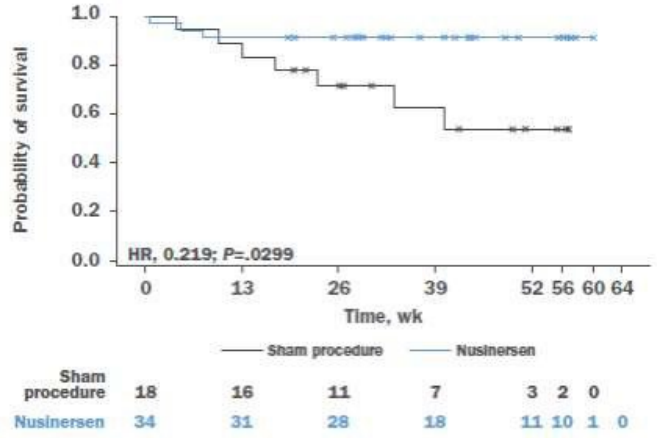
Spinraza

In the short-term model for patients in the Spinraza arm, the exact overall and event-free survival in the subgroup analysis of ENDEAR was not available. However, a graphical representation of these had been made available as part of the NICE committee papers for the HTA appraisal of Spinraza in the UK (National Institute for Health and Care Excellence 2018). In order to utilise the subgroup OS and EFS data, the Kaplan Meier graphs were imported using the method explained below (Figure 2 and Figure 3) .

Figure 2 and Figure 3 were loaded as images within a web-based digitisation software. After tracing over the graphs, the software produced co-ordinates for both OS and EFS data which were then imported into RStudio to finalise the digitisation process. RStudio code was run and produced two separate CSV files containing the digitised data. However, as there was a lack of empirical data for OS/EFS for the period of ~20 months age (14 months ENDEAR follow-up) to 36 months of age for the subgroup, extrapolation had to be made for the remaining time. A parametric distribution was fitted based upon the recorded data, however, given the short time for which data was available it was eventually determined that the preferred approach would be to just utilize the Kaplan-Maier data and assumed that the last observation could be carried forward to month 36. More details about survival extrapolations for each health state is provided in section 5.11.5 (and in section14.1 Appendix A).

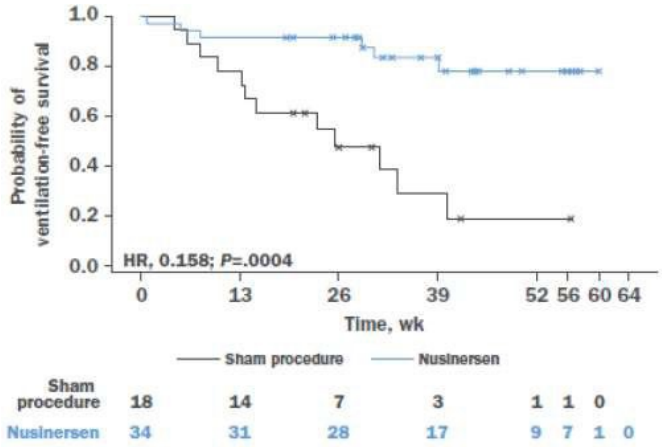
Note that since START and STR1VE-US were single-arm trials, direct comparisons made to Spinraza in the model are unanchored, naïve comparisons and no adjustment has been made for differences (known or unknown) in trial populations or settings. Therefore, caution is required in any interpretation of results.

FIGURE 2: OVERALL SURVIVAL OF PATIENTS WITH DISEASE DURATION ≤12 WEEKS AT SCREENING IN ENDEAR



Abbreviations: HR, Hazard ratio, wk, weeks.
Source: NICE committee papers (National Institute for Health and Care Excellence 2018)

FIGURE 3: EVENT-FREE SURVIVAL FOR PATIENTS WITH DISEASE DURATION ≤12 WEEKS AT SCREENING IN ENDEAR



Abbreviations: HR, Hazard ratio, wk, weeks.
Source: NICE committee papers (National Institute for Health and Care Excellence 2018)

5.11.5 Survival extrapolation

For all survival data, parametric survival curves were fitted to the empirical data to extrapolate survival and calculate transition probabilities using published methods (Diaby 2014). All reconstructions of individual patient data and fitting of parametric curves were conducted using the R software package ‘flexsurv’ procedure (details of R code used can be found in the 'Survival_R_Code' tab of the executable model) using published methods (Tierney 2007, Hoyle 2011).

Selection of models for survival modelling was informed by NICE decision support unit (DSU) (National Institute for Health and Care Excellence Decision Support Unit (NICE DSU)) and technical review by an independent academic group as part the development of this model(AveXis 2019b). Goodness-of-fit was assessed by the following methods:

- Statistically via Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Visual inspection

Parametric curves fitted to the survival data included exponential, log-normal, log-logistic, Weibull, generalized gamma, and Gompertz curves. The parametric models with the lowest AIC and BIC were used for all parametric curves but for OS and EFS curves in the D state. All curves were accelerated failure time curves. Following guidance in NICE DSU 14 (National Institute for Health and Care Excellence Decision Support Unit (NICE DSU)), the same types of parametric models were used for Zolgensma and Spinraza within a health state, i.e. generalised Gamma distributions were used for C state OS in both the Spinraza and Zolgensma arms. To avoid long curve tails leading to clinically implausible survival, curves were terminated based on observed life expectancy, input from clinical expert opinion, or based on feedback from an independent assessment review for this model (AveXis 2019b). The specific parametric models used in the base case model are shown in Table 9.

TABLE 9: SUMMARY OF SURVIVAL CURVES USED FOR THE TRIAL PERIODS AND BEYOND (BASE CASE)

Survival curve	Model used for trial period	Model used beyond trial period
State E – Non-invasive ventilation	Exponential	Exponential
State E - Tracheostomy	Gompertz	Gompertz
State D – BSC OS	Kaplan-Meier (Empirical)	Weibull
State D – BSC EFS	Kaplan-Meier (Empirical)	Weibull
State D – Spinraza OS	Kaplan-Meier (Empirical)	Weibull†
State D – Spinraza EFS	Kaplan-Meier (Empirical)	Weibull†
State D – Zolgensma OS	Kaplan-Meier (Empirical)	Weibull†
State D – Zolgensma EFS	Kaplan-Meier (Empirical)	Weibull†
State C – Spinraza OS	Generalised Gamma	Generalised Gamma
State C – Zolgensma OS	Generalised Gamma	Generalised Gamma
State B – Spinraza OS	Danish Life Tables	Danish Life Tables
State B – Zolgensma OS	Danish Life Tables	Danish Life Tables
State A – Spinraza OS	Danish Life Tables	Danish Life Tables
State A – Zolgensma OS	Danish Life Tables	Danish Life Tables

Abbreviations: EFS, event-free survival; OS, overall survival.
† Uses aggregated and disaggregated curves from natural history trial (NeuroNext) beyond the trial period

E-state (permanent assisted ventilation) – All arms

For the model base case analysis, E-state patients requiring permanent assisted ventilation are assumed to have long-term survival consistent with an observational study of SMA type

1 patients in Italy (Gregoretti 2013). Because there are no data suggesting that patients who receive disease-modifying treatment experience improved survival after experiencing respiratory insufficiency, it was assumed that all patients in the E state would experience the same survival function with no adjustment by treatment arm.

In Gregoretti et al. 2013 (Gregoretti 2013) patients were treated with tracheostomy (n = 42) or non-invasive ventilation (n=31, defined as continuous non-invasive respiratory muscle aid [NRA], including non-invasive ventilation and mechanically assisted cough is the study). However, due to large between-country differences in the prevalence of tracheostomy treatments, patients with tracheostomy and NIV were analysed as separate treatment arms, so pooling of the data was required. For pooling, the individual patient data (IPD) for the tracheostomy and NIV arms of the study were each reconstructed using published methods (Tierney 2007, Hoyle 2011) and the dataset from each arm was merged based on the time points. The published study results did not include number at risk so these were estimated using the method described in Tierney et al. 2007 (Tierney 2007). It is noted that in the non-invasive ventilation group, Gregoretti et al 2013 state that seven patients (7/31 [22.6%]) went on to receive tracheostomy, but it is not clear whether these patients are included in the survival estimates in the non-invasive ventilation curve (Gregoretti 2013).

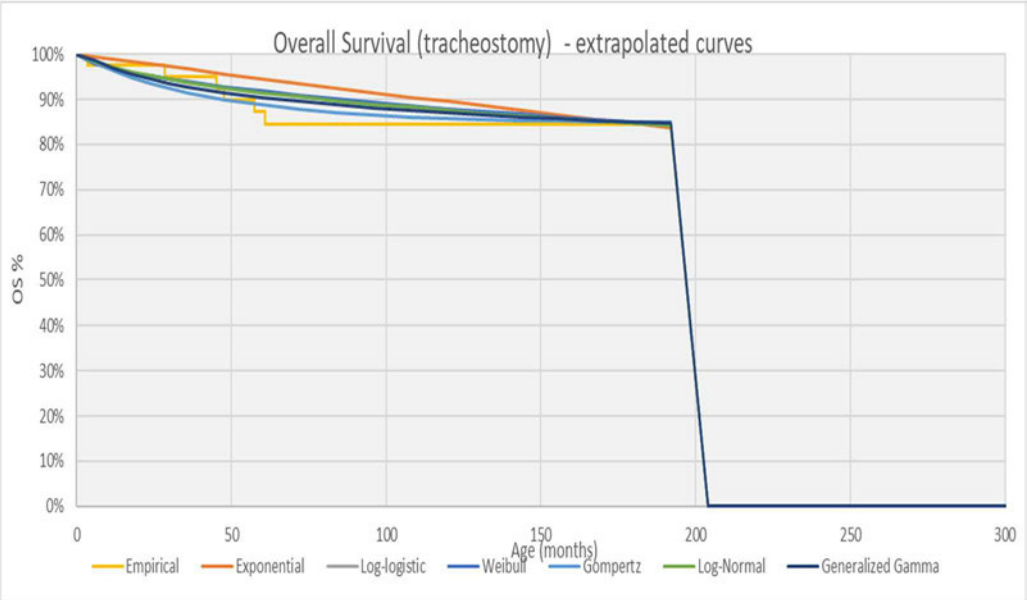
Clinical experts were consulted to estimate the proportion of patients receiving tracheostomy in the Nordics. This was deemed highly uncommon, but assigned a probability of 5% since it could not be ruled out that such treatment may be applicable in individual cases (Eklund 2019, Sejersen 2019, Tulinius 2019). With the exception of tracheostomy prevalence, the inputs and assumptions match those described in the interim ERG report that was commissioned as part of the ongoing NICE appraisal of Zolgensma (Edwards 2020).

The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the observational trial (192 months). This approach is to avoid over-fitting the model to the study population observed in Gregoretti et al. 2013 (Gregoretti 2013) and to ensure that transition probabilities remained relatively constant over time.

The mathematically best fitting curves for state E survival following tracheostomy was the Gompertz curve. However, the pooled curve plateaued and was deemed to be clinically implausible. To maintain clinically plausible results, the fitted curve is truncated at 16 years (the longest available follow-up in the study by Gregoretti et al. (Gregoretti 2013)); using this limit, the fitted curve models the probability of death as 1 by 17 years. For non-invasive ventilation, the best fitting curves were obtained using the Exponential distribution (lowest BIC). The parametric models are visualised in Figure 4 and Figure 5, and the final modelled survival is visualised below in Figure 6. The AIC and BIC values for different distributions

among the two treatment options are shown in Table 10. The curve in Figure 6 is the weighted average of tracheostomy (5%; Gompertz distribution) and non-invasive ventilation (95%, exponential distribution).

FIGURE 4: HEALTH STATE E (TRACHEOSTOMY) – OVERALL SURVIVAL DATA AND PARAMETRIC EXTRAPOLATION



Abbreviations: OS, Overall survival.

FIGURE 5: HEALTH STATE E (NON-INVASIVE VENTILATION) – OVERALL SURVIVAL DATA AND PARAMETRIC EXTRAPOLATION

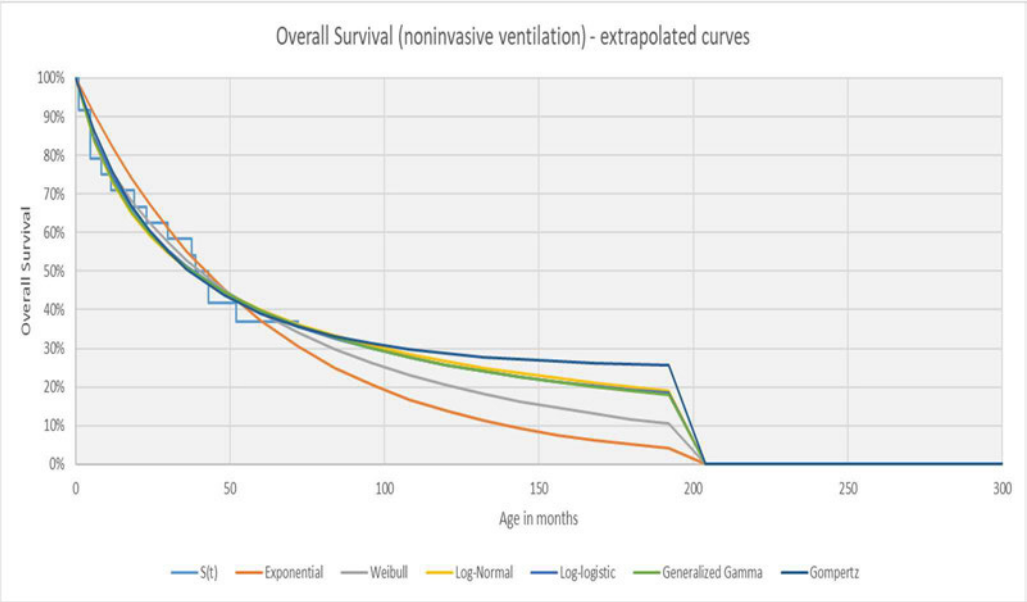


FIGURE 6: MODELLED SURVIVAL FOR HEALTH STATE E

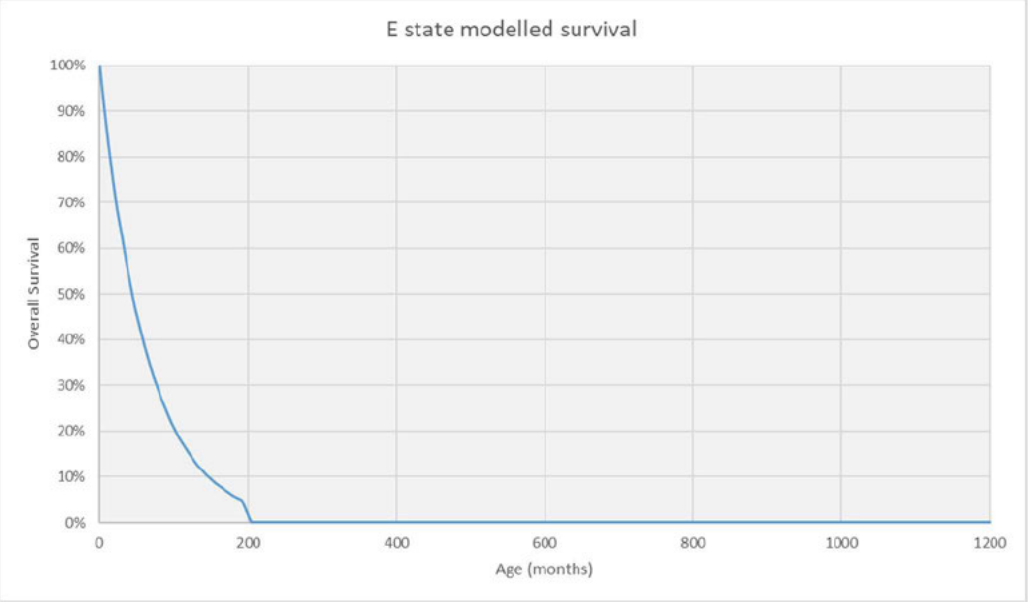


TABLE 10: ASSESSMENT OF CURVE FITS FOR THE E STATE

Parametric model	Tracheostomy		Non-invasive ventilation	
	AIC	BIC	AIC	BIC
Exponential	97.832	99.570	155.088	156.266
Weibull	97.628	101.104	155.399	157.755
Log-Normal	96.835	100.311	154.974	157.330
Log-Logistic	97.446	100.921	155.250	157.606
Generalized Gamma	97.908	103.121	156.960	160.494
Gompertz	94.117	97.593	155.443	157.799

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

As per DMC request, distributions for State C Kaplan-Meier extrapolations have been fitted separately on data before 350 months and on data after 350 months. Please see section 14.1, Appendix A for a complete description.

D state (non-sitting)

For patients in the Zolgensma arm, empirical KM survival data from the START and STR1VE-US trials were used directly for the first six model cycles (up to 36 months of age). As STR1VE-US patients only provide survival data up to 18 months of age, they are censored from survival curves in the short-term model from 18 months to 36 months of age in the POOLED model. For patients in the Spinraza arm, the empirical KM survival data from the ENDEAR subgroup analysis based upon ≤12 weeks disease duration at screening were used directly(National Institute for Health and Care Excellence 2018, page 676 to 677). Data for overall and event-free survival for this subgroup was available for the timepoint when the ENDEAR trial was

terminated, i.e. corresponding to a mean follow-up of 307 days and an approximate mean age of 60 weeks (1.15 years). Given the short time for which data was available it was determined that the preferred approach for both Zolgensma and Spinraza would be to utilize the Kaplan-Maier data and assume that the last observation could be carried forward to the end of the model's 6th cycle (36 months of age).

For the long-term part of the model, extrapolations were generated based on the natural history data for SMA type 1 patients treated with best supportive care only, i.e. no active treatment. This assumption was made in the absence of long-term evidence of continued survival benefit for non-sitting pharmacotherapy treated SMA type 1 patients. After the observed trial periods, patients who remain in the D state (non-sitting) are assumed to follow the natural history . Parametric natural history curves were fitted from the NeuroNext study (Kolb 2017). These extrapolations were then appended to the clinical trial data beyond the trial period. This process was performed separately for both overall survival and event-free survival.

AIC and BIC values for the overall survival curve and the event free survival curve assessed in the D state for BSC are shown below in Table 11 and Table 12. The parametric models are visualized below in Figure 7 and Figure 8.

TABLE 11: ASSESSMENT OF CURVE FITS FOR D STATE OVERALL SURVIVAL: BEST SUPPORTIVE CARE

Parametric model	NeuroNext	
	AIC	BIC
Exponential	68.68	69.45
Weibull	69.83	71.38
Log-Normal	67.29	68.83
Log-Logistic	68.08	69.62
G.Gamma	65.00	67.32
Gompertz	70.68	72.23

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 7: State D overall survival for best supportive care (NeuroNext)

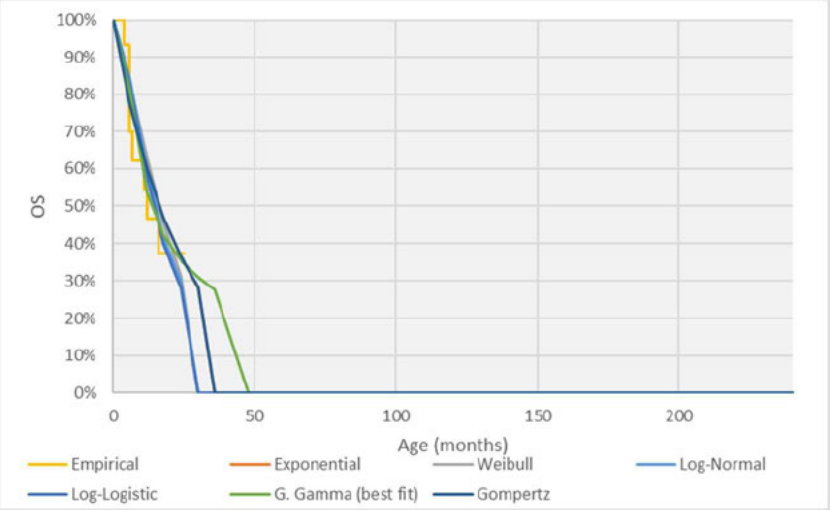
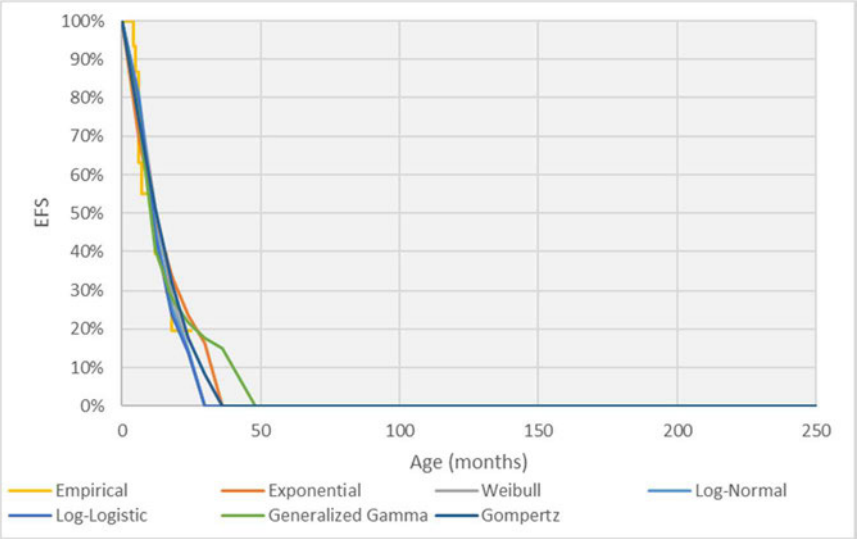


Table 12: Assessment of curve fits for the D state event free survival: best supportive care

Parametric model	NeuroNext	
	AIC	BIC
Exponential	78.19	78.96
Weibull	77.56	79.11
Log-Normal	74.63	76.18
Log-Logistic	75.33	76.87
G.Gamma	72.93	75.25
Gompertz	79.56	81.10

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

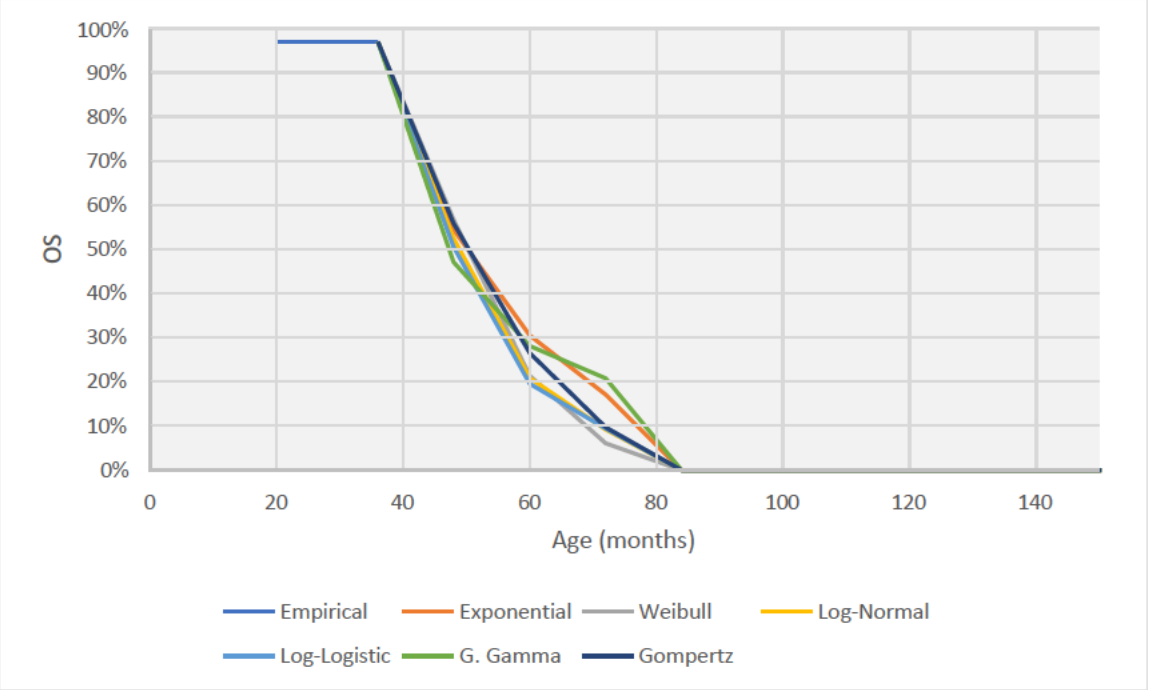
FIGURE 8: STATE D EVENT FREE SURVIVAL FOR BEST SUPPORTIVE CARE (NEURONEXT)



For the survival extrapolation based upon NeuroNext, survival did not extend beyond 4 years of age. An independent academic review (AveXis 2019b) suggested that a 4 year survival limit be applied to the model to prevent unrealistic survival in health state D from becoming a major driver of model results. Since survival extrapolations from NeuroNext was appended to the clinical trial data beyond the trial period for Zolgensma and Spinraza, the observed trial period was added to the 4 year survival limit. In other words, D state survival was capped at 7 years. The same survival limit was applied to both the Zolgensma and Spinraza treatment arms, although the model has the functionality to allow amending the survival limits for each arm individually. The impact on results from increasing the survival limit are explored in scenario analysis.

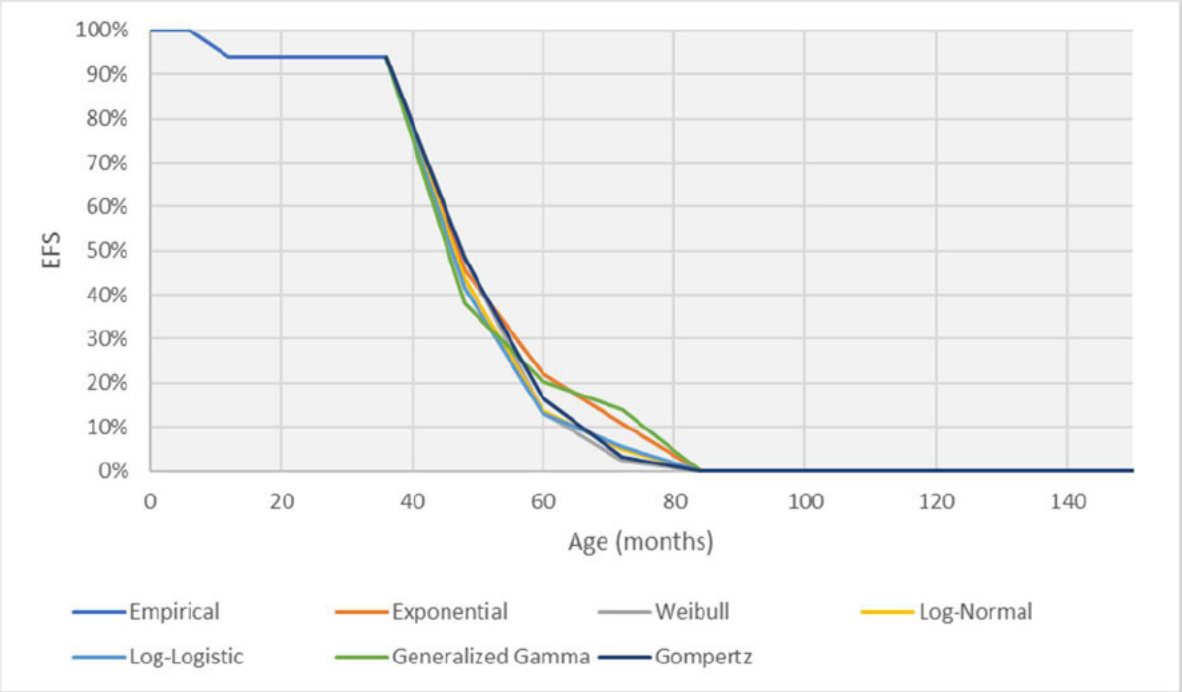
The overall survival and event-free survival curves for Zolgensma are shown below in Figure 9, Figure 10 and Figure 11. The overall survival and event-free survival curves for Spinraza are shown below in Figure 12, Figure 13 and Figure 14.

FIGURE 9: STATE D OVERALL SURVIVAL FOR ZOLGENSMA (KM FOLLOWED BY PARAMETRIC MODELS BASED ON NEURONEXT IN THE BASE CASE)



Abbreviations: OS, Overall survival.

FIGURE 10: STATE D EFS FOR ZOLGENSMA (KM FOLLOWED BY PARAMETRIC MODELS BASED ON NEURONEXT IN THE BASE CASE)



Abbreviations: EFS, Event free survival.

FIGURE 11: STATE D, OVERALL SURVIVAL AND EVENT-FREE SURVIVAL CURVES FOR ZOLGENSMA

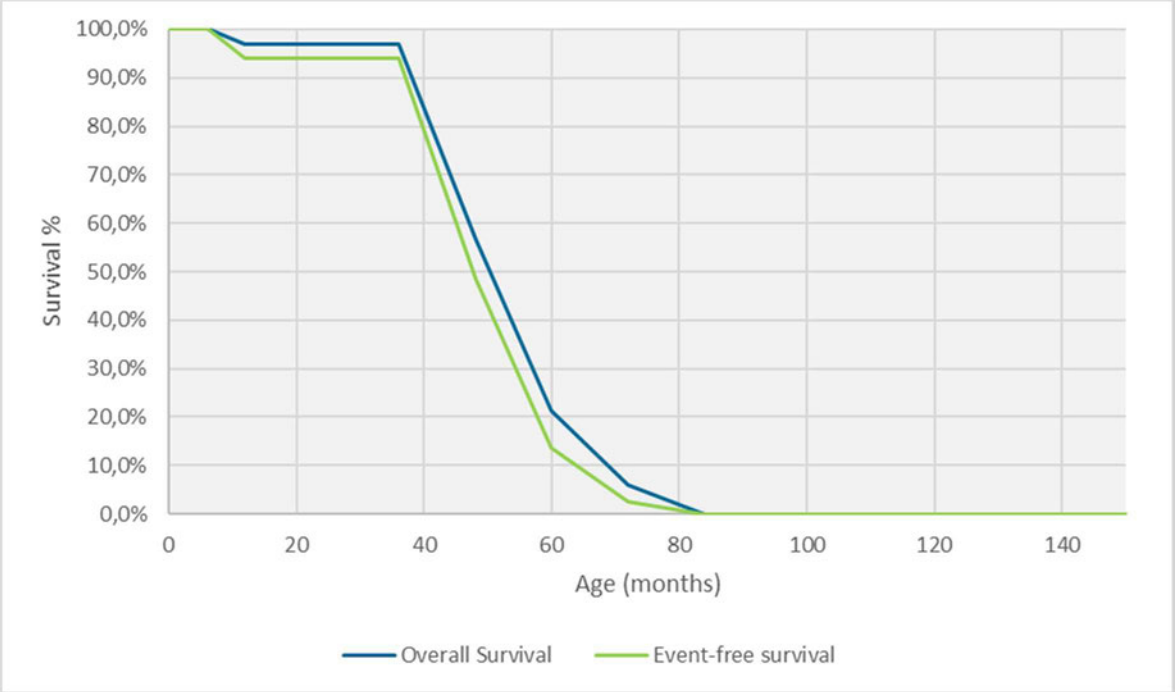
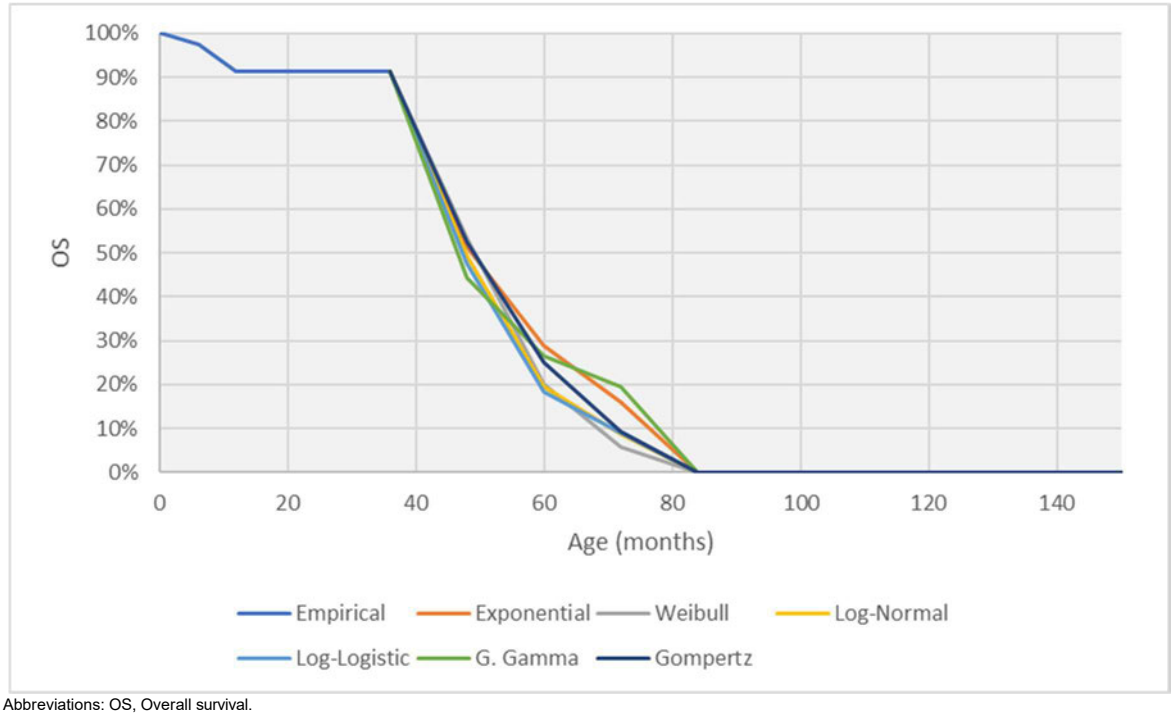
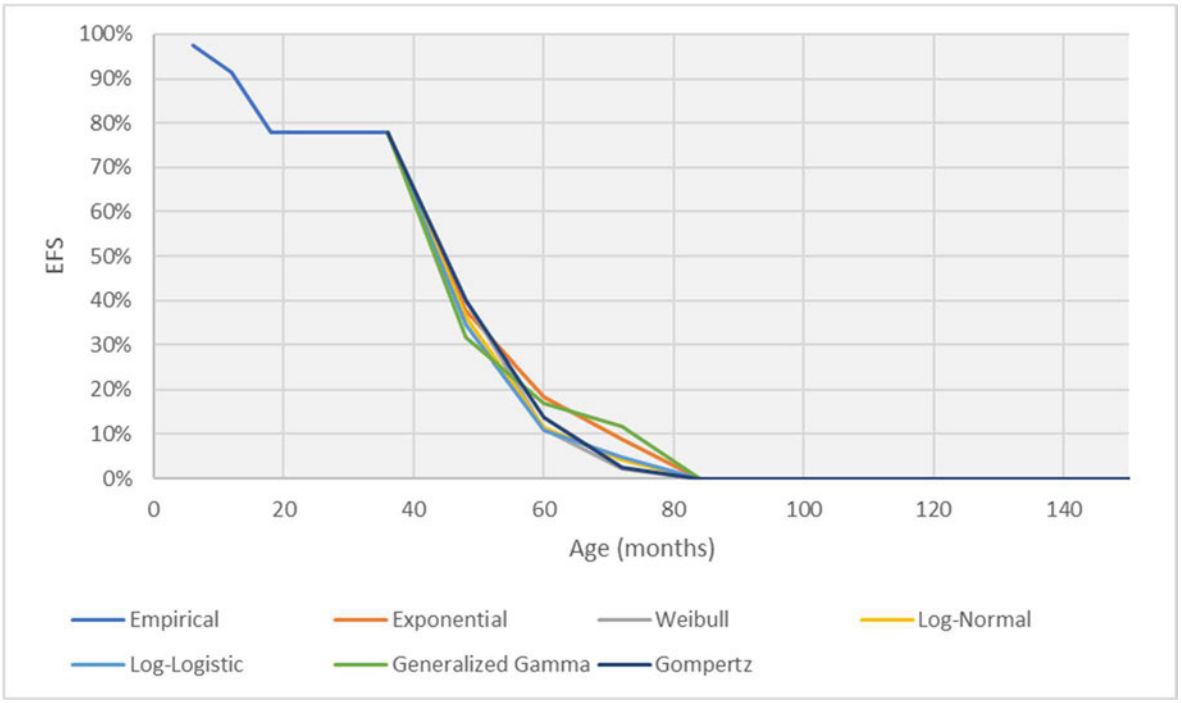


FIGURE 12: STATE D OVERALL SURVIVAL FOR SPINRAZA (KM FOLLOWED BY PARAMETRIC MODELS BASED ON NEURONEXT IN THE BASE CASE)



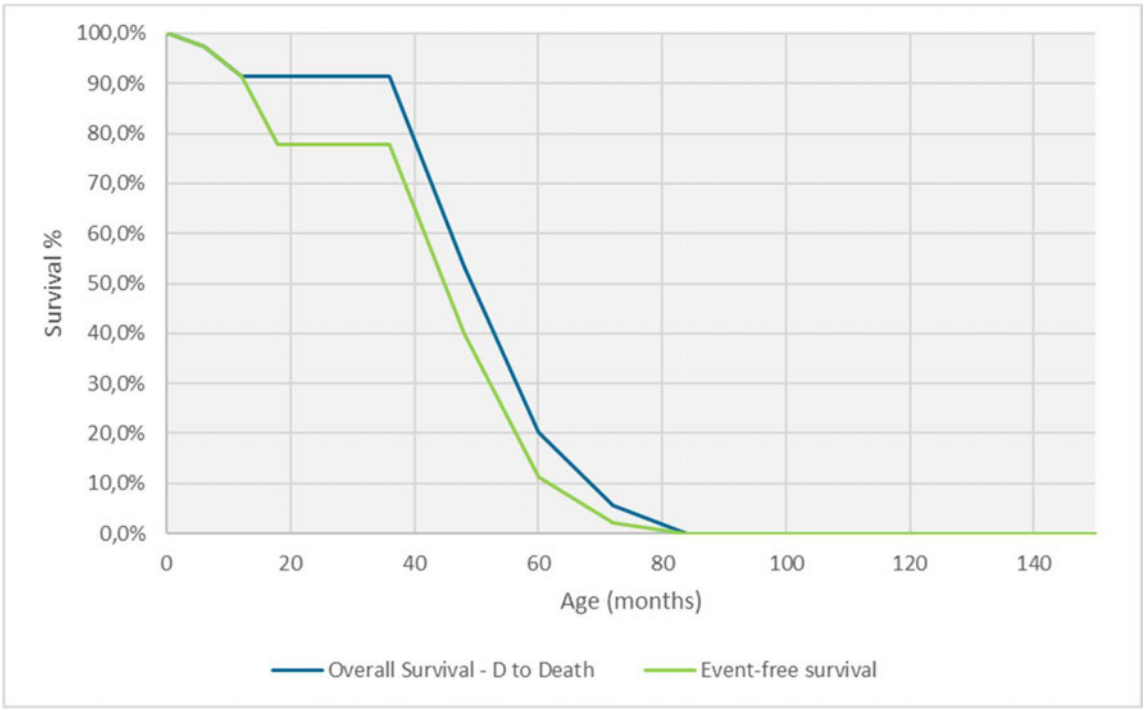
Abbreviations: OS, Overall survival.

FIGURE 13: STATE D EFS FOR SPINRAZA (KM FOLLOWED BY PARAMETRIC MODELS BASED ON NEURONEXT IN THE BASE CASE)



Abbreviations: EFS, Event free survival.

FIGURE 14: STATE D, OVERALL SURVIVAL AND EVENT-FREE SURVIVAL CURVES FOR SPINRAZA



C state (sits independently)

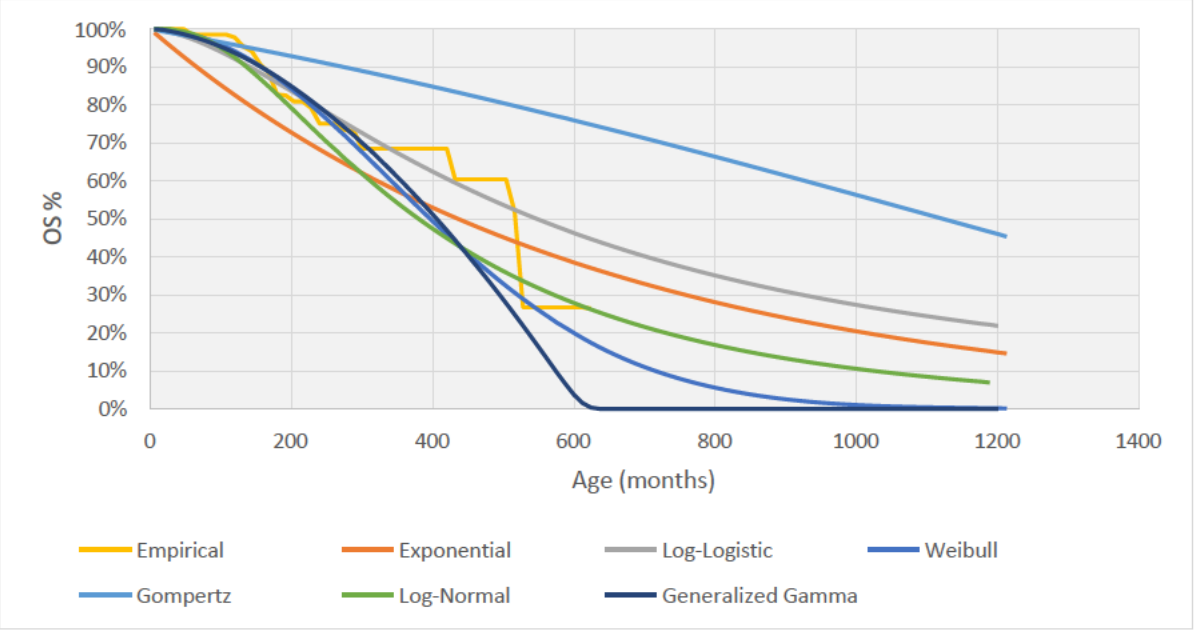
As a result of the underpinning assumption of the model that survival is improved in correlation with motor milestone achievement, and life expectancy can be estimated using proxies, SMA type 1 patients treated with Zolgensma or Spinraza are modelled from the long-term survival of the 52-year prospective and retrospective genetic study of SMA type 2 patients, as reported by Zerres et al. 1997 (Zerres 1997). The individual patient data were reconstructed using published methods (Tierney 2007, Hoyle 2011). Survival was projected with parametric estimation using the generalised gamma curve (best fit). Goodness-of-fit is shown in terms of the AIC and BIC in Table 13 and shown visually in Figure 15. The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the study. This approach is to avoid over-fitting the model to the study population observed and to ensure that transition probabilities remained relatively constant over time.

TABLE 13: ASSESSMENT OF CURVE FITS FOR HEALTH STATE C

Parametric model	AIC	BIC
Exponential	1151.27	1154.66
Weibull	1093.97	1100.76
Log-Normal	1103.72	1110.50
Log-Logistic	1131.50	1138.28
Generalized Gamma	1087.90	1098.08
Gompertz	1263.74	1270.53

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

FIGURE 15: STATE C OVERALL SURVIVAL FOR SPINRAZA AND ZOLGENSMA

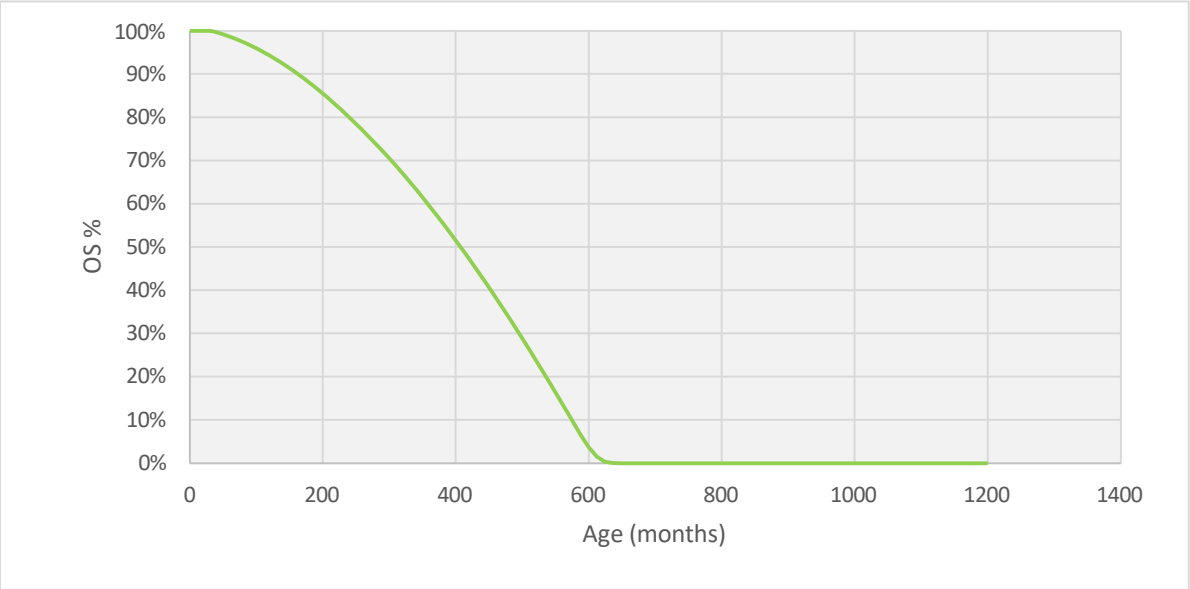


Abbreviations: OS, Overall survival.

The cost-analysis base case applies 100% survival in the first 5 cycles (up to 30 months of age) for the C and B states, to reflect the empirical survival data available for sitting and walking patients treated with Zolgensma from START and STR1VE-US. This aligns with the base case recommended by an independent academic review of this model (AveXis 2019b). From cycle 6 onwards, the generalised gamma curve fitted to the data from Zerres et al. 1997 (Zerres 1997) has been used. For Spinraza, the fitted generalised gamma curve was applied for the entire time horizon.

Figure 16 shows the modelled overall survival in C state for the Zolgensma arm. The C state survival curve for the Spinraza arm can be found in the tab 'C_Survival' of the model file.

FIGURE 16: STATE C, OVERALL SURVIVAL CURVES FOR ZOLGENSMA



Abbreviations: OS, Overall survival.

B state (walks unassisted) and A state (within broad range of normal) – treatment arms

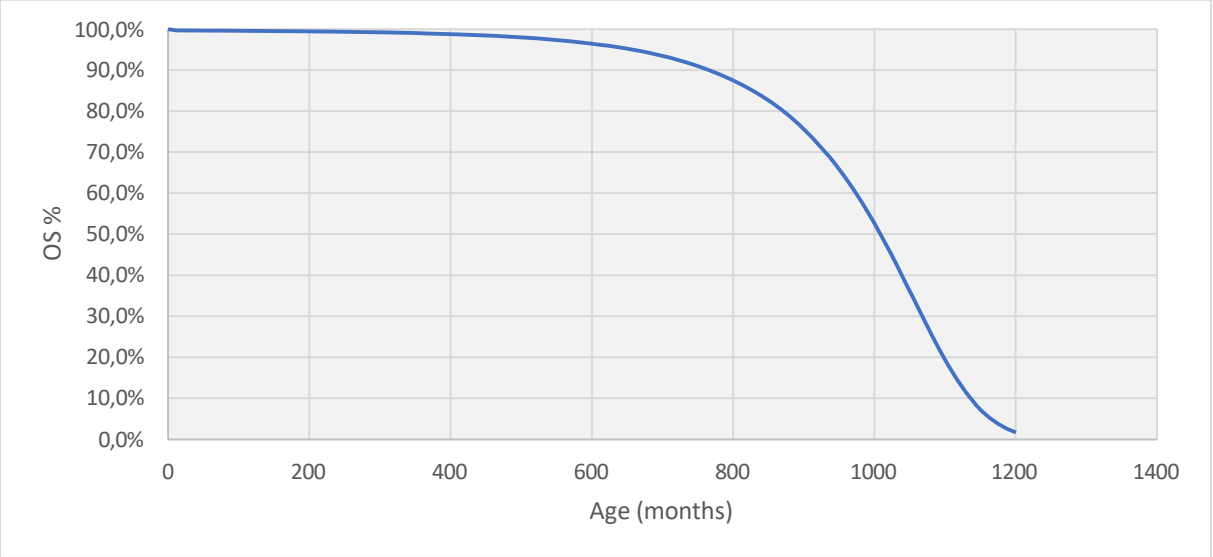
Patients who could walk unassisted were assumed to have survival consistent with the natural history of SMA type 3 patients, which is reported to not significantly differ from the survival of the general population (Zerres 1997).

Thus, for both the B state (walks unassisted) and A state (within broad range of normal development) SMA type 1 patients treated with Zolgensma or Spinraza are modelled to experience survival consistent with that of the general population. However, for Zolgensma, it has been assumed for the first five model cycles (up to 30 months of age) that the survival is 100% in both B and A states to match the 'ERG-preferred base case' assumptions; please see description above.

To estimate survival in these health states the 2020 Danish life tables were used to determine the probability of death in each cycle (Statistics Denmark 2020). The survival curve for this

health state is shown below in Figure 17. The B/A state survival curve for the Spinraza arm can be found in the tab 'B_A_Survival' of the model file.

FIGURE 17: B STATE AND A STATE OVERALL SURVIVAL FOR TREATMENT ARMS



Abbreviations: OS, Overall survival.

5.12 Healthcare resource utilization and costs

The cost-analysis considered drug and drug administration costs, adverse event costs, and medical costs associated with health states, as well as patient costs. The costs and resource use were obtained from the Nordic HRCU study (see section 5.12.2) and from the DMC (Lægemiddelsstyrelsen 2020, Danish Medicines Council 2020c). The detailed inputs and assumptions are described below and in greater detail in section 14.2 Appendix B.

5.12.1 Drug acquisition and dosing

Drug acquisition costs are based on the pharmacy purchase prices (PPP) excluding value added taxes derived from DMC's online price lists (Lægemiddelsstyrelsen 2020). The costs do not include any discounts negotiated with AMGROS. An overview of all drug costs input values for the treatments included in the analyses is presented in the Table 14 (Zolgensma) and Table 15 (Spinraza) below.

The overall cost of drug acquisition, drug administration, and patients' transportation and time for one treatment with Zolgensma is 14 537 122 DKK. These costs are incurred in the first year only, as it is a one-off treatment. This includes costs for patient transportation and time amount to 854 DKK. For subsequent years, no drug acquisition and administration costs are applied, however, the cost of patients' transportation and time for other medical services amount to 1 708 DKK annually (see Section 5.12.4).

The total cost associated with drug acquisition, drug administration, and patients' transportation and time for one treatment with Spinraza is 566 020 DKK. Patient

transportation and care costs include both drug administration and other health services, for a total of 8 events during year one, and 5 events in subsequent years; more details are presented in section 5.12.4. This means an annual total cost for patient transportation and time of 6 832 DKK (first year), and 4 270 DKK (subsequent years). The total annual cost associated with drug acquisition, administration and patient's transportation and time for Spinraza among surviving patients who continue treatment is 3 396 120 DKK for the first year (6 administrations) and 1 698 060 DKK for subsequent years (3 administrations per year).

TABLE 14: COSTS PER TREATMENT AND ADMINISTRATION FOR A PATIENT TREATED WITH ZOLGENSMA IN THE COST-EFFECTIVENESS MODEL

Items	Value (DKK)	Source
Price of the technology per treatment/patient	14 531 555	Zolgensma price at www.medicinpriser.dk
Treatment administration cost	2 341	Sundhedsdatastyrelsen (2020). Interactive DRG: spinal muscle atrophy general anesthesia 01MA99 MDC01 1-day group, Pat. 0-6 years. Available at: http://interaktivdrg.sundhedsdata.dk/
Anti-AAV9 diagnostic test	2 341	Sundhedsdatastyrelsen (2020). Interactive DRG: spinal muscle atrophy clinical genetic examination (ZZ4247) 01MA99 MDC01 1-day group, Pat. 0-6 years. Available at: http://interaktivdrg.sundhedsdata.dk/*
Prednisolone	38.43	Danish Medicines Agency (2020). Prednisolon Takeda AB. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=398747
Patient transportation and time cost	854	Calculation, see section 5.12.4
Total cost per treatment/patient	14 537 122	Calculation

Abbreviations: DKK: Danish kronor
*Note that the anti-AAV9 test is provided for free by Novartis Gene Therapies

TABLE 15: COSTS PER TREATMENT WITH INTRATHECAL ADMINISTRATION FOR A PATIENT TREATED WITH SPINRAZA IN THE COST-EFFECTIVENESS MODEL

Items	Value (DKK)	Source
Price of the technology per treatment/vial	557 927	Danish Medicines Agency (2020). Medicinpriser Spinraza (nusinersen). Available at: https://www.medicinpriser.dk/Default.aspx?id=15&vnr=458838
Treatment administration cost (Inpatient)	4 898	Sundhedsdatastyrelsen (2020). Interactive DRG: spinal muscle atrophy 09PR04 Biopsy and fluid extraction, superficial. Available at: http://interaktivdrg.sundhedsdata.dk/
Anesthesia	2 341	Sundhedsdatastyrelsen (2020). Interactive DRG: spinal muscle atrophy general anesthesia 01MA99 MDC01 1-day group, Pat. 0-6 years. Available at: http://interaktivdrg.sundhedsdata.dk/
Patient transportation and time cost	854	Calculation, see section 5.12.4
Total cost per treatment/patient	566 020	Calculation

Abbreviations: DKK: Danish kronor.

5.12.2 Health-state costs

Table 16 shows an overview of the cost categories that are applied to each of the health states in the model. A de novo healthcare resource utilisation (HCRU) study with 16 UK clinical experts, was conducted by AveXis to determine the HCRU costs associated with BSC, to ensure the model accurately captured the current UK clinical pathway of care for SMA patients (AveXis 2019c). A modified version of this study has also been conducted with Nordic clinical experts (one in Denmark, four in Sweden, one in Norway), to capture current HCRU patterns in the Nordics, post introduction of Spinraza (Born 2019, Eklund 2019, Rootwelt 2019, Sejersen 2019, Tulinius 2019, Weichbrodt 2019). The results from the interviews (in the UK and the Nordics) are listed in section 14.2, Appendix B.

Aligned with the expert advice provided and literature searched, the model structure accounts for the following costs:

- Consultations with the medical doctor responsible for the care of SMA patients (e.g., neuromuscular specialists, pulmonologists, physiotherapists, nutritionists, nurses [community and hospital based], etc.)
- Hospitalisations (accident and emergency department [A&E] and overnight admissions)
- Pharmacotherapies for treatment of SMA-related symptoms and comorbidities
- Tests, devices and surgeries – including those required for ventilatory and nutritional support
- Health materials necessary to the patient
- Patient and caregiver out of pocket costs

The model structure is based upon different health states (A-E) corresponding to different levels of functional mobility. In the absence of HCRU data by mobility status, the HCRU for health state D and E was assumed to correspond to the resource use for SMA type 1 patients in the HCRU study. The HCRU for patients with SMA types 2 and 3 were used as proxies for health states C and B, respectively. The HCRU for health state A was assumed to be identical to that of health state B.

The HCRU costs depend on the setting in which patients are treated, which in turn is influenced by their need for ventilation support, either non-invasive or through tracheostomy. The UK HCRU study estimated that the proportion of patients receiving ventilatory support for health states D, C, and B were 84%, 56% and 20%, respectively. The AveXis clinical advisory board for England (AveXis 2019a) estimated that ventilatory support, if needed, would be given in the following settings, per health state:

- For patients on NIV>16 hours per day (State E), 15% would be treated in the ITU, 15% in the high dependency unit and 70% at home
- For tracheostomy patients (State E), 10% would be treated in the ITU, 30% in the high dependency unit and 60% at home
- For patients on NIV<16 hours per day (states C and D), 5% would be treated in the ITU, 5% in the high dependency unit and 90% at home and;
- For patients able to walk independently (States A and B), 100% would be treated at home.

All HCRU costs have been adjusted by the location of the service provided, to avoid double counting costs for patients treated in hospital, as it was assumed that any costs stemming from health care resource usage would already be accounted for within the unit cost of intensive or high-dependency care. For patients treated in ITU or high dependency unit, costs were instead based upon daily admission costs to these settings in Denmark. The daily costs for patients admitted to high dependency unit (i.e. permanently hospitalised patients outside of intensive care) was 2 341 DKK per day, i.e. an annual cost of 855 050 DKK (Sundhedsdatastyrelsen 2020). The daily cost for patients treated in intensive care unit was 2 784 DKK per day, i.e., an annual cost of 1 016 856 DKK (Sundhedsdatastyrelsen 2020).

TABLE 16: LIST OF HEALTH STATES AND ASSOCIATED COSTS IN THE COST-EFFECTIVENESS MODEL

Cost categories	Health State				
	E Permanent assisted ventilation	D Not sitting	C Sits independently	B Walks unassisted	A Within broad range of development
Technology	Zolgensma: all patients receive gene therapy at baseline Spinraza: all patients receive drug unless discontinued; patients who move to E state do not receive drug				
Technology administration	Zolgensma: all patients incur administration costs at baseline. As the technology is a one-time, single IV administration, no ongoing administration costs are incurred Spinraza: all patients incur drug administration costs per dose, which is for lifetime unless the patient discontinues or dies. Patients who move to the E state do not receive Spinraza and do not incur administration costs				
SMA treatment costs	E state costs in each cycle times probability patient is in the cycle	D state costs in each cycle times probability patient is in the cycle	C state costs in each cycle times probability patient is in the cycle	B state costs in each cycle times probability patient is in the cycle	B state costs in each cycle times probability patient is in the cycle (base case)†

† In the base case, A state costs have been assumed to be the same as B state costs.

The total annual health care resource utilization cost per health state is presented in Table 17. These costs are applied equally for both treatment arms. Appendix B: Health care resource use and costs, in Section 14.2 present these costs with a higher level of granularity.

TABLE 17: ANNUAL HEALTH CARE RESOURCE UTILIZATION COSTS, PER HEALTH STATE (DKK)

Note that the costs associated with supporting medication that holds general reimbursement (i.e. amoxicillin, air salbutamol inhalation spray and Nexium) have been included in the results for the cost-analysis and the results for the budget consequence analysis. See Table 77, Table 78 and Table 79 in Appendix B (section 14.2) for detailed information about the resource use and unit costs for supporting medication.

TABLE 18: REIMBURSEMENT STATUS FOR SUPPORTING MEDICATION

Type of resource	Source	Reimbursement status
Amoxicillin	medicinpriser.dk (2020). Imacillin. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=079442	General reimbursement
Nebusal (sodium chloride for nebulizer)	Not sourced as expected to be very low cost and KOL noted patients use lower dose of label.	n/a
Airsalb salbutamol inhalation spray	medicinpriser.dk (2020). Airomir. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=376434	General reimbursement
Duphalac (lactullse laxantia)	Webapoteket.dk. Lactulose Pharma novia. Available at: https://www.webapoteket.dk/soeg/#!/term=/lactullse%20laxantia	Over the counter
D-vitamin oil 80 IE/drop	Webapoteket.dk. Apovit D-dråber til Børn. Available at: https://www.webapoteket.dk/mor-og-barn/vitaminer-til-baby-boern/apovit-d-draaber-til-boern-p-212137	Over the counter
Synagis (palivizumab, RS prophylaxis)	Not sourced as only applied to under 2 years of age, and the model is designed for HCRU costs to be applied every year.	n/a
Nexium oral suspension	medicinpriser.dk (2020). Nexium. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=528267	General reimbursement
Paracet 60 mg suppositories	Webapoteket.dk. Pinex Junior Mikstur. Available at: https://www.webapoteket.dk/mor-og-barn/smertestillende-til-boern/pinex-junior-mikstur-p-078578	Over the counter

5.12.3 Adverse-event costs

For Spinraza, as no serious AEs were reported in either arm of ENDEAR and no AEs were considered by trial investigators to be related to treatment in ENDEAR, AEs were excluded from consideration in the model. Adverse events associated with lumbar puncture (e.g. headache and back pain) were observed but the incidence and severity of these were consistent with events expected to occur with lumbar puncture. In addition, these events could not be assessed because of the limited communication abilities in the infant population treated with Spinraza.

All patients in Zolgensma clinical studies were treated with prophylactic oral prednisolone, except for the first patient enrolled into START, who developed elevated transaminases >20 x the upper limit of normal, which appeared to respond to prednisolone. However, since the cost of prednisolone is minor, no AEs are included in the cost-effectiveness model in terms of cost or health impacts.

5.12.4 Patient costs

For the total patient costs, the cost of transportation and the cost of patient and relative time (i.e. 'Patientomkostninger') as reported by DMC (AMGROS 2018) were summed and inputted in the model.

No direct estimate for transportation costs could be obtained for neither treatment with Zolgensma nor Spinraza. For this reason, transportation costs were obtained by multiplying the estimated frequency of transport for medical services with the unit cost of the average transportation. The unit cost for the average transportation including return trip was calculated to ~100 DKK (assuming a cost of 3.52 DKK/km and an average travel distance of 14 km), in line with guidance from the DMC. The cost of patients' time was valued to 179 DKK per hour (Statistics Denmark 2020, Danish Medicines Council 2020c), and it was assumed that the average treatment would require two hours of the patient's time. This result in a total unit cost per event of 458 DKK.

Patient costs included two types of events. First, all drug administrations for the respective treatment were included; Spinraza (European Medicines Agency 2017) 6 times during the first year and 3 times annually in subsequent years; Zolgensma: one-time administration only. Second, visits to medical services were estimated as the highest number of visit to any hospital-based service as estimated by KOLs (2 times) (Sejersen 2019, Tulinius 2019). For Spinraza, this meant a total of 8 events during the first year and 5 events in subsequent years. For Zolgensma, this resulted in 3 events during the first year, and 2 events annually in subsequent years. In total, this resulted in an annual patient cost for Zolgensma of 1 374 DKK (first year) and 916 DKK (subsequent years) for Zolgensma. For Spinraza, the costs were 3 664 DKK (first year) and 2 290 DKK (subsequent years). The frequencies and unit costs used for this analysis are presented in Table 19.

TABLE 19: BASE CASE SETTINGS FOR COSTS RELATED TO PATIENT TRANSPORTATION AND TIME

Parameter	Value	Source
Administration events Zolgensma	1	Zolgensma only requires a one-time administration, https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma#product-information-section
Administration events Spinraza (first year)	6	Spinraza dosing, https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza
Administration events Spinraza (subsequent years)	3	Spinraza dosing, https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza
Frequency of patient engagements (except drug administration)	2	Estimation provided by Nordic clinical experts, (Sejersen 2019, Tulinius 2019).
Patient hours per engagement (incl transportation)	2	Estimation provided by Nordic clinical experts, (Sejersen 2019, Tulinius 2019).
Valuation of patients' time (per hour)	179 DKK	Per DMC guidelines, (Danish Medicines Council 2020c)
Cost per transportation (incl. return trip)	100 DKK	Per DMC guidelines, (Danish Medicines Council 2020c)

Note that the costs associated with supporting pharmacological treatment available over the counter only (i.e. Duphalac, D-vitamin oil and paracetamol), have been included in patient costs in the results for the cost-analysis but not in the results for the budget consequence analysis. See Table 77, Table 78 and Table 79 in Appendix B (section 14.2) for detailed information about the resource use and unit costs for supporting medication.

5.13 Analysis

5.13.1 Base-case settings

Using the base-case model inputs, the costs for each treatment arm were evaluated and compared. Base-case model settings are depicted at Table 20.

TABLE 20: BASE CASE SETTINGS OF THE COST-EFFECTIVENESS ANALYSIS

Factor	Chosen values	Justification
Comparators	Spinraza	Spinraza was granted reimbursement in Denmark in 2017 (Danish Medicines Council 2017)
Time horizon of model	Lifetime horizon.	SMA type 1 is a progressive, lifelong, life-limiting disease and patients will continue to need management and/or treatment for the whole of their lives. DMC guidance states that model time horizons should be long enough to capture all benefits of the treatment.
Discount rate	4.0% (first 35 years); 3.0% (beyond 35 years)	In line with DMC guidance.
Perspective	Danish restricted societal perspective	In line with DMC guidance.
Cycle length	6-month cycles for first 3 years, 12-month cycles for remainder of model	A 6-monthly model cycle was chosen in the first three years, to allow changes in childhood development and milestone achievement to be adequately captured.
Outcomes	Costs	In line with DMC guidance.
HCRU	BSC costs, treatment costs, AE costs	From Nordic clinical expert study where possible, otherwise from public sources and interviews with UK clinical experts

Abbreviations: ICER, Incremental cost-effectiveness ratio, LY, life years, DMC, Danish Medicines Council, QALY, Quality adjusted life years

5.13.2 Sensitivity analyses

To assess the robustness of the model results, DSAs were conducted by varying one model input or assumption at a time. The modelled parameters were varied by ± 20% from their respective base-case values where logically feasible; for health state utility values ± 5% was used instead. Variables tested in one-way sensitivity analysis are reported in Table 21.

The main outcome of the DSA was to assess how the total cost for Zolgensma versus Spinraza is affected by changes in input values to the model's parameters.

TABLE 21: VARIABLES USED IN ONE-WAY DETERMINISTIC SENSITIVITY ANALYSIS

[redacted]

Spinraza discontinuation rate and rate of milestone loss	Proportion discontinuing Spinraza in C state	3.0%	2.4%	3.6%
	Proportion discontinuing Spinraza in D state	3.0%	2.4%	3.6%
	Rate of milestone loss for patients that discontinue Spinraza: state A	90.0%	72.0%	100.0%
	Rate of milestone loss for patients that discontinue Spinraza: state B	90.0%	72.0%	100.0%
	Rate of milestone loss for patients that discontinue Spinraza: state C	90.0%	72.0%	100.0%
	Rate of milestone loss for patients that discontinue Spinraza: state D	90.0%	72.0%	100.0%
Zolgensma costs	Zolgensma drug acquisition cost	14 531 555	11 625 244	17 437 866
	Zolgensma administration cost	5 567	4 453	6 680
Survival limits	Survival limit (years) for E state	16.0	12.8	19.2
	Survival limit (years) for D state	4.0	3.2	4.8

Abbreviations: GP, general practitioner; DKK, Danish krone, SMA, spinal muscular atrophy.
† For the base case analysis the costs for A state are the same as for B state.

5.13.3 Scenario analysis

In order to further assess the robustness of the model, some of its core assumptions were varied in scenario analyses. A list of key scenario analyses is provided in Table 22. For all scenarios, all non-specified settings were kept from the base case analysis.

TABLE 22: SCENARIO ANALYSES

Variable	Base case	Scenario analyses
Scenario 1. Discount rate	No discounting	0% (costs) and 0% (QALYs)
Scenario 2. Optimistic scenario	Base case extrapolations of effect	Improved survival for any patients who sit
Scenario 3. Milestone achievement	Improved milestone achievement beyond trial data	One additional sitter in STR1VE-US after 18 months of age †
Scenario 4. Milestone achievement	Improved milestone achievement beyond trial data	One additional walker in STR1VE-US after 18 months of age †
Scenario 5. Milestone achievement	Improved milestone achievement beyond trial data	One additional sitter and one additional walker in STR1VE-US after 18 months of age †
Scenario 6. Milestone achievement	Improved milestone achievement beyond trial data	4 new sitters and 4 new walkers in STR1VE-US (half in cycle ending 30 months; half in cycle ending 36 months) †
Scenario 7. Health state costs	Lower health state costs for patients broadly in line with normal development	Costs for health state A are 50% lower than for health state B
Scenario 8. Improved survival for health state D	Base case settings with alternative survival cut-off for health state D	Survival limit cut-off within state D increased to 10 years for all treatment arms
Scenario 9. Reduced survival for health state D	Base case settings with alternative survival cut-off for health state D	Survival limit within health state D set strictly at 4 years.
Scenario 10. Exclusion of patient transportation and time costs	Strict health care payer perspective	Patient transportation costs and patient time costs excluded from analysis
Scenario 11. Zolgensma administration costs	Reduced administration cost, Zolgensma	Anti-AAV9 diagnostic test provided for free by the company

Abbreviations: QALY, Quality-adjusted life year
† The base case assumes no additional walkers or sitters.

6 Budget impact analysis SMA type 1

6.1 Model approach

To estimate how the reimbursement of Zolgensma may affect the overall health care budget in Denmark, a budget impact model was developed. The budget impact model was constructed as a module within the cost-effectiveness model. The numbers of patients who would be eligible for treatment within each year of a 10-year period and the current treatment options that Zolgensma would replace for each year are selected.

All costs and health outcomes data for the analysis are drawn from the cost-effectiveness model. Discounting is not applied within the budget impact model. The model calculates the total cost of treatment for patients treated through Years 1 to 10 inclusive by reference to the model underlying the cost-effectiveness analysis. If a patient were to join in Year 2, then the model would begin calculation, again, from Year 1, but the Year 1 data for this patient are added to the Year 2 data for the first patient. Similarly, the Year 2 data for the second-year patient are added to the Year 3 data for the patient who joined in Year 1. The model compares the overall spending for two scenarios: a scenario in which Zolgensma receive pre-approved reimbursement, and one in which it does not. The overall cost for these two scenarios are then compared to estimate the budget impact of reimbursement for Zolgensma, in line with guidelines from DMC (AMGROS 2018).

6.2 Market share

In Denmark, there were six patients with SMA type 1, being treated Spinraza in 2016 (Rasmussen 2020, Danish Medicines Council 2020a). The number of new patients diagnosed each year is estimated to be two (Danish Medicines Council 2020a). It is expected that [redacted]

The number of expected patients per year and treatment with pre-approved reimbursement for Zolgensma is shown in Table 23. Figures in bold denotes patients treated with Zolgensma. The number of expected patients per year and treatment without pre-approved reimbursement for Zolgensma is shown in Table 24.

TABLE 23: NUMBER OF PATIENTS WITH SMA TYPE 1 TREATED WITH ZOLGENSMA (BOLD) AND SPINRAZA DURING THE FIRST 10 YEARS IF ZOLGENSMA IS REIMBURSED

[redacted]

Abbreviations: SMA, Spinal muscular atrophy.

TABLE 24: NUMBER OF PATIENTS WITH SMA TYPE 1 TREATED WITH SPINRAZA DURING THE FIRST 10 YEARS FOLLOWING THE REIMBURSEMENT DECISION IF ZOLGENSMA IS NOT REIMBURSED

6.3 Settings for budget impact model analysis

For the scenario without pre-approved reimbursement of Zolgensma, we assume that all patients will be treated with Spinraza. For the scenario with pre-approved reimbursement of Zolgensma, we assume that would switch from Spinraza to Zolgensma during the first year. All "non-switchers" would remain treated with Spinraza. Among the diagnosed patients per year, we assumed that would be treated with Zolgensma with Spinraza.

The cost inputs are directly linked with the cost-analysis model as the budget impact model is constructed as a module within the cost-analysis model. For the description of the cost see section 5.12. Patient costs, however, are not included in the budget impact calculations as per the guideline. A five-year time-horizon was used for the model; however, the total budget impact was also calculated over a 10--year time-horizon. No discounting was applied for the budget impact analysis.

7 Results of cost analysis SMA type 1

7.1 Base case results

The average time spent in each health state and survival time for Zolgensma and Spinraza in the model with a lifetime horizon is presented in Table 25.

TABLE 25: AVG. TIME IN EACH HEALTH STATE (YEARS) AND AVG. SURVIVAL (YEARS) FOR ZOLGENSMA AND SPINRAZA IN THE MODEL WITH A LIFETIME HORIZON

	E State	D State	C State	B State	A state	Avg. Survival
Spinraza(years)	1.04	2.44	7.24	0.00	0.00	10.720
Zolgensma (years)	0.405	2.113	19.626	0.279	6.697	29.120

A detailed presentation of the different cost items discounted at 4.0% (3.0% beyond year 35), is included in Table 26 below.

TABLE 26: DETAILED COSTS (DKK, DISCOUNTED) PER TREATMENT ARM, PER PATIENT

	Drug acquisition cost	Drug administration cost	Health state costs	Total costs
Spinraza	12 499 204	119 990	2 077 250	14 696 445
Zolgensma	14 531 555	5 178	3 135 480	17 672 213
Difference	2 032 351	-114 812	1 058 230	**2 975 768**

Abbreviations: DKK: Danish kronor

A further breakdown of costs is presented in Table 27 which outlines the costs which actors bears which costs in line with DMC preference. This categorization distinguishes between over the counter medicines and medicines under general reimbursement, as outlined in Table 18.

TABLE 27: DETAILED COST (DKK, DISCOUNTED) PER TREATMENT ARM, PER DMC COST CATEGORY, PER PATIENT

	Drug acquisition costs †	Hospital costs ††	Patient costs ‡	Adverse events costs ‡‡	Total
Spinraza	12 454 053	2 197 240	45 151	0	**14 696 445**
Zolgensma	14 517 407	3 140 658	14 148	0	**17 672 213**
Difference	2 063 353	943 418	-31 003	0	**2 975 768**

† Drug acquisition costs include the acquisition cost for Zolgensma/Spinraza and general reimbursement drugs
†† Hospital costs include all costs for treatment administration of Zolgensma/Spinraza plus all health state related health care resource utilization (HCRU) costs except for drugs
‡ Patient costs include patient transportation and time costs, as well as costs for "over the counter" medicines
‡‡ Adverse event costs are not included in this analysis. For more information, see section 0.

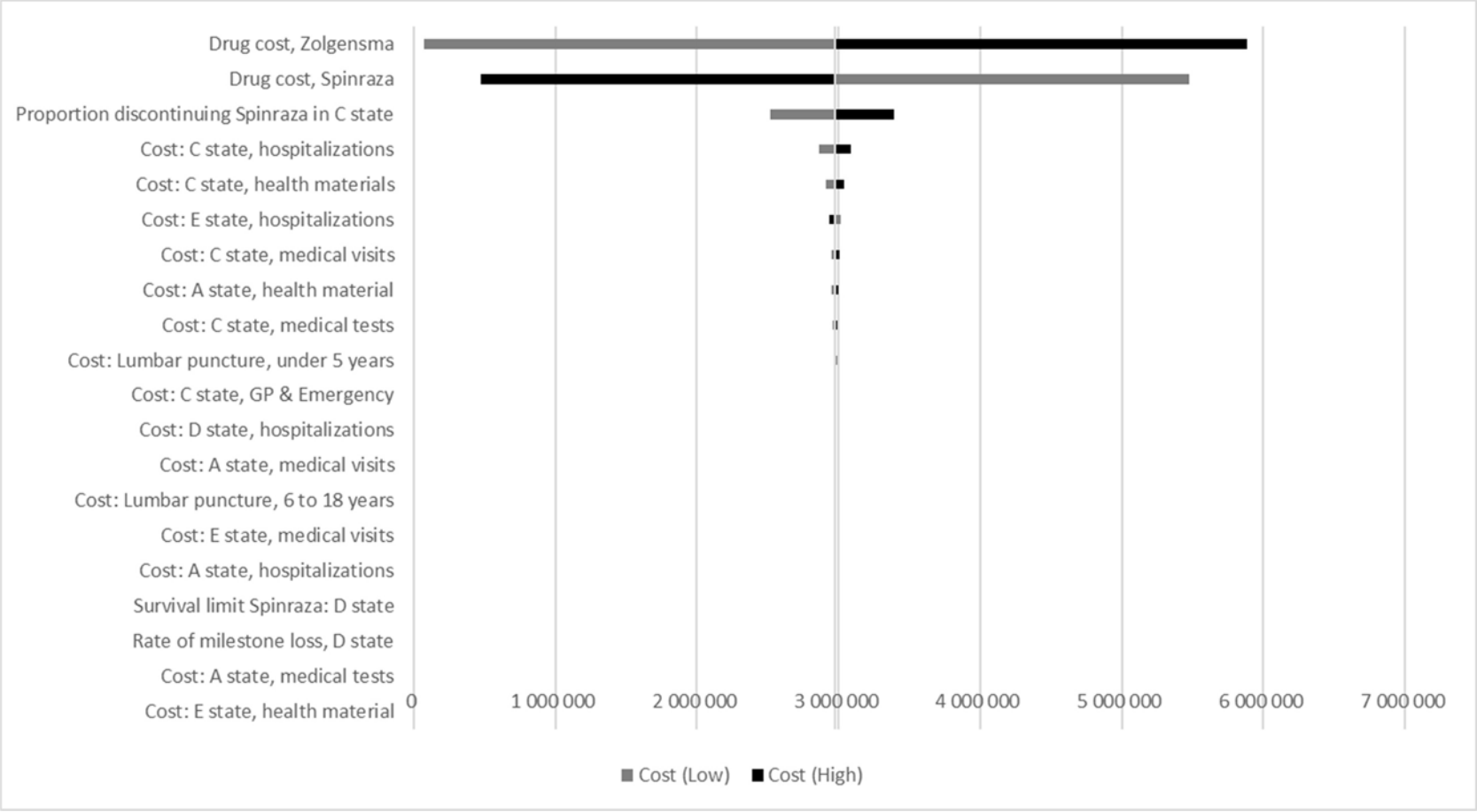
7.2 Deterministic sensitivity analysis

The deterministic sensitivity analysis explores the impact that variations of individual parameters have on the costs of Zolgensma versus Spinraza. Results are presented as a tornado diagram in Figure 18 and the values are presented in Table 28.

The DSA for Zolgensma vs Spinraza shows that the cost difference is most sensitive towards changes in the drug acquisition cost of the respective drug. Another important parameter is the discontinuation rate for Spinraza in health state C.

It is important to acknowledge that this analysis is based upon varying parameters in relative rather than absolute terms. For example, changes to health state costs for state A applies only to Zolgensma (since patients treated with the comparators are unable to reach this health state), yet still have lesser impact costs for health state D, which applies to Spinraza as well. This is partly explained by the small number of patients who reach this health state, but also by the fact that health state costs for the A state are lower than for states C, D and E. Hence, varying A state costs by ± 20% has a much smaller effect in absolute terms than what is the case for the health states associated with higher costs.

FIGURE 18: DETERMINISTIC SENSITIVITY ANALYSIS FOR THE 20 PARAMETERS WITH HIGHEST IMPACT FOR THE COST DIFFERENCE BETWEEN ZOLGENSMA AND SPINRAZA (DKK)



Note: The cost difference between Zolgensma and Spinraza is shown on the horizontal axis (values shown in DKK).
Abbreviations: DKK, Danish krone

TABLE 28: DETERMINISTIC SENSITIVITY ANALYSIS FOR THE 20 PARAMETERS WITH HIGHEST IMPACT FOR THE COST OF ZOLGENSMA VERSUS SPINRAZA

Rank	Parameter Description	Cost – Low (DKK)	Cost – High (DKK)	Range (DKK)
1	Drug cost, Zolgensma	69 457	5 882 079	5 812 622
2	Drug cost, Spinraza	5 475 609	475 927	4 999 682
3	Proportion discontinuing Spinraza in C state	2 515 653	3 389 017	873 364
4	Cost: C state, hospitalizations	[redacted]	[redacted]	[redacted]
5	Cost: C state, health materials	[redacted]	[redacted]	[redacted]
6	Cost: E state, hospitalizations	[redacted]	[redacted]	[redacted]
7	Cost: C state, medical visits	[redacted]	[redacted]	[redacted]
8	Cost: A state, health material	[redacted]	[redacted]	[redacted]
9	Cost: C state, medical tests	[redacted]	[redacted]	[redacted]
10	Cost: Lumbar puncture, under 5 years	[redacted]	[redacted]	[redacted]
11	Cost: C state, GP & Emergency	[redacted]	[redacted]	[redacted]
12	Cost: D state, hospitalizations	[redacted]	[redacted]	[redacted]
13	Cost: A state, medical visits	[redacted]	[redacted]	[redacted]
14	Cost: Lumbar puncture, 6 to 18 years	[redacted]	[redacted]	[redacted]
15	Cost: E state, medical visits	[redacted]	[redacted]	[redacted]
16	Cost: A state, hospitalizations	[redacted]	[redacted]	[redacted]
17	Survival limit Spinraza: D state	[redacted]	[redacted]	[redacted]
18	Rate of milestone loss, D state	[redacted]	[redacted]	[redacted]
19	Cost: A state, medical tests	[redacted]	[redacted]	[redacted]
20	Cost: E state, health material	[redacted]	[redacted]	[redacted]

The table shows the highest and lowest cost for Zolgensma vs Spinraza when individual parameters are varied. The base case cost difference is 2 831 148 DKK. All parameters varied by ± 20% unless logically bounded.
Abbreviations: DKK: Danish kronor; GP: General practitioner

7.3 Scenario analyses

A summary of the results from key scenarios is presented in Table 29. The scenario analyses show that total costs are fairly insensitive towards changes in the number of patients who achieve the higher milestones (sitting independently and walking independently) during the model's first 6 cycles.

The time discount rate for costs is identified as an important factor. When discount rates are set to zero, the net present value of the overall cost increase for both Zolgensma and Spinraza. However, costs mainly rise for Spinraza, since Zolgensma is a one-time treatment and its drug acquisition costs only apply at the start of treatment.

TABLE 29: RESULTS FROM SCENARIO ANALYSES

Scenario	Treatment	Cost per patient (DKK)	Cost difference (DKK)
Base case	Spinraza	14 696 445	2 975 768
	Zolgensma	17 672 213	
Scenario 1. Time discount rate set to 0% for costs and QALYs	Spinraza	20 423 531	-404 524
	Zolgensma	20 019 007	
Scenario 2. Improved survival for any patients who sit	Spinraza	16 773 789	2 161 442
	Zolgensma	18 935 231	
Scenario 3. One additional sitter in STR1VE-US after 18 months of age, but no additional walker †	Spinraza	14 696 445	3 038 900
	Zolgensma	17 735 345	
Scenario 4. One additional walker in STR1VE-US after 18 months of age, but no additional sitter †	Spinraza	14 696 445	2 961 669
	Zolgensma	17 658 114	
Scenario 5. One additional walker and one additional sitter in STR1VE-US after 18 months of age †	Spinraza	14 696 445	3 024 801
	Zolgensma	17 721 245	
Scenario 6. 4 new sitters and 4 new walkers in STR1VE-US (half in cycle ending 30 months; half in cycle ending 36 months) †	Spinraza	14 696 445	3 165 538
	Zolgensma	17 861 983	
Scenario 7. Costs for health state A are 50% lower than for health state B	Spinraza	14 696 445	2 878 251
	Zolgensma	17 574 695	
Scenario 8. Survival limit cut-off within state D increased to 10 years for all treatment arms	Spinraza	14 709 666	2 962 718
	Zolgensma	17 672 384	
Scenario 9. Survival limit within state D set strictly at 4 years	Zolgenmsa	14 157 971	3 391 255
	Spinraza	17 549 226	
Scenario 10. Exclusion of patient transportation and time costs	Spinraza	14 676 126	2 978 329
	Zolgensma	17 654 456	
Scenario 11. Cost for Anti-AAV9 diagnostic test removed from Zolgensma administration costs	Spinraza	14 696 445	2 973 427
	Zolgensma	17 669 872	

Abbreviations: DKK; Danish kronor,. † The base case assumes no additional independent sitters or walkers.

8 Results of budget impact analysis SMA type 1

The base-case analysis assumes eight patients (six prevalent + two incident) in the first year and two new patients per year added to the cohort in the subsequent years. Using this cohort

of patients, the budget impact analysis was calculated as the total cost difference of the two following scenarios:

1) Scenario with pre-approved reimbursement for Zolgensma where in the first year out of the [redacted] and in the following years out of the [redacted] while the other patients are treated with Spinraza (see Table 23). The detailed results of this scenario is shown in Table 30.
2) Scenario without pre-approved reimbursement for Zolgensma where all the patients are treated with Spinraza in every year (see Table 24). The detailed results of this scenario is shown in Table 31.

The budget impact per year for introducing Zolgensma in Denmark is presented in Table 32. The budget impact analysis shows that the budget impact is the largest in the first year (where also two treatment switches from Spinraza to Zolgensma is assumed) and then drops significantly already in the second year and thereafter decreases annually during the first 10 years. The total cumulative budget impact over 5 and 10 year time horizons is shown in Table 33 and shows that after the 10 years the total budget impact would b[redacted] of introducing Zolgensma to the Danish market.

Table 30: SMA Type 1 cohort cost per year (DKK) with pre-approved reimbursement for Zolgensma

Abbreviations: DKK: Danish kronor. SMA, Spinal muscular atrophy

Table 31: SMA Type 1 cohort cost per year (DKK) without pre-approved reimbursement for Zolgensma

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

Table 32: Budget impact per year (DKK) for introduction of Zolgensma for SMA Type 1 cohort

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

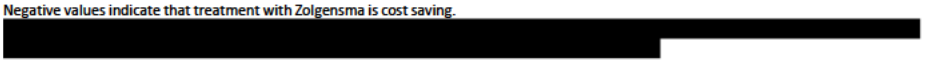


Table 33: Cumulative budget impact (DKK) for introduction of Zolgensma for SMA Type 1

Negative values indicate that treatment with Zolgensma is cost saving.

The cost of treating one SMA Type 1 patient with Zolgensma over a 10 year-time horizon is shown in Table 34, while the cost of treating one SMA Type 1 patient with Spinraza over a 10 year-time horizon is shown Table 35. The budget impact per year for treating one SMA Type

1 patient with Zolgensma instead of Spinraza is displayed in Table 36 and shows that the total cost per year per patient is less with Zolgensma in the second year and onwards. The cumulative budget impact is presented in Table 37 for the first 5 and first 10 years. After 10 years the total budget impact at the patient level of introducing Zolgensma would be 5 588 377 DKK.

Table 34: SMA Type 1 cost per year (DKK) of treating 1 patient with Zolgensma

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Zolgensma: drug acquisition costs	14 531 555	0	0	0	0
Zolgensma drug administration costs	4 820	0	0	0	0
Zolgensma: total drug costs	14 536 375	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	14 536 375	0	0	0	0
SMA medical costs	336 316	272 224	217 899	185 133	163 578
Total SMA care costs	336 316	272 224	217 899	185 133	163 578
Total costs	14 872 692	272 224	217 899	185 133	163 578
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Zolgensma: drug acquisition costs	0	0	0	0	0
Zolgensma drug administration costs	0	0	0	0	0
Zolgensma: total drug costs	0	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	155 011	149 808	145 352	141 369	137 763
Total SMA care costs	155 011	149 808	145 352	141 369	137 763
Total costs	155 011	149 808	145 352	141 369	137 763

Abbreviations: DKK: Danish kronor. SMA, Spinal muscular atrophy

Table 35: SMA Type 1 cost per year (DKK) of treating 1 patients with Spinraza

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Nusinersen: drug acquisition costs	2 595 133	1 235 017	1 195 695	907 758	673 361
Nusinersen: drug administration costs	23 248	11 063	10 711	8 132	6 032
Total drug costs	2 618 380	1 246 081	1 206 406	915 890	679 393
SMA medical costs	320 893	274 700	264 912	200 738	146 736
Total SMA care costs	320 893	274 700	264 912	200 738	146 736
Total costs	2 939 274	1 520 781	1 471 318	1 116 629	826 129
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Nusinersen: drug acquisition costs	551 293	509 555	489 771	470 319	451 220
Nusinersen: drug administration costs	4 939	4 565	4 387	4 213	4 042
Total drug costs	556 231	514 119	494 159	474 532	455 262
SMA medical costs	119 382	103 944	94 648	86 560	79 482
Total SMA care costs	119 382	103 944	94 648	86 560	79 482
Total costs	675 613	618 064	588 807	561 092	534 744

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

Table 36: Budget impact per year (DKK) for treating one SMA Type 1 patient with Zolgensma instead of Spinraza

Time horizon	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	11 917 995	-1 246 081	-1 206 406	-915 890	-679 393
SMA care budget impact	15 423	-2 477	-47 013	-15 606	16 842
Total budget impact	11 933 418	-1 248 557	-1 253 419	-931 496	-662 551
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Pharmacy budget impact	-556 231	-514 119	-494 159	-474 532	-455 262
SMA care budget impact	35 629	45 864	50 704	54 809	58 281
Total budget impact	-520 602	-468 255	-443 455	-419 723	-396 981

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

Table 37: Cumulative budget impact (DKK) for treating one SMA Type 1 patient with Zolgensma instead of Spinraza

Time horizon	Years 1-5	Years 1-10
Pharmacy budget impact	7 870 224	5 375 921
SMA care budget impact	-32 831	212 456
Total	7 837 393	5 588 377

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

9 Cost-analysis pre-symptomatic patients

Unlike for patients with SMA type 1, there is insufficient clinical evidence on the effect of Zolgensma treatment for pre-symptomatic patients to support the development of an independent cost-analysis model. However, a simplified analysis can still be performed based upon the costs for Zolgensma and Spinraza treatments.

For this analysis, we utilise the cost-effectiveness model for SMA type 1 patients. For the treatment cost comparison, it was assumed that Zolgensma would have the same clinical effect as Spinraza for pre-symptomatic patients. To model this effect, Spinraza was given the same survival and transitional probabilities as Zolgensma. Further, the same milestone achievements were applied during the model's first cycles. As a consequence, the survival and milestone achievements are identical for Zolgensma and Spinraza in the base case, so any differences in costs are due to differences in drug acquisition and drug administration costs only. Health state costs are included in the analysis but applied equally to both treatment arms. Any patient disutility related to the treatment burden stemming from repeated intrathecal injections are not taken into account in the model.

For this analysis, it was assumed that that all patients become "sitters" (health state C) during the model's second or third cycle, it was assumed that half of these transitions would occur within each cycle. The analysis focuses on two separate patient groups: those with 2 SMN2 copies and those with 3 SMN2 copies. For patients with 2 SMN2 copies, it was assumed that 80% of surviving patients would also achieve independent walking, based upon the share of independent walkers in NURTURE (Castro 2018). Remaining patients would stay in health state C (sitting independently). For patients with 3 SMN2 copies, the base case assumption was that 100% would achieve independent walking (De Vivo 2019). For both groups it was assumed that patients who achieve independent walking would do so within the fourth or fifth model cycle. It was further assumed that half of these transitions would happen within each cycle. The proportion of alive and event-free patients within each health state is shown in Table 38 for patients with 2 SMN2 copies. The transition probabilities for these patients are shown in Table 39. For patients with 3 SMN2 copies, the proportion of alive and event-free patients within each health state is shown in Table 40 and the transitional probabilities are shown in Table 41.

Table 38: Proportion of alive and event-free patients attaining milestones by model cycle, pre-symptomatic patients with 2 SMN2 copies

Model cycle	Age at end of cycle (mo.)	Not sitting	Sitting but not walking	Walking
1	6	100%	0%	0%
2	12	50%	50%	0%
3	18	0%	100%	0%
4	24	0%	60%	40%
5	30	0%	20%	80%
6	36	0%	20%	80%
7	48	0%	20%	80%
8	60	0%	20%	80%

Table 39: Transitional probabilities for pre-symptomatic patients with 2 SMN2 copies

Cycle	Age at end of cycle (mo.)	D to C	C to B	B to A
1	6	0.0%	0.0%	0.0%
2	12	50.0%	0.0%	0.0%
3	18	100.0%	0.0%	0.0%
4	24	0.0%	40.0%	0.0%
5	30	0.0%	66.7%	0.0%
6	36	0.0%	0.0%	0.0%
7	48	0.0%	0.0%	0.0%
8	60	0.0%	0.0%	0.0%
9	72	0.0%	0.0%	100.0%

† Patients achieving independent walking are assumed to transition to health state A during cycle 9

Table 40: Proportion of alive and event-free patients attaining milestones by model cycle, Pre-symptomatic patients with 3 SMN2 copies

Model cycle	Age at end of cycle (mo.)	Not sitting	Sitting but not walking	Walking
1	6	100%	0%	0%
2	12	50%	50%	0%
3	18	0%	100%	0%
4	24	0%	50%	50%
5	30	0%	0%	100%
6	36	0%	0%	100%
7	48	0%	0%	100%
8	60	0%	0%	100%

TABLE 41: TRANSITIONAL PROBABILITIES FOR PRE-SYMPTOMATIC PATIENTS WITH 3 SMN2 COPIES

Cycle	Age at end of cycle (mo.)	D to C	C to B	B to A
1	6	0.0%	0.0%	0.0%
2	12	50.0%	0.0%	0.0%
3	18	100.0%	0.0%	0.0%
4	24	0.0%	50.0%	0.0%
5	30	0.0%	100.0%	0.0%
6	36	0.0%	0.0%	0.0%
7	48	0.0%	0.0%	0.0%
8	60	0.0%	0.0%	0.0%
9	72	0.0%	0.0%	100.0%

† Patients achieving independent walking are assumed to transition to health state A during cycle 9

By default, all patients start the model in health state D during the first cycle. Before transitioning to higher health states, a substantial proportion of patients with SMA type 1 would die or transfer to state E during these first cycles. However, for this analysis mortality and transition probabilities to health state E has been set to 0% during the first six cycles. This difference compared to patients with SMA type 1 is motivated by pre-symptomatic patients resembling normally developing children more than patients with symptomatic SMA. Once in health states C and B, mortality applies the same as for the SMA type 1 analysis; C state survival is based upon Zerres et al. (Zerres 1997) and B state survival is based upon survival for the general Danish population (Statistics Denmark 2020).

We assume that no transition between health states occur after model cycle 9, although mortality still applies. For this analysis, the discontinuation rate for Spinraza has been set to 0%. Since health state achievement is assumed to be the same, the two treatment arms will yield identical QALY gains. A discount rate of 4.0% was applied for the first 35 years, beyond this the discount rate was 3.0%.

10 Results of cost- analysis pre-symptomatic patients

The results from the cost analysis for pre-symptomatic patients is shown in Table 42 (2 SMN2 copies) and Table 43 (3 SMN2 copies). Since the clinical effects by assumption are identical for the two treatment arms, the only difference is the costs required for Zolgensma and Spinraza, respectively. Since Zolgensma is a one-time infusion whereas Spinraza requires repeated administrations, the cost difference between the two treatment depends on the survival of the patients. Overall cost increases with increased survival for both treatment arms due to health state costs, however, the cost increase will be sharpest for Spinraza given the need for continuous drug acquisition and administration. Any disutility stemming from the treatment burden with Spinraza has not been considered in this analysis.

TABLE 42: COSTS FOR PRE-SYMPTOMATIC PATIENTS WITH 2 COPIES OF SMN2, DISCOUNTED

Treatment	Costs (DKK)
Zolgensma	17 710 309
Spinraza	47 275 601
Difference	**-29 565 291**

Zolgensma: 80% walkers, 20% sitters; Spinraza: 80% walkers, 20% sitters
Discount rate: 4.0% for the first 35 years, 3.0% beyond 35 years

TABLE 43: COST FOR PRE-SYMPTOMATIC PATIENTS WITH 3 COPIES OF SMN2, DISCOUNTED

Treatment	Costs (DKK)
Zolgensma	17 604 485
Spinraza	50 469 232
Difference	**-32 864 746**

Zolgensma: 100% walkers; Spinraza: 100% walkers
Discount rate: 4.0% for the first 35 years, 3.0% beyond 35 years

11 Budget impact analysis pre-symptomatic patients

The budget impact analysis of the pre-symptomatic patients is based on the similar assumptions for prevalence and incidence as for patients with SMA type 1 (see Table 23 in Section 6.2). The assumptions of patients treated with Zolgensma vs Spinraza are also the same, except for the differences applied in the cost analysis of pre-symptomatic patients. In the cost analysis for pre-symptomatic patients, clinical effects of treatment were assumed to be similar across the two treatment arms which is also the case in the budgetary consequence analysis. Similarly, milestone achievements for patients with two and three copies of SMN2 are the same as for the pre-symptomatic cost analysis (shown in Table 38 and Table 40), and transitions probabilities from health state D to permanent assisted ventilation or death have been set to 0% for the first 6 model cycles (see section 9).

12 Results of budget impact analysis for pre-symptomatic patient

12.1 Result for pre-symptomatic patients with 2 SMN copies

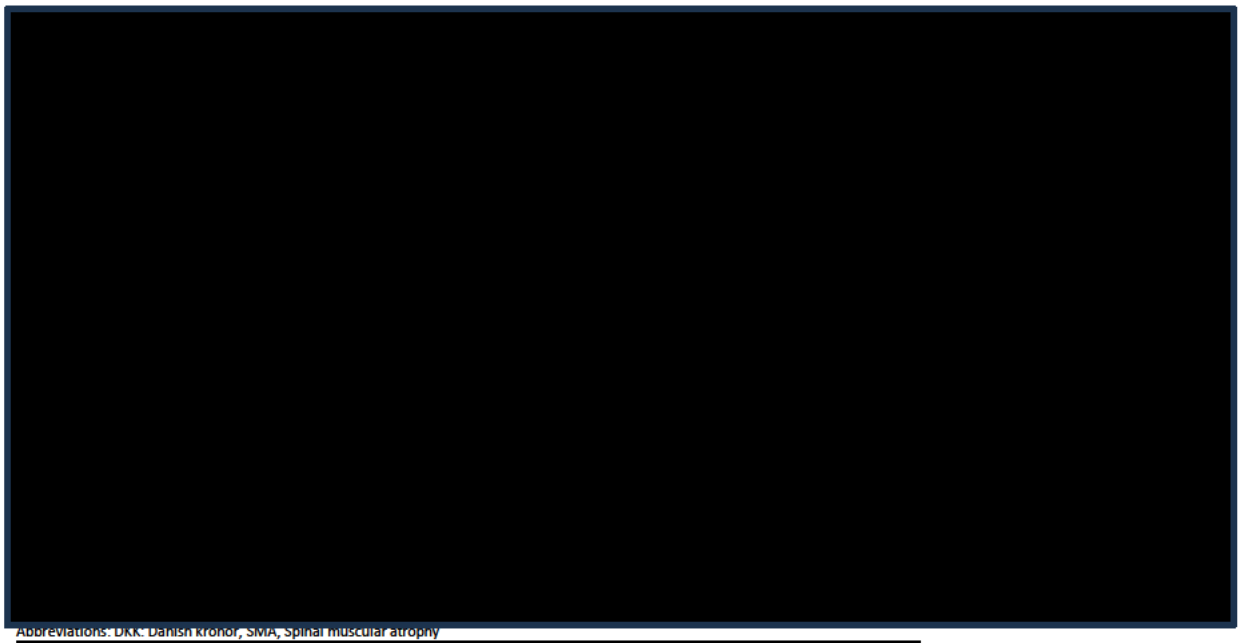
The results of the budget impact analysis for pre-symptomatic patients with 2 SMN copies are displayed in Table 44, Table 45 and Table 46 below. The results show that based on similar assumptions of incident and prevalent cases of SMA type 1, the budget impact is the largest in the first year (where also two treatment switches from Spinraza to Zolgensma is assumed) and then drops significantly already in the second year and thereafter. The cumulative budget impact over 5 and 10 years is presented in Table 47 and shows that the total additional cost by introducing Zolgensma to pre-symptomatic patients with 2 SMN copies would be [redacted] DKK over 5 years, and [redacted] DKK over 10 years.

TABLE 44: COST PER YEAR (DKK) FOR PRE-SYMPTOMATIC COHORT WITH 2 SMN COPIES WITH PRE-APPROVED REIMBURSEMENT FOR ZOLGENSMA

[redacted]

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
*In the first year, [redacted] prevalent patients would receive Zolgensma an [redacted] would receive Zolgensma
**In the second year and onwards, [redacted] incident patients would be initiated on Zolgensma

Table 45: cost per year (DKK) for pre-symptomatic cohort with 2 SMN copies without pre-approved reimbursement for Zolgensma



Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

Table 46: Budget impact per year (DKK) for introduction of Zolgensma for PRE-SYMPTOMATIC cohort with 2 SMN copies

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

Table 47: Cumulative budget impact (DKK) for introduction of Zolgensma for Pre-symptomatic cohort with 2 SMN copies

The cost of treating one pre-symptomatic patient with 2 SMN copies with Zolgensma over a 10 year-time horizon is shown in Table 48, while the cost of treating one pre-symptomatic

patient with 2 SMN copies with Spinraza over a 10 year-time horizon is shown in Table 49. The budget impact per year for treating one pre-symptomatic patient with 2 SMN copies with Zolgensma instead of Spinraza is displayed in Table 50 and shows that that the total cost per year per patient is less with Zolgensma in the second year and onwards. The cumulative budget impact over 5 and 10 years is presented in Table 51. The analyses show that treating one pre-symptomatic patient with 2 SMN copies with Zolgensma instead of Spinraza would yield an additional cost of 3 996 964 DKK over a 10-year time horizon.

TABLE 48: COST PER YEAR (DKK) OF TREATING 1 PRE-SYMPTOMATIC PATIENT WITH 2 SMN COPIES WITH ZOLGENSMA

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Zolgensma: drug acquisition costs	14 531 555	0	0	0	0
Zolgensma drug administration costs	4 820	0	0	0	0
Zolgensma: total drug costs	14 536 375	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	14 536 375	0	0	0	0
SMA medical costs	305 913	181 084	122 270	119 923	118 306
Total SMA care costs	305 913	181 084	122 270	119 923	118 306
Total costs	14 842 289	181 084	122 270	119 923	118 306
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Zolgensma: drug acquisition costs	0	0	0	0	0
Zolgensma drug administration costs	0	0	0	0	0
Zolgensma: total drug costs	0	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	116 891	115 642	114 521	113 504	112 566
Total SMA care costs	116 891	115 642	114 521	113 504	112 566
Total costs	116 891	115 642	114 521	113 504	112 566

Abbreviations: DKK: Danish kronor. SMA, Spinal muscular atrophy

Table 49: cost per year (DKK) of treating 1 pre-symptomatic patient with 2 SMN copies with Spinraza

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Nusinersen: drug acquisition costs	2 650 371	1 302 593	1 300 121	1 025 376	784 132
Nusinersen: drug administration costs	23 742	11 669	11 647	9 185	7 024
Total drug costs	2 674 113	1 314 261	1 311 768	1 034 562	791 157
SMA medical costs	320 217	269 572	258 542	192 344	136 821
Total SMA care costs	320 217	269 572	258 542	192 344	136 821
Total costs	2 994 330	1 583 834	1 570 310	1 226 906	927 978
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Nusinersen: drug acquisition costs	662 159	630 650	624 913	618 652	611 887
Nusinersen: drug administration costs	5 932	5 649	5 598	5 542	5 481
Total drug costs	668 091	636 300	630 511	624 194	617 368
SMA medical costs	110 903	99 468	94 249	89 750	85 840
Total SMA care costs	110 903	99 468	94 249	89 750	85 840
Total costs	778 994	735 768	724 760	713 944	703 208

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

Table 50: Budget impact per year (DKK) for treating one Pre-symptomatic SMA patient with 2 SMN copies with Zolgensma instead of Spinraza

Time horizon	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	11 862 262	-1 314 261	-1 311 768	-1 034 562	-791 157
SMA care budget impact	-14 304	-88 489	-136 273	-72 421	-18 515
Total budget impact	11 847 959	-1 402 750	-1 448 040	-1 106 983	-809 672
Time horizon	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Pharmacy budget impact	-668 091	-636 300	-630 511	-624 194	-617 368
SMA care budget impact	5 988	16 174	20 273	23 754	26 726
Total budget impact	-662 103	-620 126	-610 238	-600 440	-590 642

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

Table 51: Cumulative budget impact (DKK) for treating one Pre-symptomatic SMA patient with 2 SMN copies with Zolgensma instead of Spinraza

Time horizon	Years 1-5	Years 1-10
Pharmacy budget impact	7 410 515	4 234 050
SMA care budget impact	-330 001	-237 087
Total	7 080 514	3 996 964

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

12.2 Result for pre-symptomatic patients with 3 SMN copies

The results of the budget impact analysis for pre-symptomatic patients with 3 SMN copies are displayed in Table 52, Table 53 and Table 54 below. The results show that based on similar assumptions of incident and prevalent cases of SMA type 1, the budget impact is the largest in the first year (where also two treatment switches from Spinraza to Zolgensma is assumed) and then drops significantly already in the second year and thereafter. The cumulative budget impact over 5 and 10 years is presented in Table 55 and shows that the total additional cost by introducing Zolgensma to pre-symptomatic patients with 2 SMN copies would [redacted] DKK over 5 years, and [redacted] DKK over 10 years.

Table 52: cost per year (DKK) for pre-symptomatic cohort with 3 SMN copies with pre-approved reimbursement for Zolgensma

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

[redacted]

Table 53: cost per year (DKK) for pre-symptomatic cohort with 3 SMN copies without pre-approved reimbursement for Zolgensma

[redacted]

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

[redacted]

Table 54: Budget impact per year (DKK) for introduction of Zolgensma for PRE-SYMPTOMATIC cohort with 3 SMN copies

[redacted]

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

[redacted]

Table 55: Cumulative budget impact (DKK) for introduction of Zolgensma for Pre-symptomatic cohort with 3 SMN copies

[redacted]

The cost of treating one pre-symptomatic patient with 3 SMN copies with Zolgensma over a 10 year-time horizon is shown in Table 56, while the cost of treating one pre-symptomatic

patient with 3 SMN copies with Spinraza over a 10 year-time horizon is shown in Table 57. The budget impact per year for treating one pre-symptomatic patient with 3 SMN copies with Zolgensma instead of Spinraza is displayed in Table 58 and shows that that the total cost per year per patient is less with Zolgensma in the second year and onwards. The cumulative budget impact over 5 and 10 years is presented in Table 59. The analyses show that treating one pre-symptomatic SMA patient with 3 SMN copies with Zolgensma instead of Spinraza would yield an additional cost of 3 848 464 DKK over a 10-year time horizon.

TABLE 56: COST PER YEAR (DKK) OF TREATING 1 PRE-SYMPTOMATIC PATIENT WITH 3 SMN COPIES WITH ZOLGENSMA

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Zolgensma: drug acquisition costs	14 531 555	0	0	0	0
Zolgensma drug administration costs	4 820	0	0	0	0
Zolgensma: total drug costs	14 536 375	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	14 536 375	0	0	0	0
SMA medical costs	305 913	176 359	103 373	101 222	99 837
Total SMA care costs	305 913	176 359	103 373	101 222	99 837
Total costs	14 842 289	176 359	103 373	101 222	99 837
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Zolgensma: drug acquisition costs	0	0	0	0	0
Zolgensma drug administration costs	0	0	0	0	0
Zolgensma: total drug costs	0	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	98 687	97 739	96 950	96 294	95 746
Total SMA care costs	98 687	97 739	96 950	96 294	95 746
Total costs	98 687	97 739	96 950	96 294	95 746

Abbreviations: DKK: Danish kronor. SMA, Spinal muscular atrophy

Table 57: cost per year (DKK) of treating 1 pre-symptomatic patient with 3 SMN copies with Spinraza

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Nusinersen: drug acquisition costs	2 650 371	1 302 593	1 300 121	1 025 376	784 132
Nusinersen: drug administration costs	23 742	11 669	11 647	9 185	7 024
Total drug costs	2 674 113	1 314 261	1 311 768	1 034 562	791 157
SMA medical costs	320 217	269 572	258 542	192 344	136 821
Total SMA care costs	320 217	269 572	258 542	192 344	136 821
Total costs	2 994 330	1 583 834	1 570 310	1 226 906	927 978
	Year 6	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Nusinersen: drug acquisition costs	662 159	630 650	624 913	618 652	611 887
Nusinersen: drug administration costs	5 932	5 649	5 598	5 542	5 481
Total drug costs	668 091	636 300	630 511	624 194	617 368
SMA medical costs	110 903	99 468	94 249	89 750	85 840
Total SMA care costs	110 903	99 468	94 249	89 750	85 840
Total costs	778 994	735 768	724 760	713 944	703 208

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy

Table 58: Budget impact per year (DKK) for treating one Pre-symptomatic SMA patient with 3 SMN copies with Zolgensma instead of Spinraza

Time horizon	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	11 862 262	-1 314 261	-1 311 768	-1 034 562	-791 157
SMA care budget impact	-14 304	-93 213	-155 169	-91 122	-36 985
Total budget impact	11 847 959	-1 407 474	-1 466 937	-1 125 684	-828 142
Time horizon	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Pharmacy budget impact	-668 091	-636 300	-630 511	-624 194	-617 368
SMA care budget impact	-12 216	-1 729	2 701	6 544	9 905
Total budget impact	-680 306	-638 029	-627 810	-617 650	-607 463

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

Table 59: Cumulative budget impact (DKK) for treating one Pre-symptomatic SMA patient with 3 SMN copies with Zolgensma instead of Spinraza

Time horizon	Years 1-5	Years 1-10
Pharmacy budget impact	7 410 515	4 234 050
SMA care budget impact	-390 793	-385 586
Total	7 019 722	3 848 464

Abbreviations: DKK: Danish kronor, SMA, Spinal muscular atrophy
Negative values indicate that treatment with Zolgensma is cost saving.

13 Discussion

Using economic modelling, this analysis has estimated the long-term costs of treatment with Zolgensma for SMA Type 1. This estimation is based upon the achievement of clinically important milestones during the follow-up times in currently available clinical trials. Beyond this, extrapolation of survival and health care needs have been made using data for SMA types 2 and 3 as a proxy.

The cost-analysis for SMA type 1 shows that compared to treatment with Spinraza, Zolgensma is associated with increased costs (2 975 768DKK per patient over a lifetime, discounted at 4.0% for the first 35 years, and 3.0% thereafter). In part, this increase stem from the higher survival (18.40 undiscounted life years gained, and 7.50 discounted life years gained) achieved through the treatment.

Among surviving patients, the annual costs are expected to be lower for patients treated with Zolgensma than for patients treated with Spinraza, due to the higher proportion of patients achieving higher motor milestones and health states.

Sensitivity analysis show that the drug acquisition cost for Zolgensma and Spinraza are the biggest individual drivers of overall costs. Other important parameters are the rate of discontinuation for Spinraza treatment. For the cost-effectiveness analysis, the health stat utility values are important as well, particularly for health state C.

There are no head-to-head trials comparing Zolgensma to Spinraza so all base case pairwise analyses use naïve, unanchored comparisons, all in line with the protocol retrieved from the Danish Medicine's council. Thus, the model makes no adjustment for differences in patient characteristics between the studies used for each treatment arm. To address this, efforts have been made to source natural history data for overall survival and event-free survival in a SMA type 1 population that resembles START and STR1VE-US as close as possible. For Spinraza, a subgroup analysis of ENDEAR was used to make the data as comparable to the pooled data from START and STR1VE-US as possible, whilst also aligning well with Danish clinical practice.

The modelling approach used (Markov state-transition) was deemed the most adequate to reflect the natural history of SMA type 1, with the data available. The model also accounts for the chronic nature of the condition by taking a lifetime perspective and accommodates a spectrum of motor function health states. The primary strength of this economic analysis is that the model framework was conceptualised with clinical experts, drawing on frameworks developed for Spinraza and models for similar rare genetic disorders. This enabled the model to capture the patient experience in a reasonable number of health states.

The cost-analysis for pre-symptomatic patients where it was assumed that Zolgensma would have the same clinical effect as Spinraza (similar survival and milestone achievement),

demonstrated that treatment with Zolgensma could lead to substantial cost-savings compared to Spinraza if the treatment duration is long. Treatment with Zolgensma incurs a high one-time cost but avoids the cost of continuous treatment with Spinraza. The cost-analysis shows that over a lifetime, introducing Zolgensma would save a total of 29 565 291 DKK per patient with 2 copies of SMN2, assuming a discount rate of 4.0% (3.0% beyond year 35). For patients with 3 SMN2 copies, a total of 32 864 746 DKK could be saved per patient.

The budget impact analysis for SMA type 1 patients and for pre-symptomatic patients where all costs and health outcomes data are drawn from the cost-effectiveness models for SMA type 1 and pre-symptomatic patients, shows that the additional costs would highest in the first year (where it is assumed that two patients would receive Zolgensma instead of Spinraza) and then drops significantly already in the second year and thereafter decreases annually during the first 10 years.

14 Appendix

14.1 Appendix A: Extrapolations to the C- state based on a segmented approach

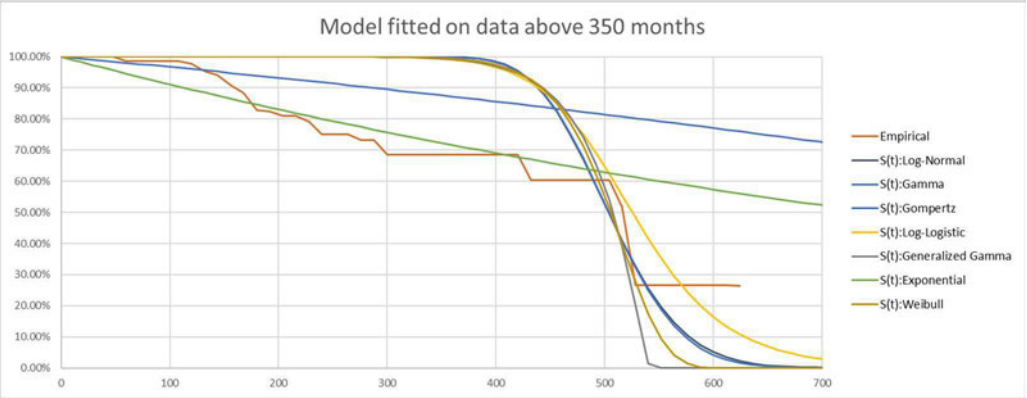
In order to address DMC's concerns regarding the selected distributions of the State C Kaplan-Meier extrapolations, we have conducted a segmented model where data have been fitted separately up to 350 months and after 350 months. On both the data below 350 months and above 350 months the Log-Normal distribution proved to be the best fitting model according to AIC and BIC (see Table 60, Figure 19 and Figure 20).

TABLE 60: MODELS FIT ON DATA BELOW AND ABOVE 350 MONTHS

Parametric model	C-state	
	AIC	BIC
Fit statistics on data below 350 months		
Exponential	915.8963	919.0083
Weibull	897.4798	903.7037
Log-Normal	890.5588	896.7828
Log-Logistic	940.0844	946.3083
Generalized Gamma	892.5585	901.8945
Gompertz	996.0828	1002.307
Gamma	894.6347	900.8586
Fit statistics on data above 350 months		
Exponential	311.7527	313.7417
Weibull	192.5866	196.5645
Log-Normal	192.1536	196.1316
Log-Logistic	198.6562	202.6341
Generalized Gamma	194.2878	200.2547
Gompertz	316.3249	320.3029
Gamma	192.1633	196.1412

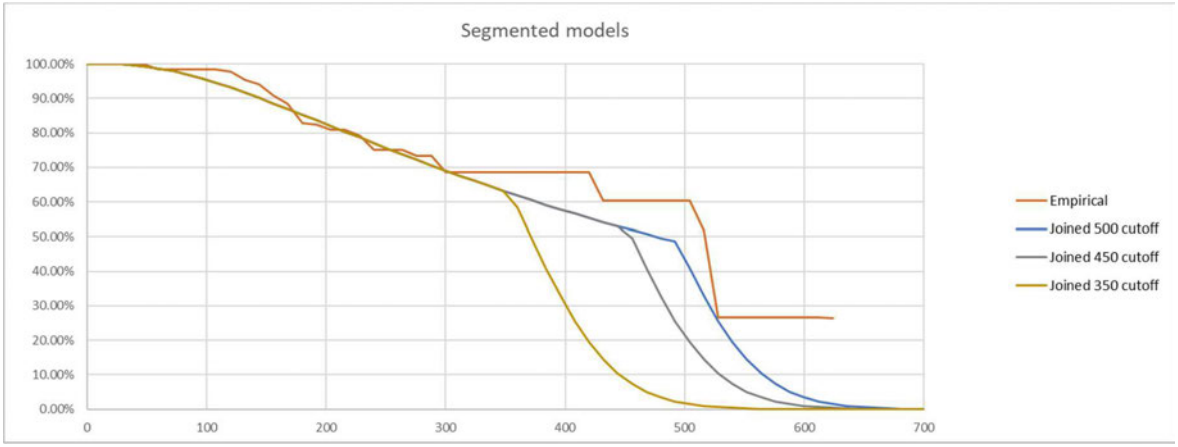
FIGURE 19: MODELS FITTED ON DATA BELOW 350 MONTHS

FIGURE 20: MODELS FITTED ON DATA ABOVE 350 MONTHS



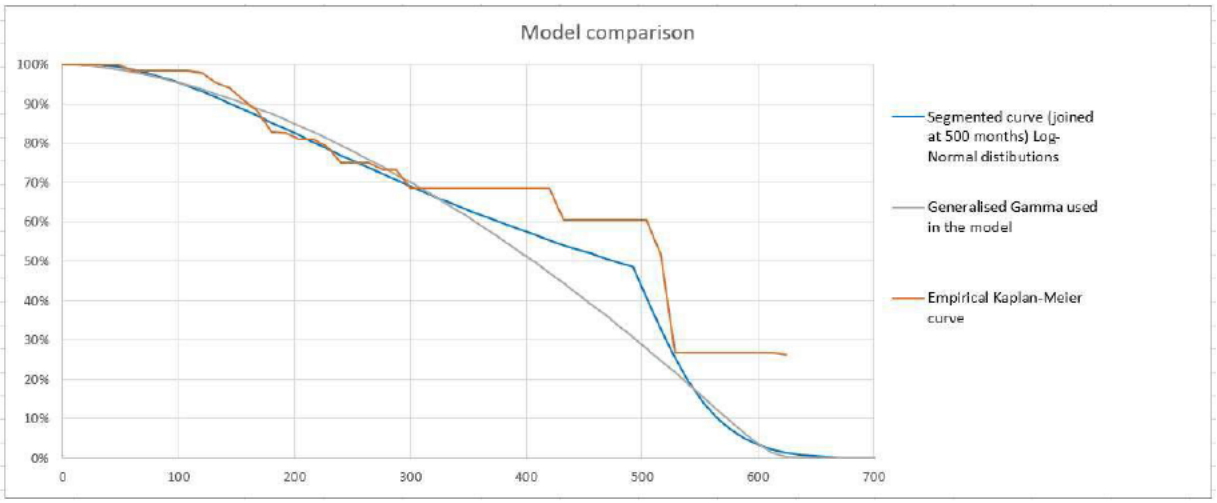
Thereafter we have used the two Log-Normal models to create a segmented model as per DMC's suggestion. We have tested several different timepoints to join the two curves, for example at 350 months, 450 months and 500 months (Figure 21).

FIGURE 21: SEGMENTED MODEL, WITH MODELS FITTED SEPARATELY ON DATA ABOVE AND BELOW 350 MONTHS



The visually best fitting segmented curve was deemed to be the one where we joined the two survival curves at 500 months. We have then compared this segmented survival curve to the Generalized Gamma distribution used in the model (see Figure 22) and compared the area under the curve (AUC) of the two models.

FIGURE 22: MODEL COMPARISON



We observed marginal differences in the AUC until 300 months (25 years) and until 400 months (34 years): 3.11 months less and 0.43 months for the Generalized Gamma model, respectively. The difference increased by the end of the tail at 600 months (50 years) to 13.2 months more for the segmented model. However, considering the fact that the CE model predicts lower survival for the CF patients (<30 years) than the timepoint where we start seeing differences between the curves (>35 years), it is highly unlikely that implementing this segmented curve would have a significant effect on the ICER. Thus, we have not implemented this curve in the CE model.

Furthermore, as per original request by DMC, we also included the results of applying a cut-off of 300 months (Figure 23 and Figure 24), as well as the segmented model using these extrapolations (Figure 25). The statistics for the models fitted on data below and above 300 months are presented in Table 61.

The main reason we deemed that fitting models on data below and above 350 months was more appropriate than using the suggested 300 cut-offs is the better fits obtained at the tail (i.e. on data above 350 months). Please see Figure 21 in comparison with Figure 20.

TABLE 61: MODELS FITTED ON DATA BELOW AND ABOVE 300 MONTHS

Parametric model	C-state	
	AIC	BIC

Fit statistics on data below 300 months		
Exponential	847.9621	850.9457
Weibull	831.9281	837.8954
Log-Normal	**825.1456**	**831.1128**
Log-Logistic	867.7826	873.7498
Generalized Gamma	827.1439	836.0947
Gompertz	918.8261	924.7933
Gamma	829.1593	835.1265
Fit statistics on data above 300 months		
Exponential	385.3861	387.6902
Weibull	250.569	255.1771
Log-Normal	**248.0356**	**252.6438**
Log-Logistic	263.3183	267.9264
Generalized Gamma	249.624	256.5361
Gompertz	395.1455	399.7537
Gamma	248.2598	252.8679

FIGURE 23:MODELS FITTED ON DATA BELOW 300 MONTHS

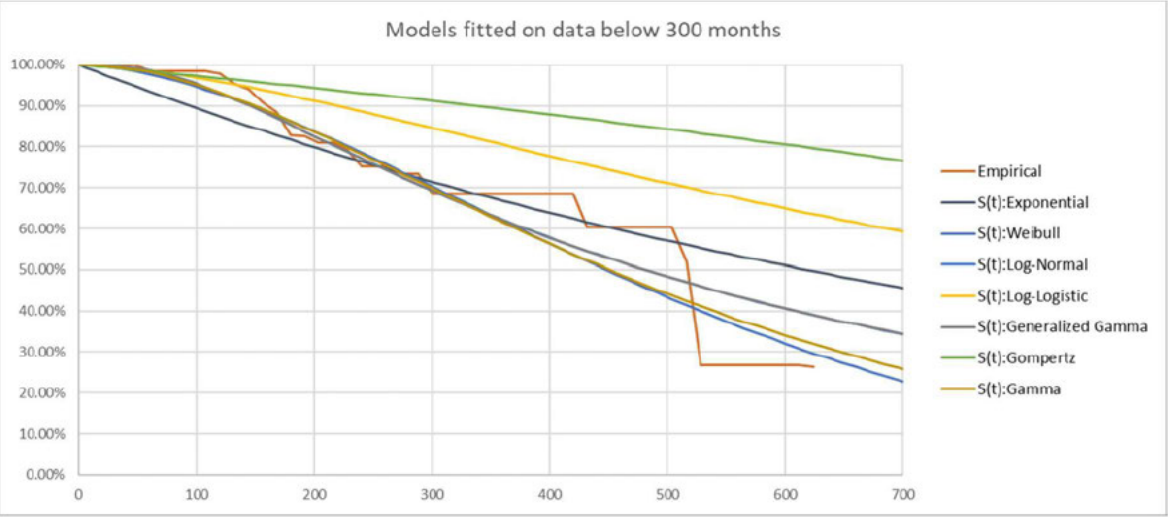


FIGURE 24: MODELS FITTED ON DATA ABOVE 300 MONTHS

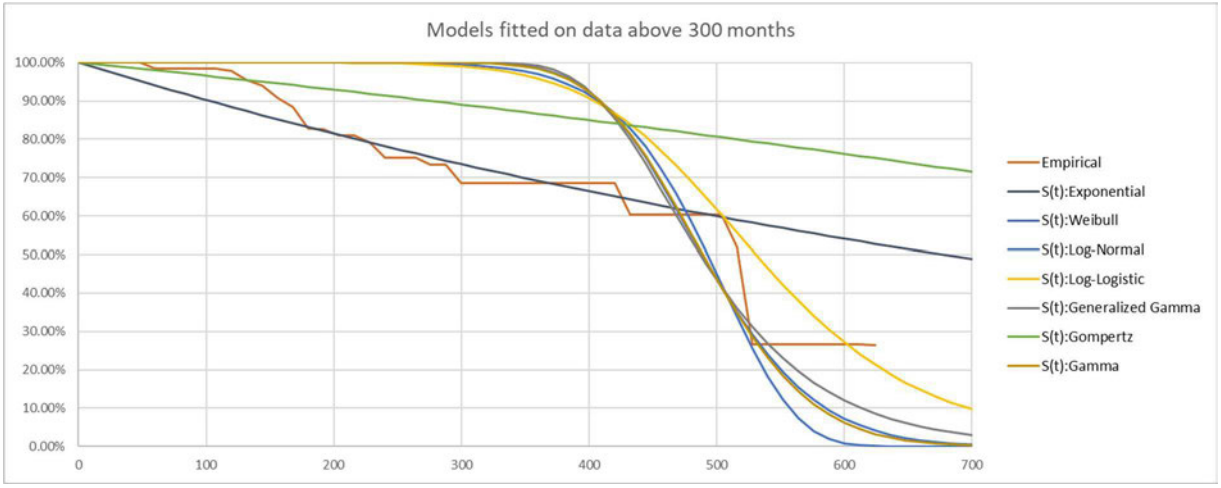
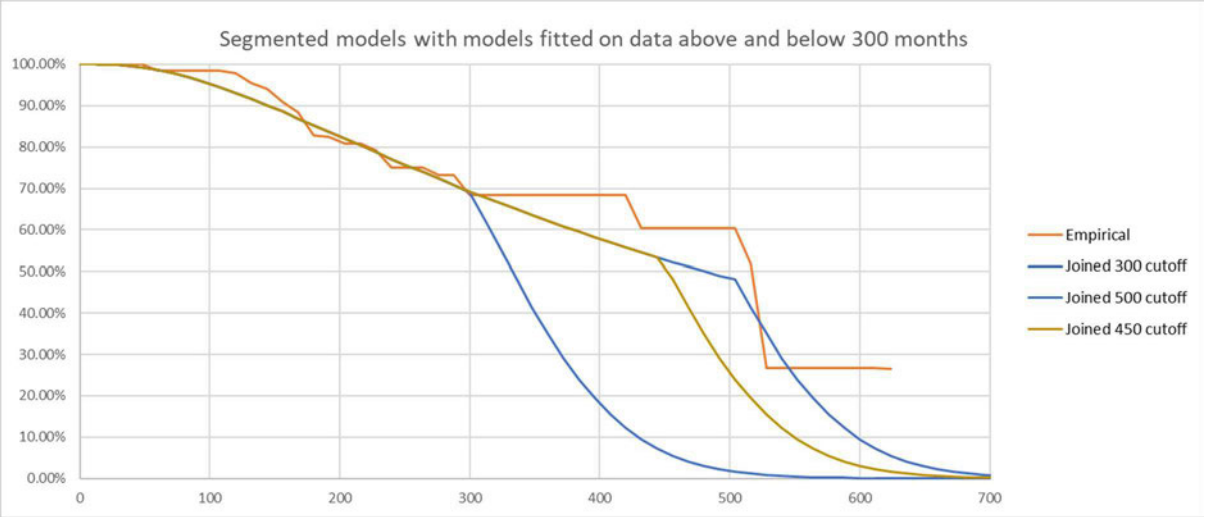


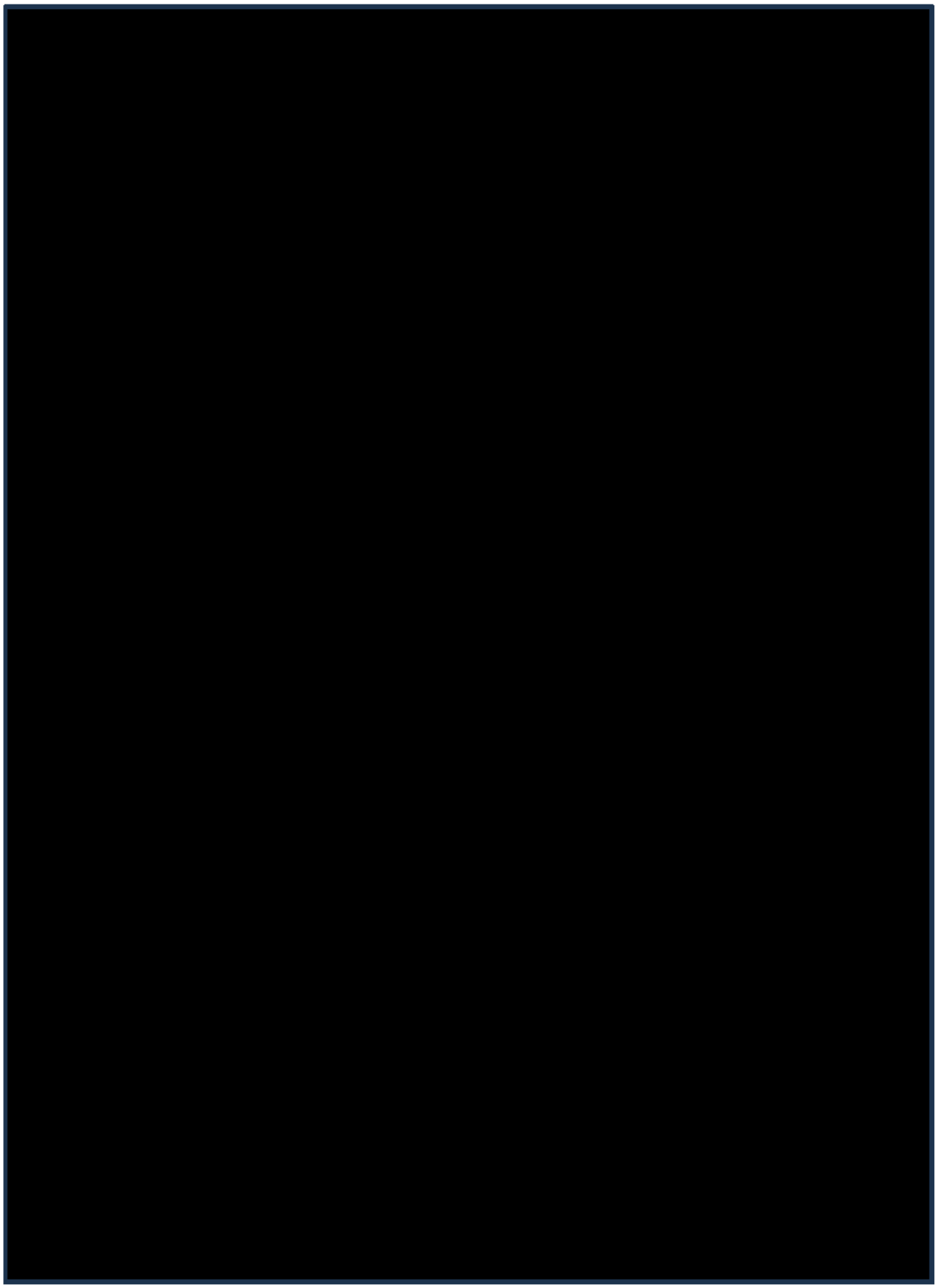
FIGURE 25: SEGMENTED MODEL, WITH MODELS FITTED SEPARATELY ON DATA ABOVE AND BELOW 300 MONTHS

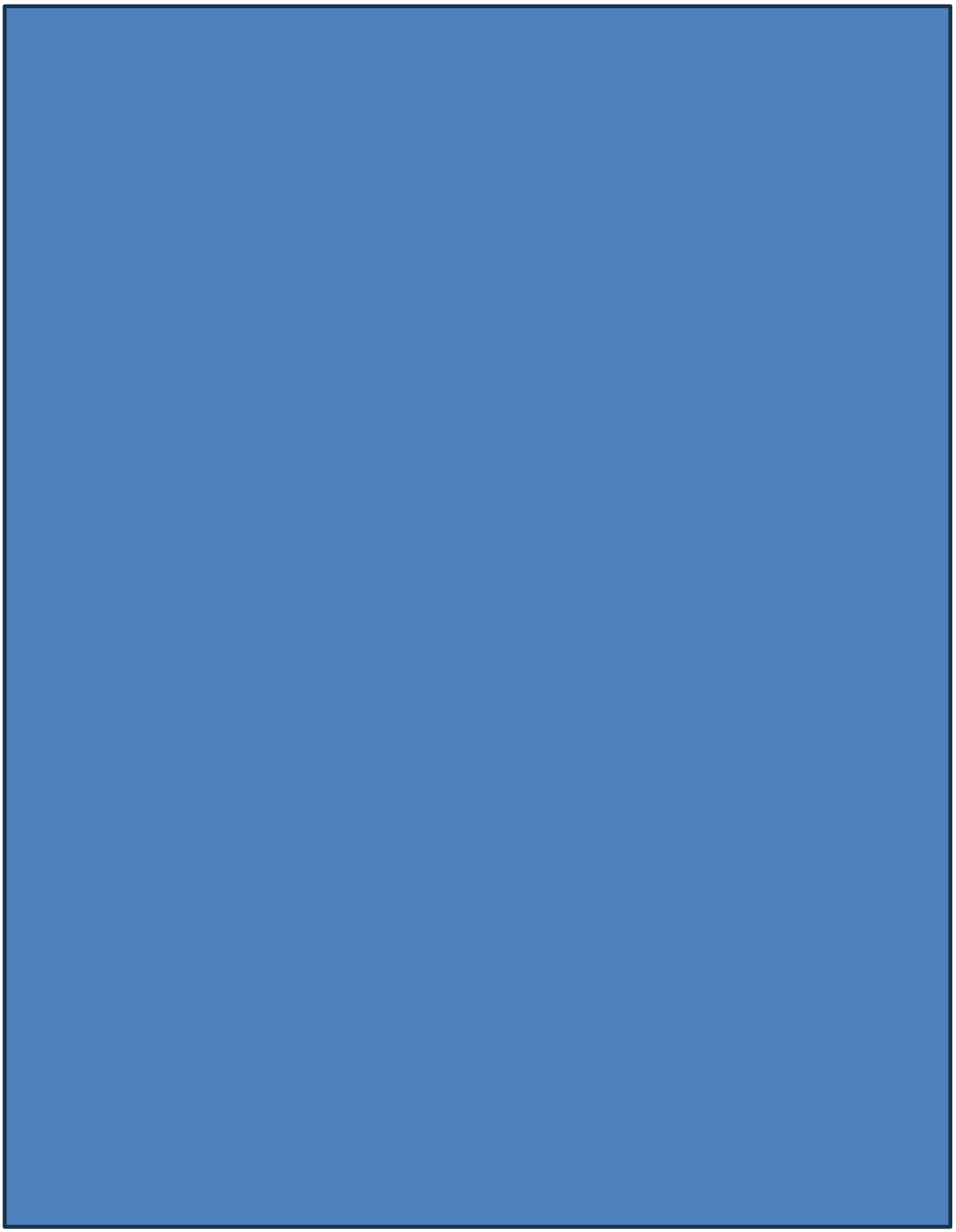


14.2 Appendix B: Health care resource use and costs

This section includes all the health care resource use assumptions and unit costs that has been used in the model. Pharmaceutical prices have been sourced from Medicinpriser.dk, DRGs from sundhedsdata.dk and specialist care costs are sourced from Kommunernes og Regionernes Løndatakontor. See below Table 62 to Table 80 for details.

Table 62. Estimated HCP medical visits per quarter, in SMA Type 1, including Danish unit costs





[redacted]

TABLE 63. ESTIMATED HCP MEDICAL VISITS PER QUARTER, IN SMA TYPE 2, INCLUDING DANISH UNIT COSTS

[redacted]

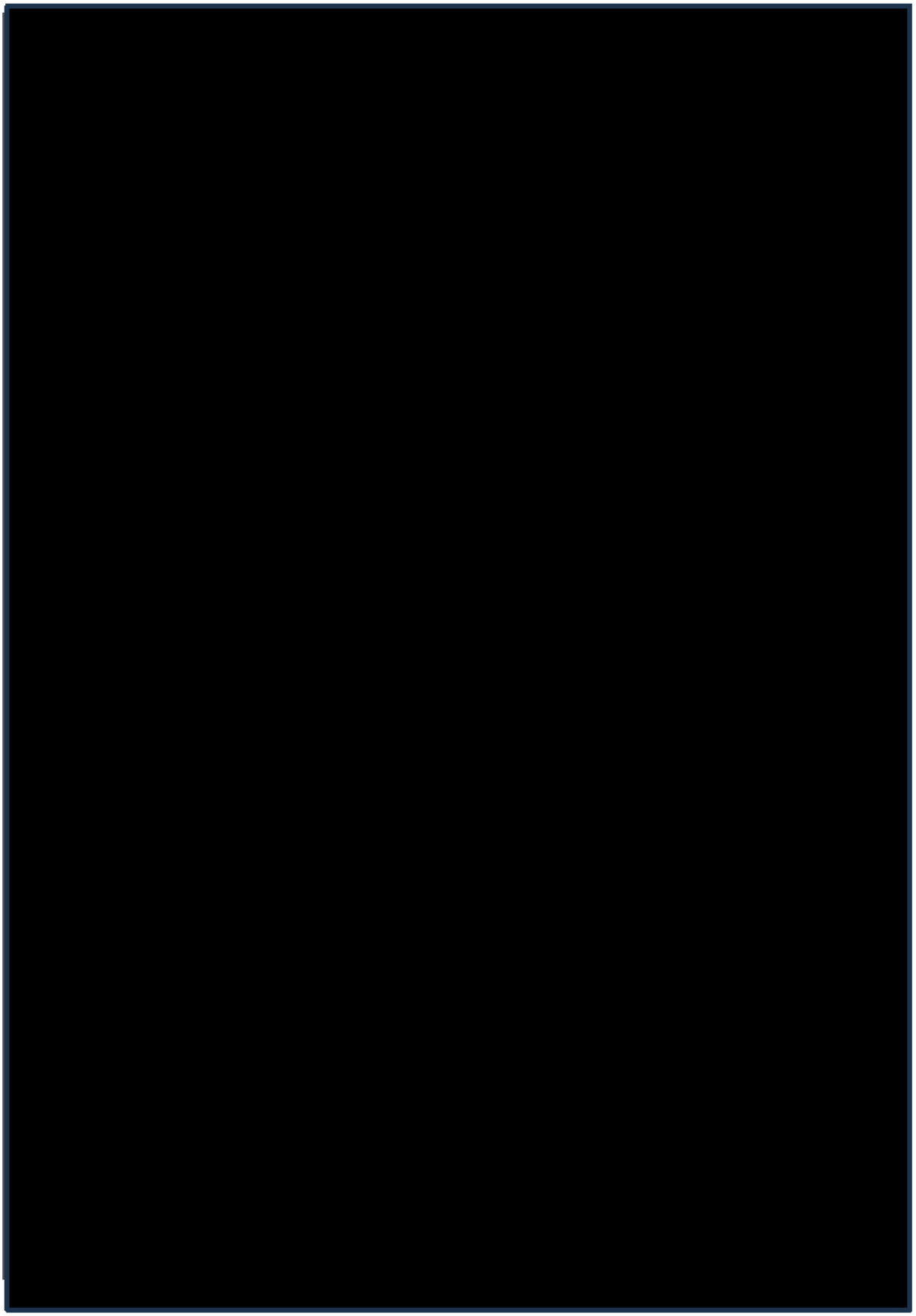
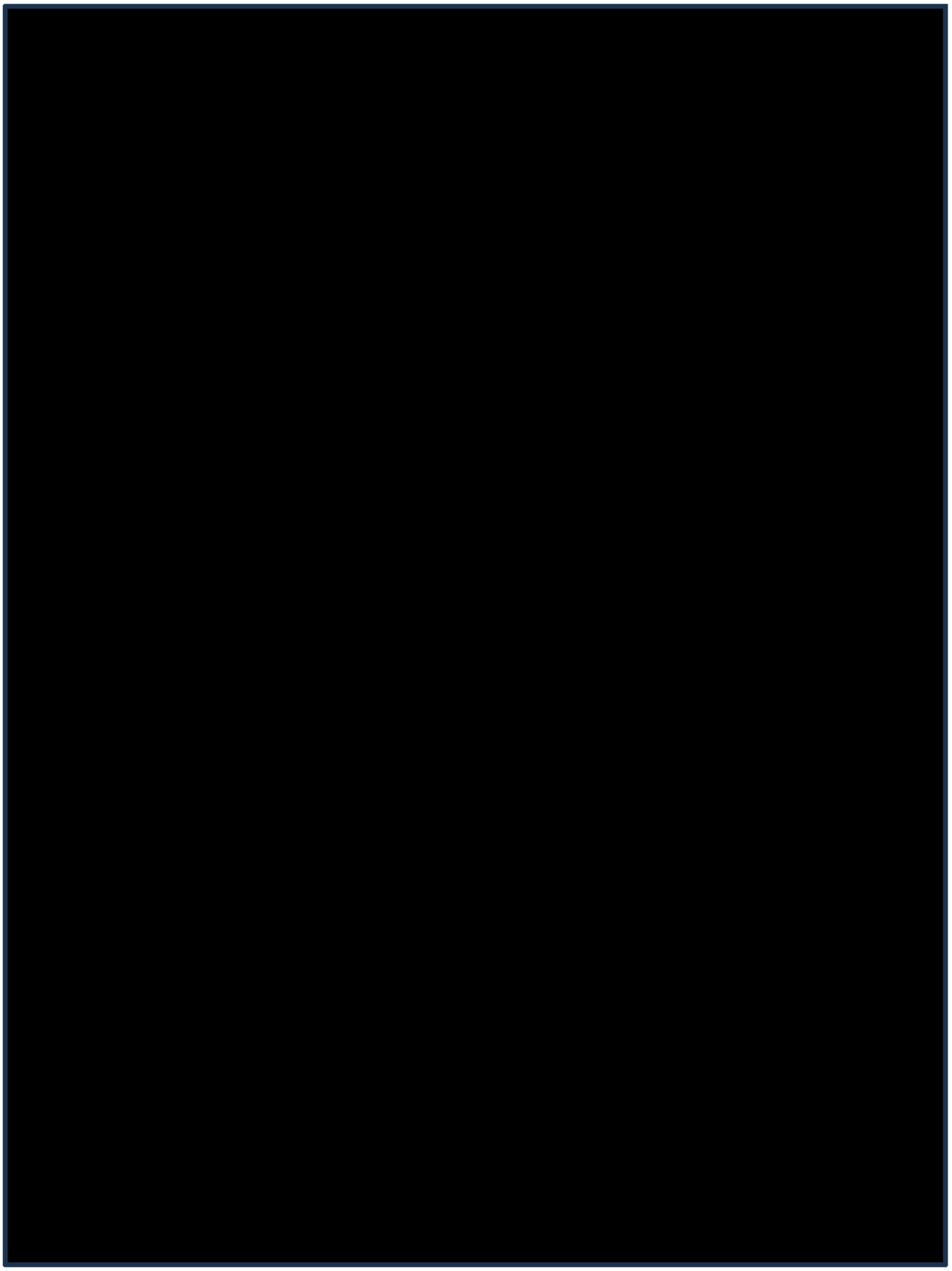
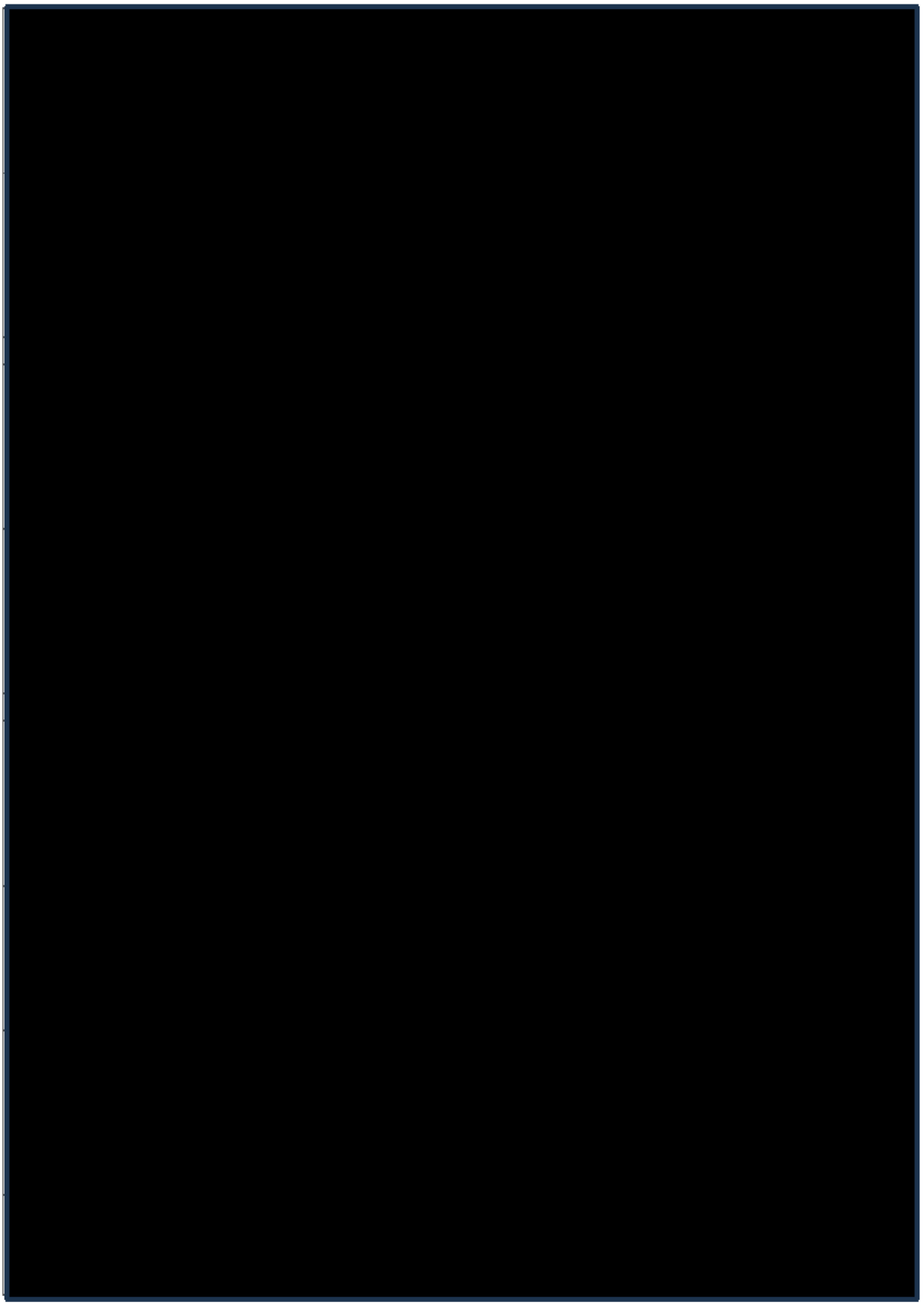


Table 64. Estimated HCP medical visits per quarter, in SMA Type 3, including Danish unit costs





[redacted]

Table 65. Estimated general practitioner and emergency visits per quarter, in SMA Type 1, including Danish unit costs

[redacted]

Table 66. Estimated general practitioner and emergency visits per quarter, in SMA Type 2, including Danish unit costs

[redacted]

Table 67. Estimated general practitioner and emergency visit per quarter, in SMA Type 3, including Danish unit costs

[redacted]

TABLE 68. ESTIMATED HOSPITALISATIONS PER QUARTER IN SMA TYPE 1, INCLUDING DANISH UNIT COSTS

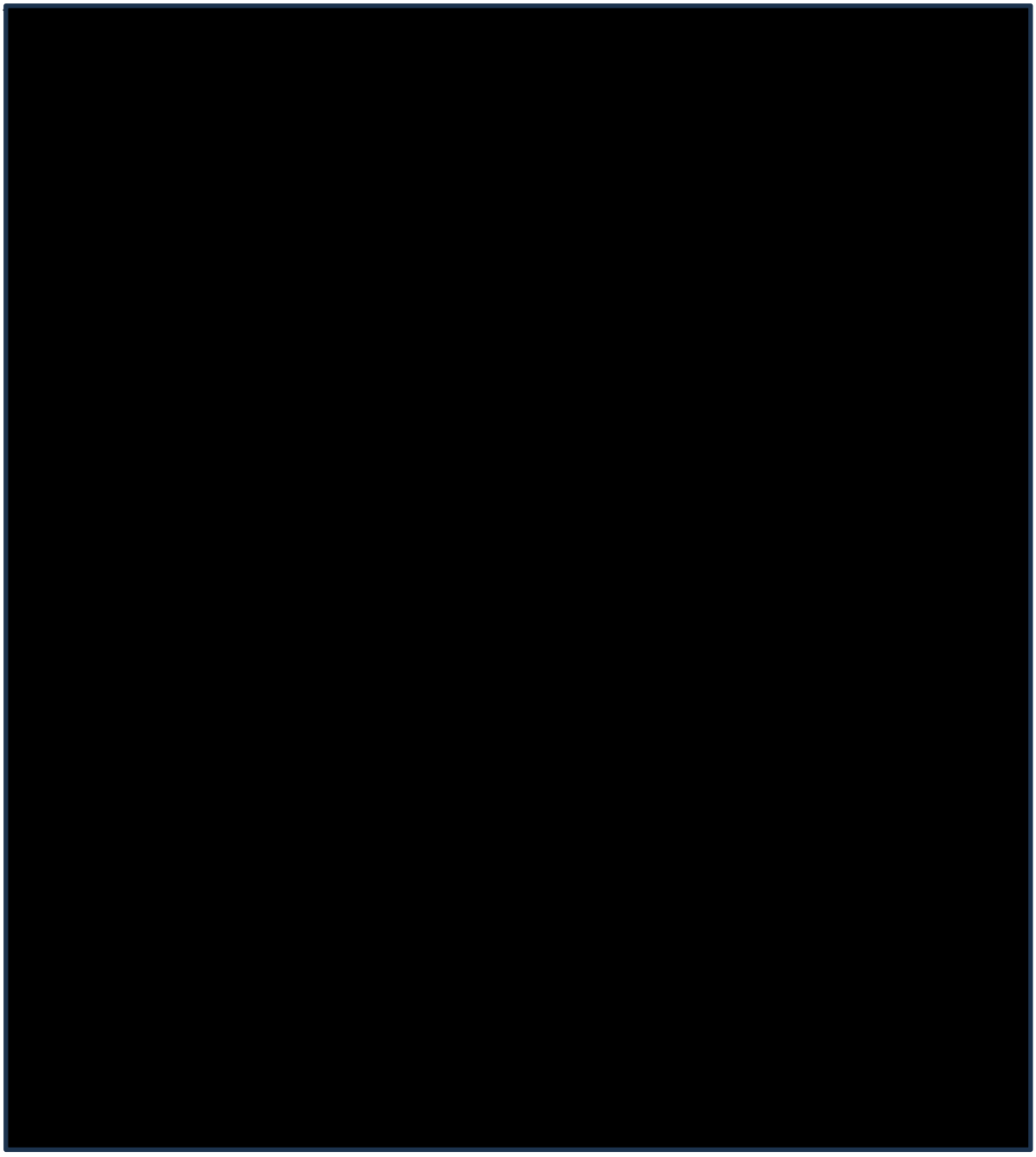


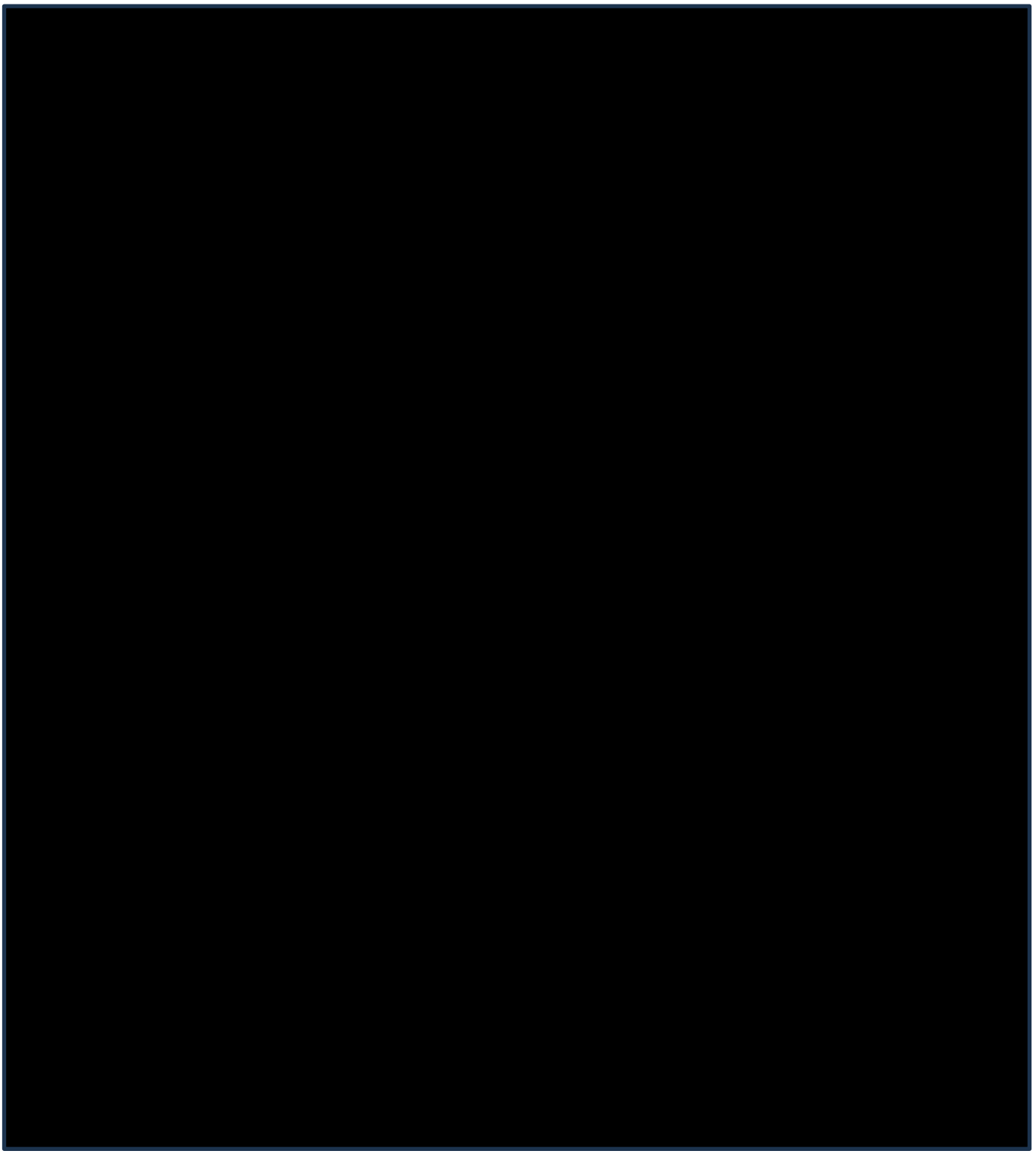
Table 69. Estimated hospitalisations per quarter in SMA Type 2, including Danish unit costs

Table 70. Estimated hospitalisations per quarter in SMA Type 3, including Danish unit costs

[redacted]

Table 71. Mobility equipment & devices for SMA Type 1, number of times resource is being used per quarter, including Danish unit costs

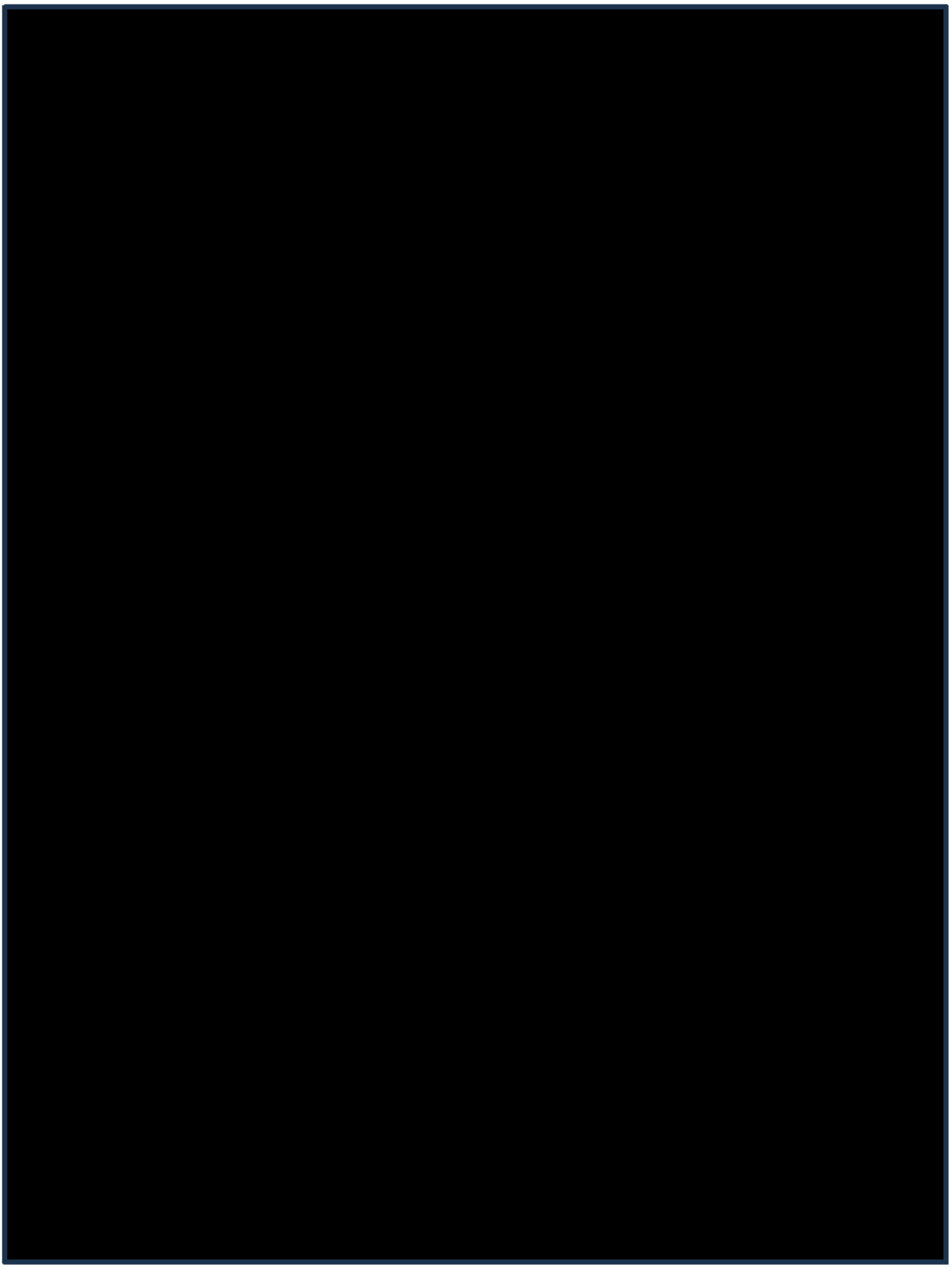
[redacted]

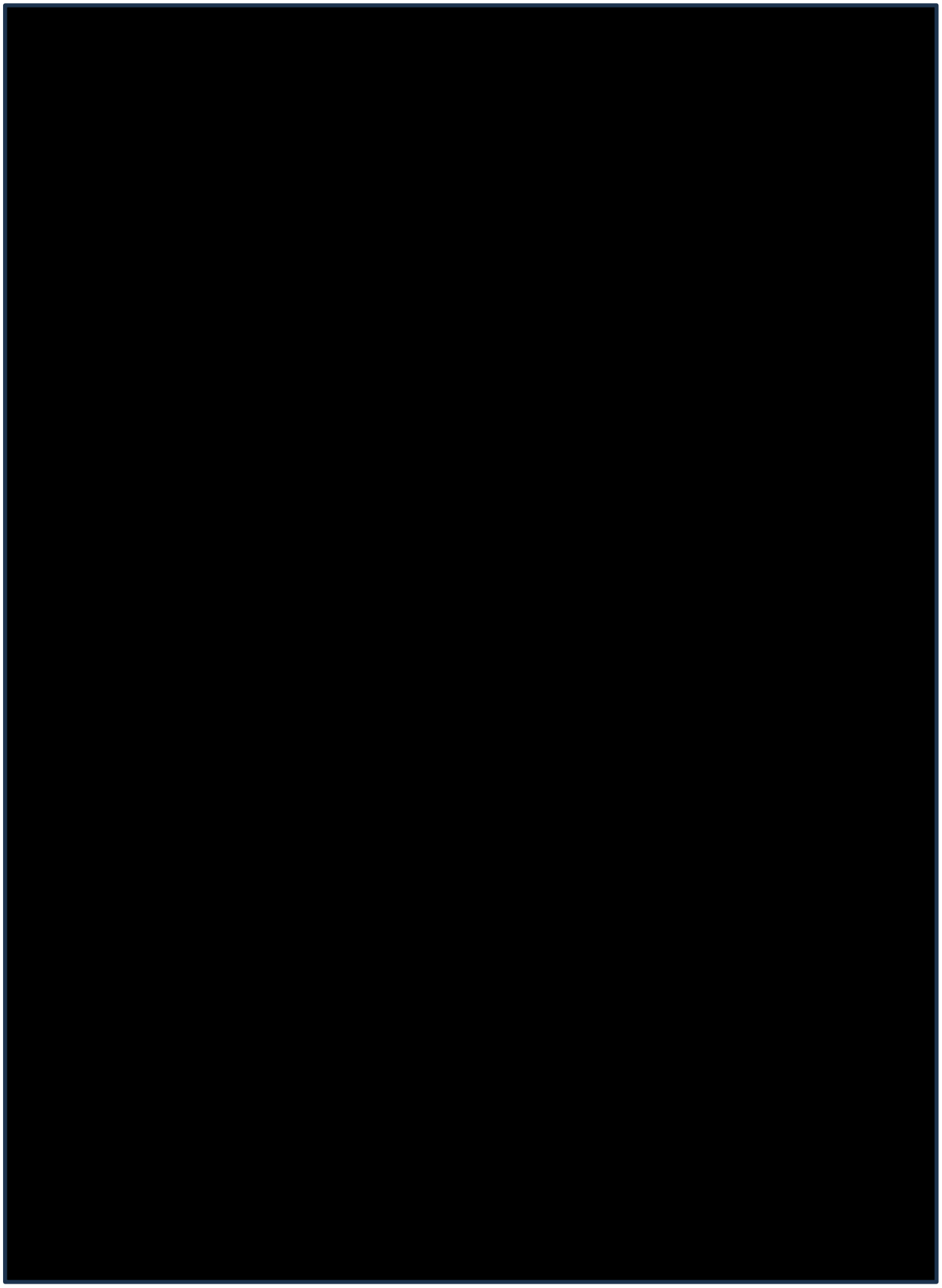


† No cost for the machine could be found for the Danish setting. As the patient would be using the machine at home, prices for respiratory assistance in the hospital setting would greatly overestimate the actual expect cost. Costs for machines from the manufacturer were considered but were not available on the website. The NICE document as is referenced, provides an estimate of daily cost of the machine in an at home setting, as is to be the most aligned value to what is expected in the Danish setting. Thus, these costs have been currency converted from GBP to DKK

Note that VAT is included where relevant.

TABLE 72. MOBILITY EQUIPMENT & DEVICES FOR SMA TYPE 2, NUMBER OF TIMES RESOURCE IS BEING USED PER QUARTER, INCLUDING DANISH UNIT COSTS

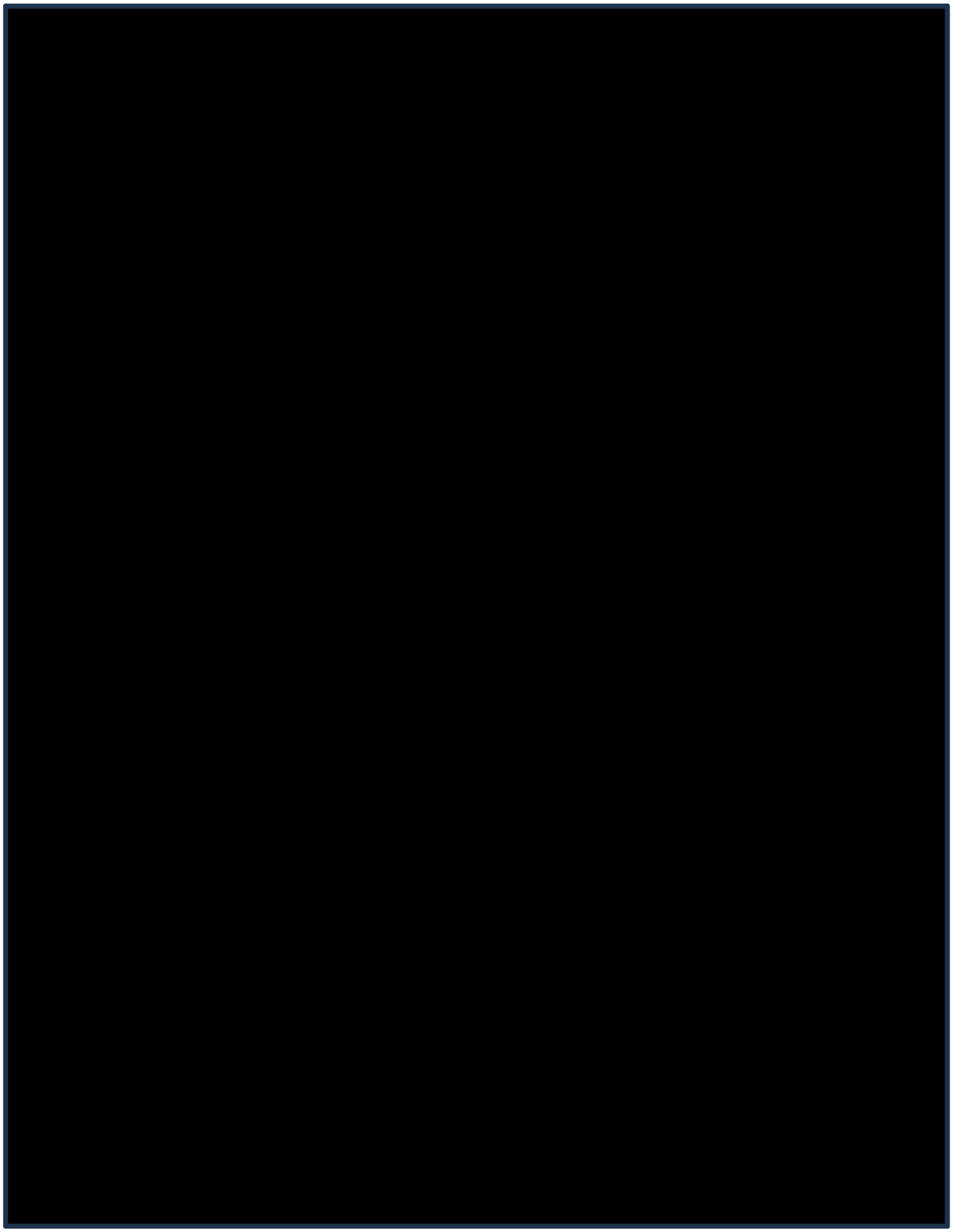


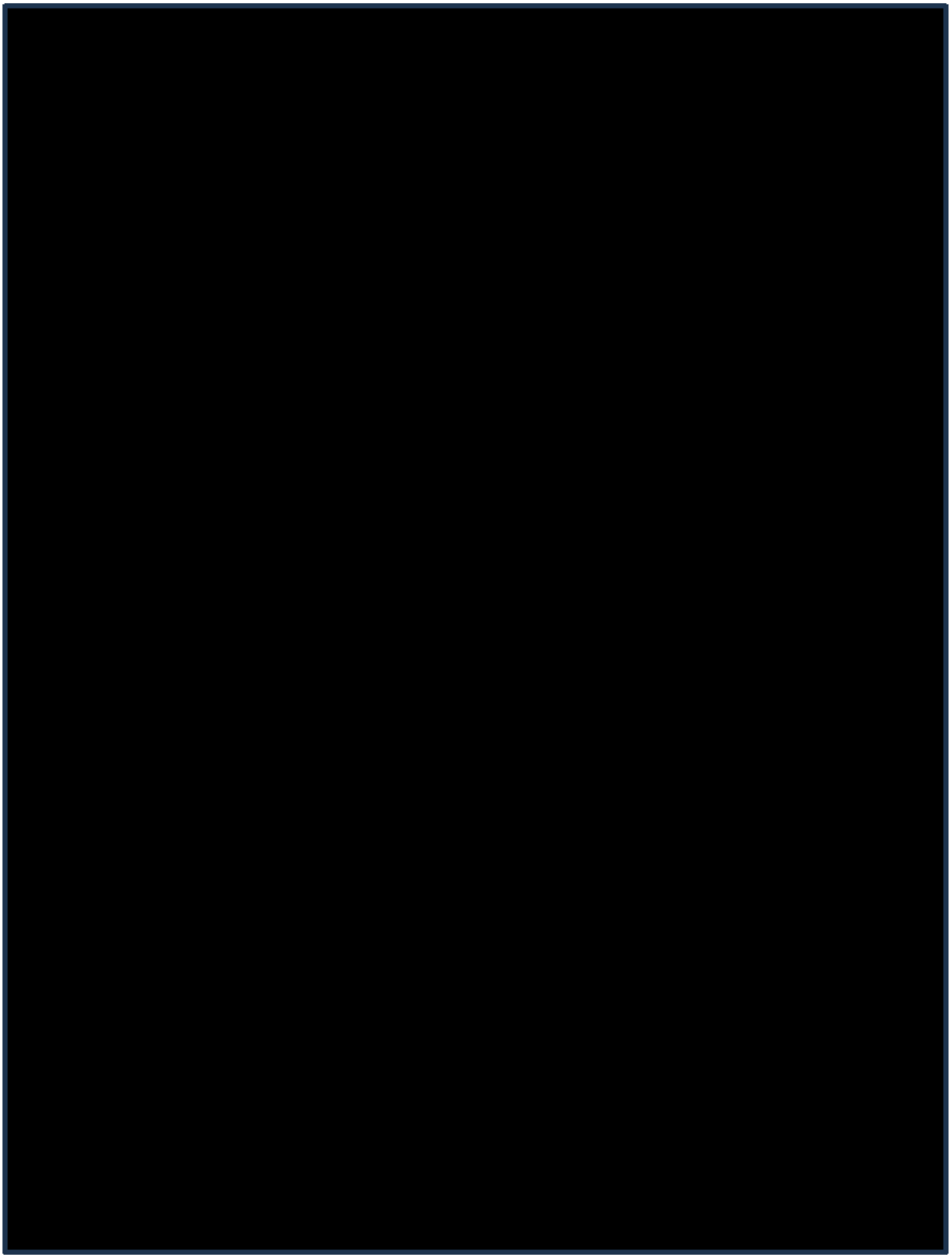


† No cost for the machine could be found for the Danish setting. As the patient would be using the machine at home, prices for respiratory assistance in the hospital setting would greatly overestimate the actual expect cost. Costs for machines from the manufacturer were considered but were not available on the website. The NICE document as is referenced, provides an estimate of daily cost of the machine in an at home setting, as is to be the most aligned value to what is expected in the Danish setting. Thus, these costs have been currency converted from GBP to DKK

Note that VAT is included where relevant.

TABLE 73. MOBILITY EQUIPMENT & DEVICES FOR SMA TYPE 3, NUMBER OF TIMES RESOURCE IS BEING USED PER QUARTER, INCLUDING DANISH UNIT COSTS

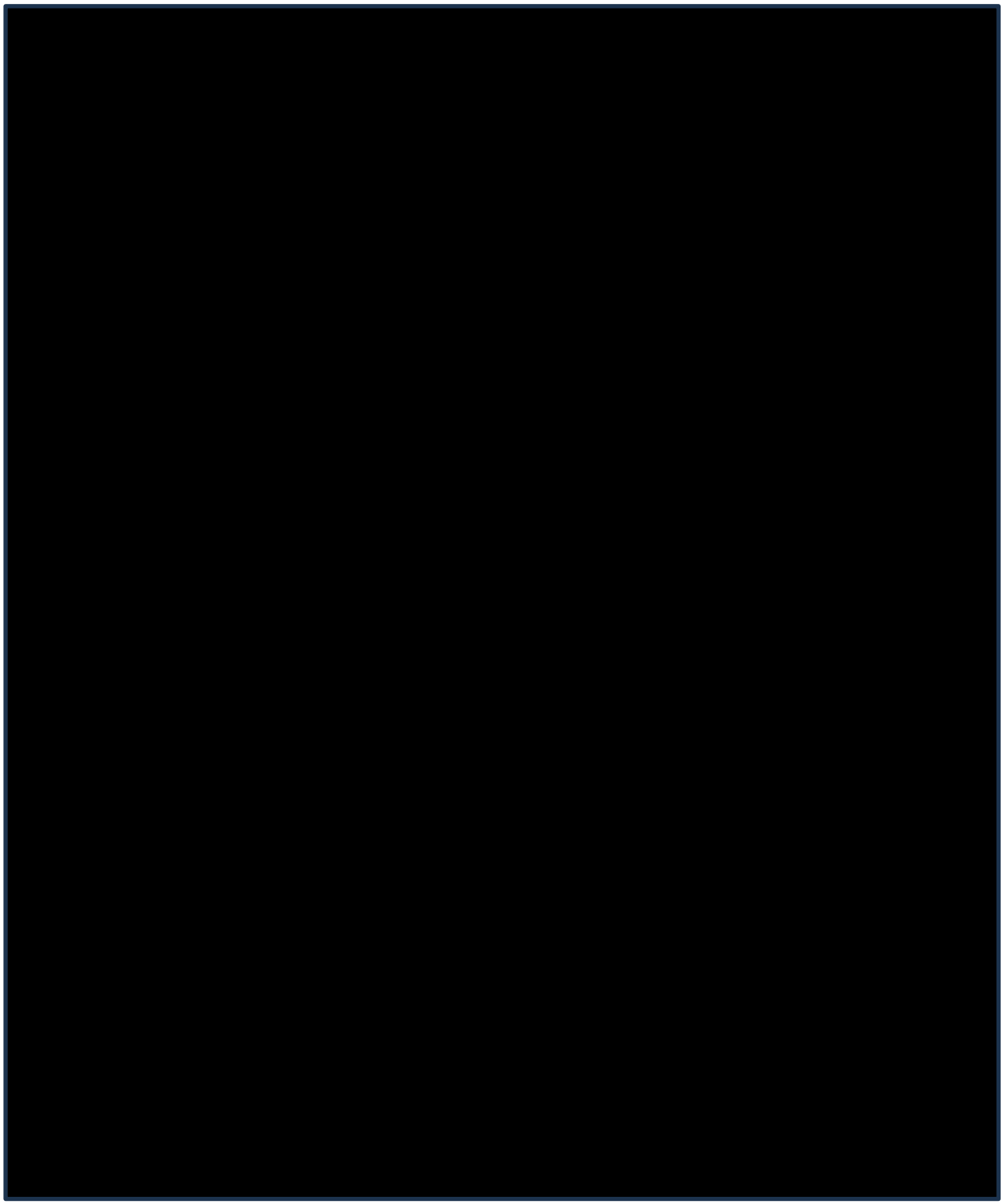




† No cost for the machine could be found for the Danish setting. As the patient would be using the machine at home, prices for respiratory assistance in the hospital setting would greatly overestimate the actual expect cost. Costs for machines from the manufacturer were considered but were not available on the website. The NICE document as is referenced, provides an estimate of daily cost of the machine in an at home setting, as is to be the most aligned value to what is expected in the Danish setting. Thus, these costs have been currency converted from GBP to DKK

Note that VAT is included where relevant.

TABLE 74. MEDICAL TESTS FOR SMA TYPE 1, NUMBER OF TIMES RESOURCE IS BEING USED PER QUARTER, INCLUDING DANISH UNIT COSTS



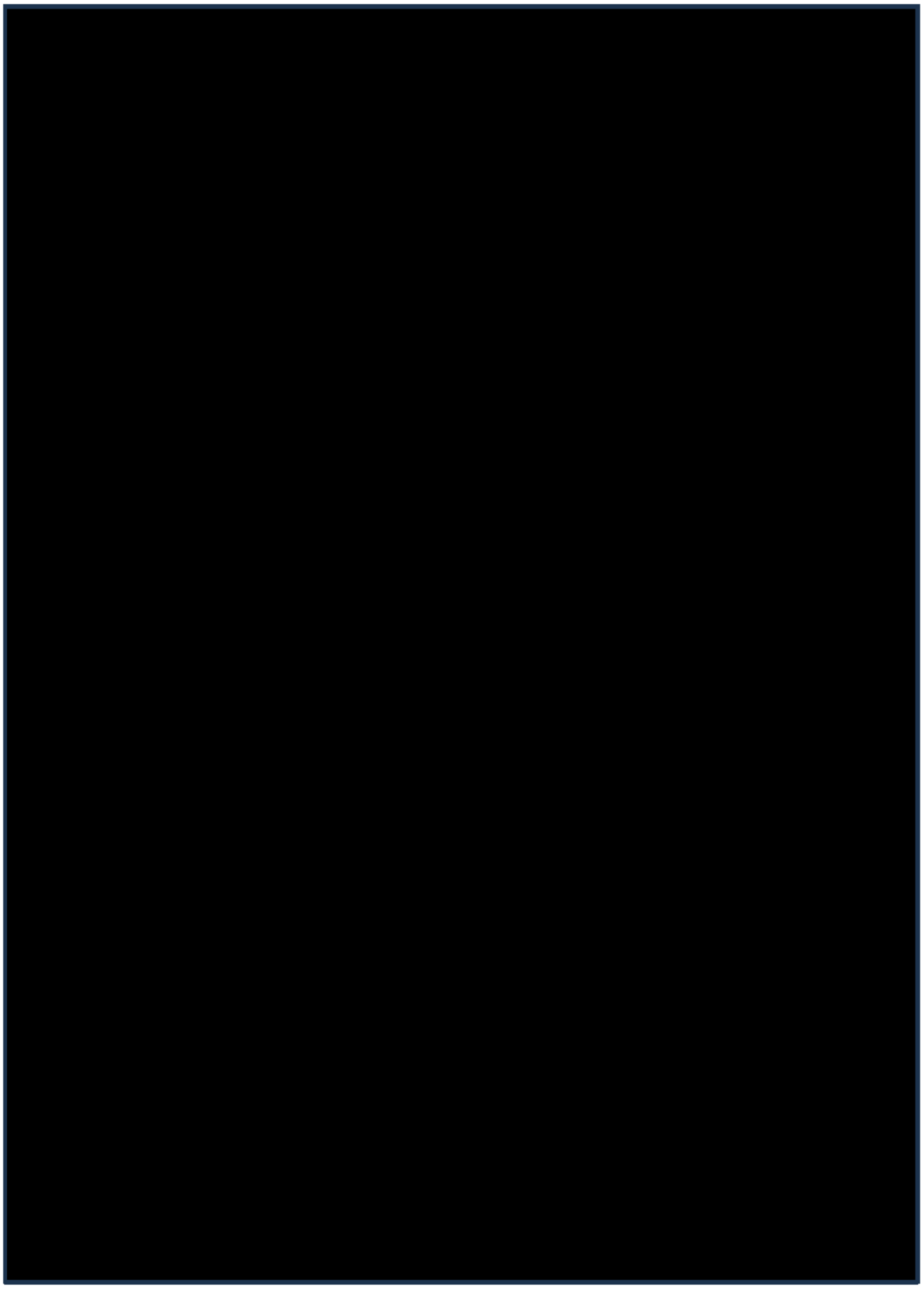
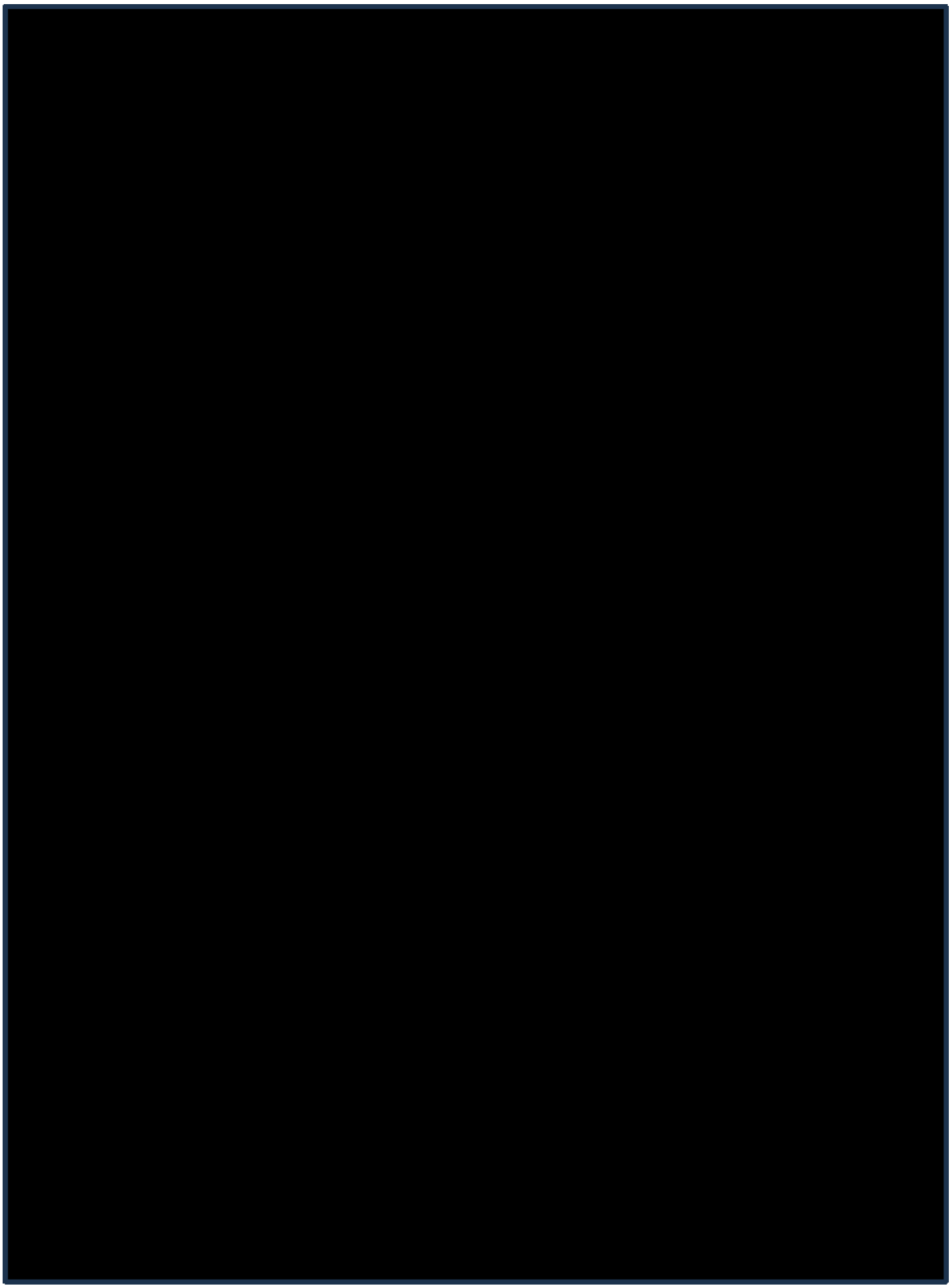
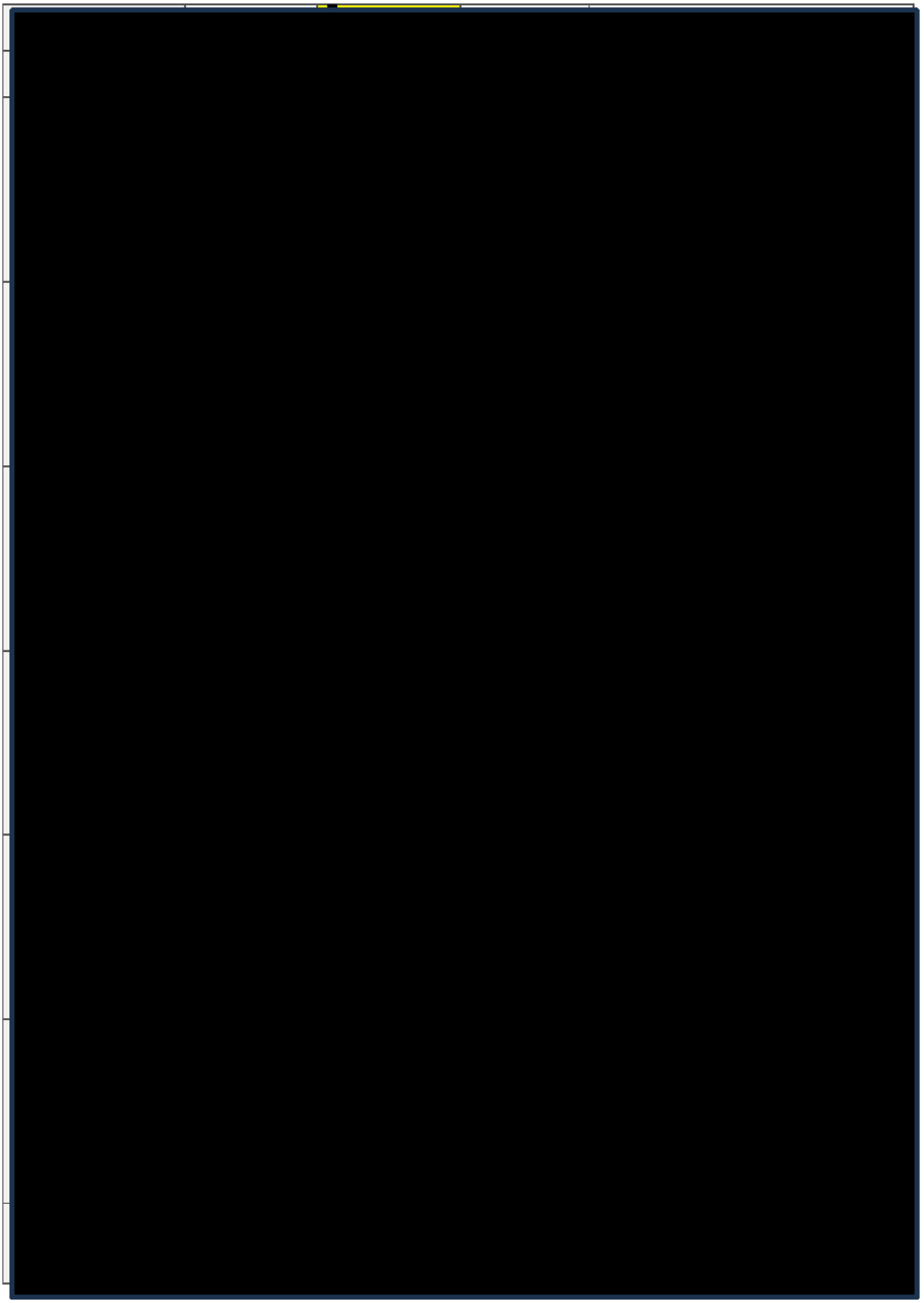


TABLE 75. MEDICAL TESTS FOR SMA TYPE 2, NUMBER OF TIMES RESOURCE IS BEING USED PER QUARTER, INCLUDING DANISH UNIT COSTS





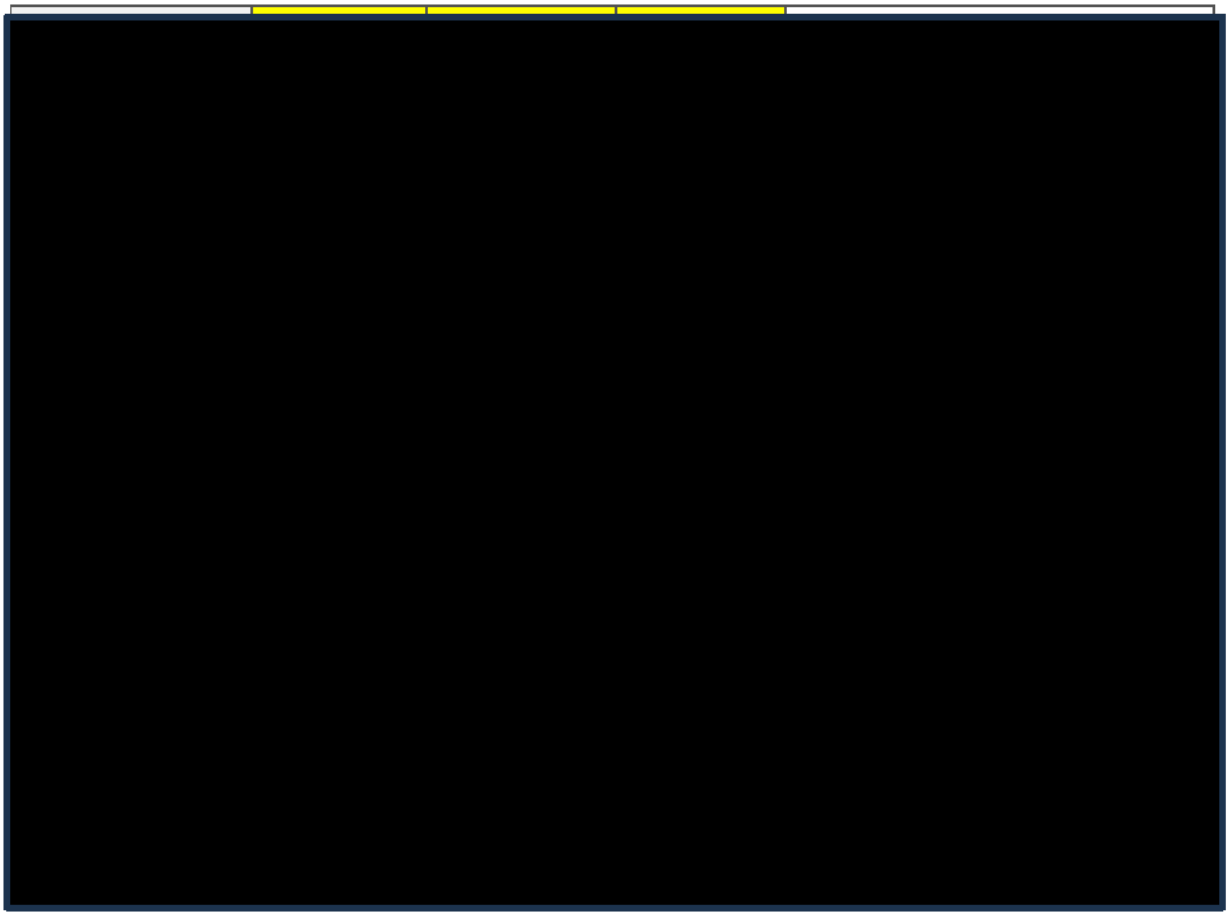
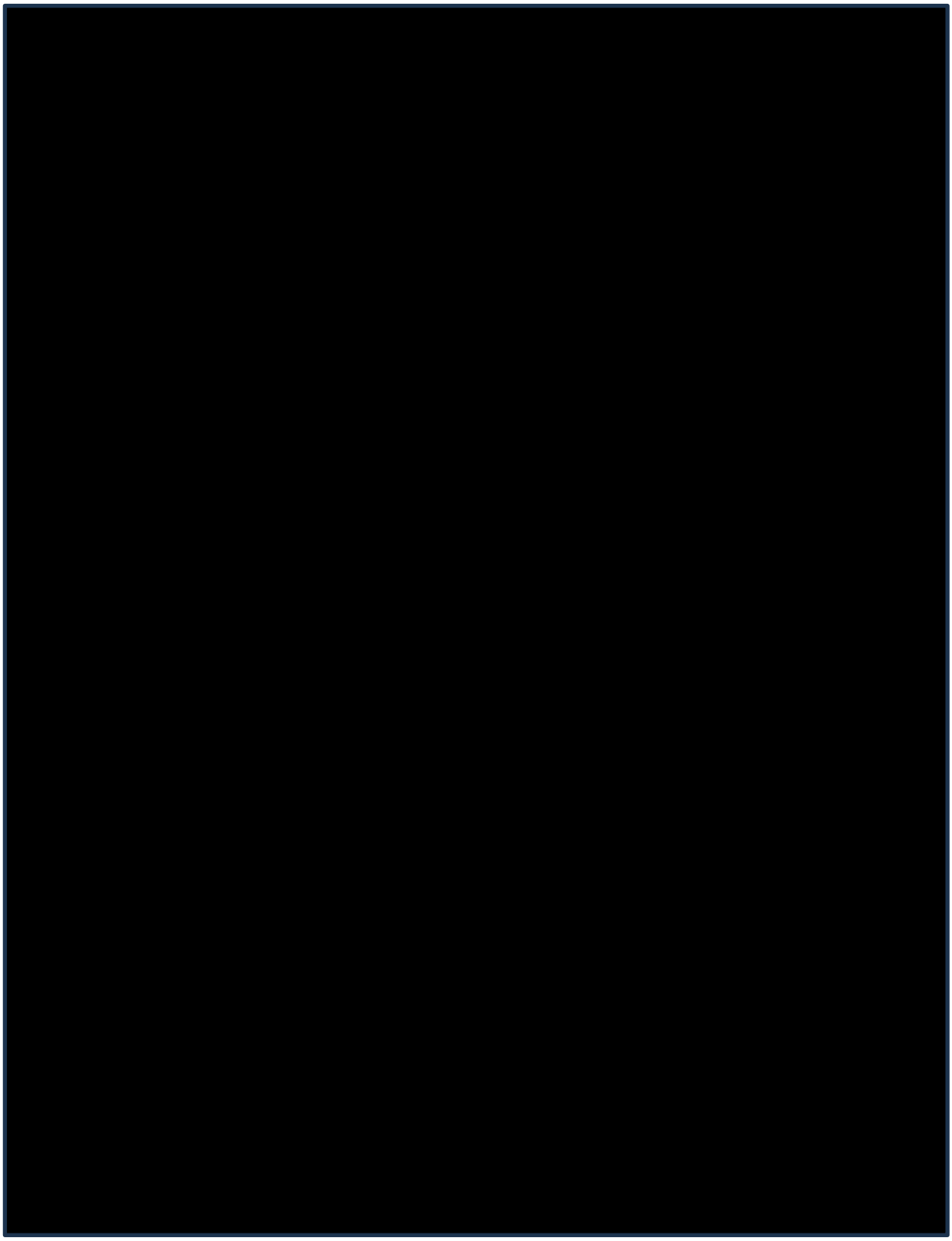
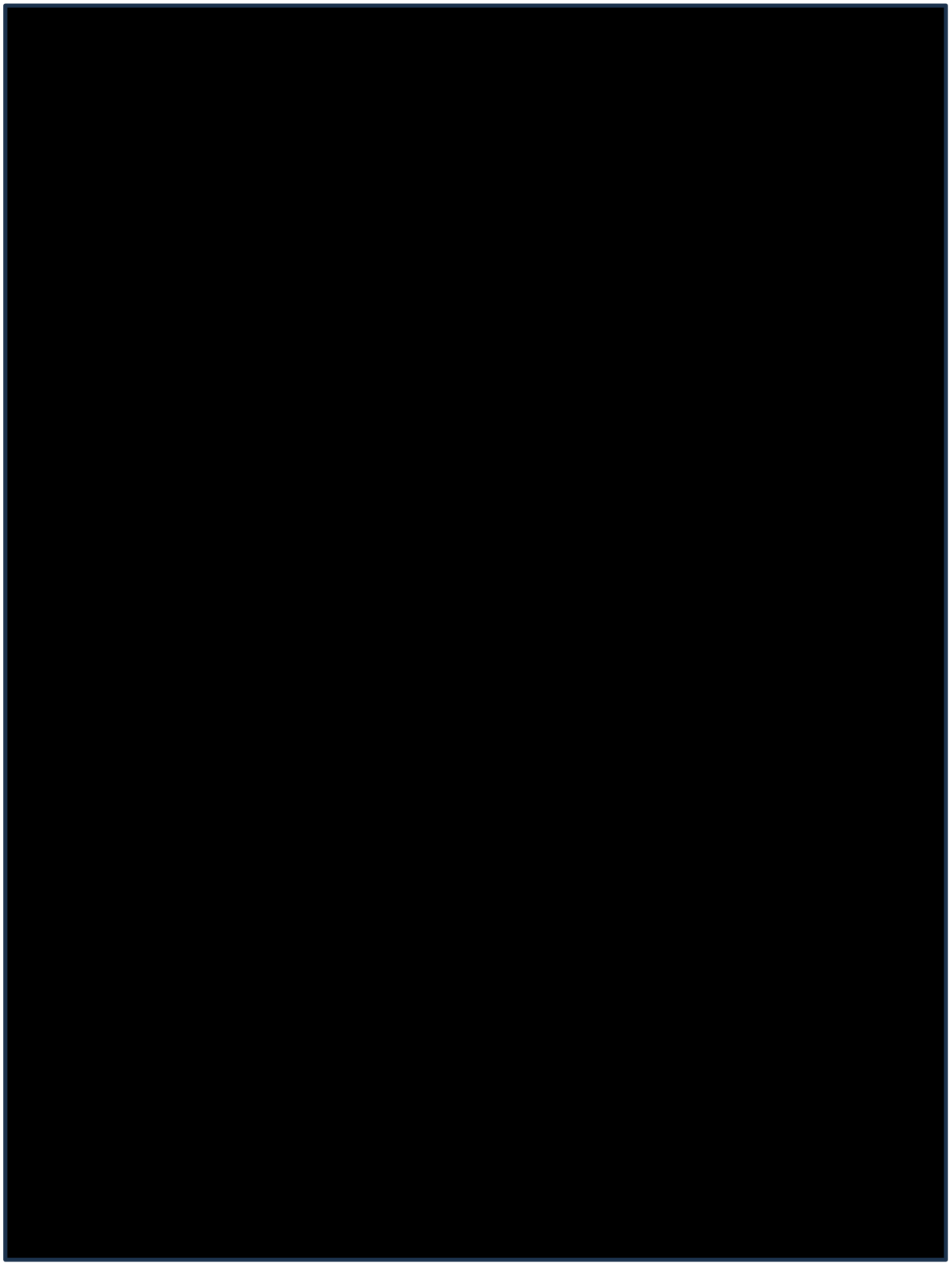


TABLE 76. MEDICAL TESTS FOR SMA TYPE 3, NUMBER OF TIMES RESOURCE IS BEING USED PER QUARTER, INCLUDING DENMARK UNIT COSTS





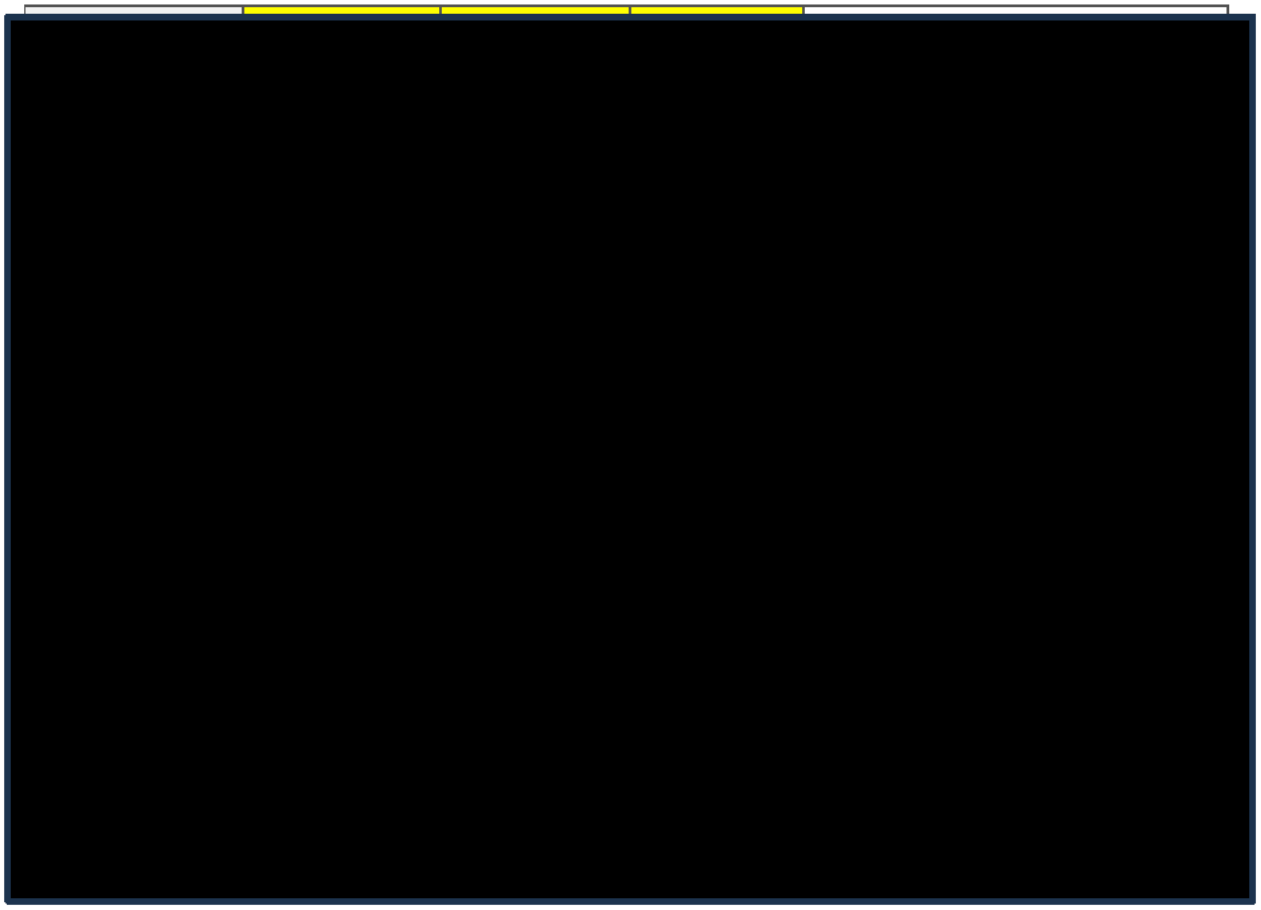


Table 77. Medication for SMA Type 1, number of times resource is being used per quarter, including Danish unit costs

Table 78. Medication for SMA Type 2, number of times resource is being used per quarter, including Danish unit costs

TABLE 79. MEDICATION FOR SMA TYPE 3, NUMBER OF TIMES RESOURCE IS BEING USED PER QUARTER, INCLUDING DENMARK UNIT COSTS

[redacted]

TABLE 80: COST FOR HOSPITALISATION, PER UNIT TYPE

[redacted]

14.3 Appendix C: Inputs and results of the cost-utility analyses

14.3.1 SMA type 1

14.3.1.1 Input values- utilities

Base case – health state utility values

The base case patient health state utility values used in the cost-effectiveness model are drawn from the recent US ICER assessment of SMA therapies (Institute for Clinical and Economic Review 2019) and UK expert clinical advice independently sourced by the NICE ERG (AveXis 2019b). These values are presented below and were derived from multiple sources:

- E state [0.000]: The utility value of 0.000 for the E state (permanent assisted ventilation) is sourced from clinical expert advice sourced independently by the NICE ERG (AveXis 2019b), which indicated that the E state should have a lower utility value than the D state.
- D state [0.190]: The utility value of 0.190 for the D state is adopted in the US ICER assessment (Institute for Clinical and Economic Review 2019). It is sourced from Thompson et al. 2017 (Thompson 2017), which is a cross-sectional study of individuals with SMA in Europe; investigators collected parent-proxy–assessed quality of life using the EuroQol-5 Dimensions (EQ-5D) 3-level version. The mean utility value for patients with SMA type 1 was 0.190 (n=7 parent-proxy assessments).
- C state [0.600]: The utility value of 0.600 for the C state (sits independently) is adopted in the US ICER assessment (Institute for Clinical and Economic Review 2019). It is sourced from the ERG report evaluating the Spinraza submission for NICE. Tappenden et al. 2018

(Tappenden P HJ 2018) reported utilities elicited (these estimates were described as 'not preference-based') from the clinical experts who advised the ERG, who were asked to provide plausible utility estimates for the different health states.

- B state and A state [general population]: The utility for the B state (walks unassisted) and A state (within broad range of normal development) are sourced from general population utilities and calculated annually as per the well-established methodology of Ara and Brazier (Ara 2010) using the equation below. The sex coefficient used is male= 44.1% as male proportion across the START and STR1VE-US trials. Table 82**Error! Reference source not found.** presents approximate utility values using this approach; all annual ages between 0–100 are not included in for brevity sake. The equation below was used to calculate the age- and sex specific utilities (Ara 2010).

$$Utility\ (EQ\text{-}5D) = 0.9508566 + (0.0212126 \times male) - (0.0002587 \times age) - (0.0000332 \times age^2)$$

TABLE 81: SUMMARY OF PATIENT UTILITY VALUES USED IN THE BASE CASE COST-EFFECTIVENESS ANALYSIS

State	Description	Utility value	Reference	Justification
E state	Permanent assisted ventilation	0.000	Thompson et al. 2017 (Thompson 2017)	• Approach taken by US ICER • Uses parent-proxy via EQ-5D-3L for UK-specific SMA type 1 population
D state	Not sitting	0.190		
C state	Sits independently	0.600	Tappenden et al. 2018 (Tappenden P 2018)	• Approach taken by US ICER • Informed by UK expert clinical advice, sourced by an independent research group (AveXis 2019b)
B state	Walks unassisted	General population	Ara and Brazier 2010 (Ara 2010)	• Approach taken by US ICER, adapted to UK general population
A state	Broad range of normal development			

Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; EQ-5D-3L, 3-level EuroQol 5-dimension; SMA, spinal muscular atrophy; UK, United Kingdom; US ICER, United States Institute for Clinical and Economic Review.

TABLE 82: GENERAL POPULATION UTILITIES USED FOR A STATE AND B STATE

Description	Utility value †	Reference	Justification
Age 0–24 years	0.954	Calculation as reported in Ara and Brazier 2010 (Ara 2010)	Walking unassisted by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children. Therefore, general population utility values are applied for the B state and A state
Age 25–34 years	0.925		
Age 35–44 years	0.899		
Age 45–54 years	0.867		
Age 55–-64 years	0.829		
Age 65–74 years	0.783		
Age ≥75 years	0.685		

Abbreviations: WHO, World Health Organization.
† Approximate values, categorised in broad age groups. The exact values for each year are calculated using the methodology for Ara and Brazier, described above.

On-treatment utilities

The base case cost-effectiveness model adopted by US ICER also included additional utility benefits – often referred to as 'on-treatment utility' – in the treatment arms (Zolgensma and Spinraza) for achieving interim milestones such as head control, rolling, standing, crawling, etc. The US ICER implemented these on-treatment utilities as an additional utility of 0.1 and 0.05 compared to BSC in the non-sitting and sitting health states, respectively. This amend to include on-treatment utilities as part of the base case also reflects the recommended base case settings from an independent academic review as part of the ongoing NICE appraisal of Zolgensma (AveXis 2019b). These utility values were considered most appropriate by the US ICER independent assessment group (Institute for Clinical and Economic Review 2019) and the clinical experts advising the NICE ongoing evaluation of Zolgensma in the UK (AveXis 2019b).

The interim milestones (i.e. head control, rolling, crawling and standing with/without assistance) and other non-motor milestone features that may be achieved with pharmacotherapy (e.g. improvements in talking and non-verbal communication, fine motor control and learning etc.) could not be explicitly modelled as health states due to limitations with the Markov state model structure. However, omitting the utility implications of such interim milestones from the base case would result in an underestimation of the true benefits of treatment. Instead, the impact of omitting these on-treatment utility increments are explored in scenario analysis.

14.3.1.2 Results- base case

Treatment with Zolgensma is associated with increased costs compared to the alternative. Compared to Spinraza, treatment with Zolgensma has an incremental cost of 2 975 768 DKK per patient, over a patient's lifetime (discounted at 4.0% during the first 35 years and 3.0% thereafter). The main results from the base case analysis are presented in Table 83.

TABLE 83: COST AND HEALTH OUTCOMES PER TREATMENT ARM, BASE CASE

Treatment	Health outcomes				Costs	
	Life years (undiscounted)	Life years (discounted)	QALYs (undiscounted)	QALYs (discounted)	Total cost per patient (DKK, undiscounted)	Total cost per patient (DKK, discounted)
Spinraza	10,720	7,37	5,380	3,428	20 423 531	14 696 445
Zolgensma	29,120	14,86	19,451	9,324	20 019 007	17 672 213
Difference	18.40	7.50	14.07	5.90	-404 524	**2 975 768**

Abbreviations: DKK: Danish kronor, QALY, Quality-adjusted life year

The ICERs for Zolgensma vs. Spinraza is presented in Table 84. At a discount rate of 4% (3.0% beyond year 35), Zolgensma has a cost per QALY gained of 504 756 DKK vs. Spinraza. The cost per life year gained is 396 887 DKK (Table 84).

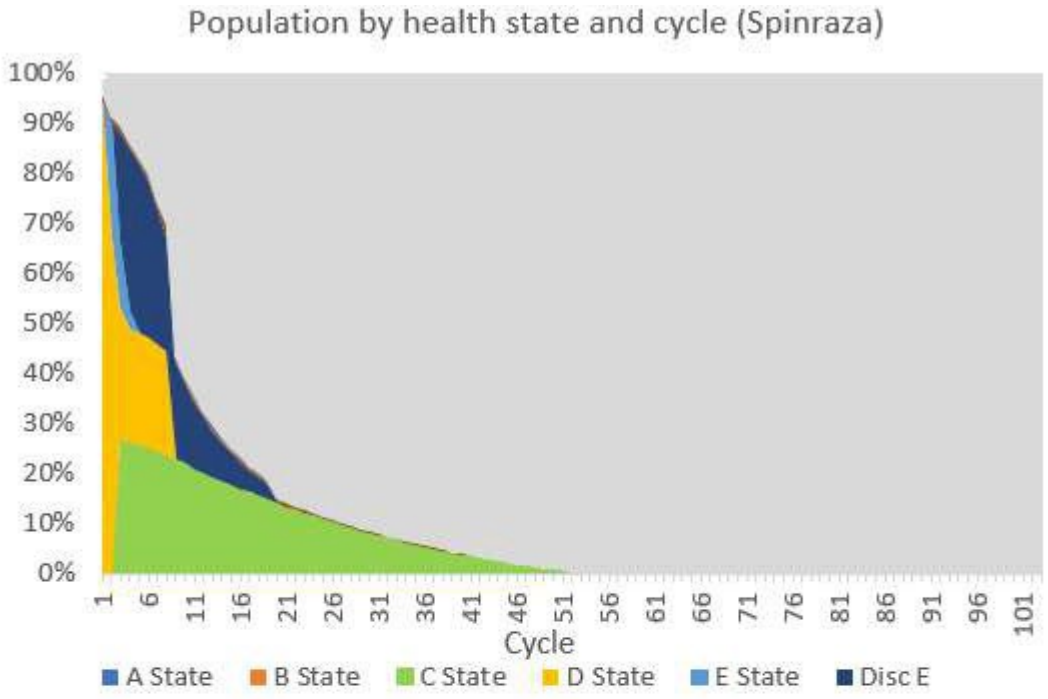
TABLE 84: INCREMENTAL COST-EFFECTIVENESS RATIOS (DKK, DISCOUNTED), BASE CASE

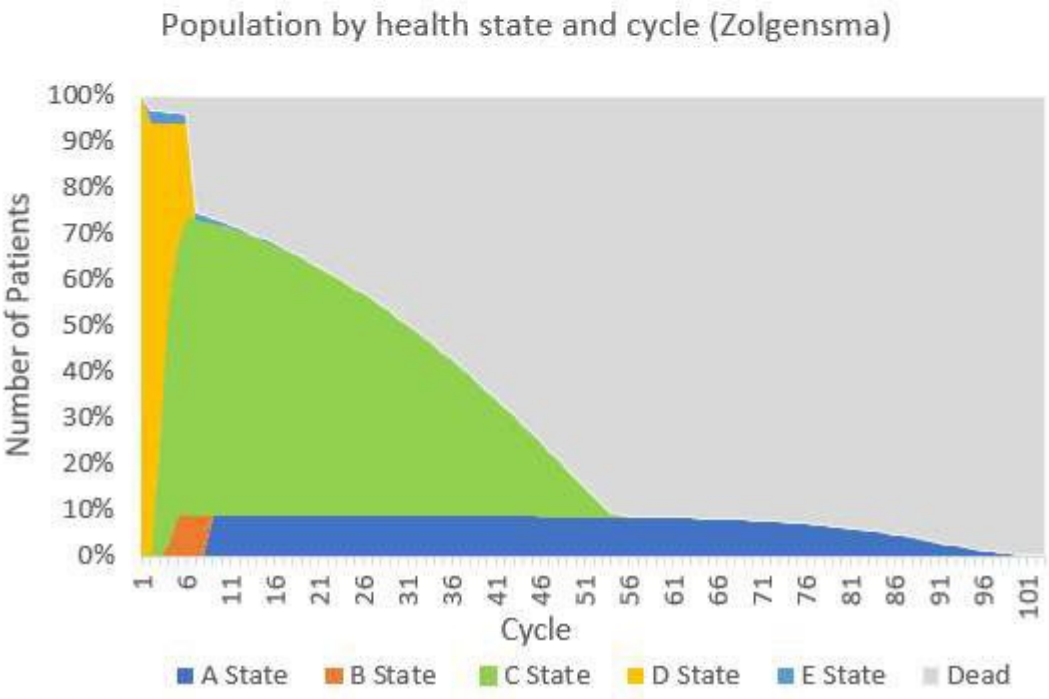
Comparison	Outcomes	
	Total cost per QALY gained	Total cost per life-year gained
Zolgensma vs. Spinraza	504 756	396 887

Abbreviations: BSC, Best supportive care; QALY, Quality-adjusted life year

The main QALY gains associated with Zolgensma stem from the higher proportion of patients achieving health states C (sitting without support) and A (broadly in line with normal development). These differences become more pronounced if no discounting is used. A visual breakdown of the survival per health state for each treatment is presented in Figure 26.

FIGURE 26: PROPORTION OF PATIENTS PER HEALTH STATE AND TREATMENT ARM



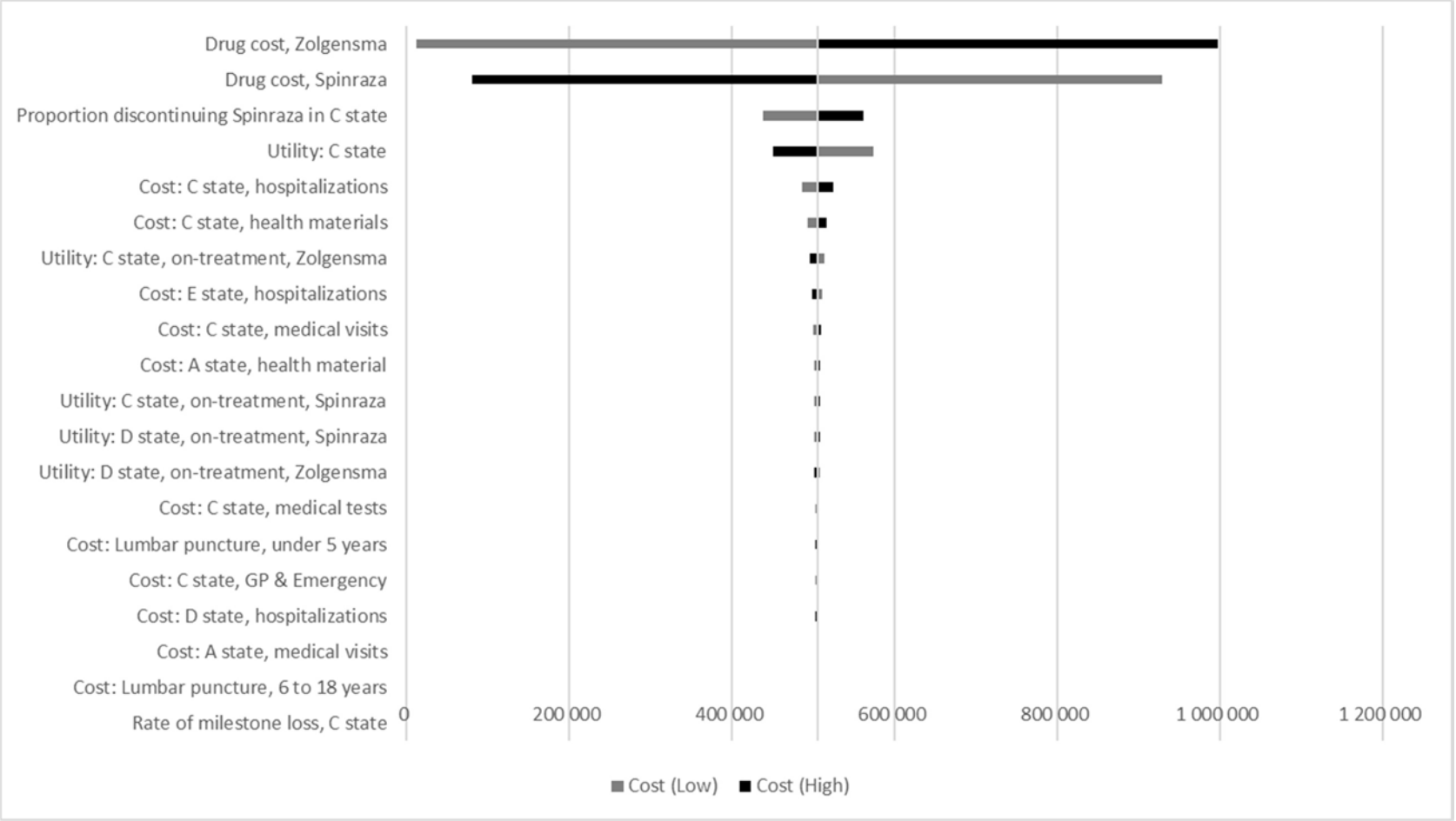


Abbreviations: BSC, best supportive care; AVXS-101, Zolgensma; Nsn, Spinraza.
Figure shows proportion of patients per health state when treated with Spinraza(top) and Zolgensma (bottom).

14.3.1.3 Results- deterministic sensitivity analysis

The deterministic sensitivity analysis explores the impact that variations of individual parameters have on the ICER of Zolgensma versus Spinraza. Results for the effect on the ICER are presented in Figure 27 and in Table 85.

FIGURE 27: DETERMINISTIC SENSITIVITY ANALYSIS FOR THE 20 PARAMETERS WITH HIGHEST IMPACT FOR THE ICER FOR ZOLGENSMA VERSUS SPINRAZA



Note: The ICER for Zolgensma versus Spinraza is shown on the horizontal axis (values shown in DKK).
Abbreviations: DKK, Danish krone; ICER, Incremental cost-effectiveness ratio

TABLE 85: DETERMINISTIC SENSITIVITY ANALYSIS FOR THE 20 PARAMETERS WITH HIGHEST IMPACT FOR THE ICER OF ZOLGENSMA VERSUS SPINRAZA

Rank	Parameter Description	ICER – Low (DKK)	ICER – High (DKK)	Range (DKK)
1	Drug cost, Zolgensma	11 782	997 730	985 949
2	Drug cost, Spinraza	928 784	80 728	848 056
3	Proportion discontinuing Spinraza in C state	437 727	562 124	124 396
4	Utility: C state	574 391	450 179	124 212
5	Cost: C state, hospitalizations	485 560	523 952	38 392
6	Cost: C state, health materials	493 634	515 878	22 244
7	Utility: C state, on-treatment, Zolgensma	513 703	496 115	17 587
8	Cost: E state, hospitalizations	511 472	498 040	13 431
9	Cost: C state, medical visits	500 030	509 482	9 452
10	Cost: A state, health material	501 077	508 435	7 359
11	Utility: C state, on-treatment, Spinraza	501 201	508 361	7 160
12	Utility: D state, on-treatment, Spinraza	501 227	508 335	7 109
13	Utility: D state, on-treatment, Zolgensma	508 254	501 306	6 949
14	Cost: C state, medical tests	502 342	507 169	4 827
15	Cost: Lumbar puncture, under 5 years	506 997	502 515	4 482
16	Cost: C state, GP & Emergency	503 220	506 292	3 071
17	Cost: D state, hospitalizations	506 269	503 243	3 027
18	Cost: A state, medical visits	503 663	505 849	2 186
19	Cost: Lumbar puncture, 6 to 18 years	505 804	503 707	2 097
20	Rate of milestone loss, C state	505 909	504 071	1 838

The table shows the highest and lowest ICER for Zolgensma vs Spinraza when individual parameters are varied. The base case ICER is 480 225 DKK. All parameters except utility values varied by ± 20% unless logically bounded. Utility values varied by ± 20% unless logically bounded.
ICER, Incremental cost-effectiveness ratio

14.3.1.4 Results- scenario analyses

A summary of the results from key scenarios is presented in Table 86. The scenario analyses show that total costs are fairly insensitive towards changes in the number of patients who achieve the higher milestones (sitting independently and walking independently) during the model's first 6 cycles. These relative impact from milestone achievement is greater for QALYs and the ICER, since higher milestone achievements are associated with better quality of life.

The time discount rate for costs and QALYs is identified as an important factor. When discount rates are set to zero, the net present value of the overall cost increase for both Zolgensma and Spinraza. However, costs mainly rise for Spinraza, since Zolgensma is a one-time treatment and its drug acquisition costs only apply at the start of treatment. Further, the corresponding increase in QALYs is even greater in relative terms for Zolgensma than Spinraza. The result is that Zolgensma dominates Spinraza (i.e. yields both lower costs and higher QALYs) when no discounting is applied.

TABLE 86: RESULTS FROM SCENARIO ANALYSES

Scenario	Treatment	Cost per patient (DKK)	QALYs per patient	ICER (DKK)
Base case	Spinraza	14 696 445	3.428	504 756 kr
	Zolgensma	17 672 213	9.324	
Scenario 1. Time discount rate set to 0% for costs and QALYs	Spinraza	20 423 531	5.380	-28 749 kr
	Zolgensma	20 019 007	19.451	
Scenario 2. Improved survival for any patients who sit	Spinraza	16 773 789	4.167	230 268 kr
	Zolgensma	18 935 231	13.554	
Scenario 3. One additional sitter in STR1VE-US after 18 months of age, but no additional walker †	Spinraza	14 696 445	3.428	492 298 kr
	Zolgensma	17 735 345	9.601	
Scenario 4. One additional walker in STR1VE-US after 18 months of age, but no additional sitter †	Spinraza	14 696 445	3.428	471 566 kr
	Zolgensma	17 658 114	9.709	
Scenario 5. One additional walker and one additional sitter in STR1VE-US after 18 months of age †	Spinraza	14 696 445	3.428	461 244 kr
	Zolgensma	17 721 245	9.986	
Scenario 6. 4 new sitters and 4 new walkers in STR1VE-US (half in cycle ending 30 months; half in cycle ending 36 months) †	Spinraza	14 696 445	3.428	369 686 kr
	Zolgensma	17 861 983	11.991	
Scenario 7. Costs for health state A are 50% lower than for health state B	Spinraza	14 696 445	3.428	488 215 kr
	Zolgensma	17 574 695	9.324	
Scenario 8. Survival limit cut-off within state D increased to 10 years for all treatment arms	Spinraza	14 709 666	3.429	502 584 kr
	Zolgensma	17 672 384	9.324	
Scenario 9. Survival limit within state D set strictly to 4 years	Zolgensma	14 157 971	3.356	570 934 kr
	Spinraza	17 549 226	9.296	
Scenario 10. Exclusion of patient transportation and time costs	Spinraza	14 676 126	3.428	505 190 kr
	Zolgensma	17 654 456	9.324	
Scenario 11. Cost for Anti-AAV9 diagnostic test removed from Zolgensma administration costs	Spinraza	14 696 445	3.428	504 359 kr
	Zolgensma	17 669 872	9.324	

Abbreviations: DKK; Danish kronor, ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year. † The base case assumes no additional independent sitters or walkers

14.3.2 Pre-symptomatic

14.3.2.1Results- base case

The results from the cost analysis for pre-symptomatic patients is shown in Table 87 (2 SMN2 copies) and Table 88 (3 SMN2 copies). Since the clinical effects by assumption are identical for the two treatment arms, the only difference is the costs required for Zolgensma and Spinraza, respectively. Since Zolgensma is a one-time infusion whereas Spinraza requires repeated administrations, the cost difference between the two treatment depends on the survival of the patients. Overall cost increases with increased survival for both treatment arms due to health state costs, however, the cost increase will be sharpest for Spinraza given the

need for continuous drug acquisition and administration. Any disutility stemming from the treatment burden with Spinraza has not been considered in this analysis.

TABLE 87: COST AND QALYS FOR PRE-SYMPTOMATIC PATIENTS WITH 2 COPIES OF SMN2, DISCOUNTED

Treatment	Life years	Health outcomes (QALYs)	Costs (DKK)	ICER
Zolgensma	24.98	21.048	17 710 309	**N/A**
Spinraza	24.98	21.048	47 275 601	
Difference	**0**	**0**	**-29 565 291**	

Zolgensma: 80% walkers, 20% sitters; Spinraza: 80% walkers, 20% sitters
Discount rate: 4.0% for the first 35 years, 3.0% beyond 35 years
ICER: Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

TABLE 88: COST AND QALYS FOR PRE-SYMPTOMATIC PATIENTS WITH 3 COPIES OF SMN2, DISCOUNTED

Treatment	Life years	Health outcomes (QALYs)	Costs (DKK)	ICER
Zolgensma	26.93	23.630	50 469 232	**N/A**
Spinraza	26.93	23.630	17 604 485	
Difference	**0**	**0**	**-32 864 746**	

Zolgensma: 100% walkers; Spinraza: 100% walkers
Discount rate: 4.0% for the first 35 years, 3.0% beyond 35 years
ICER: Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year

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Medicinrådet

Medicinrådets protokol for vurdering af onasemnogene abeparvovec til behandling af spinal muskelatrofi

Versionsnr.: 1.0

Medicinrådet

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 deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi 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, 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 ansøgende virksomhed få besked.

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Indhold

1 Begreber og forkortelser

ARR	Absolut risikoreduktion
CHOP-INTEND	*The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders*
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EPAR	*European Public Assessment Report*
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
ITT	*Intention-to-treat*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
SMA	Spinal muskelatrofi
SMD	*Standardized Mean Difference*
SMN	*Survival motorneuron*

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Avexis, som ønsker, at Medicinrådet vurderer onasemnogene abeparvovec (Zolgensma) til spinal muskelatrofi. Vi modtog den foreløbige ansøgning den 2. juni 2020.

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 [1]. Incidensen i Skandinavien er estimeret til 1 ud af 6000 fødte børn [2].

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 [2]. 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) [3,4].

Ved SMA type 1 har barnet symptomer, før han/hun er seks måneder. Der er ofte symptomer allerede fra fødslen. Uden medicinsk behandling kommer barnet aldrig til at sidde selv og bliver sjældent mere end et par år. Levealderen er afhængig af, hvor intensiv vejrtrækningshjælp, der bliver iværksat.

Tabel 1. Klinisk klassifikation af spinal muskelatrofi [3]

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

1. Ifølge fagudvalget, februar 2020: 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.

2.2 Onasemnogene abeparvovec

Onasemnogene abeparvovec er en genterapi, som erstatter det defekte *SMN1*, så patienten selv kan danne SMN-protein, som er afgørende for funktionen af motorneuronerne. Lægemidlet gives intravenøst som vægtbaseret engangsdosis iht. produktresumé [6]. Behandlingen ændrer sygdomsforløbet, så barnet får et mildere sygdomsforløb eller potentielt udvikler sig inden for normalområdet.

Onasemnogene abeparvovec fik positiv opinion i EMA den 26. marts 2020 og blev godkendt den 18. maj til indikationen patienter med 5q SMA med bi-allelic mutation i *SMN1*-genet og:

- klinisk diagnosticeret SMA type 1 eller
- op til 3 kopier af *SMN2*-genet.

Indikationsteksten rummer således ikke en afgrænsning på alder eller sværhedsgrad af sygdommen. Ifølge det godkendte produktresumé er virkning og sikkerhed på godkendelsestidspunktet ikke klarlagt hos patienter over 2 år eller hos patienter, som vejer over 13,5 kg. Ved fremskreden SMA, hvor der formodes at være sket irreversibel skade af motorneuroner, afhænger effekten af graden af muskelsvækkelse på behandlingstidspunktet. Effekten formodes markant reduceret hos patienter med udtalt muskelsvækkelse og respirationssvigt, patienter i permanent ventilation samt patienter, der ikke kan synke. Benefit/risk-profil hos patienter med fremskreden SMA, der behandles med permanent ventilation, og som ikke tager på, er ikke klarlagt [6].

I produktresuméet fremgår også, at studieopfølgningstiden for patienter med 3 *SMN2*-kopier er for kort til at drage nogen definitive konklusioner om fordelene i denne patientpopulation i øjeblikket.

2.3 Nuværende behandling

Nye patienter med SMA type 1, som ikke er i permanent ventilationsbehandling, samt præsymptomatiske børn, bliver i dag tilbudt behandling med nusinersen iht. Medicinrådets anbefaling fra 2017 [7]. Målet med behandlingen er at nedsætte sygdomsprogressionen og derigennem øge barnets overlevelse, funktionsniveau og livskvalitet.

Behandlingen varetages på tre centre i hhv. København, Aarhus og Odense. I Danmark tilbydes patienter med SMA type 1 almindeligvis ikke invasiv ventilationsbehandling, men der er enkelte SMA type 1 patienter, der efter forældrenes ønske får invasiv respiration.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel, vi undersøger (interventionen), af den behandling, vi sammenligner med (komparator(er)), og af effektmålene.

De kliniske spørgsmål opdeles i de to populationer: 1: Børn med klinisk diagnosticeret SMA 1. 2: præsymptomatiske spædbørn. Fagudvalget vurderer, at alle nye patienter, som udgangspunkt, bliver tilbudt nusinersen, som dermed er den relevante komparator.

3.1 Klinisk spørgsmål 1

Hvilken værdi har onasemnogene abeparvovec sammenlignet med nusinersen for børn med klinisk diagnosticeret SMA type 1?

Population
Populationen omfatter børn med klinisk diagnosticeret SMA type 1 defineret iht. den kliniske klassifikation i tabel 1.

Der vil i vurderingen blive taget højde for forskelle i studiernes inklusionskriterier og patientkarakteristika, såsom alder ved symptomdebut samt alder og ventilationsbehovs behandlingsstart. En præspecificeret subgruppeanalyse for nusinersen har vist betydelig forskel i effekt ved sygdomsvarighed under 12 uger [8]. Derfor vil populationen så vidt muligt blive yderligere opdelt i subgrupper iht. sygdomsvarighed < 12 uger ift. > 12 uger.

Fagudvalget vil herudover diskutere, om patienter, der allerede har modtaget en eller flere doser af nusinersen, evt. også kan være kandidater til onasemnogene abeparvovec (se afsnit 5 vedr. særlige forhold for denne protokol).

Intervention
Onasemnogene abeparvovec.

Komparator
Nusinersen (dosis iht. produktresumé).

Effektmål
De valgte effektmål står i tabel 2.

3.2 Klinisk spørgsmål 2

Hvilken værdi har onasemnogene abeparvovec sammenlignet med nusinersen for præsymptomatiske spædbørn?

Population
Præsymptomatiske spædbørn med verificeret 5q SMA-gendefekt og op til 3 *SMN2*-kopier.

Fagudvalget vil herunder vurdere evidensen for subpopulationen med 3 *SMN2-kopier,* hvoraf nogle vil udvikle SMA type 1, men størstedelen vil udvikle SMA type 2., samt nyfødte børn med én *SMN2-kopi* (SMA type 0).

Intervention
Onasemnogene abeparvovec.

Komparator
Nusinersen (dosis iht. produktresumé).

Effektmål
De valgte effektmål står i tabel 2.

3.3 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 2. For hvert effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel. I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 2. Effektmål

Effektmål	Vigtighed	Effektmål gruppe*	Måleenhed	Klinisk spørgsmål nr.#	Mindste klinisk relevante forskel
Overlevelse	*Kritisk*	*1*	Andel p.t. i live	1 2	5 %-point (efter 10-14 mdr.) (efter 24 mdr.)
Kombineret mortalitet eller permanent ventilations-behandling	*Kritisk*	*2*	Andel p.t., som enten er døde eller anvender respirator > 16 timer/døgn	1 2	15 %-point (10-14 mdr.) (efter 24 mdr.)
Permanent ventilations-behandling	*Vigtigt*	*2*	Andel p.t., som ikke anvender respirator > 16 timer/døgn	1 2	10 %-point (efter 12-18 mdr.) (efter 24 mdr.)
Motoriske milepæle	*Kritisk* *Vigtigt*	*2*	Respondere (andel patienter med min 4 point bedring på CHOP-INTEND) Andel p.t., der opnår evnen til at: • Sidde uden støtte • Gå uden støtte	1 1 2 1 2	20 %-point (efter 12-18 mdr.) 10 % efter 12-18 mdr. 5 % efter 24 mdr. 5 % efter 12-18 mdr. 10 % efter 24 mdr.
Alvorlige bivirkninger (relateret til behandlingen)	*Vigtigt*	*2*	Andel patienter, som oplever mindst én alvorlig bivirkning	1 2	10 %-point (efter 12-18 mdr.) (efter 24 mdr.)
Livskvalitet	*Vigtigt*	*2*	Kun kvalitativ bedømmelse	1 2	-

*Effektmålsgruppe refererer til de væsentlighedskriterier i Medicinrådets metodehåndbog, der ligger til grund for kategoriseringen af de relative effektestimater. Effektmålsgruppe 1: Dødelighed. 2: Alvorlige symptomer og bivirkninger eller livskvalitet. 3: Ikkealvorlige symptomer eller bivirkninger.
De kliniske spørgsmål refererer til populationerne.
1. Klinisk diagnosticeret SMA type 1.
2. Præsymptomatiske spædbørn med verificeret 5q SMA-gendefekt og op til 3 SMN2-kopier.

3.3.1 Kritiske og vigtige effektmål

Definitionen af de absolutte mindste kliniske relevante forskelle tager udgangspunkt i hændelsesrater fra studierne af nusinersen hos hhv. børn med klinisk diagnostiseret SMA type 1 (ENDEAR) [8] og præsymptomatiske børn (NURTURE) [9].

Overlevelse (Kritisk)

SMA type 1 patienter har ubehandlet en gennemsnitlig forventet levetid under to år og er derfor et kritisk effektmål. Selvom dødeligheden ved SMA type 1 bliver reduceret markant ved behandling med nusinersen (komparator) er den høj (i ENDEAR-studiet var 16 % døde efter 13 mdr.) [8]. 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). I NURTURE-studiet, hvor der indgik præsymptomatiske spædbørn med 2-3 SMN2-kopier, var alle i live efter 24 mdr. [9]. Fagudvalget vurderer på baggrund af disse hændelsesrater, at en forskel på ARR på 5 %-point i overlevelsesrate efter hhv. 10-14 mdr. ved SMA type 1 og 24 mdr. for præsymptomatiske spædbørn er klinisk relevant ift. nusinersen som aktiv komparator.

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 allerede er i permanent ventilationsbehandling, er almindeligvis ekskluderet fra studierne. I ENDEAR-studiet af børn med SMA type 1 endte 22 % i nusinersengruppen og 32 % i kontrolgruppen i permanent ventilationsbehandling efter 13 måneder [8]. I NURTURE opnåede ingen af de præsymptomatiske børn dette effektmål. Fagudvalget vurderer på denne baggrund, at en ARR på 10 %-point efter 12-18 mdr. ved SMA type 1 og 24 mdr. hos præsymptomatiske børn er klinisk relevant.

Kombineret mortalitet eller permanent ventilationsbehandling (Event-free survival) (kritisk)

'*Event-free survival*' er et kombineret effektmål, der er anvendt som det primære effektmål i hovedstudierne af både onasemnogene abeparvovec og nusinersen. Effektmålet er defineret som død eller permanent ventilationsbehandling. Ved vurdering af relevansen af et kombineret effektmål er det centralt, at de hændelser, der kombineres, har samme grad af alvorlighed. Selvom død som udgangspunkt må anses som mere alvorligt, kan et liv med så svær muskelsvækkelse, at patienten er afhængig af permanent respiratorbehandling, være mindst lige så alvorligt eller endda værre. Fagudvalget vurderer derfor, at effektmålet er kritisk.

I ENDEAR-studiet opnåede 39 % i nusinersengruppen og 68 % i kontrolgruppen dette effektmål [8]. I NURTURE opnåede ingen dette effektmål [9]. Fagudvalget vurderer på baggrund af hændelsesraterne, at en ARR på 15 %-point efter 10-14 mdr. ved SMA type 1 og efter 24 mdr. for præsymptomatiske spædbørn er klinisk relevant.

Motoriske funktioner og milepæle (kritisk)

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.

Måling af motoriske milepæle før siddestadiet
Sværhedsgraden af SMA type 1 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 motorfunktion af SMA type 1-patienter. Skalaen måler i praksis på de motoriske milepæle før siddestadiet og er opdelt i 16 aktiviteter, som hver tildeles fra 0-4 point (max 64 point) [5].
Respondere er i studierne defineret som patienter, der opnår min. 4 points stigning. I ENDEAR var responsraten 71 % [8]. Fagudvalget vurderer på denne baggrund, at en forskel i respondere på 20 %-point efter 12-18 mdr. ved SMA type 1 er klinisk relevant. I NURTURE, hvor der ikke er en kontrolgruppe, opnåede 20 ud af 25 børn en maksimal score på 64 point [9]. Fagudvalget har på denne baggrund ikke defineret en mindste klinisk relevant forskel for præsymptomatiske børn på dette effektmål.

Måling af den motoriske milepæl - evne til at sidde uden støtte
Behandling af SMA type 1 gør nu, 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.

I praksis måler man i studierne, om barnet kan sidde kortvarigt uden støtte (i 5, 10 eller 30 sekunder). 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. 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 kritisk.

Der kan være forskel på, om studierne har målt effekten efter 5, 10 eller 30 sekunder, som kan give en skævhed ved sammenligning af lægemidlerne Fagudvalget finder, at det er vigtigt, at effekten er målt på samme tidspunkt. Hvis data for begge lægemidler er opgjort på flere tidspunkter (fx både 5 og 30 sekunder), vælges den længste. I ENDEAR-studiet opnåede 8 % af børnene med SMA type 1 evnen til at sidde kortvarigt uden støtte (varighed ikke angivet) [8]. Fagudvalget vurderer, at en forskel i andel patienter, der kan sidde kortvarigt uden støtte på 10 %-point efter 12-18 mdr., er klinisk relevant. I NURTURE opnåede alle præsymptomatiske børn at sidde uden støtte [9]. På denne baggrund sættes den mindste klinisk relevante forskel til 5 %-point.

Måling af den motoriske milepæl - evne til at gå uden støtte
Med nye behandlinger kan der potentielt være både præsymptomatiske børn og patienter med klinisk diagnosticeret SMA type 1, som vil opnå evnen til at gå uden støtte, hvilket vil være helt usandsynligt uden behandling. Dette er derfor også et kritisk effektmål. Raske børn går normalt omkring 12-15-månedersalderen, men der kan være stor variation selv i den raske population. Som udgangspunkt vil næsten alle raske børn kunne gå i en alder af 18 måneder. Derfor vil dette effektmål blive opgjort som andel patienter, der har opnået effektmålet i en alder af 18 mdr.

I ENDEAR opnåede ingen børn med SMA type 1 evnen til at stå eller gå uden støtte [8]. Fagudvalget vurderer på denne baggrund, at en forskel på 5 %-point målt ved alder på 18 mdr. er klinisk relevant.

I NURTURE-studiet med præsymptomatiske børn kunne 88 % gå ved 2-årsalderen [9]. Fagudvalget vurderer på denne baggrund, at en forskel på 10 %-point målt ved en alder på 24 mdr. er klinisk relevant.

Alvorlige hændelser (vigtig)

Alvorlige bivirkninger er defineret som alvorlige hændelser, som i studierne er vurderet relateret til behandlingen. I ENDEAR er alvorlige hændelser opgjort som 'alle hændelser'. Hændelsesraten var på 76 % [8]. I NURTURE-studiet af præsymptomatiske børn var hændelsesraten 48 % [9]. På baggrund af dette vurderer fagudvalget, at en forskel på 10 %-point er klinisk relevant. Opgjort efter 12-18 mdr. ved SMA type 1 og efter 24 mdr. hos præsymptomatiske børn.

Livskvalitet (vigtig)

Livskvalitet er ikke rapporteret, da det ikke er muligt at måle hos så små børn, og vil derfor ikke indgå som et kvantitativt effektmål. Ved vurdering og vægtning af de øvrige effektmål vil en forbedret overlevelse også blive set i lyset af barnets livskvalitet.

4 Litteratursøgning

Der er ingen studier, hvor onasemnogene abeparvovec er sammenlignet direkte med nusinersen. Derfor skal ansøger søge efter artikler til en indirekte sammenligning. Søgestrengen fremgår nedenfor. Derudover skal ansøger konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for begge lægemidler.

Søgestrenge til PubMed - https://pubmed.ncbi.nlm.nih.gov/advanced/

#	Søgetermer	Kommentar
#1	onasemnogene abeparvovec[tiab] OR Zolgensma*[tiab] OR avxs-101[tiab] OR avxs101[tiab]	Søgetermer for lægemidler
#2	(adeno-associated vir*[tiab] AND serotype 9[tiab]) OR scAAV9[tiab]	
#3	SMA[tiab] OR SMA1[tiab] OR SMA2[tiab] OR SMA3[tiab] OR spinal muscular atrophy[tiab] OR Spinal Muscular Atrophies of Childhood[mh] OR Muscular Atrophy, Spinal[mh]	
#4	#2 AND #3	
#5	nusinersen[nm] OR nusinersen[tiab] OR Spinraza*[tiab] OR ISIS-SMN*[tiab]	
#6	#1 OR #4 OR #5	
#7	Case Reports[pt] OR Comment[pt] OR Guideline[pt] OR Letter[pt] OR News[pt]	Eksklusion af specifikke publikationstyper
#8	#6 NOT #7	Linje #8 = endelig søgning

Søgestrenge til CENTRAL – Cochrane Library https://www.cochranelibrary.com/advanced-search/search-manager

#	Søgetermer	Kommentar
#1	(onasemnogene next abeparvovec or Zolgensma* or "avxs 101" or avxs101):ti,ab,kw	Søgetermer for lægemidler
#2	((adeno next associated next vir* and "serotype 9") or scAAV9):ti,ab	
#3	(nusinersen or nusinersen or Spinraza* or ISIS next SMN*):ti,ab,kw	

#4	#1 or #2 or #3	
#5	(clinicaltrials.gov or trialsearch):so	Eksklusion af specifikke publikationstyper
#6	"conference abstract":pt	
#7	#5 or #6	
#8	#4 not #7	Linje #8 = endelig søgning. Limit to Trials

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 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 ekskludere først 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 (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

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 Databehandling og -analyse

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 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 (jævnfør 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 (jævnfør 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’- 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

- Baselinekarakteristika og resultater for patienter med SMA type 1 skal, i det omfang det er muligt, også angives for subpopulationerne med sygdomsvarighed hhv. under og over ca. 12 uger.
- Baselinekarakteristika og resultater for præsymptomatiske børn skal angives for subpopulationerne med hhv. 2 og 3 SMN2-kopier

- Såfremt der er data for patienter, der allerede har modtaget en eller flere doser af nusinersen inden behandling med onasemnogene abeparvovec, bedes baselinekarakteristika og resultater herfor fremlagt.

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.

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 vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

Der er afgørende forskelle på de to behandlingsmodaliteter, som kan have stor betydning for både patienten og omkostningerne til behandlingen. Onasemnogene abeparvovec er éngangsbehandling. Nusinersen skal administreres intratekalt tre gange om året og er i princippet livslang behandling, med mindre patienten ophører pga. manglende effekt eller bivirkninger eller skifter til en ny oral behandling. Udfaldet af den sundhedsøkonomiske analyse vil især afhænge af, hvilke antagelser der gøres ift. forventet levetid på behandlingen. Herunder hvor mange år man forventer, at effekten holder. I forbindelse med ekstrapolering af langtidseffekten er det relevant at inddrage data med længst mulige opfølgningstid for de to lægemidler.

8 Relation til behandlingsvejledning

Der findes ikke en relevant behandlingsvejledning, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet.

9 Referencer

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10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

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

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11 Versionslog

Version	Dato	Ændring
1.0	7. juli 2020	Godkendt af Medicinrådet.