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2021016504

Datum 6 mei 2021
Betreft Pakketadvies sluisgeneesmiddel onasemnogene abeparvovec (Zolgensma®)

Onze referentie
2021016504

Geachte mevrouw Van Ark,

Zorginstituut Nederland adviseert u over onasemnogene abeparvovec (Zolgensma®) bij de behandeling van patiënten met symptomatische spinale musculaire atrofie (SMA) type 1 en presymptomatische SMA-patiënten met maximaal drie kopieën van het SMN2-gen. De aanleiding voor dit advies is de plaatsing van genoemd middel in de pakketsluis voor dure geneesmiddelen. Het Zorginstituut heeft de beoordeling binnen het 'Beneluxa Initiative' uitgevoerd en daarin samengewerkt met België en Ierland.

Onasemnogene abeparvovec (OA) is een innovatieve, veelbelovende en eenmalige behandeling die aangrijpt op de oorzaak van de ziekte en voldoet aan de stand van wetenschap en praktijk. Deze gentherapie is van groot belang voor de behandeling van een levensbedreigende aandoening bij zeer jonge kinderen. De eerste resultaten zijn veelbelovend; pre-symptomatische behandeling draagt de belofte in zich om ziekte te kunnen voorkomen. Dat is waardevol.
Er zijn echter ook grote onzekerheden over de effecten, zowel op de korte als op de lange termijn en over eventueel gebruik van aanvullende ziektemodulerende behandelingen. Verder is de kosteneffectiviteit op basis van de beschikbare data onzeker en vooralsnog ongunstig. Data die in de toekomst verzameld worden in het bestaande SMA-register, zullen hierover meer informatie geven.
Het Zorginstituut adviseert u OA op te nemen in het verzekerde pakket wanneer voldaan is aan de volgende voorwaarden:

- Uitgaande van de genoemde onzekerheden, mag het risico op een te hoge prijs niet uitsluitend bij de premiebetaler worden neergelegd. Rekening houdend met een prijsreductie van 85% voor nusinersen (huidige behandeling) en met de onzekerheid over de effectiviteit, zou een prijsverlaging van 91% op OA van toepassing moeten zijn om te komen tot een kosteneffectieve behandeling met OA. Als de claim van de fabrikant volledig uitkomt, zou geen prijsverlaging nodig zijn. Wanneer dat risico gedeeld zou worden, zou een prijsreductie rond 50% noodzakelijk zijn.
- Daarnaast adviseert het Zorginstituut een 'pay for performance'-afspraak waarbij de betaling afhangt van het al dan niet bereiken van relevante uitkomstmaten. Onderstaande relevante uitkomstmaten kunnen deel uitmaken van deze afspraak:
  - het gebruik van aanvullende ziektemodulerende behandelingen zoals

Zorginstituut Nederland
Zorg II
Infectieziekten, Bloed & Immunologie

Datum
6 mei 2021

Onze referentie
2021016504

bijvoorbeeld nusinersen;
- overleving zonder beademing;
- het bereiken van motorische mijlpalen.

Het Zorginstituut adviseert u om de (prijs)onderhandeling aan te gaan binnen de al bestaande Beneluxa-samenwerking. Over 5 jaar zou het Zorginstituut een herbeoordeling kunnen doen om te zien hoe de kosteneffectiviteit zich op basis van de dan beschikbare data heeft ontwikkeld.

In deze brief licht ik onze bevindingen en eindconclusie toe.

Algemeen

Het Zorginstituut maakt op uw verzoek vanuit het oogpunt van het uit gezamenlijke premies betaalde basispakket, de afweging of nieuwe zorg onderdeel zou moeten zijn van het verzekerde pakket. Om tot een advies te komen heeft het Zorginstituut OA beoordeeld aan de hand van de vier pakketcriteria[1]: effectiviteit[2], kosteneffectiviteit[3], noodzakelijkheid en uitvoerbaarheid. We maken hierbij een weging, zowel in wetenschappelijke zin als vanuit maatschappelijk draagvlak, en we wegen aspecten van doelmatigheid en transparantie. Het Zorginstituut wordt bij zijn pakketbeoordelingen geadviseerd door twee onafhankelijke commissies:

- de Wetenschappelijke Adviesraad (WAR) voor de toetsing van de gegevens aan de stand van de wetenschap en praktijk en het bepalen van de kosteneffectiviteit; en
- de Adviescommissie Pakket (ACP) voor de maatschappelijke afweging.

Ook hebben wij belanghebbende partijen tijdens het proces over de beoordeling geconsulteerd.

Onasemnogene abeparvovec (Zolgensma®)

Patiënten met SMA hebben een defect in het SMN1-gen. Het lichaam heeft dit gen nodig om een eiwit aan te maken dat essentieel is voor de normale werking van de zenuwen die spierbewegingen aansturen. De werkzame stof in OA bevat een functionele kopie van dit gen. Wanneer het middel wordt geïnjecteerd, gaat het (door middel van een zogenaamde AAV-vector) over in de zenuwen van waaruit het het juiste gen levert om voldoende van het eiwit aan te maken en zo de zenuwfunctie veilig te stellen. Naast het SMN1-gen, produceert ook het SMN2-gen een klein deel van het benodigde eiwit. Het aantal SMN2-kopieën is de belangrijkste bepalende factor voor de ernst van SMA, maar niet de enige.
De indicatie van OA zoals vastgesteld door de EMA omvat de behandeling van:

- patiënten met 5q spinale spieratrofie (SMA) met een bi-allelische mutatie in het SMN1-gen en een klinische diagnose van SMA-type 1; en
- patiënten met 5q SMA met een bi-allelische mutatie in het SMN1-gen en maximaal 3 kopieën van het SMN2-gen.

De aangevraagde vergoeding is smaller en wordt ondersteund door de beroepsgroep:

- alle symptomatische patiënten met SMA type 1;
- presymptomatische SMA-patiënten met maximaal 3 kopieën van het SMN2-gen.

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1 Pakketbeheer in de praktijk 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

2 Beoordeling stand van de wetenschap en praktijk: geactualiseerde versie (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

3 Rapport kosteneffectiviteit (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

Zorginstituut Nederland
Zorg II
Infectieziekten, Bloed & Immunologie

Datum
6 mei 2021

Onze referentie
2021016504

Nusinersen was het eerste geneesmiddel dat in 2017 werd goedgekeurd voor de behandeling van SMA. Behandeling met nusinersen (ongeacht het type SMA) is vergoed voor kinderen die voor de leeftijd van 9,5 jaar starten met de behandeling. Vanaf 9,5 jaar is nusinersen beschikbaar via voorwaardelijke toelating.

Integrale weging pakketcriteria

Symptomatische patiënten met SMA type 1

In de belangrijkste, afgeronde STR1VE-US-studie waren 20 (90%) van de 22 baby's die OA kregen, na 14 maanden nog in leven en ademden ze zonder een permanent beademingsapparaat. Normaal gesproken zou slechts een kwart van de onbehandelde patiënten zou overleven zonder permanent beademingsapparaat. In de SHINE-studie met nusinersen waren na 18 maanden 32 (37%) van de 63 baby's nog in leven en ademden ze zonder een permanent beademingsapparaat.

Uit de STR1VE-US-studie bleek ook dat OA baby's kan helpen zonder hulp te zitten voor ten minste 30 seconden. 14 van de 22 baby's die OA toegediend kregen, waren hiertoe na 18 maanden in staat, een mijlpaal die bij onbehandelde baby's met ernstige vormen van de ziekte nooit wordt bereikt. Op alle uitkomstmaten bij symptomatische patiënten (overleving, beademingsvrije overleving en mobiliteit), lijkt OA beter dan nusinersen. Maar door de onvergelijkbaarheid van de studies (de patiënten in de studies met nusinersen waren er bij de start van de behandeling slechter aan toe dan bij OA) kunnen we geen uitspraak doen over een klinisch relevant verschil.

Presymptomatische patiënten met 2 of 3 kopieën van het SMN2-gen

Presymptomatische patiënten kunnen worden gevonden via oudere broertjes of zusjes of via hielprikscreening. Hielprikscreening start naar verwachting in Nederland in oktober 2022.

De studie SPR1NT naar de behandeling van presymptomatische patiënten met OA is nog niet afgerond. Tot dusver zijn alle behandelde patiënten (n=29) nog in leven en ademen ze zonder een permanent beademingsapparaat (mediane follow-up is 15 maanden). In het cohort patiënten met 2 SMN2-kopieën kunnen 11 van de 14 patiënten zitten zonder hulp (10 bereikten deze mijlpaal binnen de grenzen van normale ontwikkeling) en in het cohort patiënten met 3 SMN2-kopieën kunnen 8 van de 15 patiënten staan en kunnen 6 van de 15 lopen.

Ook na presymptomatische behandeling met nusinersen (NURTURE-studie) zijn alle patiënten in leven gebleven, zonder permanente beademing.

Langere follow-up is nodig om definitieve conclusies te trekken over de effectiviteit van OA in vergelijking met nusinersen.

Stand van wetenschap en praktijk

Zorginstituut Nederland, de Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) en het Ierse National Centre for Pharmacoeconomics (NCPE) concluderen dat OA voldoet aan de stand van de wetenschap en praktijk bij de behandeling van symptomatische patiënten met SMA type 1. Het werkingsmechanisme, de brede consensus over de voordelen van een presymptomatische behandeling en het feit dat mogelijk meer dan de helft van de patiënten met 3 kopieën van SMN2 een zeer ernstige ziekte zal ontwikkelen, worden voldoende geacht om te concluderen dat OA ook voldoet aan de stand van de wetenschap en praktijk bij presymptomatische SMA-patiënten met 2 of 3 van het SMN2-gen.

Zorginstituut Nederland
Zorg II
Infectieziekten, Bloed & Immunologie

Datum
6 mei 2021

Onze referentie
2021016504

Er is onvoldoende bewijs om een conclusie te trekken over de waarde van OA in vergelijking met nusinersen. Een goede vergelijkende studie waarin OA met nusinersen wordt vergeleken, is niet uitgevoerd en zal er in de toekomst waarschijnlijk ook niet komen.

Budgetimpact
De netto budgetimpact van OA bedraagt in jaar 3 circa € 11 miljoen in Nederland. Deze budgetimpact is sterk afhankelijk van de gekozen populatie en de kosten en aannames rondom nusinersen gebruik.

Kosteneffectiviteit
De kosteneffectiviteit is bepaald voor een subgroep van patiënten met de geregistreerde indicatie, namelijk symptomatische patiënten met SMA type 1. Pre-symptomatische patiënten zijn geïncludeerd in een scenario-analyse.
De behandeleffecten van OA zijn waarschijnlijk overschat door de toepassing van enkelarmige studies en keuzes in het model zoals gemaakt door de registratiehouder, zoals keuzes voor (voordelige) langetermijneffecten. De meerwaarde van OA ten opzichte van nusinersen kan nog niet bepaald worden omdat vergelijkende effectiviteitsdata ontbreken.
De Beneluxa-landen konden zich niet vinden in de aannames die in het model gedaan werden door de registratiehouder en heeft een alternatieve 'base case'-analyse gedaan waarin onder andere het gebruik van nusinersen na toediening van OA is meegenomen. De schatting van deze 'incremental cost effectiveness ratio' (ICER) laat zien dat OA niet kosteneffectief is versus nusinersen of best ondersteunende zorg (BSC); de geschatte ICER is € 263.389 per QALY versus nusinersen.
In een eerdere beoordeling is de kosteneffectiviteit van nusinersen bepaald bij de genoemde indicatie. Voor nusinersen is de prijs onderhandeld door de minister. Omdat deze informatie niet openbaar is, heeft het Zorginstituut bij de huidige beoordeling van de kosteneffectiviteit van OA zelf een scenario opgesteld waarbij is uitgegaan van de destijds geadviseerde prijs van nusinersen (prijsdaling van 85% om de referentiewaarde te benaderen). In dat geval moet de prijs van OA dalen met 91% om binnen de referentiewaarde van € 80.000 per QALY te vallen.

Weesgeneesmiddelenarrangement
Om de inzet van OA te monitoren en te volgen, zal het bestaande weesgeneesmiddelenarrangement voor nusinersen worden uitgebreid met OA. Hierin zijn afspraken vastgelegd over start- en stopcriteria, een indicatiecommissie, dataverzameling en evaluatie. Het bestaande SMA-register dat het SMA Expertisecentrum bijhoudt, wordt hierbij als basis gebruikt. Het Zorginstituut zal dit traject verder faciliteren. Het Zorginstituut brengt daarbij onder uw aandacht dat het van groot belang is dat expertisecentra voor het uitvoeren van dergelijke weesgeneesmiddelarrangementen over voldoende middelen beschikken om de gemaakte afspraken te kunnen nakomen en om de praktijk goed te kunnen volgen. Alleen zo kan voldoende data worden verkregen voor de geadviseerde voorwaarde *pay for performance.*
De resultaten van het weesgeneesmiddelenarrangement zullen jaarlijks in de *Monitor weesgeneesmiddelen in de praktijk* worden gepubliceerd.
Daarnaast kunnen de data in het bestaande SMA-register de mogelijkheid bieden om in de loop der tijd meer zekerheid te krijgen over de lange termijn effectiviteit van OA.

Zorginstituut Nederland
Zorg II
Infectieziekten, Bloed & Immunologie

Datum
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Eindconclusie

Onasemnogene abeparvovec (OA) is een innovatieve, veelbelovende en eenmalige behandeling die aangrijpt op de oorzaak van de ziekte en voldoet aan de stand van wetenschap en praktijk. Deze gentherapie is van groot belang voor de behandeling van een levensbedreigende aandoening bij zeer jonge kinderen. De eerste resultaten zijn veelbelovend; pre-symptomatische behandeling draagt de belofte in zich om ziekte te kunnen voorkomen. Dat is waardevol.
Er zijn echter ook grote onzekerheden over de effecten, zowel op de korte als op de lange termijn en over eventueel gebruik van aanvullende ziektemodulerende behandelingen. Verder is de kosteneffectiviteit op basis van de beschikbare data onzeker en vooralsnog ongunstig. Data die in de toekomst verzameld worden in het bestaande SMA-register, zullen hierover meer informatie geven.
Het Zorginstituut adviseert u OA op te nemen in het verzekerde pakket wanneer voldaan is aan de volgende voorwaarden:

- Uitgaande van de genoemde onzekerheden, mag het risico op een te hoge prijs niet uitsluitend bij de premiebetaler worden neergelegd. Rekening houdend met een prijsreductie van 85% voor nusinersen (huidige behandeling) en met de onzekerheid over de effectiviteit, zou een prijsverlaging van 91% op OA van toepassing moeten zijn om te komen tot een kosteneffectieve behandeling met OA. Als de claim van de fabrikant volledig uitkomt, zou geen prijsverlaging nodig zijn. Wanneer dat risico gedeeld zou worden, zou een prijsreductie rond 50% noodzakelijk zijn.
- Daarnaast adviseert het Zorginstituut een 'pay for performance'-afspraak waarbij de betaling afhangt van het al dan niet bereiken van relevante uitkomstmaten. Onderstaande relevante uitkomstmaten kunnen deel uitmaken van deze afspraak:
  - het gebruik van aanvullende ziektemodulerende behandelingen zoals bijvoorbeeld nusinersen;
  - overleving zonder beademing;
  - het bereiken van motorische mijlpalen.

Het Zorginstituut adviseert u om de (prijs)onderhandeling aan te gaan binnen de al bestaande Beneluxa-samenwerking. Over 5 jaar zou het Zorginstituut een herbeoordeling kunnen doen om te zien hoe de kosteneffectiviteit zich op basis van de dan beschikbare data heeft ontwikkeld.

Hoogachtend,

Sjaak Wijma
Voorzitter Raad van Bestuur

2021016277

ACP-advies aan de Raad van Bestuur van het Zorginstituut over de gentherapie onasemnogene abeparvovec (hierna afgekort als OA) (Zolgensma®) bij de behandeling van de volgende supgroepen van spinale musculaire atrofie (SMA) patiënten:

- Alle symptomatische SMA type 1 patiënten
- Presymptomatische SMA patiënten met maximaal 3 kopieën van het SMN2 gene.

De Adviescommissie Pakket (ACP) adviseert de Raad van Bestuur (RvB) van het Zorginstituut over voorgenomen pakketadviezen. Zij toetst deze adviezen aan de pakketcriteria en kijkt of de uitkomsten daarvan maatschappelijk wenselijk zijn. Daarbij kijkt zij zowel naar de belangen van de patiënten die in aanmerking komen voor vergoeding van een bepaalde interventie, als naar de belangen van patiënten met andere aandoeningen (die ook graag willen dat de behandeling van hun aandoening wordt vergoed) en van premiebetalers. Zij doet dit vanuit het principe dat de basisverzekering maximale gezondheidswinst dient op te leveren voor de gehele bevolking. Om hier een uitspraak over te kunnen doen, hanteert de commissie normaliter zogenaamde referentiewaarden voor kosteneffectiviteit. Deze referentiewaarden moeten worden opgevat als, in beginsel maximale, bedragen die we als samenleving per gewonnen levensjaar willen investeren in een behandeling. Gaan we daarboven zitten, dan is er sprake van verdringing van andere zorg. Dat betekent dat voor hetzelfde bedrag meer gezondheidswinst kan worden verkregen door het aan andere behandelingen uit te geven.

De commissie heeft in haar vergadering van 23 april 2021 (i.v.m. corona maatregelen een videoconferentie) gesproken over de vraag of OA voor genoemde subgroepen van SMA-patiënten opgenomen moet worden in de basisverzekering.

De patiëntenorganisatie Spierziekten Nederland, het SMA Expertisecentrum en de fabrikant Novartis hebben ingesproken tijdens de vergadering. Hieronder volgt een samenvattende weergave daarvan.

Alle partijen gaven aan dat er sprake is van een belangrijke innovatieve behandeling die ingrijpt op de oorzaak van de ziekte. Ondanks alle onzekerheden over de effecten op lange termijn biedt deze gentherapie hoop op een beter leven voor SMA-patiënten, waarbij opname van SMA in de hielprik een belangrijke rol zal gaan spelen voor tijdige, presymptomatische behandeling van patiëntjes. Dit staat voor eind 2022 gepland. Spierziekten Nederland en het Expertisecentrum dringen erop aan om te kijken of dit eerder mogelijk is. Ook wijzen zij op het belang van dataverzameling over lange termijneffecten en bijwerkingen. Zij roepen de fabrikant op de data vrij te geven van alle behandelde patiënten ter wereld. Dat is ook nodig om ouders goede informatie te kunnen bieden bij hun moeilijke keuze om hun kind al dan niet te laten behandelen. Het Expertisecentrum wijst verder op de noodzaak dat expertisecentra financiering ontvangen uit een onafhankelijke bron om registers op te zetten en te onderhouden om zo optimaal bij te kunnen dragen aan gepast gebruik. Dit kan immers leiden tot grote besparingen.
Spierziekten Nederland realiseert zich dat de kosten van deze gentherapie hoog zijn en roept alle betrokken partijen op om zo snel mogelijk te komen tot realistische afspraken om deze nieuwe behandeling voor deze groep kinderen zo snel mogelijk toegankelijk te maken.
De fabrikant betwijfelt of het Zorginstituut de juiste aannames hanteert t.a.v. de prijsstelling. Hij heeft er vertrouwen in dat de gunstige effecten op termijn zullen aanhouden. Hij geeft echter ook aan open te staan voor afspraken over gespreide betaling en/of pay for performance.

De volgende punten vormen voor de commissie het vertrekpunt voor de discussie:

- het betreft een op korte termijn effectieve, en op langere termijn veelbelovende gentherapie, waarbij in theorie kan worden uit gegaan van een eenmalige behandeling;
- er is echter grote onzekerheid over de lange termijn effecten, bijwerkingen en de kosteneffectiviteit;

- de prijs is uitzonderlijk hoog.

De commissie deelt de mening van partijen over:
- de noodzaak van het verzamelen en delen van data; alsmede
- de noodzaak tot onafhankelijke financiële ondersteuning van expertisecentra om een weesmiddelen-arrangement te kunnen uitvoeren.
- Tevens heeft de commissie, gezien de ernst van de ziekte en gezien daar inmiddels een effectieve behandeling voor beschikbaar is, begrip voor de oproep van partijen om opname van SMA in de hielprik screening zo snel mogelijk te realiseren.

Ook al acht de commissie het wenselijk dat deze behandeling spoedig beschikbaar komt voor de patiënt, zij vindt de prijs, bijna twee miljoen per patiënt, echter veel te hoog. Het kosteneffectiviteitsmodel van de Beneluxa-review groep (de beoordeling heeft in een Europees samenwerkingsverband plaatsgevonden) laat zien dat, uitgaande van de referentiewaarde van €80.000 per QALY die van toepassing is bij deze aandoening met een zeer hoge ziektelast (0.94), OA niet kosteneffectief is in vergelijking met nusinersen (€263.389 per QALY). Er zou een prijsreductie van 91% van OA nodig zijn om te kunnen spreken van een kosteneffectieve behandeling. Voor de berekening van dit percentage is uitgaan van de destijds door het Zorginstituut geadviseerde prijs van nusinersen (85% prijsreductie) omdat pas bij die prijsreductie sprake zou zijn van een kosteneffectieve behandeling met nusinersen. Ook is in dit model rekening gehouden met de mogelijkheid dat een deel van de patiënten dat met OA is behandeld in de toekomst wellicht ook met nusinersen behandeld zal gaan worden. Uit real world evidence en het onderzoek dat hiernaar loopt, blijkt namelijk dat een deel van de patiënten behandeld wordt met beide middelen. Het is nog onzeker of dit meerwaarde heeft. De verwachting is dat het effect van OA levenslang behouden blijft en vervolgbehandeling met nusinersen niet nodig is. De lange termijn gegevens zullen moeten uitwijzen of dit inderdaad het geval is.

De commissie acht het nodig, gezien de grote onzekerheid over de lange termijn effecten en de kosteneffectiviteit, om een *'pay for performance'* afspraak te adviseren, waarbij de commissie het Zorginstituut en de beroepsgroep vraagt mede uitwerking te geven aan een dergelijke afspraak. De commissie vindt het verder noodzakelijk dat deze afspraken openbaar worden gemaakt door het ministerie van VWS, zodat hiervan kan worden geleerd voor de toekomstige beoordelingen van gentherapieën. Hiermee doelt de commissie op de medisch-inhoudelijke kant van de afspraken, zoals welke uitkomstmaten relevant zijn, bij welke effectgrootte over welke periode er sprake is van een langdurig effectieve behandeling en welke betaling is aangewezen. Dit betekent overigens niet dat zij in het algemeen van mening zou zijn dat de gemaakte prijsafspraken niet openbaar zouden moeten worden gemaakt door het ministerie.

Echter, naast de pay for performance afspraak acht de commissie, gezien de hoge prijs, ook een forse prijsreductie nodig. Hoewel de commissie veelbelovende innovatie wil belonen en stimuleren en daarom een zekere afwijking van de referentiewaarde acceptabel vindt, zijn er ook argumenten die daartegen pleiten:
- de grote mate van onzekerheid over de lange termijn effecten en kosteneffectiviteit;
- de kans dat de werkelijke kosten voor ontwikkeling- en registratie een stuk lager zijn dan de gevraagde prijs. De commissie heeft hier namelijk geen inzicht in;
- het feit dat het consumentensurplus volledig naar de fabrikant gaat;[1]
- de verdringing van andere zorg, die door de huidige prijs, ver boven de referentiewaarde, zal gaan toenemen;
- het moeilijk te rechtvaardigen is naar (ouders van) patiënten met andere ernstige gezondheidsproblemen die hun zorg (nog) niet of onvoldoende krijgen.

[1] Als een land de maximale willingness to pay betaalt, impliceert dat dat het hele surplus (de meeropbrengst) volledig naar de fabrikant gaat.

Waar het gaat om de grote mate van onzekerheid begrijpt de commissie dat dit (deels) opgevangen wordt door een pay for performance afspraak. Het gewicht dat aan de mate van onzekerheid wordt toegekend is daarom afhankelijk van de aard van de gemaakte prijsafspraken.

Alles afwegende komt de commissie tot het advies om OA bij deze subgroepen van patiënten niet te vergoeden tenzij er een pay for performance afspraak gemaakt wordt én prijsonderhandeling leidt tot een zeer forse prijsreductie, waarvan de omvang mede afhankelijk is van de aard van de gemaakte pay for performance afspraken. Door de grote onzekerheden over de werking van het middel op de lange termijn en de te maken afspraken, is het voor de commissie lastig te zeggen welke prijsreductie noodzakelijk is om te kunnen spreken van een kosteneffectieve behandeling. De commissie baseert zich bij haar advies op de onafhankelijke kosteneffectiviteitsbepaling van de Beneluxa-review groep en op de publicatie van Broekhoff et al. (2021) in Value in health[2] over de kosteneffectiviteit van OA voor de Nederlandse situatie.
Beide berekeningen wegend en het innovatieve aspect in acht nemend, acht de commissie een prijsreductie van minimaal 50% noodzakelijk om tot een maatschappelijk verantwoorde opname van OA in de basisverzekering te komen.

[2] Early cost-effectiveness of onasemnogene abeparvovec-xioi (Zolgensma) and nusinersen (Spinraza) treatment for spinal muscular atrophy I in the Netherlands with relapse scenario's.

National Health Care Institute

Relative effectiveness report onasemnogene abeparvovec (Zolgensma®) 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 up to three copies of the SMN2 gene

Element of the initial assessment of specialty medicines

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Content

Abbreviations

Abbreviation	Description
AAV	Adeno-associated viruses
ASO	Antisense oligonucleotide
OA	Onasemnogene abeparvovec (Zolgensma®)
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
CRM	Commission Reimbursement of Medicines
CTG	Commissie Tegemoetkoming Geneesmiddelen
EMA	European Medicine Agency
EPAR	European public assessment reports
FU	Follow-up
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HINE-2	The Hammersmith Infant Neurological examination
HR	Hazard ratio
NA	Not available
NCPE	National Centre for Pharmacoeconomics
NR	Not eported
MCID	Minimal clinically important difference
PNCR	Paediatric Neuromuscular Clinical Research
RCT	Randomized controlled trial
RIVM	National Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu*)
RR	Relative risk (risk ratio)
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMN	Survival motor neuron gene
SMD	Standardized mean difference
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TEAE	Treatment emergent adverse event
WAR	Scientific Advisory Board (*Wetenschappelijke adviesraad)*
WHO	World Health Organisation

Summary

In this relative effectiveness report, The Beneluxa assessment team including *Zorginstituut Nederland* (ZIN: the National Healthcare Institute), the Belgian Commission Reimbursement on Medicines (CRM) and the Irish National Centre for Pharmacoeconomics (NCPE) describes the substantive assessment of the benefit of onasemnogene abeparvovec (Zolgensma®) for the treatment of symptomatic SMA type 1 patients and presymptomatic SMA patients with up to three copies of the SMN2 gene.

Onasemnogene abeparvovec (OA) is compared with nusinersen (Spinraza®) and best supportive care based on the criteria favourable effects, unfavourable effects, experience, applicability and usability. Zorginstituut Nederland has been advised in this regard by its Scientific Advisory Board (*Wetenschappelijke adviesraad*: WAR) and by the Belgian Commission Reimbursement of Medicines *(CTG)*. The evaluation is part of a common evaluation in the context of the Beneluxa Initiative project. This report, as well as the pharmacoeconomic report and the budget impact analysis will be used both by ZIN, the CRM and the NCPE. The relative effectiveness report has been prepared by ZIN, the cost-effectiveness model and the budget impact analysis by the NCPE. All assessment procedures are running in parallel according to the national legislations.

Spinal muscular atrophy (SMA) is a serious, progressive muscle disease that leads to strongly reduced mobility, curvature of the spine, loss of the arm and hand functions and paralysis of the respiratory muscles. Nusinersen (Spinraza®) was the first drug that received approval for treatment of SMA in 2017 and is reimbursed in all Beneluxa Initiative countries. The current classification of the type of SMA (type 0-4) is based on the age at which the first symptoms occur and the motor function/milestones achieved. Type 1 SMA is characterized by onset before 6 months of age, failure to achieve sitting without support, and a life expectancy of 2 years or less. When treated with the best supportive care, life expectancy improves a little with a median survival of 2 years. Traditional SMA types alone are however not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict the severity of the disease. In presymptomatic patients SMN2 copy number is the most important predictor of clinical severity and age of onset.

OA is a single-dose intravenous infusion of gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells to address the cause of the SMA. To date only open label, single arm studies are available. Registration of OA was based on two clinical trials in 22 and 12 symptomatic SMA type 1 patients (STR1VE-US and START) who received a therapeutic dose of the product. One similar trial with 33 patients (STR1VE_EU) and one other trial investigating 29 presymptomatic SMA patients with two or three copies of SMN2 (SPR1NT) are still ongoing. Survival, ventilation-free survival and mobility outcomes such as CHOP-INTEND and motor milestones were evaluated. OA is used as an adjunct to best supportive care. Only patients younger than 6 months of age at the time of gene infusion were included in these trials.

The quality of the evidence is (very) low due to the limited setup of the trials: single arm trials without controls and a limited number of patients. Two of the four studies are still ongoing and the follow-up time is limited. Data from historical controls are available but there are differences in study design and patient population. This

affects the comparability with the OA trials (differences in baseline characteristics e.g. mobility scores, ventilation and nutritional support). The use of these data is accepted by the regulatory authorities. In absence of a direct comparative trial between OA and best supportive care or nusinersen, a naïve indirect comparison had to be made. Given the progressive nature of SMA in type 1 patients it is considered unethical to include placebo arms in the trials that followed on the first phase 1/2 OA trial (START). No other active treatments were available for this patients at the start of the OA studies. Therefore non-comparative studies or indirect treatment comparisons are the highest achievable at the moment of this assessment and therefore considered appropriate.

Symptomatic SMA type 1 patients
The relative effectiveness of OA compared with nusinersen is highly uncertain given the lack of direct comparative evidence and the heterogeneity in clinical trials used for the naïve indirect treatment comparison. Less patients have been studied compared to nusinersen. The indirect comparison suggested that OA is at least associated with comparable effects on overall survival and has possibly more effect on event-free survival (survival without permanent assisted ventilation) compared with nusinersen at 18 months of time on study. For the mobility outcome CHOP-INTEND score, a statistically significant difference was observed in favour of OA when compared to nusinersen, but clinical relevance has not been conclusively demonstrated. Nusinersen treated patients seem to be more affected at start of treatment, based on differences in CHOP-INTEND and ventilation support at baseline. Follow-up data from the nusinersen studies are much longer than the immature data from the OA studies. A convincing added benefit of OA versus nusinersen cannot (yet) be concluded. Further the robustness of a naïve unanchored comparison is problematic in determining benefit objectively.

All estimated effects of OA on survival, ventilation free survival and the mobility outcomes are substantial and within the standards of clinical relevance. The Beneluxa assessment team considers the beneficial effects of OA to be clinically relevant compared to standard of care. However, more information on both number of patients and follow-up time is needed to assess the maintenance of the treatment effect.

Presymptomatic patients
One single-arm trial with 29 presymptomatic OA treated children is still ongoing (14 patients with 2 copies and 15 patients with 3 copies of SMN2). A comparable single-arm trial of nusinersen was carried out. Both OA and nusinersen subjects were treated before 6 weeks of age. Since none of the OA and nusinersen presymptomatic treated patients experienced an event of permanent ventilation or death so far, the effect of both products on this outcome measure seems to be comparable. In addition, the results on the motor milestones and CHOP-INTEND score of OA and nusinersen treated patients point in the same direction. However, the follow-up of the patients in the OA trial is much shorter with median follow-up <15 months of age vs. 35 months in the latest nusinersen data cut. A longer follow-up is needed in order to draw conclusions about milestones that still need to be met. An equal or added benefit of OA versus nusinersen in presymptomatic patients cannot be concluded based on these immature presymptomatic trials.

Presymptomatic patients with two copies of SMN2
In the absence of data to determine benefit in presymptomatic patients, it could be the case that the effectiveness of OA in symptomatic patients is at least similar in presymptomatic patients with 2 copies of SMN2. The results of the latest, unpublished data cut of June 2020 suggests at least 4 of the patients are developing

within the normal range of healthy children measured by the standing and walking alone milestones of the WHO. But there are also patients staying behind in development. Three (3) of the 14 treated presymptomatic patients did not develop the motor milestone sitting without support, although they exceeded the upper bound of the normal development window. One did not achieved walking alone within the normal range of development. Only longer term follow-up can conclude whether these children will indeed continue to lag behind healthy children.

Presymptomatic patients with three copies of SMN2
More variation of the course of the disease is seen in patients with three copies of SMN2; most of these patients will develop type 1 c or 2a (very severe) SMA without effective treatment. Patients with type 2 SMA will never learn to walk and their life expectancy is still limited to 20-40 years. With the introduction of nusinersen in the treatment regime of SMA patients, the prognosis of patients with 3x SMN2 has changed. Treatment with nusinersen in patients with 3x SMN2 (both symptomatic and presymptomatic treated patients) is effective.

Conclusive evidence of the effectiveness of OA in SMA patients with 3 copies of SMN2 has not yet been provided. SPR1NT is ongoing and includes 15 presymptomatic patients with 3 SMN2 copies. The results from the latest unpublished June 2020 data cut suggests most children in this cohort can sit without support within or slightly behind the normal development window. But the data is still immature as more than half of the patients are too young to make conclusions on group level on the development of the milestones walking and standing alone. The data from the 15 patients with 3 SMN2 copies treated with OA is immature to the extent that no firm conclusions can be drawn regarding efficacy. Longer follow-up data are needed to draw conclusions about the relative effect of OA versus nusinersen in these patients.

Based on the mechanism of action, the more mature data from the symptomatic treated patients is an indication for the longer term efficacy of OA in the presymptomatic patients. It is widely supported in i.e. the EU consensus document that presymptomatic children with SMA will benefit even more from active treatment than patients that already experienced symptoms of the disease.
Together with the arguments that it is not possible to distinguish between presymptomatic patients with 2 or 3 copies of SMN2 based on the data an added benefit of OA versus best supportive care for the pre-symptomatic SMA patients with 2 **and** 3 SMN2 copies is concluded. Although direct evidence is lacking and only long-term follow-up studies can find out what the magnitude of the added benefit is of OA in presymptomatic patients.

Concomitant use of nusinersen
OA is a gene therapy targeting the underlying pathophysiology of the disease, from which it would be expected that no further treatment would be necessary. Nusinersen modulates alternative splicing of the SMN2 gene, functionally converting it into SMN1 gene, thus increasing the level of SMN protein in the central nerve system. Real world evidence and registered clinical trials have noted concomitant use of nusinersen. This is now being explored in clinical trials (Biogen). The company provided data from long term follow up studies LT-001 (N=13) which indicate that 40-50% of patients who received OA subsequently received therapy with nusinersen (4/10 who received the higher dose in phase I/IIa study and all three patients who received the lower dose in this study are on nusinersen). We cannot rule out that this will also happen in clinical practice, although there is no published evidence that combination of these two disease modifying therapies is superior to any single treatment alone.

Other aspects
From the available safety data it seems that OA will result in more treatment-related adverse events than treatment with nusinersen. Although the number of serious adverse events, whether or not related to the treatment seem to be lower when treated with OA versus nusinersen, the data remains very limited due to the short follow-up. The CHMP concluded that OA and nusinersen have at least a comparable safety profile. However, the burden of treatment with OA should not be underestimated. Available data suggest that treatment with OA is well tolerated by very young children, but children receiving OA should be treated with high doses of prednisone to prevent liver failure.

The long-term follow up of the adverse events of OA are unknown. The adverse events related to the immune response are not likely to have long term safety consequences. However, the long-term safety of gene expression is less clear. Though the carcinogenicity risk is considered low as AAV vectors mainly do not integrate in the host genome as compared to e.g. lentivirus, it can also not be fully excluded. Much about OA and AAV vector use in general is still unknown, particularly regarding long-term side effects. Children have died in the studies, and death has also been reported in other AAV gene therapy trials. Intensive monitoring of safety is of great importance in children treated with OA. Treated patients will be followed up till 15 years.

The experience and applicability of OA versus nusinersen is comparable but the usability of OA (single intravenous infusion) and dose regime (only once) was considered a clinically relevant advantage as compared to the repeated intrathecal injections of nusinersen.

Conclusion

The Beneluxa assessment team (Zorginstituut Nederland, the Belgian CRM and the Irish NCPE) conclude that onasemnogene abeparvovec (Zolgensma®) is considered established medical science and medical practice in the treatment of symptomatic SMA type 1 patients. The mechanism of action, the wide consensus about the advantages of presymptomatic treatment and the fact that possibly more than half of the patients with 3 copies of SMN2 will develop very severe disease is considered sufficient to conclude established medical science and medical practice for OA in presymptomatic SMA patients with 2 or 3 copies the SMN2 gene. There is insufficient evidence to draw a conclusion on the comparative benefit of OA compared with nusinersen.

The discussion of the concept of this relative effectiveness report was completed by the Scientific Advisory Board of Zorginstituut Nederland at its meeting on 29 March 2021 and by the Belgian Commission Reimbursement of Medicines at its meeting on 30 March 2021

Dutch Summary (Nederlandse samenvatting)

In dit farmacotherapeutisch rapport beschrijft het Beneluxa beoordelingsteam, inclusief Zorginstituut Nederland, de Belgische Commissie Vergoeding Geneesmiddelen (CRM) en het Ierse Nationale Centrum voor Farmacoeconomie (NCPE) de inhoudelijke beoordeling van de waarde van onasemnogene abeparvovec (Zolgensma®) bij de behandeling van symptomatische spinale musculaire atrofie (SMA) type 1 patiënten en presymptomatische SMA patiënten met maximaal drie kopieën van het SMN2 gen.

Onasemnogene abeparvovec (OA) is daarbij vergeleken met nusinersen en best ondersteunende zorg op de criteria gunstige effecten, ongunstige effecten, ervaring, toepasbaarheid en gebruiksgemak. Zorginstituut Nederland heeft zich hierbij laten adviseren door haar Wetenschappelijke Adviesraad (WAR) en door de Belgische Commissie Tegemoetkoming van Geneesmiddelen (CTG*)*. De beoordeling maakt deel uit van een gezamenlijke evaluatie in het kader van het Beneluxa Initiatief project. Dit rapport, evenals het farmaco-economische rapport en de budgetimpactanalyse worden zowel door ZIN, de Belgische commissie voor de vergoeding van geneesmiddelen (*Commission Reimbursement of Medicines*: CRM) en het Ierse nationale centrum voor farmacoeconomie (*National Centre for Pharmacoeconomics*: NCPE) gebruikt. Het farmacotherapeutische rapport is opgesteld door ZIN, het farmaco-economische rapport en de budgetimpactanalyse door de NCPE. Alle beoordelingsprocedures lopen parallel volgens de nationale wetgeving.

Spinale spieratrofie (SMA) is een ernstige, progressieve spierziekte die leidt tot sterk verminderde mobiliteit, kromming van de wervelkolom, verlies van de arm- en handfuncties en verlamming van de ademhalingsspieren. Nusinersen (Spinraza®) was het eerste geneesmiddel dat in 2017 werd goedgekeurd voor de behandeling van SMA en wordt in alle landen van het Beneluxa Initiatief vergoed. SMA wordt momenteel getypeerd op basis van klinische kenmerken zoals leeftijd waarop de eerste symptomen zich manifesteren en behaalde motorische mijlpalen. Waarbij type 1 patiënten zeer ernstig zijn aangedaan en zonder effectieve behandeling een mediane survival van slechts 2 jaar hebben. Patiënten met type 2 kunnen, al dan niet met handicaps, wel 20-40 jaar oud worden. Er is ook een genetische onderverdeling te maken op basis van het aantal SMN2 kopieën. Patiënten met 2 kopieën van SMN2 ontwikkelen meestal type 1 SMA. Patiënten met 3 kopieën ontwikkelen meestal type 2 SMA en zijn minder aangedaan dan de patiënten met 2 kopieën. Het klinisch beeld bij patiënten met 3 kopieën is echter zeer heterogeen. De traditionele klinische SMA typering is niet voldoende om de patiëntenpopulaties te kunnen definiëren die het meest zouden kunnen profiteren van gentherapie. Bij symptomatische SMA patiënten zijn de leeftijd bij aanvang van de behandeling, de duur van de ziekte en de motorische functie bij aanvang van de behandeling belangrijkst factoren die de ernst van de ziekte kunnen voorspellen. Bij presymptomatische patiënten is het aantal SMN2 kopieën de belangrijkste voorspeller van de klinische ernst en de leeftijd van het begin.

OA is een eenmalig intraveneuze toediening van gentherapie, ontworpen om een functionele kopie van het *survival of motor neuron 1* (SMN1) gen in de getransduceerde cellen te introduceren om de oorzaak van SMA aan te pakken. Tot op heden zijn alleen open label, single arm studies beschikbaar. De registratie van OA was gebaseerd op twee klinische studies bij 22 en 12 symptomatische SMA type 1 patiënten (STR1VE-US en START) die een therapeutische dosis van het product kregen. Een soortgelijk onderzoek met 33 patiënten (STR1VE-EU) en een ander onderzoek met 29 presymptomatische SMA-patiënten 2 of 3 kopieën van SMN2

(SPR1NT) lopen nog. Overleving, beademingsvrije overleving en mobiliteit zoals de CHOP-INTEND score en motorische mijlpalen werden geëvalueerd. OA wordt gebruikt als aanvulling op de beste ondersteunende zorg. Alleen patiënten jonger dan 6 maanden op het moment van gen toediening werden in deze studies opgenomen.

De kwaliteit van het bewijs is zeer laag door de beperkte opzet van de trials: single arm trials zonder controles en een beperkt aantal patiënten. Twee van de vier studies lopen nog en de follow-up tijd is beperkt. Gegevens van historische controles zijn beschikbaar maar er zijn verschillende in het studiedesign en in de patiënten populaties. Dit beïnvloedt de vergelijkbaarheid van deze studies met de OA studies (verschillen in baselinekarakteristieken zoals mobiliteit scores en ventilatie- en voedingssupport). Het gebruik van deze data is geaccepteerd door de *European Medicines Agency* (EMA). De patiënten in de historische cohorten blijken gebaseerd op de baselinekarakteristieken van de studies (beademings- en voedingsondersteuning) mogelijk ernstiger te zijn aangedaan. Omdat een direct vergelijkend onderzoek tussen OA en de beste ondersteunende zorg of nusinersen niet voor handen is, moest een naïeve indirecte vergelijking worden gemaakt. Er waren geen andere actieve behandelingen op de markt ten tijde van het starten van de OA trials en door het progressieve karakter van SMA type 1 wordt het als onethisch gezien om na de resultaten die werden behaald in de fase 1/2 OA studie (START) een placebo arm te includeren. Daarom zijn niet-vergelijkende studies of indirecte vergelijkingen van behandelingen het hoogst haalbare op het moment van deze beoordeling en worden daarom als passend bewijs gezien.

Symptomatische SMA type 1-patiënten
De relatieve effectiviteit van OA in vergelijking met nusinersen is zeer onzeker gezien het gebrek aan direct vergelijkend bewijs en de heterogeniteit in de klinische studies die gebruikt worden voor de naïeve indirecte vergelijking. Er zijn minder patiënten onderzocht in vergelijking met nusinersen. De indirecte vergelijking suggereerde dat behandeling met OA (na 18 maanden) minstens geassocieerd is met vergelijkbare effecten op algehele overleving en mogelijk meer effect heeft op event vrije overleving (overleving zonder permanente ventilatie) vergeleken met nusinersen. Voor de mobiliteitsuitkomst CHOP-INTEND score is een statistisch significant verschil waargenomen in het voordeel van OA ten opzichte van nusinersen, maar de klinische relevantie is niet aangetoond. Patiënten uit de nusinersen studies lijken aan het begin van de behandeling minder ernstig te zijn aangedaan dan de patiënten uit de OA studies, gebaseerd op de baseline scores van CHOP-INTEND en ventilatie support. De follow-up tijd van de nusinersen studies is veel langer dan de immature data die op dit moment beschikbaar is voor OA. Een overtuigende meerwaarde van OA ten opzichte van nusinersen kan nu (nog) niet worden geconcludeerd. Waarbij de robuustheid van een naïeve indirecte vergelijking problematisch is bij het bepalen van het verwachte voordeel.
Alle geschatte effecten van OA op de overleving, tijd tot beademing en de mobiliteitsresultaten zijn substantieel en binnen de normen van klinische relevantie wanneer wordt vergeleken met de best ondersteunende zorg. Het Beneluxa beoordelingsteam acht de gunstige effecten van OA klinisch relevant in vergelijking met de best ondersteunende zorg. Er is echter meer informatie nodig in zowel patiënten aantallen als de follow-up om het behoud van het behandelingseffect op de lange termijn te kunnen beoordelen.

Presymptomatische patiënten
Een single-arm trial met 29 presymptomatische OA behandelde kinderen loopt nog (14 patiënten met 2 kopieën en 15 patiënten met 3 kopieën van SMN2). Er is een vergelijkbare eenarmige studie van nusinersen uitgevoerd. Zowel OA als nusinersen

patiënten werden behandeld voor de leeftijd van 6 weken. Aangezien geen van de OA- en nusinersen presymptomatisch behandelde patiënten tot nu toe permanent wordt beademd of is overleden, lijkt het effect van beide producten op deze uitkomstmaat vergelijkbaar te zijn. Daarnaast wijzen de resultaten op de motorische mijlpalen en de CHOP-INTEND score van de met OA en nusinersen behandelde patiënten in dezelfde richting. De follow-up van de patiënten in de OA-studie is echter veel korter met een mediane follow-up <15 maanden vs. 35 maanden in de laatste nusinersen data cut. Een langere follow-up is nodig om conclusies te kunnen trekken over de mijlpalen die nog gehaald moeten worden. Een gelijke of toegevoegde waarde van OA versus nusinersen in presymptomatische patiënten kan niet worden geconcludeerd op basis van deze immature presymptomatische studies.

Presymptomatische patiënten met twee kopieën van SMN2
Bij gebrek aan gegevens om het verwachte voordeel bij presymptomatische patiënten te bepalen, zou het kunnen dat de effectiviteit van OA bij symptomatische patiënten ten minste vergelijkbaar is met die bij presymptomatische patiënten met 2 kopieën van SMN2. De resultaten van de laatste ongepubliceerde datacut suggereren dat er ten minste 4 patiënten zijn die motorische eindpunten behalen zoals zelf staan of lopen binnen de leeftijdsnorm die door de WHO is gesteld voor gezonde kinderen. Maar er zijn ook patiënten die toch nog achter blijven in de ontwikkeling. Drie (3) van de 14 presymptomatisch behandelde patiënten kunnen nog niet zitten zonder hulp, terwijl zij de leeftijd waarin gezonde kinderen dit kunnen al wel hebben overschreden. Eén (1) van de patiënten uit hetzelfde cohort kan nog niet alleen lopen op een leeftijd dat gezonde kinderen dit al wel kunnen. Alleen een langere follow-up kan concluderen of deze kinderen inderdaad achter blijven lopen op gezonde kinderen.

Presymptomatische patiënten met drie kopieën van SMN2
Meer variatie in het verloop van de ziekte wordt gezien bij patiënten met drie kopieën van SMN2; de meeste van deze patiënten zullen type 2 SMA ontwikkelen zonder effectieve behandeling. Patiënten met type 1c of 2a (zeer ernstige) SMA zullen nooit leren lopen en hun levensverwachting is nog steeds beperkt tot 20-40 jaar. Met de introductie van nusinersen in het behandelingsregime van SMA-patiënten is de prognose van patiënten met 3 kopieën van SMN2 veranderd. De behandeling met nusinersen bij deze patiënten (zowel symptomatisch als presymptomatisch) is effectief.

Er is nog geen sluitend bewijs geleverd over de effectiviteit van OA in SMA patiënten met drie SMN2 kopieën. De lopende SPR1NT studie heeft 15 presymptomatisch behandelde patiënten met drie kopieën geïncludeerd. De ongepubliceerde resultaten van de laatste dat cut van Juni 2020 suggereren dat de meeste kinderen uit dit cohort kunnen zitten zonder hulp binnen of net iets na de leeftijdsnorm die door de WHO is gesteld voor gezonde kinderen. De data is echter nog zeer immatuur want meer dan de helft van de patiënten is nog te jong om conclusies hierover op groepsniveau te kunnen maken. Langere follow-up gegevens zijn nodig om conclusies te trekken over het relatieve effect van OA versus nusinersen bij deze patiënten.

De meer mature data van de symptomatisch behandelde patiënten met SMA type 1 is, gebaseerd op het werkingsmechanisme een indicatie voor de lange termijn effectiviteit van OA in de presymptomatische patiënten. In het EU consensus document wordt ondersteund dat presymptomatisch behandelde kinderen meer voordeel zullen hebben van actieve behandeling dan patiënten die al symptomen van de ziekte ervaren. Samen met het argument dat het eigenlijk niet mogelijk is om te differentiëren tussen patiënten met 2 of 3 kopieën op basis van de data wordt

een toegevoegde waarde van OA ten opzichte van best ondersteunende zorg voor presymptomatische SMA patiënten met 2 en 3 kopieën geconcludeerd. Hoewel direct bewijs ontbreekt en alleen follow-up studies op lange termijn kunnen uitwijzen wat de omvang van het toegevoegde voordeel is van OA bij presymptomatische patiënten.

Gelijktijdig gebruik van nusinersen
OA is gentherapie die zich richt op de onderliggende pathofysiologie van de ziekte, waarvan dan ook verwacht wordt dat er geen verdere behandeling nodig is. Nusinersen moduleert alternatieve splicing van het SMN2-gen, waarbij het functioneel wordt omgezet in het SMN1-gen, waardoor het niveau van SMN-eiwit in het centraal zenuwstelsel wordt verhoogd. *Real world data* en geregistreerde klinische studies hebben echter toch gelijktijdig gebruik van nusinersen opgemerkt. Dit wordt nu onderzocht in klinische studies (Biogen). De registratiehouder heeft data van de long-term follow-up studie(LT-001 (N-13) aangeleverd waaruit blijkt dat 40-50% van de patiënten die werden behandeld met OA vervolgens ook therapie met nusinersen ontvingen (4/10 van de patiënten die de hogere dosis OA kregen in de START studie en alle 3 patiënten uit dezelfde studie die de lage dosis OA kregen worden nu behandeld met nusinersen). We kunnen niet uitsluiten dat dit ook in de klinische praktijk zal gebeuren, hoewel er geen gepubliceerd bewijs is dat de combinatie van deze twee therapieën superieur is aan monotherapie.

Andere aspecten
Uit de beschikbare veiligheidsgegevens blijkt dat OA zal leiden tot meer behandelingsgerelateerde bijwerkingen dan behandeling met nusinersen. Hoewel het aantal ernstige ongewenste bijwerkingen, al dan niet gerelateerd aan de behandeling, lager lijkt te zijn bij behandeling met OA dan bij behandeling met nusinersen, blijven de gegevens zeer beperkt vanwege de korte follow-up. De CHMP concludeerde dat OA en nusinersen ten minste een vergelijkbaar veiligheidsprofiel hebben. De belasting van behandeling met OA moet echter niet worden onderschat. De beschikbare gegevens suggereren dat behandeling met OA goed verdragen wordt door zeer jonge kinderen, maar kinderen die OA krijgen toegediend moeten worden behandeld met hoge doses prednison om leverfalen te voorkomen.

De follow-up van de bijwerkingen op lange termijn van OA is onbekend. De bijwerkingen die verband houden met de immuunrespons zullen waarschijnlijk geen gevolgen hebben voor de veiligheid op lange termijn. De veiligheid op lange termijn van de genexpressie is echter minder duidelijk. Hoewel het risico op carcinogeniteit gering wordt geacht omdat AAV-vectoren in het algemeen niet in het genoom van de gastheer integreren in vergelijking met bijvoorbeeld lentivirus, kan het ook niet volledig worden uitgesloten. Over OA en het gebruik van AAV-vectoren in het algemeen is nog veel onbekend, vooral wat de neveneffecten op lange termijn betreft. Er zijn in de studies kinderen overleden, en overlijden is ook gemeld in andere AAV gentherapie trials. Intensieve controle van de veiligheid is van groot belang bij kinderen die met OA worden behandeld. Behandelde patiënten zullen tot 15 jaar worden gevolgd.

De ervaring en de toepasbaarheid van OA ten opzichte van nusinersen is vergelijkbaar, maar de bruikbaarheid van OA (enkelvoudige intraveneuze infusie) en het doseringsregime (slechts één keer) wordt beschouwd als een klinisch relevant voordeel ten opzichte van de herhaalde intrathecale injecties van nusinersen.

Conclusie

Zorginstituut Nederland, het Belgische CRM en het Ierse NCPE concluderen dat onasemnogene abeparvovec (Zolgensma®) voldoet aan de stand van de wetenschap en praktijk bij de behandeling van symptomatische patiënten met SMA type 1. Het werkingsmechanisme, de brede consensus over de voordelen van een presymptomatische behandeling en het feit dat mogelijk meer dan de helft van de patiënten met 3 kopieën van SMN2 een zeer ernstige ziekte zal ontwikkelen, wordt voldoende geacht om te concluderen dat OA ook voldoet aan de stand van de wetenschap en praktijk bij presymptomatische SMA-patiënten met 2 of 3 van het SMN2-gen, hoewel er onvoldoende bewijs is om een conclusie te trekken over de waarde van OA in vergelijking met nusinersen.

De bespreking van dit farmacotherapeutisch rapport is door de Wetenschappelijke Adviesraad van Zorginstituut Nederland afgerond in haar vergadering van 29 maart 2021 en door de Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) in haar vergadering van 30 maart 2021.

1 Introduction

1.1 Scope of the report

Zorginstituut Nederland assesses the relative clinical benefit of onasemnogene abeparvovec (OA) for the treatment of symptomatic SMA type 1 patients and presymptomatic SMA patients with up to three copies of the SMN2 gene. compared to best supportive care and nusinersen.

Onasemnogene abeparvovec (Zolgensma®) solution for injection 2.0x10^{13} vg/mL in 5.5 ml and 8.3 ml vials[1, 2]	
Registered indication:	*- 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.*
Reimbursement claim of the company:	*- all symptomatic SMA type 1 patients, and* *- presymptomatic SMA patients with up to three copies of the SMN2 gene*[1]
Posology:	*Single-dose intravenous infusion only.* *Patients will receive a dose of nominal 1.1 x 10^{14} vg/kg OA. The total volume is determined by patient body weight.* *Recommended dosing for patients who weigh 2.6 to 21.0 kg can be found in the SmPC. Treatment should be initiated and administered in clinical centres and supervised by a physician experienced in the management of patients with SMA. Before administration of onasemnogene abeparvovec, baseline laboratory testing is required, including:* *• adeno-associated viruses 9 (AAV9) antibody testing using an appropriately validated assay* *• liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin,* *• platelet count, and* *• troponin-I.*
Mechanism of action:	*OA is a gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells to address the monogenic root cause of the disease. By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons.* *OA is a non-replicating recombinant AAV vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene. The ability of the AAV9 capsid to cross the blood brain barrier and transduce motor neurons has been demonstrated.* *The SMN1 gene present in OA is designed to reside as*

[1] The claim of the company is smaller than the registered indication. All –thus also symptomatic type 2 and 3– SMA patients with 3x SMN2 are included in the registered indication, but only **presymptomatic** SMA patients with 3x SMN2 are included the claim of the company.

	episomal DNA in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The AAV9 virus is not known to cause disease in humans. The transgene is introduced to target cells as a self-complementary double-stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken β-actin hybrid), which results in continuous and sustained SMN protein expression. Proof of the mechanism of action has been supported by non-clinical studies and by human bio distribution data.
Particularities:	OA has received a conditional marketing authorisation and is designated as an orphan medicinal product as it is indicated for treatment life-threatening disease.

1.2 Background

1.2.1 Symptoms and severity

Symptoms of SMA are general weakness and atrophy of the skeletal muscles. The rate at which the muscles weaken differs per person and per type of SMA. Symptoms, disease course and life expectancy differ per type of SMA. The different types of SMA are part of a wide continuum without clear boundaries[9, 7, 12, 13]:

- **SMA type 1** or Werdnig-Hoffmann disease. Children with SMA type 1 have the first symptoms before the age of 6 months. The children usually do not survive till age of two. With improved attention to nutrition and respiration, survival has increased to a median survival of 2 years. SMA type 1 is subdivided into type 1a, 1b and 1c.
  - SMA type 1a (catastrophic) (also referred to as SMA type 0 or prenatal SMA): the most severe form, which begins before birth. Symptoms after birth: severe muscle weakness, forced positions of joints; sometimes bone fractures and extremely thin ribs. Subsequently problems with swallowing and breathing occur. These children rarely survive beyond the age of 6 months.
  - SMA type 1b (catastrophic): manifests between 0 and 6 months with symptoms: difficulty with sucking and swallowing, breathing problems. In the course of its life, the child will become increasingly paralyzed. In general these children will never be able to sit independently.
  - SMA type 1c (very severe): children have similar symptoms to type 1b, but survive longer [14].
- **SMA type 2 (very severe or severe)**. Start of symptoms between 7 and 18 months. The muscle strength of these children will increase at first, so they can learn to sit independently, but (according to the classification definition of type 2) they will never be able to walk. Halfway through the teens they lose the ability to sit independently. Frequent: scoliosis, flaccidity and vibration of the finger. Also in SMA type 2, life expectancy is limited (due to reduced lung function). But there is a wide range in life expectancy: from teens up to 40 years old.
- **SMA type 3 (severe)** or Wohlfart-Kugelberg-Welander disease. Start of symptoms from eighteen months to thirty years of age. Symptoms: problems with stairs and running, frequent falling. In approximately 50%: scoliosis. Patients with SMA type 3 can eventually become wheelchair dependent. Life expectancy with SMA type 3 depends on the clinical course of the disease.
  - Two subtypes are distinguished, SMN type 3a and 3b: start of symptoms respectively between 18 months - 3 years and from 3 years and up.

- **SMA type 4 (mild)** and Finkel SMA. These forms of SMA develop in adults from the age of 30 years. The first symptoms are loss of strength in thighs and upper arms, with the result that climbing stairs, getting up out of a chair or hanging the laundry become more difficult. Life expectancy with SMA type 4 is not necessarily shortened, but it does depend on the clinical course of the disease. A truly 'mild' course of the disease is considered rare.

A problem in the classification of SMA is that the type of SMA is determined afterwards, by the age at which the first symptoms occurred and the motor milestones reached. When diagnosing SMA, there can be no certainty about the clinical type of SMA, because the achieved milestone is part of the classification. In a German study on the natural course of SMA, 19% (46/240) of the patients with an expected SMA type 2 based on onset of symptoms < 18 months were still able to walk independently and therefore were no longer classifiable as SMA type 2. In this report we will therefore always refer to the expected type of SMA in the included studies, based on the age of the first symptoms in that study.

In SMA, there are large differences in the severity of the condition: in type 1, the disorder develops in the first weeks or months of life and the life expectancy is severely shortened. For the other types, the symptoms start later (> 6 months) or arise in childhood or even adulthood. There is a broad spectrum of very severe to less severe disease progression.

Within the classification into types there is great variation in severity and course of the disease. This partly depends on the number of SMN2 copies; see table 1. The more SMN2 genes (SMN2 copies) a person has, the more SMN protein is produced, which postpones the age at which the patient may face the possible limitations of this progressive muscle disease. Whilst intensive care (e.g. nutritional support and/or ventilatory support) provided as part of best supportive care may improve overall survival/ maximum life expectancy in patients with SMA, best supportive care does not fundamentally alter or improve disease progression.

1.2.2 *Prevalence and incidence*

SMA is a rare disease. The estimated incidence differs somewhat between populations, but is estimated to be approximately 1: 6,000 - 1: 10,000 births per year[15]. In the Netherlands, an estimated 15-20 children are born with SMA per year. About half of these children have the most severe form of SMA (type 1)[7, 16, 17]. The incidence of SMA reported from published newborn screening programmes ranges from 1 in 28,137 births (New York State, US)[18] to 1 in 7,000 in Belgium[19]. The incidence of SMA in Ireland was 5.6 per 100,000 live births in 2015 and 6.7 per 100,000 live births for 2011-2015[20].

1.2.3 Newborn screening

There is strong evidence that the irreversible loss of motor neurons in patients with SMA type 1 begins early in the perinatal period, with severe denervation in the first three months and loss of more than 90% of motor units within six months of age. Furthermore, preclinical studies looking at the timing of drug delivery in mouse models of severe SMA consistently show that the best results are obtained when drugs are given as early as possible, before significant motor weakness or loss is present[21].

A European consensus document on gene replacement therapy for SMA stated that SMA is a good candidate for inclusion in newborn screening programs. Published and

unpublished data from clinical trials and newborn screening programs indicate that presymptomatic initiation of treatment is often associated with normal motor development during infancy. In addition, several studies indicate that age and functional status at initiation of treatment are key predictors for the effect size of disease modifying treatments. Especially type 1 (early-onset) SMA is a rapidly progressing disease in which the clinical status can deteriorate within a week[21].

In Belgium, an ongoing screening project is being conducted in Southern Belgium. This pilot study is assessing the feasibility, efficacy, and cost-effectiveness of a newborn screening programme which was initiated in 2018; a full evaluation will be conducted after three years to consider the inclusion of SMA screening in the publicly funded NBS programme in Southern Belgium[22]. In Northern Belgium and the Netherlands, newborn screening for SMA is not yet in place.

The Health Council of the Netherlands (*de Gezondheidsraad*) gave a positive recommendation for including SMA in the neonatal blood spot screening in July 2019, whereby the committee emphasized the importance of evaluating the screening after 5 and 10 years[23]. The feasibility study performed by the National Institute for Public Health and the Environment (*Rijksinstituut voor Volksgezondheid en Milieu*: RIVM) shows that SMA can be added to the newborn blood spot screening. RIVM expects the screening for SMA to become operational throughout the Netherlands in October 2022. The Netherlands will then be one of the first countries in Europe to screen babies for SMA. The next step is acquisition of an effective test method for detecting children with SMA. A study must be carried out to determine whether the used method can also effectively detect children with SMA in the Dutch situation. As soon as screening for SMA is introduced, all screening laboratories in the Netherlands will use the test[24].

Newborn screening is not in place in Ireland.

The implementation of newborn screening will make a substantial change in how the disease is diagnosed. Diagnosis will possibly shift from a clinical diagnosis based on the age at which the first symptoms occurred and the motor milestones reached, to a genetic diagnosis based on SMN2 copy number. As explained in 1.1.1 the SMN2 copy number is not perfectly correlated with the SMA disease type and especially in children with 3 copies this is challenging. In addition, all of these studies predict that less than 10% of SMA cases would first present in children older than three years, and these would typically be classified as having SMA type 3.

1.2.4 Standard treatment

Best supportive care
Standard treatment is symptomatic, supportive care and it targets the primary symptoms and (prevention of) secondary complications and does not target the cause of the disease. Components of the treatment depend on the type of SMA and stage of the disease progression[25].

- nutritional assistance such as feeding tube, gastrostomy (due to problems with sucking and swallowing and fatigue);
- coughing and breathing support (by progressive deterioration of pulmonary function); hospital admissions for respiratory tract infection (no strength to cough; especially with types 1 and 2);
- aids (wheelchair, inlays in adapted or ready-to-wear shoes, arm support);
- physiotherapy, occupational therapy, speech therapy, psychology and social work.

- fixation (surgery) of the back (type 2)
- striving to prevent deconditioning through inactivity.

A multidisciplinary approach is the key element in the management of SMA patients (see figure 2). This should be coordinated by one of the physicians, generally the neurologist or paediatric neurologist, who is aware of the disease course and potential issues[26].

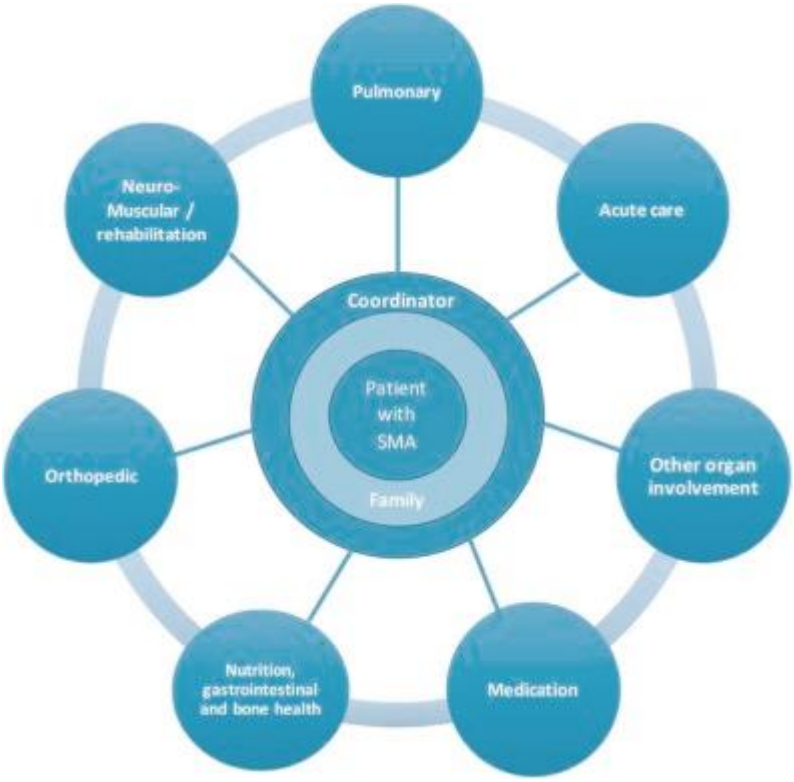


Figure 1: Multidisciplinary approach in the management of SMA patients[26]

Nusinersen (Spinraza®)

Nusinersen improves functional SMN protein expression by altering SMN2 transcript splicing using an antisense oligonucleotide approach, was recently approved by the EMA (May 2017) and is now commercially available. The registered indication is treatment of 5q SMA. Nusinersen is administered intrathecal by lumbar puncture. The recommended dose is 12 mg (5 ml) per administration. Nusinersen treatment should be initiated as early as possible after diagnosis with 4 loading doses on days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter[27].

Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts, by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the SMN2 pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2mRNA is produced, it can be translated into the functional, full length SMN protein[27]. See figure 3 for the mechanism of action of nusinersen.

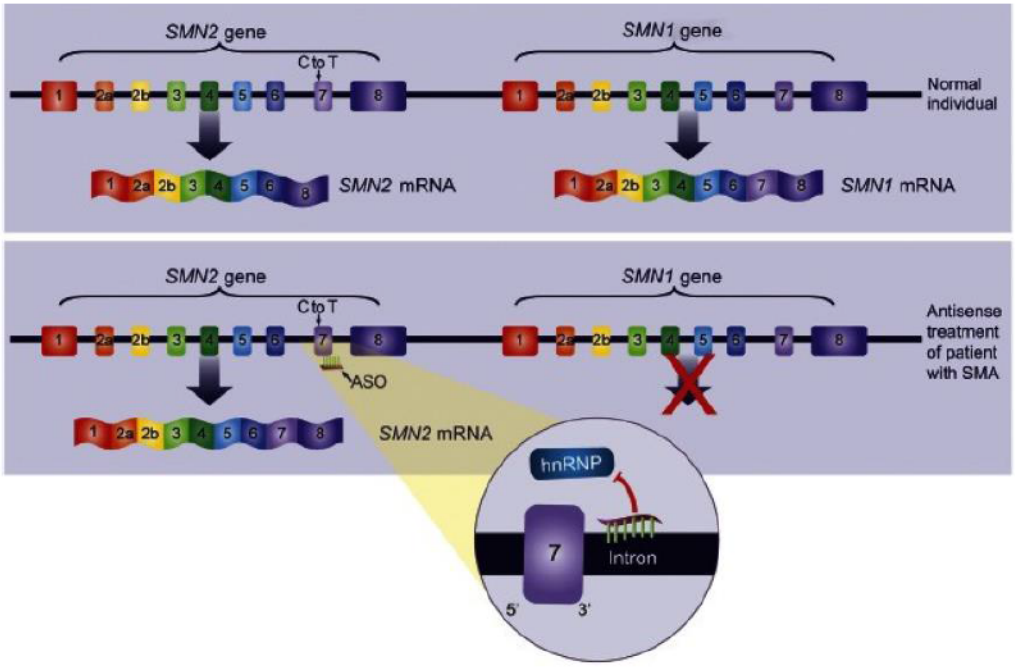


Figure 2: Mechanism of action of nusinersen[28]

Nusinersen is reimbursed in Belgium, Ireland and the Netherlands, sometimes subject to certain conditions. The reimbursement status and restrictions per country can be found in table 2.

Table 1. The reimbursement status and restrictions per country

Country	**Date of reimbursement decision**	**Restrictions of reimbursement**
Belgium	1 September 2018	Complete reimbursement of registered indication. Reimbursement is discontinued when patients receives permanent invasive ventilation.
Ireland	1st July 2019	Partial reimbursement of registered indication for children under the age of 18 with genetically confirmed SMA type 1, 2 or 3. Individual treatment approval by the HSE-Medicines Management Programme (MMP) is required. Also explicit stop-criteria are formulated.
The Netherlands	11 July 2018	Complete reimbursement for (as of 1 August 2018): - infant-onset SMA patients (< 6 months of age) with a disease duration <26 weeks at the start of treatment. - later-onset SMA patients (from 6-20 months) with a disease duration <94 months at the start of treatment. - presymptomatic infants with a genetic diagnosis of 5q SMA and with 2 or 3 copies of SMN2. Conditional reimbursed for (as of 1 January 2020): - SMA patients ≥9.5 years of age as of 1 January 2020.

In all countries patients are eligible for reimbursement of nusinersen if they meet one of the following conditions:

- 5q SMA with symptom onset <6 months of age and disease duration <26 weeks
- 5q SMA with symptom onset between 6-20 months of age and disease duration <94 months
- Presymptomatic patients 5q SMA with two or three copies of SMN2

In Belgium, all patients outside these conditions who are eligible within the registered indication meet the criteria for reimbursement as well. In the Netherlands, a conditional inclusion program for nusinersen has been implemented for SMA patients >9.5 years of age.

The CHMP describes the continued unmet medical need for SMA 1 patients in the EPAR of OA: nusinersen treatment is associated with significant burden for the patient since it requires lifelong intrathecal injection, which is associated with safety risks. OA effectively targets the disease mechanism in 5q SMA, 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. The benefits to public health of the immediate availability of OA outweigh the risks inherent in the fact that additional data are still required. Early access to OA would be highly important for especially SMA Type 1 patients, who without treatment have a life expectancy of less than two years. In 2017, nusinersen was authorised as a disease-modifying treatment resulting in advances in SMA patient care and outcomes. However, not all treated patients have improved their muscular functions as demonstrated by the ability to sit or walk unassisted[2].

2 Method of systematic literature search

2.1 Question

What is the therapeutic benefit of onasemnogene abeparvovec (Zolgensma®) for the treatment of symptomatic SMA type 1 patients and presymptomatic SMA patients with up to three copies of the SMN2 gene compared to best supportive care and nusinersen.

2.1.1 PICO

Table 2: PICO

Patient population *(claim of the applicant)*	1. All symptomatic SMA type 1 patients *Type 1 SMA is diagnosed in infants who develop the first symptoms of SMA before 6 months of age* 2. Presymptomatic SMA patients with up to three copies of the SMN2 gene. *Presymptomatic patients can be found/diagnosed by elderly siblings or by new-born screening (NBS)*
Intervention	OA as an adjunct to best supportive care. *A single-dose intravenous infusion with a nominal recommended dose of 1.1x10^{14} vector genome copies (vg)/kg body weight OA. Recommended dosing for patients who weight 2.6-21.0 kg can be found in the SmPC.*
Controls	-Nusinersen (Spinraza®) -Best supportive care
Outcomes	-Survival -Ventilation free survival -Mobility / muscle function. Measured with motor milestones or CHOP-INTEND -Incidence treatment-related serious adverse events (SAEs) -Discontinuation due to adverse events
Relevant follow-up period	Sufficient duration of study to indicate an effect on mortality or disease progression. The median survival without invasive ventilation of SMA type 1 patients is 6-13 months[7] The treatment duration is preferably longer than 1 year for the crucial outcome measures. Clinical studies with shorter follow-up periods can support the evidence found and for that reason are not excluded.
Study design	In order to support the therapeutic benefit of OA compared with nusinersen, preference is given to direct comparative randomised controlled phase 3 trials. Given the progressive nature of SMA in type 1 patients it is considered unethical to include placebo arms in the trials that followed on the first phase 1/2 OA trial (START). No other active treatments were not available for this patients at the start of the OA studies. Therefore an indirect comparison can be considered.

2.1.2 *Outcome measures and clinical relevance*

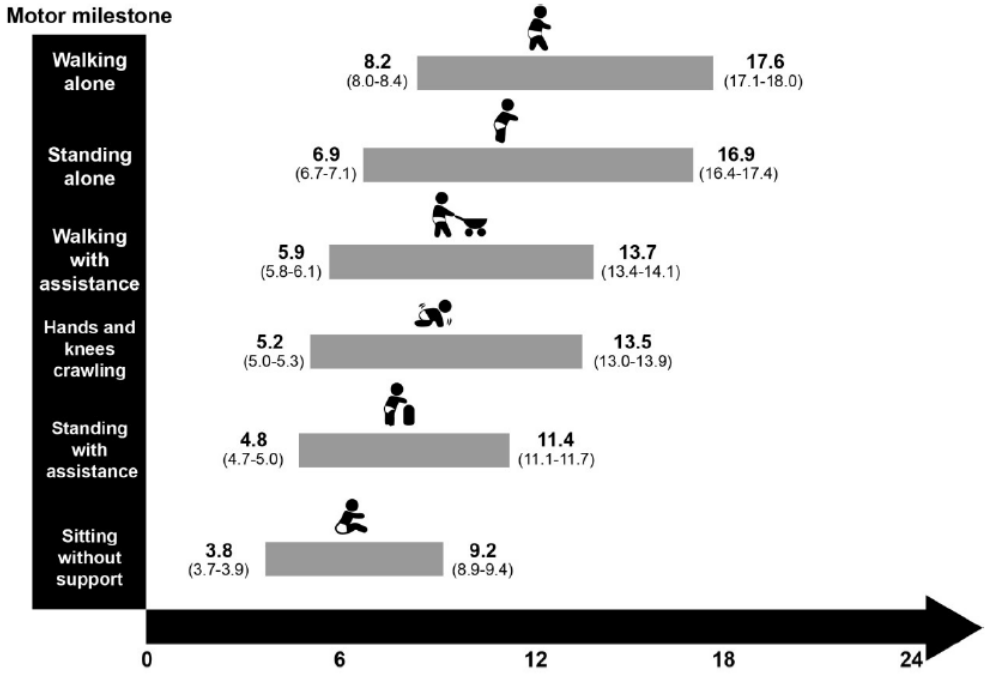
The choice of the crucial outcome measures for SMA is based the European consensus from the ENMC SMA Workshop Study Group[29].

Mobility and muscle function
To measure an effect on mobility and muscle function in young children in a study over a relatively short period the SMA validated Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP-INTEND) is used. The Hammersmith Infant Neurological Examination (HINE-2) is also used in nusinersen studies but is not specifically validated for SMA. WHO motor milestones are an universal way to represent the functioning of children.

CHOP-INTEND (Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease) is an outcome measure validated for SMA patients until the age of two. The CHOP-INTEND consists of 16 items expressing the motor function and strength of the child, scored by a physician. The outcomes range from a score of 0 (worst possible sum score) to 64 (best possible sum score). Mean CHOP-INTEND score was statistically significant lower in SMA type 1 infants compared with the control group of healthy subjects in the NeuroNext prospective, longitudinal natural history study of infants with genetically confirmed SMA (n=26) and healthy control infants (n=27) (21.4 ± 9.6 at mean age of 3.7 months versus 50.1 ± 10.2 at mean age of 3.3 months, $P < 0.01$)[30].

WHO motor milestones[31] are a set of six milestones considered to be universal and fundamental to acquiring the ability to walk independently. Children will typically progress sequentially through this order of milestones with the exception of crawling. An international study conducted in Ghana, India, Norway, Oman, and the US, recorded ages of achievement of each milestone in healthy children between 4 months and 24 months of age, providing windows of achievement representing the 1st to 99th percentiles (see table 4).

Table 3: WHO motor milestones windows of achievement of 1st to 99th percentile in healthy children.



<u>*Overall survival and ventilation free survival*</u>
Overall survival and ventilation free survival are dependent on the supportive care, which possibly differentiates per country, institute and clinician. The ventilation endpoint definition can differ between studies. Permanent ventilation is mostly described as the requirement of invasive ventilation or more than x hours of respiratory assistance per day (including non-invasive ventilator support) continuously for >x days in the absence of an acute reversible illness. The specific definition used is reported in the results section of this report.

<u>*Serious adverse events*</u>
Serious adverse events are also considered as crucial outcomes. Therefore the incidence of adverse events grade 3-5, as well as discontinuations due to adverse events will be analysed as short term parameters. Long term follow-up and registry data are necessary in order to evaluate the potential low frequency serious adverse events, as well as detrimental effects in the long term.

Zorginstituut Nederland uses a default limit to define added benefit for the outcome measures in which a minimal clinically important difference (MCID) is missing. A minimal clinically relevant difference (MCID) is not determined for any of the outcome measures described. The default limit of the standardized mean difference (SMD) is 0.5. When using a relative risk (RR or HR), the default limit value is 0.75 and 1.25.

2.1.3 Disease

Spinal muscular atrophy (SMA) is an autosomal recessive disease of the motor anterior horn cells of the spinal cord and brain stem, that almost always develops in childhood. SMA manifests clinically as slowly progressive muscle weakness. This disease is caused by a homozygous deletion of the survival motor neuron (SMN) 1 gene on chromosome 5q and is the leading genetic cause of early-life mortality[3, 4]. The disease is transmitted autosomal recessively, which means both parents are

carriers. Both copies of the SMN1 gene on chromosome 5q are absent or mutated in 5q-SMA. Approximately 80-90% of all SMA is 5q SMA. When we refer to SMA in this report, we always mean 5q SMA.

SMN is essential for the function and survival of motor neurons (nerve cells from the spinal cord that control muscle movements). Absence or a substantial shortage of SMN protein causes degeneration of the motor neurons in the motor anterior horn cells of the spinal cord. This results in muscle weakness and atrophy of the muscles, including the respiratory muscles. The muscle weakness is symmetrical, more proximal than distal, and progressive[5].

The SMN protein is encoded by two genes, SMN1 and SMN2. In all patients with SMA there is no functional SMN1 gene. Therefore, SMA patients rely on the SMN2 gene, a kind of "reserve" gene, for the production of SMN. This gene is very similar to SMN1, but makes much less functioning SMN protein. Most of the mRNA transcripts of the SMN2 gene lack exon 7 (~90%). Therefore the SMN2 gene only produces ~ 10% normally functioning SMN protein. The number of copies of the SMN2 gene present on chromosome 5 varies in healthy people from 0 to 5. A higher number of SMN2 copies is believed to lead to more functional SMN protein and therefore to a milder clinical picture. The number of SMN2 copies correlates (but not perfectly) with the SMA types (Table 1). In general, patients with 3 or more copies of SMN2 have a relatively milder course of the disease (types 3, 4)[6]. Three asymptomatic individuals with an SMN1 deletion and 5 copies of SMN2 have been described in the literature.

The current classification of the type of SMA is based on clinical criteria. A distinction is made between four types of SMA that vary from the most severe phenotype that manifests in newborns to less severe phenotypes that can occur in children or adults. Type 1 SMA (Werdnig-Hoffman disease; acute SMA; severe SMA) is characterized by onset before 6 months of age, failure to achieve sitting without support, and a life expectancy of 2 years or less. Type 2 usually becomes symptomatic between ages 6 and 18 months, but may start earlier. These patients ultimately attain independent sitting and may live into adolescence or longer. SMA type 3 (juvenile SMA or Kugelberg-Welander disease) becomes symptomatic after 18 months, and all patients walk independently at some time. Patients with SMA type 3 may survive longer than 60 years[4, 7]. Traditional SMA types alone are however not sufficient to define patient populations who might benefit most from gene therapy.

In **symptomatic** patients, number of SMN2 copies, age at onset, disease duration and motor function status at the start of treatment are the most important factors that can predict the severity of the disease[8].

In **presymptomatic** patients SMN2 copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on SMN2 copy number via newborn screening. Determination of SMN2 copy number needs to be performed in an expert laboratory with adequate measures of quality control as discrepancies have been noted in the literature [8].

Although SMN2 copy number is known to be the primary determinant of SMA severity, it is clearly not the only phenotypic modifier. Other modifiers (e.g. c.859G>C exon 7 mutation) have been described and more are expected as the understanding of the molecular pathogenesis of SMA is refined. Thus, the SMA phenotype cannot be deduced solely from the SMN2 copy number determination, a

crucial fact when conducting genetic counselling for patient families[9]. See table 1 for the relation between SMA disease type and the number of SMN2 copies.

Table 4: Spinal Muscular Atrophy Classification[2]

Type	**Age at Symptom Onset**		**Maximum Motor Function**	**Life Expectancy**	**SMN2 Copy No.**
0	Fatal		None	Days – Weeks	1
1	< 6 months	1A: Birth – 2 weeks 1B: < 3 months 1C: >3 months	Never sits	< 2 years	1, **2**, 3
2	6 – 18 months		Never walks	20-40 years	2, **3**, 4,
3	1.5 – 10 years	3A: < 3 years 3B: > 3 years	Walks, regression	Normal	3, **4**, 5
4	> 35 years		Slow decline	Normal	4, 5

SMN2 = survival motor neuron 2 gene.
bold = predominant SMN2 copy number that defines the SMA Type, the other copy numbers represent a small percentage of the designated SMA Type.

In a recent compilation of 34 studies that focused on the correlation between SMN2 copy number and SMA phenotype, 3,370 non-related individuals with type 1-3 were included. The distribution of SMA types according to the number of SMN2 copies of this study is shown in figure 1. The authors concluded that in the actual scenario of SMA treatment options, it is of utmost importance to discover biomarkers that predict whether a given patient with three SMN2 copies would eventually be able to walk or not[10].

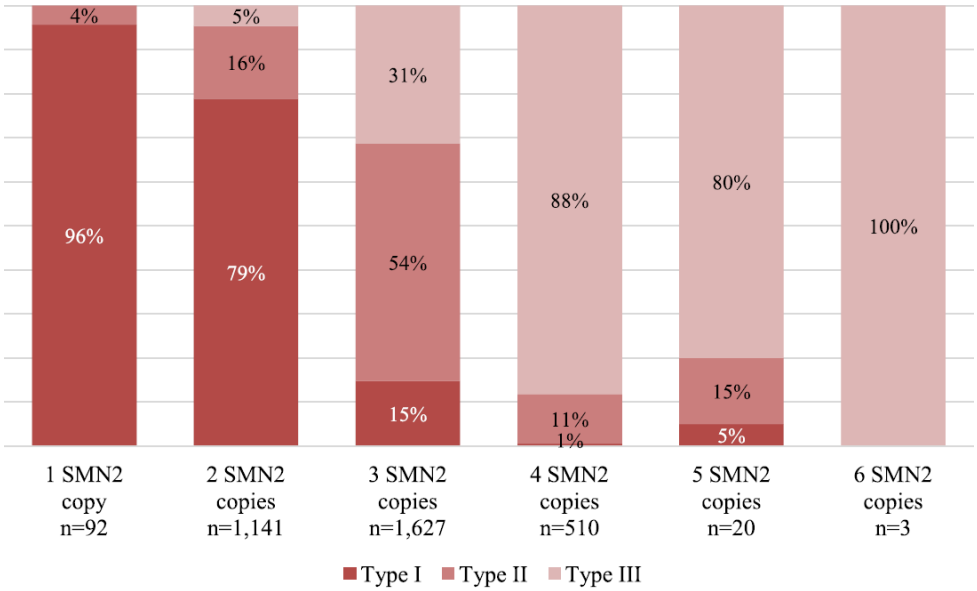


Figure 3: Distribution of SMA types according to the number of SMN2 copies[10]

In one large German study, 80% of patients with SMA type 1 had two or fewer copies of SMN2, 82% of those with SMA type 2 had three copies of SMN2, and 96% of those with SMA type 3 had three or four copies of SMN2. This relationship of phenotype to genotype enables prediction of SMA type from the SMN2 copy number before the onset of symptoms. Infants found to have two or three copies of SMN2

are highly likely to manifest SMA type 1 or 2, which are associated with high early mortality and substantial morbidity. Conversely, those with four or more copies of SMN2 are unlikely to present with the most severe SMA type 1. In addition, all of these studies predict that less than 10% of SMA cases would first present in children older than three years, and these would typically be classified as having SMA type 3. Thus, identification of homozygous deletion of SMN1 combined with determination of SMN2 copy number is a powerful predictor of disease and identifies a group who would benefit substantially from new and emerging therapies[11].

2.2 Search strategy

In the assessment, the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) of OA and nusinersen have been used.

In order to obtain relevant data out of scientific research we performed a literature search in PubMed and the Cochrane library in November 2020 concerning publications on OA and nusinersen treatment in SMA patients. The exact search strategy has been described in annex 1.

2.3 Selection criteria

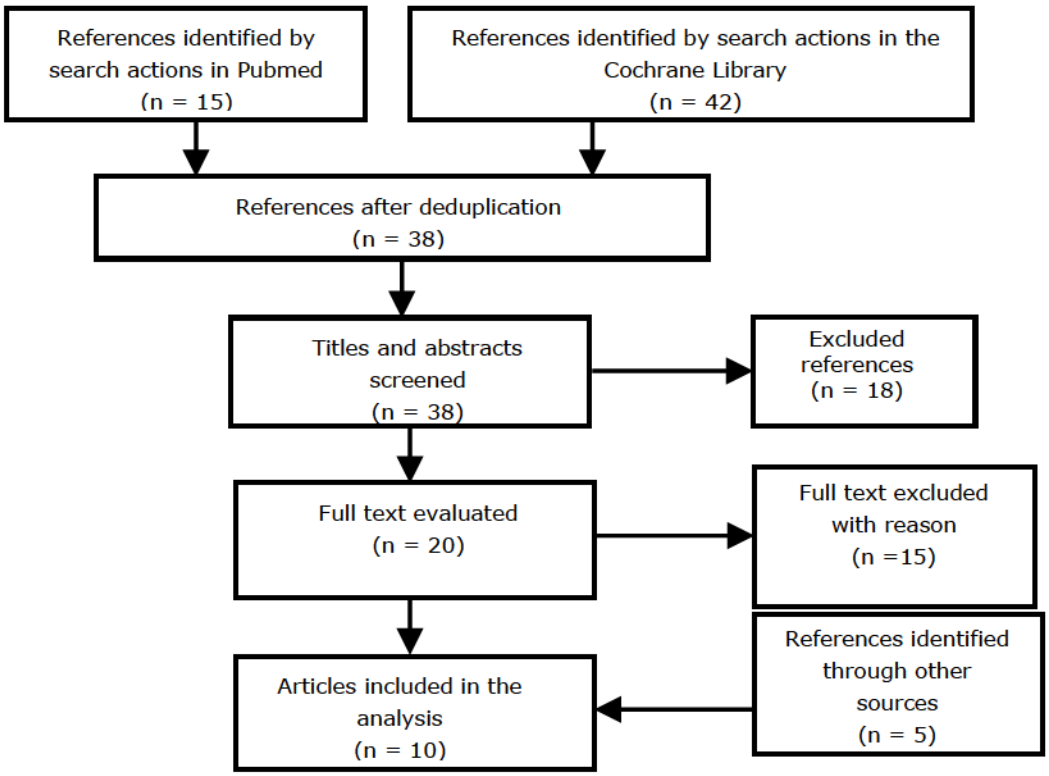
Inclusion and exclusion of detected literature was based on abstracts. If articles could not be excluded based on the abstract, full text articles were viewed.

Clinical trials evaluating the survival, ventilation free survival (lung function) and mobility outcomes, as well as trials evaluating adverse events of OA in patients with infantile onset SMA and presymptomatic patients with up to three copies of SMN2 were included. Also European and national SMA guidelines were included. Case reports (≤5 patients) and animal studies were excluded.

3 Results

3.1 Results search strategy

The search strategy resulted in 38 references. Ten (10) trials met the inclusion criteria. The PRISMA flowchart below visualizes the selection process.



The characteristics of the selected studies are shown in appendix 2. The excluded studies with reason for exclusion are shown in appendix 3. The included guidelines and other sources are shown in appendix 4.

Three (3) relevant clinical trials with OA in symptomatic SMA type 1 patients have been identified; START, STR1VE-EU, STR1VE-US and one trial in presymptomatic SMA patients (SPR1NT). All 4 studies have been used for registration or in support of registration. LT-001 and LT-002 are long-term follow-up studies. One publication reports results of the START-trial[32]. The other clinical trials are reported in the EPAR with the data cut of 31 December 2019. The company has provided the latest clinical study reports of STR1VE-US with data cut 22 April 2020, this provides data with a follow-up of 18 months.

Of the clinical OA program, only the START and the STR1VE-US study provide outcomes with a follow-up of ≥18 months. To provide the most comprehensive overview of all patients treated with OA, all four studies will be included in the assessment, however only the studies with follow-up data ≥18 months will be used in the GRADE evidence profile.

Four (4) nusinersen studies in infantile onset SMA patients have been identified: ENDEAR/SHINE, CS3A and NURTURE. Interim results of these studies have been

published. To provide the most up to date nusinersen data, the NICE committee papers of the single technology appraisal (STA) of nusinersen [ID1069] will be used[33].

3.2 Characteristics and study design of the included studies

3.2.1 OA studies

The four OA studies (START, STR1VE-EU, STR1VE-US and SPR1NT) identified by the literature search and the two long-term follow-up studies (LT-001 and LT-002) included in the clinical study program are reported in table 5. START is a phase 1/2 ascending dose, single centre study to evaluate the safety and efficacy of OA manufactured through process A[2] in symptomatic patients with type 1 SMA. STR1VE-US and STR1VE-EU are phase 3, open-label, single-arm, single-dose study of OA manufactured through process B in symptomatic SMA Type 1 patients with no functional SMN1 gene and 1 or 2 copies of SMN2 and who are < 6 months (< 180 days) of age at the time of gene replacement therapy. The STR1VE-EU study is ongoing and has a median follow-up of 11.9 months (range 1.8-15.4) at the 31 December 2019 data cut. SPR1NT is a phase 3, single-arm, multicentre study of OA manufactured through process B in presymptomatic SMA Type 1 patients with no functional SMN1 gene and 2 or 3 (and one patient with 4) copies of SMN2 and who are <6 weeks of age at the time of gene replacement therapy.

Table 5: Overview clinical trials with intravenous OA

Phase	Name	Study design	Status	Patients	Data availability
1 / 2	START (CL-101)	Open-label dose-escalation ***process A***	Completed	Symptomatic SMA type 1 2x SMN2	Al-Zaidy 2019[34], Mendell 2017[35] Unpublished data: Clinical overview 31 Dec 2019; 20 June 2020 Follow-up: 2 years post-dose
4	LT-001	Long term follow-up of START	*Ongoing*	Symptomatic SMA type 1 2x SMN2	Al-Zaidy 2019[34] Unpublished data – Clinical overview 31 Dec 2019; 20 June 2020 Follow-up: 56.7-72.9 months of age
3	STR1VE-EU (CL-302)	Single-arm ***process B***	*Ongoing*	Symptomatic SMA type 1 2x SMN2	Unpublished data - Clinical overview 31 Dec 2019; 20 June 2020 Follow-up: 56.3% ≥14 months 57.6% ≥18 months of age
3	STR1VE-US (CL-303)	Single-arm ***process B***	Completed	Symptomatic SMA type 1 2x SMN2	Unpublished data – Clinical overview 22 April 2020 data cut Follow-up: 100% >18 months of age
3	SPR1NT (CL-304)	Single-arm ***process B***	Ongoing	Presymptomatic SMA 2/3/4x SMN2	Unpublished data - Clinical overview 31 Dec 2019; 20 June 2020 Follow-up: 2x SMN2: 15.6 (8.8-18.8) months of age 3x SMN2: 15.2 (3.3-21.1) months of age
4	LT-002	Long term follow-up of STR1VE and SPR1NT) *process B*	*Ongoing*	Pre- and symptomatic SMA 2/3/4x SMN2	-

[2] Two different processes, A and B, have been used to manufacture vectors for clinical evaluation. One batch is manufactured at a research institute, called Process A. This Process A batch is only used in the START study. Subsequent batches are referred to as Process B batches and claimed to be manufactured with the commercial process. These Process B batch is used in STR1VE-US, STR1VE-EU and SPR1NT

Outcome measures
Event free survival was defined as time from birth to either ≥16-hour of respiratory assistance per day continuously for ≥2 weeks or death in START and as tracheostomy or ≥16-hour of respiratory assistance per day continuously for ≥2 weeks or death in the other three trials. Event free survival at 14 months of age was the primary or secondary endpoint in all studies. Co-primary endpoint was event-free survival (time from birth to either death or permanent ventilation), analysed when all patients reached 13.6 months of age (which is associated with the 25% survival rate of the natural history cohort of the PNCR study).
Efficacy analyses in START were conducted at 3 time points, the first two time points corresponded with those of the major efficacy endpoints of the natural history study (13.6 and 20 months of age), and the third time point corresponded with at least two years follow up for all patients (24 months post-dose). The efficacy endpoint of time to death or permanent ventilation was compared to the natural history estimate using a 1-sample binomial test at the time patients were 13.6 or 20 months of age (corresponding to 25% and 8% survival in the natural history study).

A variety of scales and measures were used to assess motor function and muscle strength. CHOP-INTEND scores are assessed in all four studies with OA. All four studies included safety outcome measures.

3.2.2 *Nusinersen studies*

The clinical trial program of nusinersen consists of 4 trials considering SMA type 1 patients with up to three copies of SMN2. One phase 2 open-label dose-escalating study (CS3A), 2 RCT's and a long-term follow-up of these 2 RCT's (SHINE). In addition, one single-arm trial considering presymptomatic SMA type 1 or 2 patients started (NURTURE) and has some interim-analysis available but is not completed yet. An overview is given in table 6.

*Table 6: Overview clinical trials with intrathecal nusinersen**

Phase	Name	Study design	Status	Patients	Data availability
2	CS3A (NCT01839656)	Open-label dose-escalating	Completed	Symptomatic SMA patients expected type 1 2/3x SMN2	Finkel et al. 2016[36]
2	EMBRACE	RCT	*Terminated early, no published results (yet)*	Symptomatic SMA patients type 1/2	Shieh et al. 2018[37]
3	ENDEAR	RCT	Completed	Symptomatic SMA type 1 2x SMN2	Finkel et al. 2017[38] NICE nusinersen[33]
4	SHINE	Long-term follow-up of ENDEAR and EMBRACE	*Ongoing*	Symptomatic SMA type 1 2x SMN2	Finkel et al 2018[39], NICE nusinersen[33]
3	NURTURE (NCT02386553)	Single arm	*Ongoing*	Presymptomatic SMA type 1 or 2 2/3x SMN2	De Vivo et al. 2018[40] Follow-up: 34.8 (25.7-45.4) months

** Clinical trials in patient populations outside the registered indication of OA are not taken into account in this overview (see appendix 3 for an overview of the excluded studies)*

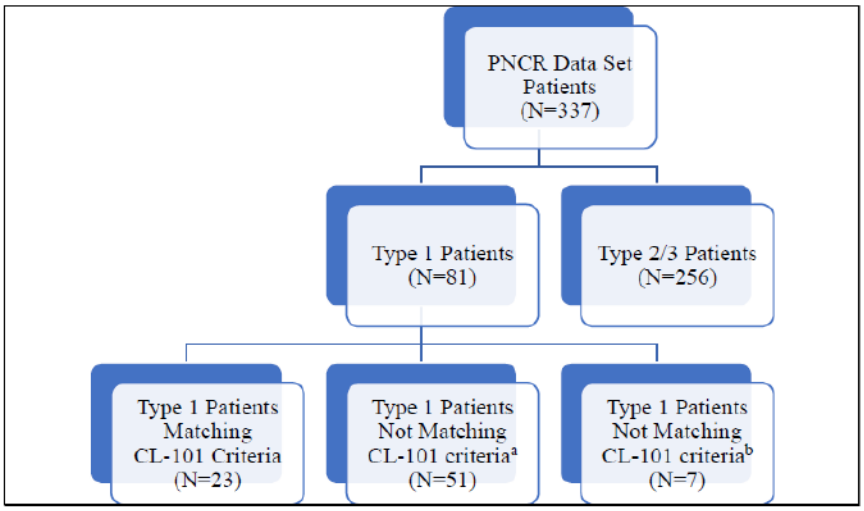
3.2.3 *Natural history cohort studies*

All clinical trials with OA are single-arm trials. To provide information about the relative effectiveness of OA compared to best supportive care, natural history information is used.

PNCR database[7, 2]

The Paediatric Neuromuscular Clinical Research network history study (PNCR) is a natural history study of 337 patients with any form of SMA followed at 3 large tertiary medical centres in the US. Inclusion of the patients ranged from May 2005 to April 2009. The study enrolled both previously identified patients followed in PNCR site clinics and newly diagnosed patients. The SMA standard of care guidelines published in 2007[25] were used as a basis for providing uniform care among the study sites. Children who were unable at any point to achieve the milestone 'sit independently for >10 seconds' (the World Health Organization-Multicentre Growth Reference Study [WHO-MGRS] criteria) were classified as SMA Type 1. To allow development of an appropriate comparator cohort for the START and the STR1VE-US study, a natural history control population was drawn from this PNCR Natural History Dataset[7]. This cohort consists of all patients with age of onset ≤6 months, bi-allelic deletion of survival motor neuron 1 gene (SMN1) (exon 7/8 common homozygous deletion) and 2 copies of SMN2 for whom enrolment data (retrospective and prospective) were available see figure 4 for the patient disposition. All patients with SMA Type 1 in the PNCR natural history study were affected by bi-allelic deletions of SMN1. The SMN2 modifier mutation (c.859G>C) was not assessed in the PNCR study cohort. Primary endpoints in the PNCR study were age at death and age at reaching the combined endpoint of either death or requiring at least 16 hours/day of non-invasive ventilation support for at least 14 days in the absence of an acute reversible illness or peri-operatively (as a surrogate for death). CHOP-INTEND scores and motor milestone achievement were obtained.

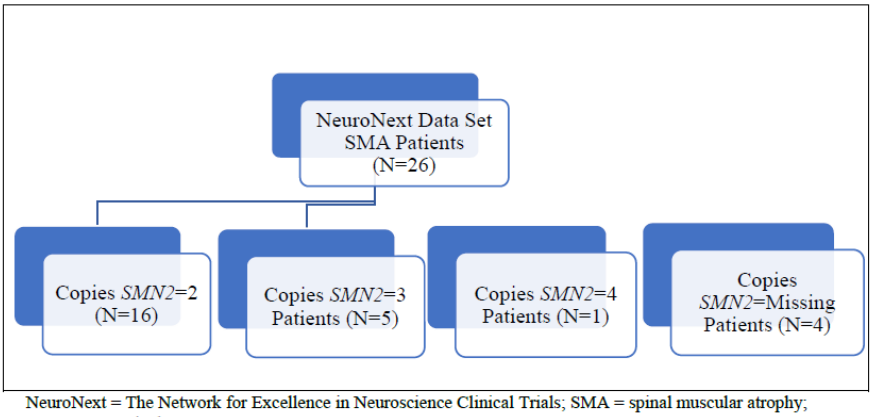
The PCNR database also contains data on patients with 3 SMN2 copies, which were not included in the PCNR natural history cohort but are used for comparison in SPR1NT.



PNCR = Pediatric Neuromuscular Clinical Research, *SMN2* = survival motor neuron 2 gene.
[a] Not 2 copies of *SMN2* (ie, 1 with 1 copy, 12 with 3 copies, 38 missing).
[b] Age of onset after 6 months or age at diagnosis > 24 months.

Figure 4: Patient disposition in PNCR dataset[41]

NeuroNext database[16, 2]
The NeuroNext natural history study was a longitudinal, multi-centre, prospective natural history study that enrolled 26 SMA infants <6 months of age (and 27 healthy control infants) at 14 centres across the US. The study was designed to mimic the inclusion and timing of future SMA clinical trials targeting treatment of SMA infants[30, 16]. Enrolment was restricted to infants who were <6 months of age and born between 36 and 42 weeks of gestation. SMA was confirmed by genetic testing prior to enrolment. All patients had bi-allelic deletions of SMN1 exon 7. SMN2 copy number was measured in all patients except for 4 who died before confirmation samples were obtained but who were presumed to have 2 copies of SMN2 based upon disease course. Sixteen (16) infants had 2 copies of SMN2, 5 infants had 3 copies, and 1 infant had 4 copies. See figure 4 for the patient disposition. Exclusion of the SMN2 gene modifier mutation c.859G>C was confirmed in all but the 4 patients. Patients were excluded if they required non-invasive ventilator support for >12 hours/day, had a comorbid illness, were on any therapy thought to increase SMN expression, or were enrolled in a therapeutic study. The NeuroNext cohort of 16 patients with SMN2 copy number of 2 served as a secondary natural history control population for additional exploratory analyses.



NeuroNext = The Network for Excellence in Neuroscience Clinical Trials; SMA = spinal muscular atrophy; *SMN2* = survival motor neuron 2 gene.

Figure 5: Patient disposition in NeuroNext dataset[41]

Detailed baseline characteristics can be found below in table 10 and in appendix 5.

3.2.4 *Study population of included studies*

START only included SMA patients younger than 6 months with 2 copies of SMN2 with an age of onset up to 6 months of age. STR1VE-US and STR1VE-EU both included SMA patients younger than 6 months with one or two copies of the SMN2 gene (see table table 7 for the key in- and exclusion criteria of the studies in symptomatic SMA patients).

Table 7. Key inclusion criteria of symptomatic SMA patient trials

Inclusion criteria					
OA			nusinersen	natural history	
START[32] (CL-101)	STR1VE-EU[2] (CL-302)	STR1VE-US[2, 42] (CL-303)	ENDEAR/SHINE[33]	PNCR[7]	NeuroNext[16]
SMA diagnose based on bi-allelic SMN1 mutation Type 1 based on disease onset <6 months of age 2x SMN2	SMA diagnose based on bi-allelic SMN1 mutation 1/2x SMN2	SMA diagnose based on bi-allelic SMN1 mutation 1/2x SMN2	SMA diagnose based on bi-allelic SMN1 mutation Type 1 based on disease onset <6 months of age 2x SMN2	SMA diagnose based on bi-allelic SMN1 mutation Type 1 based on milestone sitting independently 2x SMN2	SMA diagnose based on bi-allelic SMN1 mutation 2x SMN2
<6 months of age at the time of OA treatment	<6 months of age at the time of OA treatment	<6 months of age at the time of OA treatment	<7 months of age at screening	-	< 6 months of age at enrolment
Exclusion criteria					
antibody to adeno-associated virus serotype 9 (anti-AAV9) titres >1:50 as determined by enzyme-linked immunosorbent assay binding immunoassay; signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding; Low oxygen-saturation level; tracheostomy or non-invasive ventilator support >16 hours/day.	*Low oxygen-saturation level; tracheostomy or non-invasive ventilator support ≥12 hours/day over the 2 weeks prior to dosing; signs of aspiration based on swallowing test or weight for age below third percentile (WHO Child Growth Standards) and unwilling to use alternative method to oral feeding.*	Low oxygen-saturation level; Tracheostomy or non-invasive ventilator support ≥ 6 hours/day over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilator support while awake over the 7 days; inability to tolerate non-thickened liquids	Low oxygen-saturation level; active infection; history of brain or spinal cord disease affecting lumbar puncture, circulation of CSF or safety.	Age of onset after 6 months or age at diagnosis > 24 months.	non-invasive ventilator support (i.e., bi-level positive airway pressure [BiPAP]) for ≥12 hours/day, had a comorbid illness or were enrolled in a SMA therapeutic clinical trial.

ENDEAR with follow-up study SHINE has published results and is used to make the indirect treatment comparison with OA. ENDEAR is a double-blind sham-controlled phase 3 trial in 121 genetic confirmed SMA infants with expected type 1. Randomization was 2: 1 (n = 81: 41). The dose of nusinersen was: approx. 12 mg intrathecal (depending on age estimated cerebrospinal fluid volume (CSF)) administered on days 1, 15, 29, 64, 183, and 302. Before each intrathecal injection 4-5 ml cerebrospinal fluid (CSF) was taken. The control arm received a sham treatment: a fake epidural where the infant was only superficially placed a needle in the same place as with the real epidural. The same plaster was then placed in the same way as in the nusinersen-arm.

The SPR1NT study is the only OA study considering presymptomatic SMA patients with two or three copies of SMN2. SPR1NT is an ongoing phase 3 open-label, single-arm study to evaluate the safety and efficacy of OA in presymptomatic SMA patients

with 2 or 3 copies of SMN2. NURTURE is a comparable nusinersen trial in presymptomatic patients and is used to make an indirect comparison. See table 8 for the key inclusion criteria of these studies.

Table 8: Key inclusion criteria of presymptomatic SMA patient trials

OA	Nusinersen
SPR1NT (CL-304)	**NURTURE**
Presymptomatic SMA diagnose based on bi-allelic SMN1 mutation 2/3x SMN2 obtained from an acceptable new-born or pre-natal screening method	Presymptomatic SMA diagnose based on bi-allelic SMN1 mutation 2/3x SMN2
<6 weeks of age at the time of treatment	<6 weeks of age at start of treatment

The definitions of the endpoint "event-free survival" in the symptomatic SMA patient studies are shown in table 9.

Table 9. Definition of endpoint in event-free survival.

START	STR1VE-EU	STR1VE-US	ENDEAR/SHINE	PNCR	NeuroNext
Death or requirement of ≥16-hour respiratory assistance per day (includes bi-level positive airway pressure [BiPAP]) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation	Death or tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilator support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.	Death or requirement of invasive ventilation or ≥16 hours of respiratory assistance per day (including non-invasive ventilator support) continuously for ≥14 days in the absence of an acute reversible illness, excluding perioperative ventilation.	Death or the use of permanent assisted ventilation (tracheostomy or ventilator support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event).	Death or requiring at least 16 hours/day of non-invasive ventilation support for at least 14 days in the absence of an acute reversible illness or peri-operatively (as a surrogate for death).	Death or tracheostomy

The PNCR and NeuroNext cohorts are included in this report as comparator for the single-arm OA trials. In the RCT of nusinersen (ENDEAR) a SHAM control arm was used. The baseline characteristics of the (historic) control study/arms can be found in table 10.

Table 10. Baseline characteristics of (historic) control studies/arms of symptomatic SMA patients

Variable	PNCR	NeuroNext	ENDEAR (SHAM) control
SMA type	1		1
SMN2 copies	2	2	2
N	23	16	41
Age at symptom onset (months) **Mean (SD)** **Median**	 3.0 (1.6) (range: 0.5-6) NR	 NA	 9.6 (1-20) weeks 8 weeks NR
Age at baseline (months) **Mean (SD)** **Median (min, max)**	Age at enrolment: 29.0 (41.7) (2-171)	Age at enrolment: 4.1 (1.7) (0-6)	 5.9
Female, n (%)	12 (52.2)	8 (50.0)	24 (59)
Race, n (%) **White** **Black or African American** **Asian** **Other**	 16 (69.6)	 15 (93.8)	 NR
Ethnicity, n (%) **Not Hispanic or Latino** **Hispanic or Latino**	 3 (13.0%)	 5 (31.3%)	 NR
Reported ventilation support n (%)	12/23 (52.2)	6/16 (37.5)	6/41 (15)
Use of gastrointestinal tube, n (%)			5/41 (12)
Ventilation support before 6 months of age.	21/23 (91.3)	10/16 (62.5)	NR
Reported Nutrition support, n (%)	18/23 (78.3)	7/16 (43.8)	NR
CHOP-INTEND **Mean (SD)** **Median (min, max)**	 24.6 (11.6) (5-40)	 20.3 (7.3) (10-33)	 28.43 (7.56)

The most important baseline characteristics of the included OA and nusinersen trials can be found in table 11. An overview of all baseline characteristics can be found in appendix 5.

Table 11: Key baseline characteristics of included studies.

	OA			**Nusinersen**	
	START	STR1VE-US	Pooled START+ STR1VE-US	ENDEAR	SHINE (extension of ENDEAR)
N	12	22	34	80	81*
Female, N (%)	7 (58%)	12 (55%)	19 (56%)	43 (54%)	44 (54%)
Mean age at study start (first dose), days (range)	103.4 (27.4-240.3)	112.5 (15.2-179.5)	108.6 (15.2-240.3)	163 (60.8-242)	164.3 (60.8-456.3)
Mean age at symptom onset, days (range)	42.6 (0-91.3)	57.8 (0-121.7)	52.5 (0-120)	55.3 (14-126)	48.7 (0-121.7)
Mean age at genetic diagnosis, days (range)	60 (0-136)	63.9 (15.2-121.7)	62.5 (0-136)	88.2 (0-203)	NR
Mean weight, kg (range)	5.7 (3.6-8.4)	5.8 (3.9-7.5)	5.8 (3.6-8.4)	NR	NR
CHOP-INTEND score, mean (range)	28 (12-50)	32 (18-52)	30.8 (12-52)	26.6 (8.1)*	26.7 (8.1)*
HINE-2 score, mean (range)	NR	NR	NR	1.3 (1.1)*	1.3 (1.1)*
Nutritional support, n (%)	5 (42%)	0	5 (15%)	7 (9%)	NR
Ventilation support, n (%)	2 (17%)	0	2 (6%)	21 (26%)	NR

*One infant randomized to receive nusinersen in ENDEAR was not dosed, but was dosed in SHINE

3.2.5 *Discussion study characteristics*

The open-label single arm study design of the studies was considered appropriate given the rarity of the disease and the lack of therapeutic options. The outcomes observed in the phase II START study made it unethical to include a placebo arm in the phase III studies given the universally dismal prognosis of SMA type 1. The results of OA trials are compared with the nusinersen trial SHINE (extension of ENDEAR). The natural history studies PNCR and NeuroNext are used to provide information of the natural course of the disease. Overall, demographic and baseline disease characteristics of the study populations are consistent with a population highly likely to develop type 1 SMA. Inclusion of the patients in the PNCR cohort ranged from May 2005 to April 2009. Enrolment in the NeuroNext cohort ranged from December 2012 – September 2014.

The STR1VE-US study is considered the pivotal study for the assessment of the efficacy in the patients with 2x SMN2 in the EPAR. The START study in which the product was manufactured using process A is considered supportive by the CHMP because based on quality assessment comparability of process A and B cannot be concluded.

The age at baseline of the OA studies and nusinersen-arm of the ENDEAR trial were comparable. Patients in the OA studies were younger at baseline (mean age of 103.4 days in the therapeutic dose cohort of START, 112.5 days in the STR1VE-US and 164.3 days in the nusinersen-arm of the ENDEAR study). None of the patients in the STR1VE-US study needed ventilation support at baseline compared to 26% in the nusinersen treated patients in the ENDEAR trial. Also ~10% of patients had a gastrointestinal tube in the ENDEAR trial vs. 0% in the STR1VE-US. Mean CHOP-INTEND baseline scores were higher (less severe) in the STR1VE-US cohort compared to the nusinersen treated patients, 32.0 (SD: 9.9) and 26.63 (SD: 8.13) respectively.

In the PNCR cohort, children were classified as SMA type 1 when they were unable at any point to achieve the milestone 'sit independently for >10 seconds' (the World Health Organization -Multicentre Growth Reference Study [WHO-MGRS] criteria). Only then were they assigned to the cohort (when they met the inclusion criteria as set in the START study).

There were some differences between the PNCR, NeuroNext and the OA studies. At baseline, 12/23 (52.2%) in PNCR and 6/16 (37.5%) of patients in the NeuroNext studies reported ventilation support. In the START study 2/12 (17%) patients reported ventilation support. In STR1VE-US none of the patients had ventilator support or nutritional support at baseline. In the historic cohorts 78.3% and 43.8% reported nutrition support in PNCR and NeuroNext respectively. This suggests that the patients in the historic control studies were more severely affected, which can result in bias and possible overestimation of the treatment effect of OA from this comparison. In particular the STR1VE-US patients seem to be less affected as nutrition and ventilation support rates are zero.

The PNCR cohort was older at disease onset (median 3.0 months), than the START (median 42.6 days) and STR1VE-US (median 57.8 days) patients. The mean CHOP-INTEND scores at baseline of the PNCR (mean 24.6 range: 5-40) and NeuroNext (mean 20.3 range: 10-33) cohorts were lower than the scores in START (mean 28 range: 12-50) and STR1VE-US (mean 32 range: 18-52). Considering the differences combined the cohorts are not similar in terms of severity. The START and the historic control baseline characteristics are more comparable.

Event-free survival within NeuroNext was defined as alive without tracheostomy(surgically created hole in the trachea that provides an alternative airway for breathing), a somewhat less stringent definition than that used in the clinical studies (event defined by death, tracheostomy or requirement of ≥16 hours of ventilator support for ≥2 weeks, excepting acute reversible illness or perioperative use). Comparing with the NeuroNext data on this endpoint will possibly give an underestimation of the effect of the intervention since a stricter endpoint definition is used in the clinical studies of OA. In the nusinersen ENDEAR/SHINE trial, the definition of permanent ventilation was somewhat less strict since permanent ventilation was reached when received longer than 21 consecutive days, instead of 14 days as defined in the OA trials.

3.3 Favourable effects of the intervention

A direct comparison of OA vs. nusinersen in patients with SMA type 1 or presymptomatic patients with up to three copies of SMN2 is considered not feasible since nusinersen was not yet available at the start of the trials with OA. Since only single-arm trials are available for determining the effect of OA an indirect (unanchored) treatment comparison with nusinersen has to be made. Since this unanchored comparison is surrounded by insecurities, the indirect comparison of OA vs. best supportive care - received from historic cohorts - is included in the report as well. The results of the single arms of the studies on the crucial outcome measures will be compared by calculating the relative risk (RR) or standardized mean difference (SMD). These calculated measures can only give an indication of the size and direction of the effect of OA since the quality of evidence is considered very low as explained below.

Risk of bias and quality of evidence
The assessment of the risk of bias can be found in appendix 5. The efficacy of the intervention and the quality of the evidence is combined in the *GRADE evidence* profiles (appendix 6). The quality of the evidence is reviewed through the GRADE methodology. The quality of evidence is determined per outcome measure and there are, next to risk of bias, some essential factors of interest: inconsistency, indirect evidence, imprecision and publication bias. Presence of one or more of these factors can result in downgrading the quality of evidence by one or two levels. This will result in a gradation of the quality of evidence of high, moderate, low or very low. As in this assessment use is made of an naïve (unanchored) indirect treatment comparison which results in low or very low quality of evidence for all outcome measures. In absence of a randomized controlled trial, the risk of bias is considered to be very serious. The use of hard outcomes as primary or co-primary efficacy endpoints, such as survival and event-free survival, in the clinical trial programme lowers the risk of bias the risk of bias that could be associated with lack of blinding. Motor milestone outcomes were video-confirmed and centrally reviewed.

Also the follow-up differed widely between the included studies. Therefore the results are described in detail in addition to the GRADE assessment. The most recently published Kaplan-Meier curves of the OA and nusinersen trials are included as well as descriptions and figures of the CHOP-INTEND scores and achieved motor milestones.

3.3.1 Symptomatic SMA patients

3.3.1.1 Event free survival

OA
The event-free survival at 14 months of age is determined in two OA trials (START and STR1VE-US). 22 patients enrolled in study STR1VE-US, 20 (90.9%) patients were reported alive and without permanent ventilation (event-free) at 14 months of follow-up. One patient died at the age of 7.8 months and one patient was reported to be on permanent ventilation at age of 11 months, and withdrew consent at age of 11.9 months. Of the 12 patients treated with the therapeutic dose (cohort 2.2.0E14 vg/kg) of OA in START (with OA produced in process A), 12/12 (100%) survived ventilation free at 14 months of age.

Nusinersen
The 18 month follow-up of SHINE is calculated by the applicant from the Kaplan-Meier (figure 7) that was published in the NICE committee papers of the single technology appraisal (STA) of nusinersen [ID1069][33]. This data is from the interim-analysis with data cut 30 June 2017. Treatment with nusinersen resulted in an event free survival of 32 out of 63 patients (36.5%) at 18 months follow-up.

OA vs. nusinersen
When the result of the SHINE study is naively compared with the STR1VE-US trial at a follow-up of 18 months a RR of 0.14 (95% CI: 0.02, 0.54) is calculated by the assessment group. When the pooled data from the START and STR1VE-US trials is used at a follow-up of 18 months, a **RR of 0.09 (95% CI: 0.02, 0.36)** is calculated for the naive comparison by the assessment group for OA vs. nusinersen. The median age of experiencing an event is not reached in OA trials and not reported for nusinersen. In absolute terms this means 5.78 patients less (from 6.22 to 4.06 less) will experience an event per 10 patients treated with OA vs. nusinersen.

GRADE conclusion:
Treatment with OA versus nusinersen results in a statistically significant effect on event-free survival until 18 months of age and the effect is possibly **[evidence of very low quality]** clinically relevant.

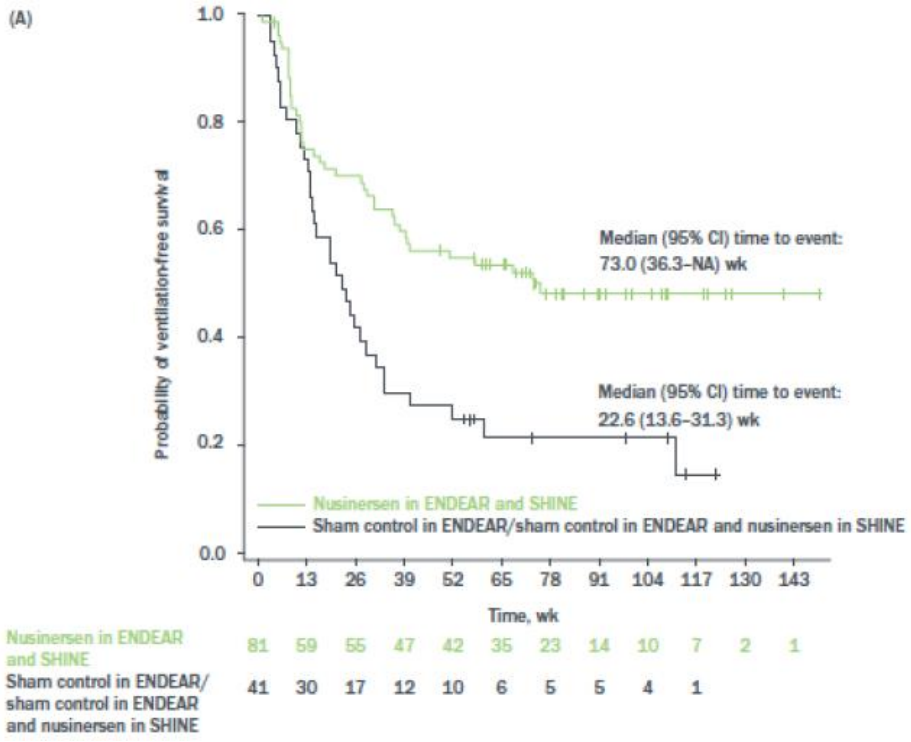


Figure 6: SHINE Time to death or permanent ventilation (interim analysis: data-cut: 30th June 2017)[33]

The company provided a naive indirect treatment comparison based on the pooled data from START and STR1VE-US and the data from the Kaplan-Meier of the long-term follow up study SHINE which was published by NICE. A hazard-ratio of 0.09 (95% CI: 0.02, 0.37) was calculated by the applicant.

Best supportive care (natural history control)
Sixteen (16) of 23 patients (70%) in the PNCR cohort reached the combined event (death or the need of non-invasive ventilation support) at 14 months. This means 7 of 23 patients survived event-free upon 14 months of age. In the EPAR a median survival in the PNCR cohort of 10.5 months is described. The patient-level survival rate of this control cohort determined at 13.6 months of age from the Kaplan-Meier curve is approximately 25%, this rate is used as comparator for the survival analysis in the START study. The data of the NeuroNext cohort reflects tracheostomy-free survival, a more lenient endpoint (a child could receive 24 hours per day of non-invasive support without triggering the combined endpoint). The applicant provided an unpublished database report with more details on the PNCR and NeuroNext cohorts dated 1 June 2018[41]. The percentage reaching the event free survival endpoint at 14 months of age is therefore lower than that in the PNCR cohort. 8 of the 16 patients (50.0%) reached the combined endpoint in the NeuroNext; which means 8 of 16 patients (50%) received tracheostomy or died before 14 months. The median age of event upon 14 month follow-up was reported in the PNCR and NeuroNext database report as 6.8 (range: 4.2 - 12.8) months and 8.5 (range 2.0 - 14.0) months respectively. When all data from the natural history cohort are included (without follow-up restriction) the *PNCR and NeuroNext database report* reported 18/23 (78.3%) of the PNCR cohort and 10/16 (62.5%) reached the combined endpoint at a median age of 9.5 (2.0 - 20.0) and 7.1 (4.2 - 18.3) months respectively. Which means only 5/23 (21.7%) of the patients in the PNCR cohort survived event-free and 6/16 (37.5%) of the NeuroNext cohort.

OA vs. best supportive care (natural history control)
When the OA study STR1VE-US and the natural history PNCR cohort data at a follow-up of 14 months are analysed through a naïve indirect comparison, a RR of 0.13 (95% CI: 0.03, 0.50) is calculated by the assessment group. This naïve indirect treatment comparison is surrounded with uncertainties and results in low quality of evidence as will be discussed in 3.3.4. Median age of experiencing an event is not reached in the OA study. The latest provided data of the STR1VE-US trial shows event-free survival for 20/22 patients up to 18 months of age. One patient withdrew due an AE at the age of 18 months, but was reported to be event free at the time of withdrawal. Of the 12 patients treated with the therapeutic dose (cohort 2.0E14 vg/kg) of OA in START (with OA produced in process A), 12/12 (100%) survived event-free at 14 months of age. In the PNCR historic cohort only 7/23 (30.4%) of patients survived event-free at 14 months of age. If all available data of STR1VE-US and START are pooled and compared with the PNCR cohort through a naïve indirect comparison, (event free-survival of 32/34 vs. 7/23) a **RR of 0.08 (95% CI: 0.02, 0.33)** is calculated by the assessment group. In absolute terms this means 6.4 patients less (from 6.82 less to 4.66 less) will experience an events before 14 months of age per 10 patients treated with OA vs. best supportive care.

GRADE conclusion:
Treatment with OA versus best supportive care results in a statistically significant effect on event-free survival until 14 months of age and the effect is possibly **[evidence of low quality]** clinically relevant.

In START (process A batch of OA) the effect on event-free survival was sustained at 24 months post-dose, 12/12 (100%) of the patients were alive without permanent ventilation versus 8% in the PNCR historic control (calculated from Kaplan-Meier[2]). The ventilation free survival defined as alive and without permanent ventilation is a primary or secondary endpoint in all OA studies. A pooled-analysis is provided in the EPAR in which all patients with 2x SMN2 treated with the OA product from process B are represented (STR1VE-US, STR1VE-EU and SPRINT at data cut 31 December 2019). This pooled analysis shows an event-free survival of 78/81 (96.3%) with a mean follow-up time since receipt of OA of 14.21 months (range: 1.8-25.7).

Kaplan-Meier analysis of event-free survival data was performed for the 2x SMN2 pool versus historical, untreated controls from the NeuroNext and PNCR studies. The survival curve of the 2-copy SMN2 pool was statistically significantly different from the curves generated from the two historical control studies (log-rank test, $P<0.0001$; Figure 6). 70 of 81 (86%) patients are followed-up until the age of 10 months at this data cut. Only 12 of 81 (15%) patients have a follow-up until the age of 20 months.

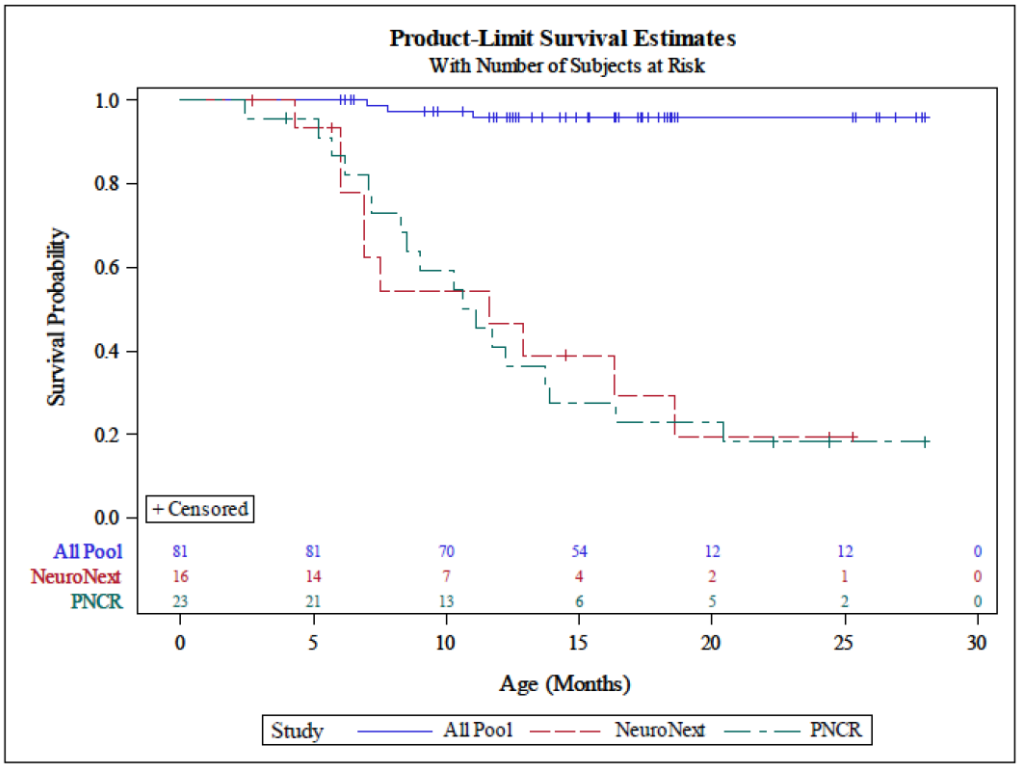


Figure 7: Kaplan-Meier Survival Curves of 2-copy SMN2 Pool vs. NeuroNext and PNCR (p<0.0001)[2]

3.3.1.2 Overall survival

OA

The survival at 14 months of age is determined in two OA trials (START used product produced via process A and STR1VE-US used product produced via process B). 22 patients enrolled in study STR1VE-US and 21 (95.5%) patients were reported alive at 14 months of age. Of the 12 patients treated with the therapeutic dose (cohort 2.2.0E14 vg/kg) of OA in START (with OA produced in process A), 12/12 (100%) survived at 14 months of age.

Nusinersen

The 18 month follow-up of SHINE is calculated by the applicant from the Kaplan-Meier (figure 8) that was published in the NICE committee papers of the single technology appraisal (STA) of nusinersen [ID1069][33]. These data are from the interim-analysis with data cut 30 June 2017. Treatment with nusinersen resulted in a survival of 39 out of 56 patients (69.6%) at 18 months follow-up.

OA vs. nusinersen

The survival of OA treated patients in STR1VE-US is naively indirectly compared with the nusinersen treated patients from the SHINE study at a follow-up of 18 months. A non-statistically significant RR of 0.15 (95% CI: 0.02, 1.06) is calculated by the assessment group. When the pooled data from the START and STR1VE-US trials are used to make the naive indirect comparison at follow-up of 18 months, a **RR of 0.10 (95% CI: 0.01, 0.70)** is calculated by the assessment group for OA vs. nusinersen. The median age of experiencing an event is not reached in the OA trials and not reported for nusinersen. In absolute terms this means 6.27 patients less (from 6.89 less to 2.09 less) will die before 18 months of age per 10 patients treated with OA vs. nusinersen.

GRADE conclusion:
Treatment with OA versus nusinersen results in a statistically significant effect on overall survival until 18 months of age and the effect is possibly **[evidence of very low quality]** clinically relevant.

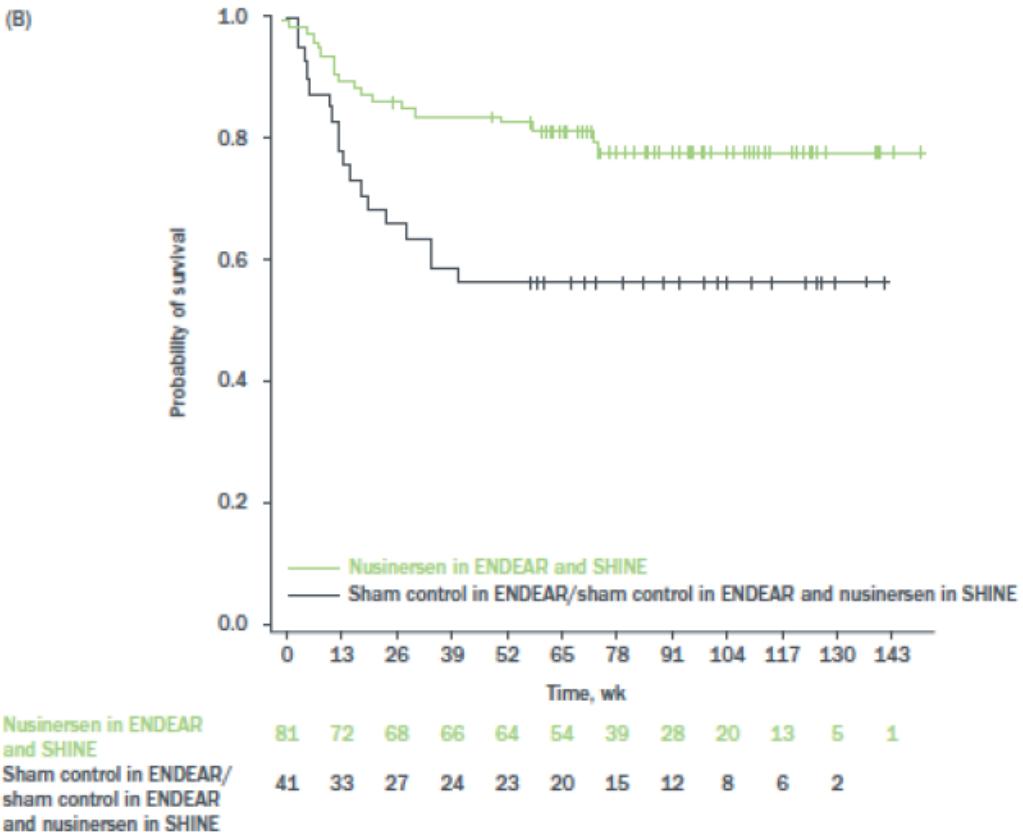


Figure 8: ENDEAR/SHINE (interim analysis: data-cut: 30th June 2017) Time to death

The company provided a naïve indirect treatment comparison based on the pooled data from START and STR1VE-US and the data from the by Kaplan-Meier of the long-term follow up study SHINE which was published by NICE . A non-statistically significant hazard-ratio of 0.35 (95% CI: 0.09, 1.32) was calculated by the applicant.

Best supportive care (natural history control)
In the PNCR historic cohort 16 out of 23 (69.6%) patients survived at 14 months of age with a median survival of 7.0 months (range: 3.0 – 12.0). In the NeuroNext cohort 9 of the 16 (56.3%) patients survived at 14 months of age with a median survival of 7.0 months (range: 4.0 - 13.0). When all data of the natural history cohort is included (without follow-up restriction), 12/23 (52.2%) of the PNCR cohort and 8/16 (50.0%) survived at a median age of 12.0 (3.0 - 176.0) and 7.0 (4.0 – 16.0) months respectively[41].

OA vs. *Best supportive care (natural history control)*
Indirectly comparing the STR1VE-US and PNCR cohort data at an follow-up of 14 months gives a non-statistically significant RR of 0.15 (95% CI: 0.02, 1.12). If all available data of STR1VE-US and START is pooled and naively compared with the

PNCR cohort a **RR of 0.10 (95% CI: 0.01, 0.73)** is calculated by the assessment group. In absolute term this means 2.74 patients less (from 3.01 less to 0.82 more) will experience death before 14 months of age per 10 patients treated with OA versus the historic control.

GRADE conclusion:
Treatment with OA versus best supportive care results in a statistically significant effect on overall survival until 18 months of age and the effect is possibly **[evidence of low quality]** clinically relevant.

3.3.1.3 Motor function

CHOP-INTEND

OA
In the OA STR1VE-US study the CHOP-INTEND scores of the 20 patients that were alive and ventilation free at 18 months after dosing, increased with a mean of 19.3 points (SD: 9.13) from baseline.

Nusinersen
Most recent CHOP-INTEND scores of participants in ENDEAR/SHINE are published a graph in the NICE assessment of nusinersen (see figure 9). The mean change in CHOP-INTEND at day 578 (19 months) from baseline was estimated at +14.0 (range: 11.0-17.5), measured in 32 subjects. An SD was not applicable.

OA vs. nusinersen
If the not reported SD of the ENDEAR/SHINE study is hypothetically set on 8 and then naively indirectly compared to the CHOP-INTEND scores of the OA treated patients in the STR1VE-US study, a **SMD of 0.62 (0.05, 1.19)** is calculated by the assessment group, in which the confidence interval just exceeded the limit of statistical significance.

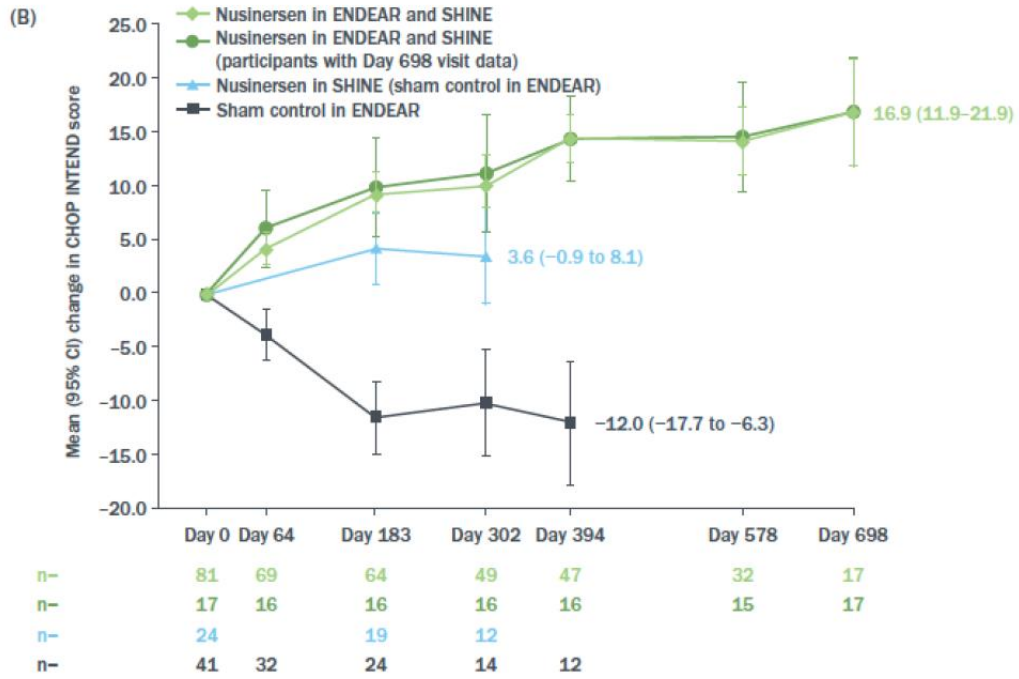


Figure 9: Mean (95% CI) change in CHOP-INTEND score over time in nusinersen studies ENDEAR/SHINE[20]

GRADE conclusion:
Although OA results in a statistically significant effect on the CHOP-INTEND score, it is unclear **[evidence of very low quality]** whether OA can result in a clinically relevant increase compared to nusinersen (default limit: SMD > 0.5).

OA vs. best supportive care (natural history control)
A pooled analysis of all SMA participants with 2x SMN2 that received process B product of OA is presented in the EPAR (figure 10), this includes presymptomatic treated patients (SPR1NT - green). The mean follow-up time was 14.21 (SD: 5.48 months) with a range of 1.8 – 25.7 months). CHOP-INTEND scores in this 2-copy SMN2 pool improved by a mean (±SD) of +6.5 (±5.91) at 1 month post-dose, +11.8 (±6.93) at 3 months post-dose, +15.4 (±8.14) at 6 months post-dose, and +19.9 (±8.54) at 12 months post-dose compared to the NeuroNext cohort were there was no mean improvement shown in CHOP-INTEND scores (grey). The mean (±SD) CHOP-INTEND score at the most recent visit prior to the data cut was 49.8 (±10.54) for the 2-copy SMN2 pool participants. The normal range of development in healthy children is visualized in yellow. At least 5 patients in the STR1VE-EU study have CHOP-INTEND scores <36 at the latest data point available.

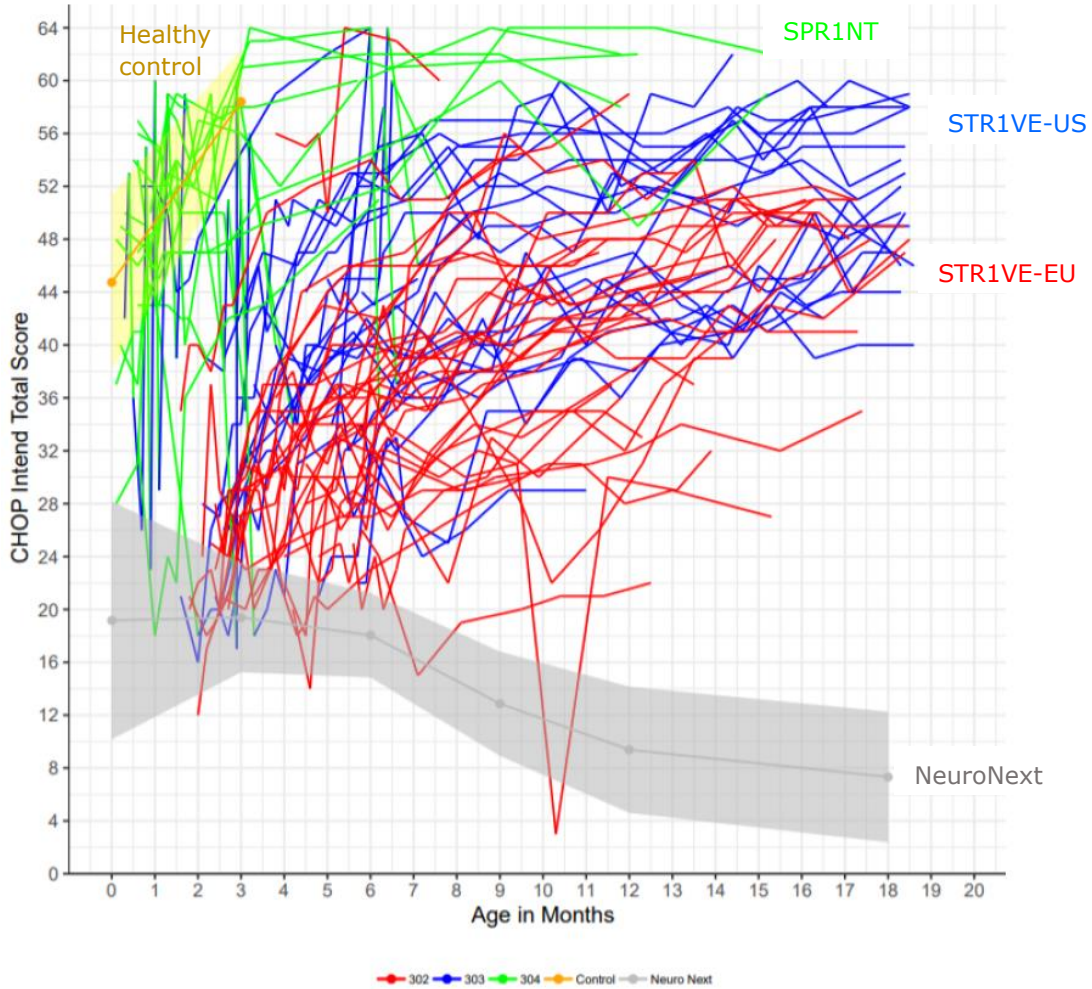


Figure 10: CHOP-INTEND Total Score in the 2x SMN2 Pooled Analysis (NeuroNext natural history cohort trend in grey)

None of the patients in the PNCR natural history cohort achieved a CHOP INTEND score >40 at or after the 6-month visit (with one transient exception). In the NeuroNext cohort, no patient achieved a CHOP INTEND score >33 at or after the 6-

month visit, and no patient had an increase in score from baseline. A mean decline of 10.7 points in CHOP-INTEND was observed between the 6 and 12 months of age visit (no SD was applicable so an SD of 5.2 was estimated from the provided graphs). A visualization of the natural course of CHOP-INTEND score in SMA infants is given in figure 11.

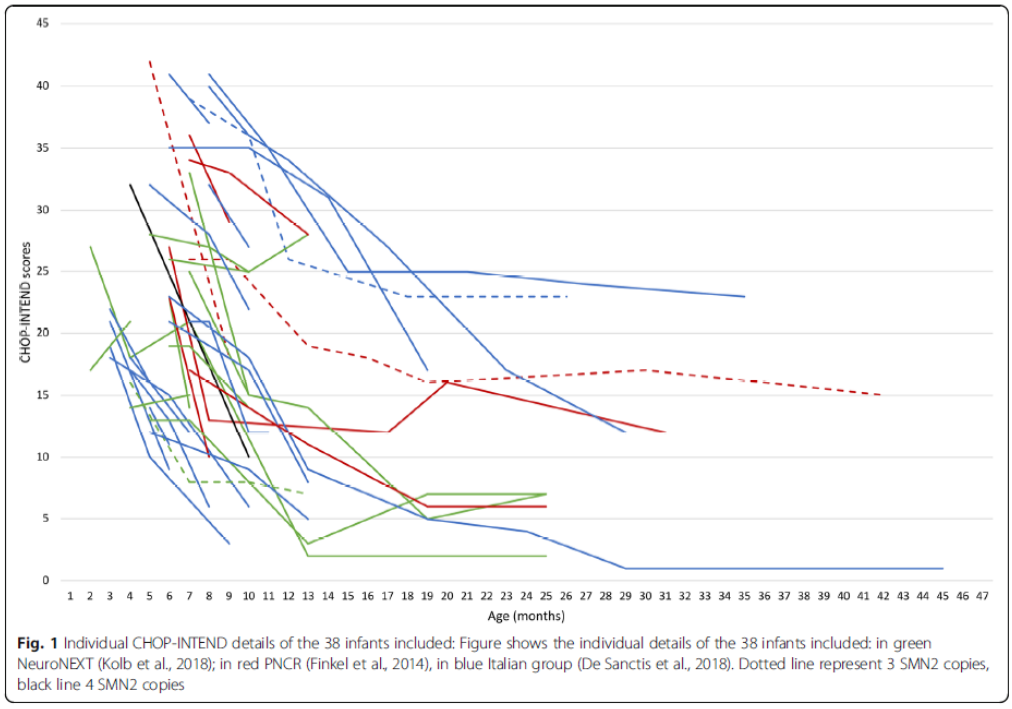


Fig. 1 Individual CHOP-INTEND details of the 38 infants included: Figure shows the individual details of the 38 infants included: in green NeuroNEXT (Kolb et al., 2018); in red PNCR (Finkel et al., 2014), in blue Italian group (De Sanctis et al., 2018). Dotted line represent 3 SMN2 copies, black line 4 SMN2 copies

Figure 11: CHOP-INTEND scores in historic cohort

In a naïve indirect comparison of patients treated with OA in STR1VE-US vs. the historic cohort of NeuroNext a decrease was observed between the 6 and 12 months of age visit and the - by the assessment group - calculated **SMD is 3.61 (95% CI: 2.37, 4.85).**

GRADE conclusion:
Treatment with OA versus best supportive care results in a statistically significant effect on CHOP-INTEND score until 18 months of age and the effect is possibly **[evidence of low quality]** clinically relevant (default limit: SMD > 0.5).

Developmental milestones

OA
In the STR1VE-US study, 14 of 22 (63.6%) of OA treated patients reached the WHO milestone sitting without support at 18 months of age.

Nusinersen
65 participants from the ENDEAR nusinersen-treated patients transitioned to SHINE. Based on the 15 October 2018 data cut with a follow-up of 19 months, 21/59 (36%) participants who received nusinersen in ENDEAR/SHINE achieved the World Health Organization motor milestone of sitting without support.

OA vs. nusinersen
When the results of the STR1VE-US study are naively indirectly compared with this results of nusinersen a RR of 1.79 (1.12, 2.85) is calculated by the assessment

group. If all available data of STR1VE-US and START at a follow-up of 18 months (20/34 58.8%) is pooled and naively indirectly compared with the nusinersen results (median follow-up 19 months) a **RR of 1.65 (95% CI: 1.06, 2.58)** is calculated by the assessment group. From an absolute perspective this means 2.31 more patients (from 0.21 more to 5.62 more) of 10 treated patients will reach the WHO milestone sitting without support when treated with OA vs. nusinersen.

GRADE conclusion:
Although OA results in a statistically significant effect on the WHO motor milestone of sitting without support, it is unclear **[evidence of very low quality]** whether OA can result in a clinically relevant increase compared to nusinersen (default limit: RR 0.75-1.25).

The milestones achieved by nusinersen treated patients in ENDEAR/SHINE can be found in table 12. 5 of 59 (8%) patients treated with nusinersen achieved standing with assistance, and 3 of 59 (5%) achieved walking with assistance. None of the patients that were randomized to sham-procedure in ENDEAR and nusinersen in SHINE (n=22) achieved these milestones.

Developmental milestones achievement was also assessed for the whole 2-copy SMN2 pool treated with OA, and the total number of treated individuals who achieved each developmental milestone at least once was tabulated. Not all milestones were assessed in all studies, but all milestones assessed were confirmed by central video review. Sitting without support as defined by the WHO motor milestones was achieved by 34 of the 81 (30%) of the patients treated with OA, 7 of them were treated in the presymptomatic trial SPR1NT. Walking alone was achieved by 4 of 69 (5.8%) treated patients, all presymptomatic treated patients. In the pooled OA trials with type 1 SMA patients with 2 copies of SMN2 4/69 patients reached the WHO milestone achievement independent walking at the data cut of 31 December 2019. At the data cut of 15 October 2018, none of the nusinersen treated symptomatic SMA type 1 patients reached this milestone in the ENDEAR/SHINE study.

The WHO milestones achieved by the largest to smallest proportion of the 2-copy SMN2 pool are shown in table 12.

Table 12. Milestones achieved in 2-copy pool of OA treated patients versus nusinersen interim data from ENDEAR/SHINE (15 October 2018)[2, 43]

Motor milestones achieved		**2x SMN2 pool OA, n (%)**	**Nusinersen, n (%)**
Holds head erect for ≥3 seconds without support (Bayley)*		58/81 (72)	NA
Turns from back to both right and left sides (Bayley)		38/81 (47)	NA
Sits without support	≥10 seconds (WHO)	34/81 (42)	21/59 (36)
	≥30 seconds (Bayley)	39/81 (48)	NA
Crawls	≥5 feet (Bayley)	3/69 (4.3)	NA
	≥3 movements (WHO)	3/69 (4.3)	NA
Stands with assistance	Supports own weight for ≥2 seconds	7/69 (10)	NA
	Holding a stable object (WHO)	7/81 (8.6)	NA
Pulls to stand (Bayley)		4/69 (5.8)	
Stands alone	≥3 seconds (Bayley)	7/81 (8.6)	NA
	≥10 seconds (WHO)	3/69 (4.3)	5/59 (8)
Walks with assistance	(Bayley)	8/81 (9.9)	NA
	(WHO)	4/69 (5.8)	3/59 (5)*
Walks alone	(Bayley) §	5/81 (6.2)	NA
	(WHO) §	4/69 (5.8)	NA
Median (range) duration of follow-up at last visit, months		Mean: 14.21 (SD: 5.48; range: 1.8 – 25.7)	19 months

NA: Not available

* It is unknown whether this represents the WHO milestone

Best supportive care (natural history control)
None of the patients in the PNCR control cohort reached the milestone of sitting without support for ≥10 seconds. In the NeuroNext cohort, no child achieved the milestone of sitting with or without support, hands and knees crawling, standing with assistance, walking with assistance, standing alone or walking alone.

OA vs. best supportive care (natural history control)
When the outcome of STR1VE-US are naively indirectly compared with the PNCR cohort a RR of 30.26 (95% CI: 1.91, 478.39) was calculated by the assessment group. In the START study 11 of the 12 (91.6%) OA treated patients were able to sit without support (follow-up 24 months). If all available data of STR1VE-US and START at 18 months is pooled and naively indirectly compared with the PNCR cohort a **RR of 28.11 (95% CI: 1.78, 442.83)** is calculated by the assessment group. An absolute effect cannot be formally calculated with 0 events the control arm.

GRADE conclusion:
Treatment with OA versus best supportive care results in a statistically significant effect on the WHO motor milestone sitting without support until 18 months of age and the effect is possibly **[evidence of low quality]** clinically relevant.

In the START study 11 of the 12 (91.7%) OA treated patients were able to sit without support for ≥5 seconds (follow-up 24 months). 2 of the 12 (16.7%) patients achieved walking without assistance. In the STR1VE-US study, 1 patient achieved walking without assistance.

3.3.2 *Presymptomatic SMA patients*

OA

The efficacy of OA in presymptomatic patients is determined in one ongoing, phase 3, single-arm study: SPR1NT. This trial included patients with 2x SMN2 in cohort 1 and patients with 3x SMN2 in cohort 2. At the data cut of 31 December 2019 the median age of the patients at the last follow-up at last visit was 10.5 months (range: 6.0 – 18.6) for patients in cohort 1 (2x SMN2, n=14) and 9.6 months (range 3.3 – 15.1) for patients in cohort 2 (3x SMN2, n=15). This data has to be considered immature. All patients were alive and free of permanent ventilation at the data cut-off. See figure 12 for the Kaplan-Meier.

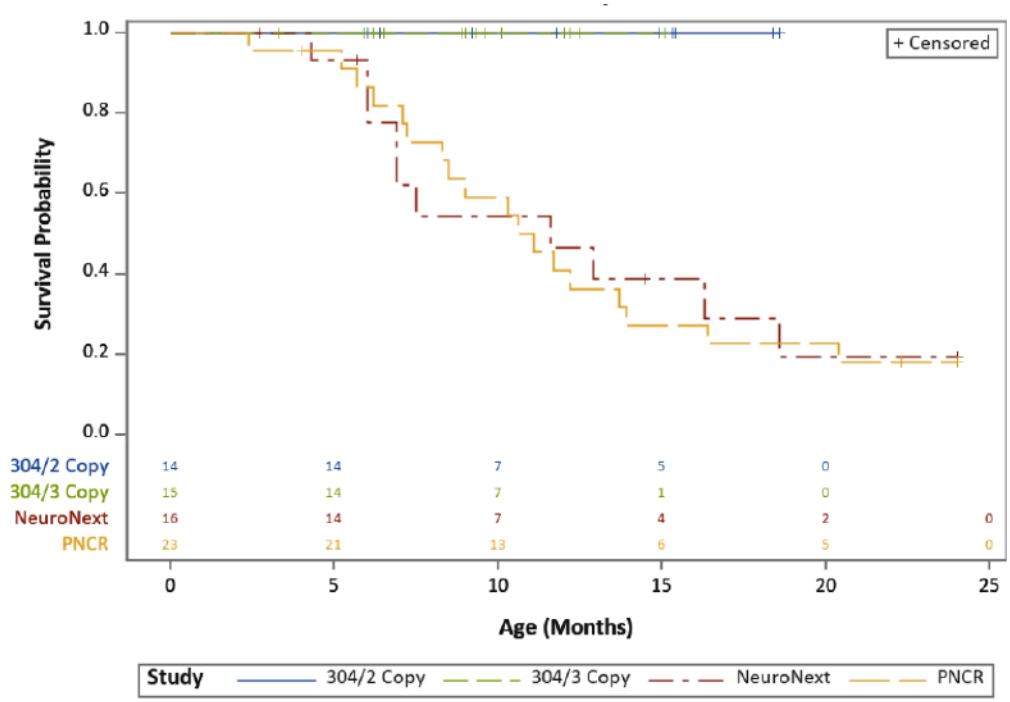


Figure 12: Kaplan-Meier plot for event-free survival in 2x SMN2 and 3x SMN2 patients in SPR1NT (31 December 2019 data cut)

The mean baseline CHOP-INTEND score was 46.1 (SD: 8.77). At the 31 December 2019 data cut, 12/14 (85.7%) of participants with 2x SMN2 had achieved a score CHOP-INTEND >60. The mean change from baseline for the 2x SMN2 patients was +16.6 points. Of the patients in cohort 1 (2x SMN2), 7 of 14 (50%) patients achieved the WHO milestone sits alone without support for at least 30 seconds and 4 of 14 (29%) reached the achievement of walking alone. In cohort 2, 10/15 (67%) patients with 3 copies of SMN2 achieved sits alone without support for at least 30 seconds and 3 of 15 (20%) reached the achievement of walking alone. Other milestones can be found in table 14.

Nusinersen

The effectiveness of nusinersen in presymptomatic subjects is examined in one observational trial (NURTURE) in which 15 patients with 2x SMN2 and 10 patients with 3x SMN2 are included. In figure 13 the Kaplan-Meier from the interim analysis of 29 March 2019 can be found[40]. At the interim analysis all patients were alive and none required permanent ventilation. The median time to death or respiratory intervention (invasive or non-invasive ventilation for ≥6 h/day continuously for ≥7

days or tracheostomy) could not be estimated, as there were too few events.

At the last visit, mean (range) CHOP INTEND total score was 62.1 (48–64) in those with two SMN2 copies and 63.4 (58–64) in those with three SMN2 copies. At the time of this interim analysis, 10/15 (67%) of participants with 2 SMN2 copies and 10/10 (100%) of those with 3 SMN2 copies had achieved a maximum score of 64.

Four (16%) infants (all with two SMN2 copies) utilized respiratory intervention for ≥6 h per day continuously for ≥7 days. As of data cut-off, all (25/25; 100%) NURTURE infants achieved the WHO motor milestone "sitting without support", while 23/25 (92%; 13/15 with two SMN2 copies and 10/10 with three SMN2 copies) achieved "walking with assistance", and 22/25 (88%; 12/15 with 2x SMN2 copies and 10/10 with 3x SMN2 copies) achieved "walking alone". See table 14 for an overview. Most participants achieved these milestones within the time window established by the WHO for healthy children. The median (95% CI) ages for first achievement of sitting without support, walking with assistance, and walking alone in two SMN2 copy participants were 7.9 (5.9–9.2) months, 16.1 (11.8– 18.8) months, and 20.4 (15.5, 29.7) months, respectively. In those with three SMN2 copies, the median (95% CI) ages for first achievement of sitting without support, walking with assistance, and walking alone were 6.4 (5.1–7.9) months, 9.6 (8.0–11.8) months, and 12.3 (11.2–14.9) months, respectively.

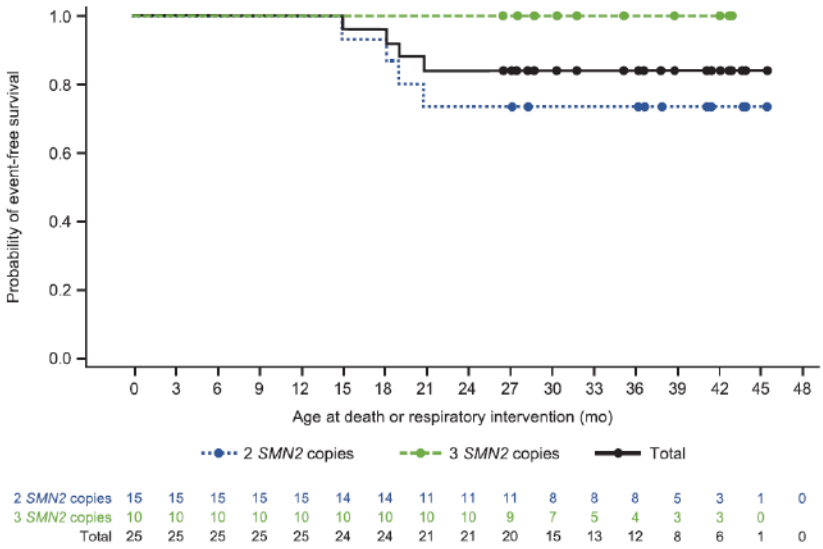


Fig. 2. Kaplan–Meier plot for age at death or respiratory intervention.[a]
SMN2, survival motor neuron 2.
No participants have died or required tracheostomy or permanent ventilation (defined as ≥16 h/day continuously for >21 days in the absence of an acute reversible event or tracheostomy).
[a]Respiratory intervention was defined as ventilator use for ≥6 h per day for ≥7 days or tracheostomy.

Figure 13: Kaplan-Meier of NURTURE (median follow-up age: 34.8 (range: 25.7–45.4) (data cut 29 March 2019)[40]

* Patients were past the expected age of symptom onset for SMA Types I or II

Table 13: Milestones achieved by OA and nusinersen treated patients in SPR1NT and NURTURE

		OA SPR1NT[2] December 2019 data cut		NURTURE [44] interim 1	Nusinersen NURTURE[40] interim 2	
Motor milestones achieved		**2x SMN2, n=14 (%)**	**3x SMN2, n=15 (%)**	**Pooled, n=25**	**2x SMN2, n=15 (%)**	**3x SMN2, n=10 (%)**
Holds head erect for ≥3 seconds without support (Bayley)*		14 (100)	15 (100)	NA	NA	NA
Turns from back to both right and left sides (Bayley)		8 (57)	9 (60)	NA	NA	NA
Sits without support	≥10 seconds (WHO)	7 (57)	10 (67)	71%	15 (100)	10 (100)
	≥30 seconds (Bayley)	8 (57)	10 (67)	NA	NA	NA
Crawls	≥5 feet (Bayley)	3 (21)	6 (40)	NA	NA	NA
	≥3 movements (WHO)	3 (21)	6 (40)	NA	NA	NA
Stands with assistance	Supports own weight for ≥2 seconds	5 (36)	9 (60)	NA	NA	NA
	Holding a stable object (WHO)	5 (36)	9 (60)	59%	NA	NA
Pulls to stand (Bayley)		3 (21)	7 (47)	NA	NA	NA
Stands alone	≥3 seconds (Bayley)	4 (29)	4 (27)	NA	NA	NA
	≥10 seconds (WHO)	3 (21)	3 (20)	18%	NA	NA
Walks with assistance	(Bayley)	4 (29)	6 (40)	NA	NA	NA
	(WHO)	4 (29)	5 (33)	29%	13 (87)	10 (100)
Walks alone	(Bayley) §	3 (21)	2 (13)	NA	NA	NA
	(WHO) §	4 (29)	3 (20)	12%	12 (80)	10 (100)
Median duration of follow-up at last visit, months (range)		9.9 (5.1 - 18.0)	9.0 (2.0 – 13.9)	10.4 (0-17.2)	unknown	
Median age at last visit, months (range)		10.5 (6.0 – 18.6)	9.6 (3.3 – 15.1)	NA	34.8 (25.7–45.4)	

* two patients in the 2x SMN2 group and five patients in the 3x SMN2 group had had control at screening
§patients achieving this milestone also met previous milestones

Best supportive care (natural history control)

The registered indication includes presymptomatic SMA patients up to three copies of SMN2. For the patients with 2x SMN2, the natural course of the disease is discussed in 3.3.1. Patients with 3 copies of SMN2 are less clearly defined in terms of the course of the disease. Life expectancy is longer but differs from 20 up to 40 years of age. A proportion of patients with 3 copies of SMN2 will fail to gain basic milestones such as independent sitting however the phenotypic variation of patients with 3 SMN2 copies is large. A recent publication of an ongoing prospective population based prevalence cohort study in 250 SMA patients shows a wide variety of SMA types of patients within the 2x SMN2 patients. 155 patients with 3x SMN2 were included and 18 (12%) were characterized as SMA type 1c (very severe), 62 (40%) as SMA type 2a (very severe), 42 (27%) as 2b (severe), 28 (18%) as type 3a and 5 (3%) as type 3b[45]. When observed as a group SMA type 1 patients with three copies of SMN2 experienced a less severe clinical course compared to the type 1 patients with 2 SMN2 copies. 25% of these patients reached 22 months of age.

Most patients experienced prolonged survival with 17% mortality during observation and an age range of between 15 months and 52 years (median 7.4 years)[2].

3.3.3 *Other considerations*

Matched adjusted indirect treatment comparison (MAIC)
The applicant performed a MAIC in order to make the comparison with nusinersen more reliable. Several methodological challenges arise in relation to heterogeneity and how the matching occurred. Since this analysis is not published and peer-reviewed it is seen as supportive in this assessment. The MAIC is informed with the presymptomatic patients of the START and STR1VE-US studies for OA and the ENDEAR/SHINE study for nusinersen. The MAIC produced weights for these individuals using the method of moments such that the weighted mean of OA some observed patient characteristics (START and STR1VE-US pooled) matched to those of nusinersen. The outcomes of the MAIC are generally in line with the outcomes of the naïve indirect treatment comparison.

Comparison with the natural history cohorts PNCR and NeuroNext
The used PNCR cohort consists of patients with age of onset ≤6 months, bi-allelic deletion of SMN1 and 2 copies of SMN2. From the NeuroNext natural history study a population is drawn with SMA type 1 patients with bi-allelic deletion of SMN1 and 2 copies of SMN2 <6 months of age. Since the PNCR cohort consists of patients with age of onset ≤6 months, the patients included are clinically defined as SMA type 1. The NeuroNext patients do not seem to have this explicit criterion.

Key secondary endpoints were change from baseline in CHOP-INTEND score and motor milestone. The CHOP-INTEND score is a validated motor function score for SMA type 1 children. Although this score is considered clinically meaningful, this is not a norm-referenced scale which hampers the assessment of the development in relation to their healthy peers. Bayley scale assessments were initiated in patients reaching the top of the CHOP-INTEND. Since this is a norm-referenced scale this outcome is expected to provide clinically meaningful information.

Ongoing trials
At the December 2019 data cut, 32 of the 33 enrolled patients (97.0%) in the ongoing STR1VE-EU had survived without permanent ventilation of which only 18 patients (56.3%) were ≥ 14 months of age and 4 (12.5%) were ≥ 18 months of age. The event-free survival is visualized in figure 14. The achieved motor milestones are shown in table 13.

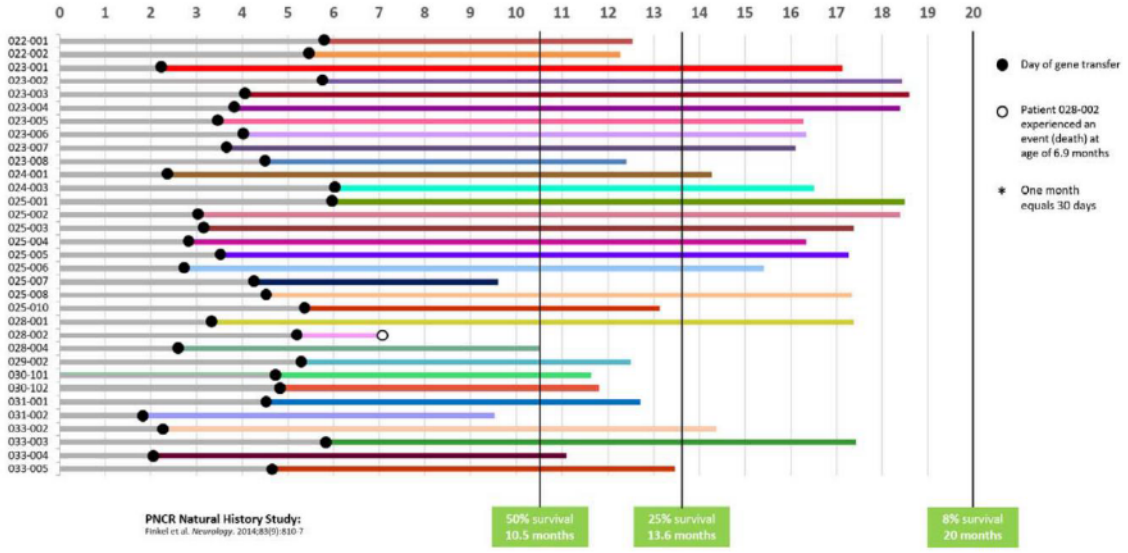


Figure 14: Event-free survival in STR1VE-EU (31 December 2019 data cut[2]

Table 14: Motor milestones achieved by patients in the STR1VE-EU trial[2].

Motor milestones achieved	N (%)
Holds head erect for ≥3 seconds without support (Bayley)*	20/33 (62.5%)
Turns from back to both right and left sides (Bayley)	8/32 (25%)
Sitting without support WHO	8/32 (25%)
Standing with assistance WHO	1/32 (3.1%)

From figure 10 (page 47 of 90) , it was noticed that at least 5 patients in the STR1VE-EU study had CHOP-INTEND scores <36 at the latest data point available.

Update of the data - data cut 20 June 2020
The company provided unpublished data from the 20 June 2020 data cut. These numbers are published in a press release on the website of the company on March 15 2021. Since these data are not published, these are only seen as supportive to the data from the December 2019 data cut. 20/22 patients of the STR1VE-US trial; 30/31 patients of STR1VE-EU and 29/29 patients of SPR1NT that were alive and without permanent ventilation in the December 2019 data cut continued to be so.
Developmental milestones in SPR1NT cohort 1: 2x SMN2 copies

- -The median age of patients was 15.6 months (range 8.8–18.8 months of age).
- -Eleven of 14 patients (79%) achieved the study's primary endpoint of sitting without support for at least 30 seconds. Ten of these patients achieved this within the WHO window of normal development. The remaining three patients were still being evaluated in the study at the time of the data cut-off.
- -Five patients (36%) could stand independently, three of whom achieved this milestone within the WHO window of normal development. Four patients (29 percent) could walk independently, three of whom achieved this milestone within the WHO window of normal development. Of those patients who had not yet achieved these milestones, the majority (seven of 9 and seven of 10, respectively) had not yet passed the normal developmental window.
- -All patients (100 percent) achieved CHOP INTEND scores of ≥50, and 13 (93 percent) achieved a CHOP INTEND score ≥58.

Developmental milestones in SPR1NT cohort 2: 3x SMN2 copies

- The median age was 15.2 months (range 3.3–21.1 months of age).
- Eight patients (53%) achieved the study's primary endpoint of standing alone for at least three seconds, and six patients (40%) walked independently.
- These motor milestones were all achieved within the WHO window of normal development. Of those patients who had not yet achieved these milestones, all were still within the WHO window of normal development.

LT-001

The LT-001 (N=13) is the long-term follow-up of the START study. Milestone achievements were recorded in study LT-001 to support persistence of efficacy. To date, there has been no loss of previously attained milestones for patients who received the therapeutic dose of OA in START. The oldest patients is 72.9 months (6 years) of agein the latest data cut (20 June 2020). The data indicates that 40-50% of patients who received OA subsequently received therapy with nusinersen (4/10 who received the higher dose and all three patients who received the lower dose are on nusinersen). New video-confirmed motor milestones of standing with assistance were achieved by 2 patients. Both of these patients have had a one-year follow-up visit and neither of these patients are reported to have used nusinersen at any point.

RESTORE

The RESTORE registry is an ongoing, prospective, multicentre, multinational, observational study of patients with a diagnosis of SMA, including patients from the OA managed access programs and from partnering clinical sites with a planned follow up of 15 years. As of December 2020, >70 patients were enrolled. Of these, 45 (64 percent) had SMA Type 1. Two deaths have been reported: one was due to respiratory arrest assessed as unrelated to OA by both the investigator and the company, and one report could not be substantiated by the site investigator.

3.3.4 *Discussion favourable effects*

Risk of bias and quality of evidence

The quality of the evidence is low or very low due to the limited setup of the trials: single arm trials without controls and limited number of patients. Two of the four studies are still ongoing and the follow-up time is limited. The patients of the nusinersen trial SHINE (extension of ENDEAR) were older than the patients in the STR1VE-US (164.3 days (60.8-456.3) versus 112.5 days (15.2-197.5) at the first dose and had slightly lower CHOP-INTEND scores at baseline (26.7 (SD: 8.1) versus 32 (range: 18-52)). With the assumption that earlier initiation of treatment is more likely to prevent a patient from deteriorating, the differences between the two studies will presumably result in bias in favour of OA. Also the differences in nutritional support (0% in STR1VE-US versus 9% in ENDEAR/SHINE) and ventilation support (0% in STR1VE-US versus 26% in ENDEAR/SHINE) at baseline show that patients in the nusinersen-arm are more affected at start of the study.

Data from historical controls is available but the cohorts are not exactly comparable. The patients in the historic controls seem to be more severely affected when comparing baseline characteristics of ventilation and nutritional support.

As noted in the discussion on study characteristics, a different batch of product was used in the START study (process A) than in the other OA studies (process B). The CHMP could not determine whether the different products were comparable in quality and/or efficacy. Since other factors as age at symptom onset or age at initiation of treatment presumably have a larger effect on the efficacy, combined

with the fact that the point estimates are comparable and confidence intervals will become smaller, it was found appropriate to pool the data of START and STR1VE-US for this assessment.

Although there are indications that the patients in the historic cohorts differ in baseline characteristics, the historical controls are in general considered adequate in the absence of any randomized controlled trial for comparison with the study population of the OA studies.

Based on the literature available it can be concluded that few if any patients suffering from SMA type 1 survive the first 18 months of life without any ventilator requirement and nutritional support. None of the patients of the PNCR and NeuroNext cohort ever achieved motor milestones as sitting or standing without support or a CHOP-INTEND score higher than 33.

3.3.4.1 Symptomatic SMA type 1 patients

Six studies with OA are identified (START, LT-001, STR1VE-US, STR1VE-EU, SPR1NT and LT-002). Low (vs. best supportive care) or very low (vs. nusinersen) quality of evidence is concluded from the GRADE evidence profile since naive indirect treatment comparisons had to be made between single-arm trials or cohort studies. Given the fast progressing nature of SMA type 1, a single-arm trial was the highest achievable in absence of another treatment at time of the start of this trials.

All estimated effects of OA on survival, ventilation free survival and the mobility outcomes are substantial and within the default set standards of clinical relevance (The default limit of the standardized mean difference (SMD) is 0.5. When using a relative risk (RR or HR), the default limit value is 0.75 and 1.25). Although the quality of evidence is limited, the sample size for which efficacy data has been provided is reasonable given the incidence of the disease. Zorginstituut Nederland considers the beneficial effects of OA to be clinically relevant compared to best supportive care. However, more information on both number of patients and follow-up time is needed to assess the maintenance of the treatment effect.

OA vs. nusinersen in symptomatic type 1 patients
From the naïve indirect treatment comparison a HR of 0.09 (95% CI: 0.02, 0.37) is calculated by the applicant which corresponds to a number needed to treat of 1.85. The results of OA versus nusinersen on event-free survival and survival seem to be statistically significant and clinically relevant from the naïve indirect comparison, although the effects on survival alone are less convincing. The applicant performed a MAIC in order to make the OA patient populations more comparable with the nusinersen study population, however this analysis was not published and is therefore not considered. The calculated effects of the MAIC are comparable with the effects of the naive comparison. The SD of the achieved effect on CHOP-INTEND score in the nusinersen population is unknown but a statistically significant difference can be extracted from the indirect comparison. Clinical relevance has not been conclusively demonstrated since the confidence interval exceeds the default limit of clinical relevance (SMD >0.5). Although the follow-up of the participants in the OA studies did not yet reach 19 months, more patients achieved WHO motor milestones independent sitting and independent walking than patients in the nusinersen study who had a follow-up of >19 months. From the naïve indirect treatment comparison it is unclear whether the difference is clinically relevant at a follow-up of 18 months and the quality of the evidence is considered very low.

The relative effectiveness of OA compared with nusinersen is highly uncertain given

the lack of direct comparative evidence and the heterogeneity in clinical trials used for the naïve indirect treatment comparison. Less patients have been studied in OA trials compared to nusinersen. The indirect comparison suggested that OA is at least equally as effective as nusinersen in preventing death and that OA is possibly more effective in preventing permanent ventilation. Given the fact that the nusinersen treatment started at an older age in the studies (treatment started at a median of 109 (range 15-240) days in OA trials versus 163 (range: 61-242) days in the nusinersen trials) and nusinersen treated patients seem to be more affected at start of treatment (based on differences in CHOP-INTEND and ventilation support at baseline) a convincing added benefit of OA versus nusinersen cannot (yet) be concluded. Further the quality of the naïve unanchored comparison is problematic in determining benefit objectively.

3.3.4.2 Presymptomatic SMA patients with 2 or 3 copies of SMN2

None of the pre-symptomatic treated patients in SPR1NT experienced an event of permanent ventilation or death so far (data cut June 2020) with a median follow-up age of 15 months. The patients in both cohorts - 2 and 3xSMN2 copies - show motor milestones development which is largely within the range for normal development. In the 2x SMN2 cohort 11 out of 14 patients have achieved sitting without support of whom 10 achieved this within the WHO window of normal development. Five (5) patients can stand independently and 4 can walk alone as well. Bayley scaled scores show motor function within 2 SD of indicating normal motor development. Also the patients in the 3x SMN2 cohort show motor milestones development which is largely within the range for normal development thus fare. Eight (8) out of 15 patients have achieved standing alone and 6 achieved walking independently as well. Of those patients who had not yet achieved these milestones, all were still within the WHO window of normal development. Bayley scaled scores show motor function within 2 SD of indicating normal motor development.

Since none of the OA and nusinersen presymptomatic treated patients in SPR1NT and NURTURE experienced an event of permanent ventilation or death so far, the effect of both products on this outcome measure seem to be comparable. Also the results on the motor milestones and CHOP-INTEND score of OA and nusinersen treated patients from the presymptomatic trials point in the same direction. However, the follow-up of the patients in the OA trial is much shorter with median follow-up age - at the June 2020 data cut - <15 months of age vs. 35 months in the latest nusinersen data cut. A longer follow-up is needed in order to draw conclusions about milestones that still need to be met. An equal or added benefit of OA versus nusinersen in presymptomatic patients cannot be concluded based on these immature presymptomatic trials.

Presymptomatic patients with two copies of SMN2
The data from the June 2020 data cut of the SPR1NT study suggests that most of the treated patients in the 2x SMN2 copy cohort of SPR1NT are developing motor milestones as sitting without support and standing or walking alone within the range of normal development. But based on these data, it can also be seen that at least 4/14 presymptomatic treated patients with 2x SMN2 copies are not developing within the upper bound of normal development (3/14 did not reach milestone "sits without support" within the normal development window, 1/14 had not yet reached milestone "walks alone" within the normal development window). Which means that not all presymptomatic OA treated patients with 2x SMN2 are developing as good as healthy children will. But only longer term follow-up can conclude whether these children will indeed continue to lag behind healthy children.

Presymptomatic patients with three copies of SMN2
The ongoing SPR1NT trial includes 15 presymptomatic patients with 3 SMN2 copies in cohort 2. The latest results from the June 2020 data cut - published on the company's website – still only represent the effects within a median follow-up age of 15.2 (range: 3.3 – 21.1) months. The data from the June 2020 data cut of the SPR1NT study suggests that most of the treated patients in the 3x SMN2 copy cohort of SPR1NT are developing motor milestones as sitting without support within the range of normal development. Almost half of them are also standing or walking alone. But for the other half of the patients in this cohort, the follow-up is still too short and no firm conclusions regarding efficacy can be drawn from this immature data for the whole 3x SMN2 cohort.

More variation of the course of the disease is seen in patients with three copies of SMN2; a significant proportion (20%) of patients who go on to develop SMA type 1 have three copies of the SMN2 gene and, in the Dutch cohort, up to 50% of patients with three copies of the SMN2 gene have SMA type 1C or 2A which mean they will suffer from very severe disease. Patients with type 2 SMA will never learn to walk and their life expectancy is still limited to 20-40 years. Hence, there is a strong clinical rationale to provide an active therapy in pre-symptomatic patients with three SMN2 copies.

The CHMP stated that the data to substantiate benefit of OA in patients with 3x SMN2 is limited. Due to the heterogeneity in the natural history for these patients, it is unclear whether the effect exceeds the expected development. The CHMP considered the efficacy for patients with 2 copies of SMN2 can be extrapolated to patients with 1 or 3 SMN2 copies (see benefit/risk assessment). The indication is therefore considered acceptable by the CHMP. The completion of the SPR1NT study is one of the conditions of the market authorization of OA. In addition the applicant has committed to further characterize the natural history from patients with 3x SMN2 and SMA type 2/3a based on available literature and patients from the RESTORE registry.

Concomitant use of nusinersen
OA is a gene therapy targeting the underlying pathophysiology of the disease, from which it would be expected that no further treatment would be necessary. Nusinersen modulates alternative splicing of the SMN2 gene. Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts which leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein, thus increasing the level of SMN protein in the central nerve system. The concomitant use of nusinersen in the long-term follow-up of OA treated patients hampers the assessment of the achievement of new milestones in these patients which cannot solely be attributed to OA. In these cases, it is difficult to disentangle whether maintenance of effect or further improvement is due to OA, nusinersen or an additive effect. Since symptomatic OA treated children, may still not achieve sufficient motor milestones in life, parents and clinicians will possibly consider the addition of nusinersen treatment. Real world evidence and registered clinical trials have noted concomitant use of nusinersen. Nusinersen was regulatory approved at the time of this study while OA was still an investigational agent. The extent to which this level of concomitant usage may be reflected in clinical practice remains to be seen. It is expected that there will be pressure from parents to give nusinersen on top of treatment with OA, even when OA becomes standard clinical practice. The concomitant use of nusinersen after OA is now being explored in clinical trials (Biogen: NCT04488133). It cannot be ruled out that this will also happen in clinical

practice, although there is no published evidence up to date that combination of these two disease modifying therapies is superior to any single treatment alone.

3.4 Unfavourable effects

OA[2, 1]

Safety data discussed in the EPAR of OA were derived from the four studies in which, at the cut-off date of 31 December 2019, 101 patients have received OA via the intravenous route of administration. 98 patients received the proposed dose of 1.1E14 vg/kg (referred to as 2.0E14 vg/kg in study in START) and 3 received a lower dose. Twelve of the 98 patients were treated with process A manufactured OA. Thus, 86 patients received intravenous OA manufactured by process B in the proposed therapeutic dose.

96 of the 98 patients (99%) experienced at least 1 treatment emergent adverse event (TEAE) and 56 patients (58%) were reported to have a TEAE considered by the investigator to be related to OA. 45 patients (46%) had at least one serious adverse event (SAE) and 39 patients (40%) had at least one TEAE that was Grade 3 severity or higher. Two patients (2.1%), 1 in STR1VE-US and 1 in STR1VE-EU, were discontinued due to TEAEs that resulted in death. In Study STR1VE-US one patient withdrew from the study because of a TEAE of respiratory distress which was considered not related to treatment with OA.

As of 31 December 2019, a total of 192 patients with 488 adverse events were retrieved from the post-marketing Argus Safety database. Because of the limited information about the cases, e.g. concomitant medication, outcome, medical history etc., no firm conclusions that confirm or deviated from the known safety profile of OA could be drawn by the CHMP. However, most reported events are consistent with the known adverse event profile of OA. In the list of spontaneous reports there seems a notable tendency of occurrence of pyrexia after administration of OA.
The long-term follow up of the adverse events of OA are unknown. The adverse events related to the immune response are not likely to have long term safety consequences. However, the long-term safety of gene expression is less clear. Though the carcinogenicity risk is considered low as AAV vectors mainly do not integrate in the host genome as compared to e.g. lentivirus, it can also not be fully excluded. Long-term data are needed to confirm this. Patients will be followed up till 15 years.

Nusinersen[27, 46]

The safety assessment of nusinersen was based on two phase 3 clinical studies in infants (ENDEAR) and children (CHERISH) with SMA, together with one Phase 2 study in infants and children with SMA (CS7) and open-label studies including presymptomatic infants (NURTURE) genetically diagnosed with SMA and infants and children with SMA. Of the 346 patients who received nusinersen up to a maximum of 5 years, 258 patients received treatment for at least 1 year.

Overall, 101 SAEs were reported in 16 nusinersen subjects (80%). SAEs reported with the highest frequency were respiratory in nature, which is consistent with the natural history of Type I SMA: SAEs were most frequently reported in the respiratory, thoracic, and mediastinal disorders SOC (46 events [45.5%] in 15 subjects [75%]) and the infections and infestations SOC (44 events [43.6%] in 13 subjects [65%]), the majority of which were respiratory in nature. Less common were cardiac disorders (5 events [5.0%] in 3 subjects [15%]), metabolism and nutrition disorders and nervous system disorders (2 events [2.0%] in 2 subjects each [10%]), and gastrointestinal disorders and musculoskeletal and connective

tissue disorders (1 event each [1.0%] in 1 subject each [5%]). None of the SAEs were considered related to study treatment or related to the LP procedure.

Five of the 20 nusinersen subjects died as a result of SAEs that were either accidental or consistent with the rapid natural progression of Type I SMA. None of the deaths or SAEs was considered related to study treatment by the Investigator.

Table 15. Unfavourable effects of OA compared with nusinersen in SMA patients

	OA[2]	nusinersen[46]
Most frequent	Transaminases increased, thrombocytopenia, vomiting, pyrexia, aspartate aminotransferase increased, alanine aminotransferase increased, troponin-I increased	Headache, vomiting, back pain*
Serious	Pneumonia, hydrocephalus±, increased transaminases	-

* Adverse events considered related to the lumbar puncture procedure. These events can be considered manifestations of post-lumbar puncture syndrome. ±This SAE was determined possibly related to OA by the site investigator

Post-marketing experience OA
Three cases of thrombotic microangiopathy (an acute and life-threatening condition characterised by thrombocytopenia, haemolytic anaemia and acute kidney injury) following administration of OA are described in literature to date. These 3 case reports indicate a plausible association between onasemnogene abeparvovec with TMA based on their temporal association. Of note, TMA has been reported following treatment with other gene therapies using an adeno-associated vector.

Post-marketing experience nusinersen
Adverse reactions have been identified during post-approval use of nusinersen. Among patients treated with nusinersen by lumbar puncture, serious infection, such as meningitis, has been observed. Communicating hydrocephalus, aseptic meningitis and hypersensitivity (e.g. angioedema, urticarial and rash) have also been reported. The frequency of these reactions is not known as they have been reported from the post marketing setting.

Incidence treatment-related adverse events.
Treatment-emergent adverse events (TEAEs) related to the study treatment are reported for 56 of the 97 (57.7%) OA treated patients. No adverse events that can (possibly) be attributed to the treatment were reported in the pooled infantile onset nusinersen treated patients. Most serious adverse events in nusinersen treated patients were inherent to the disease. A **RR of 115.00 (95% CI: 7.21, 1853.49)** was calculated by the assessment group. In appendix 7 the GRADE evidence profile can be found.

Grade conclusion:
Treatment with OA versus nusinersen results in a statistically significant effect on the incidence of treatment-related adverse events and given the magnitude of the effect this is considered **[evidence of very low quality]** clinically relevant, but the CI is extremely wide which makes the effect estimator is very uncertain

48 of the 100 (48%) pooled OA treated patients experienced a serious adverse

event (SAE). 77 of the 100 (77%) patients in the pooled infantile onset nusinersen treated patients experienced a SAE.

In 2 of 97 OA treated patients (2%) are TEAEs reported that resulted in death. One patient died due to respiratory failure possibly not related to OA and probably to the disease. The cause of death of the second patient was most likely due to hypoxic/ischemic brain damage due to respiratory tract infection requiring artificial ventilation. Respiratory insufficiency is a known feature of SMA Type 1. For nusinersen 17 patient deaths were reported in the 100 in the pooled infantile onset patients. It is not clear if these death were treatment-emergent.

Discontinuation due to adverse events
Treatment-Emergent Adverse Events (TEAEs) causing study discontinuation are reported for 3 of the 97 (3.1%) OA treated patients. In 16 of the 100 patients treated with nusinersen an adverse event was leading to discontinuation of treatment. When an indirect comparison is made, a **RR of 0.19 (0.06, 0.62)** is calculated by the assessment group. Treatment with OA vs nusinersen will result in 1.3 less (from 1.5 less to 0.61 less) patients per 10 patients treated with OA vs. nusinersen discontinuing due to adverse events.

Grade conclusion:
Although treatment with OA versus nusinersen results in a statistically significant decrease on the chance of discontinuation due to adverse events, it is unclear **[evidence of very low quality]** whether this effect is clinically relevant.

3.4.1 Other considerations

Currently there is no experience with the intravenous use of OA in patients with a bodyweight above 13.5 kg and it might be associated with additional risks due to the high amount of viral vector. If the use of gene therapy for this population is deemed appropriate, it should only be performed under a rigorous protocol and close safety monitoring, and after having carefully considered the other approved therapeutic options[8].

3.4.2 Discussion unfavourable effects

The single treatment arm clinical study design makes it difficult to disentangle whether an adverse event is due to treatment with OA, due to accompanied corticosteroid use, due to SMA type 1 or its complications or due to naturally occurring background childhood diseases. From the RCT ENDEAR of nusinersen it was concluded that the majority of AEs and SAEs reported in subjects exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA. Although a RCT for OA is not available, it is plausible that the same applies to the reported AEs and SAEs in the OA trials. Nevertheless almost half (48%) of the OA treated patients experienced treatment-emergent adverse events unknown/possibly/probably or definitely related to the OA treatment. It should be noted that since OA is a single-dose infusion, discontinuation of the drug is not possible.

Two (2) of the children in the OA studies died after the administration of OA and 1 patient experienced an event (permanent ventilation) and withdrew consent soon after. Death has also been reported in other AAV gene therapy trials. Available data suggest that treatment with OA is well tolerated by very young children, but children receiving OA should be treated with high doses of prednisone to prevent liver failure. Much about OA and AAV vector use in general is still unknown, particularly regarding long-term side effects. Intensive monitoring of safety is of

great importance in children treated with OA as highlighted in the European consensus document[8].

As a one-time treatment, any immunogenic adverse events associated with administration of OA will only occur for a short period. This is an advantage compared to chronic administration (e.g. for nusinersen).

Conclusions on clinical safety
From the available safety data can be concluded that OA will result in more treatment-related adverse events than treatment with nusinersen. Although the number of serious adverse events, whether or not related to the treatment seem to be lower when treated with OA versus nusinersen, the data remains very limited due to the short follow-up. It has to be kept in mind that it is not clear if these adverse events are reported in a comparable way. The CHMP concluded that OA and nusinersen had at least a comparable safety profile

The long-term follow up of the adverse events of OA are unknown. The adverse events related to the immune response are not likely to have long term safety consequences. However, the long-term safety of gene expression is less clear. Though the carcinogenicity risk is considered low as AAV vectors mainly do not integrate in the host genome as compared to e.g. lentivirus, it can also not be fully excluded. Much about OA and AAV vector use in general is still unknown, particularly regarding long-term side effects. Intensive monitoring of safety is of great importance in children treated with OA. Treated patients will be followed up till 15 years.

3.5 Experience

The experience with OA is shown in table 16.

Table 16. Experience with OA compared with nusinersen in SMA patients

	OA	*nusinersen*
limited: < 3 years on the market or < 100,000 prescriptions (not-chronical indication)/20,000 patient years (chronical medication)	X	X
sufficient: ≥ 3 years on the market, and > 100,000 prescriptions/20,000 patient years		
broad: > 10 years on the market		

Onasemnogene abeparvovec (Zolgensma®) was approved by the EMA in May 2020 and nusinersen (Spinraza®) in May 2017.

3.6 Applicability

Extended information on applicability is available in the SmPC's of OA and nusinersen. This paragraph only mentions the most important differences in applicability between the medicines.

Contra-indications
Both OA and nusinersen are contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Specific groups

- Renal impairment: Both OA and nusinersen have not been studied in patients with renal impairment. The safety and efficacy in patients with renal impairment has not been established in both products but treatment in these patients is not excluded for either one.
- Hepatic impairment: Both OA and nusinersen have not been studied in patients with hepatic impairment.

Interactions

- OA: Based on the mechanism of action, occurrence of clinically-significant drug-drug interactions following OA administration is unlikely. Therefore drug-drug interactions have not been evaluated. Experience with use of concomitant 5q SMA targeting agents such as nusinersen is limited.
- Nusinersen: No interaction studies have been performed. In vitro studies indicated that nusinersen is not an inducer or inhibitor of CYP450 mediated metabolism. In vitro studies indicate that the likelihood for interactions with nusinersen due to competition for plasma protein binding, or competition with or inhibition of transporters is low.

Warnings and precautions

- Pre-existing immunity against AAV9: Anti-AAV9 antibody formation can take place after natural exposure. There have been several studies on the prevalence of AAV9 antibodies in the general population that show low rates of prior exposure to AAV9 in the paediatric population. Patients should be tested for the presence of AAV9 antibodies prior to infusion with OA.
- Advanced SMA: Since SMA results in progressive and non-reversible damage to motor neurons, the benefit of OA in symptomatic patients depends on the degree of disease burden at the time of treatment, with earlier treatment resulting in potential higher benefit. While advanced symptomatic SMA patients will not achieve the same gross motor development as unaffected healthy peers they may clinically benefit from gene replacement therapy, dependent on the advancement of disease at the time of treatment. The treating physician should consider that the benefit is seriously reduced in patients with profound muscle weakness and respiratory failure, patients on permanent ventilation, and patients not able to swallow. The benefit/risk profile of OA in patients with advanced SMA, kept alive through permanent ventilation and without the ability to thrive is not established.
- Immunogenicity: Systemic immune response, including immune-mediated hepatotoxicity, has been reported in the OA clinical program.
- Hepatic injury: Several warnings are given for OA, i.e.: administration of AAV vector may result in transaminase elevations, which may be serious; acute serious liver injury has occurred; patients with pre-existing liver impairment or acute hepatic viral infection may be at higher risk of liver injury.
- Thrombocytopenia and abnormal coagulation: Cases of thrombocytopenia and abnormal coagulation have been seen after subcutaneous administration or intravenous administration of antisense oligonucleotides. Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in OA trials.
- Elevated troponin-I: Increases in cardiac troponin-I levels following infusion with OA were observed.
- Shedding: Temporary OA shedding occurs, primarily through bodily waste. Caregivers and patient families should be advised on the following instructions for the proper handling of patient stools.
- Lumbar puncture: The lumbar puncture procedure of nusinersen can have unfavourable effects (headache, back pain, vomiting). In addition,

implementation of the procedure in young, paediatric patients and in patients with scoliosis are difficult.
- Nephrotoxicity: Cases of nephrotoxicity have been seen after subcutaneous and intravenous administration of antisense oligonucleotides.
- Elevated troponin-I: Increases in cardiac troponin-I levels following infusion with OA were observed.

Clinical experts in the Netherlands have expressed their concerns about the use of OA in children >13.5 kg. This leads to dosages that have never been applied to humans before. Treatment of these groups of children should therefore be carried out only in trial settings as stated in the EU consensus document as well.

Conclusion
Given the severity of the condition, the applicability OA is acceptable. OA is a single-dose gene therapy with limited safety data, there are no outstanding applicability problems identified.

3.7 Usability

The usability of OA is shown in table 17.

Table 17. Usability of OA compared with nusinersen in SMA patients

	OA	*nusinersen*
Route of administration	Intravenous injection	Intrathecal via lumbar puncture
Administration frequency	Single-dose	4 loading doses distributed in 9 weeks, followed by maintenance treatment 1x / 4 months.

Nusinersen treatment is associated with significant burden for the patient since it requires lifelong intrathecal injection, which is associated with safety risks. In addition, the mode of administration of OA (single intravenous infusion) and dose regime (only once) was considered a clinically relevant advantage as compared to the repeated intrathecal injections of nusinersen by the CHMP.

4 Final assessment

4.1 Discussion on relevant aspects

Symptomatic type 1 patients
The relative effectiveness of OA compared with nusinersen is highly uncertain given the lack of direct comparative evidence and the heterogeneity in clinical trials used for the naïve indirect treatment comparison. Less patients have been studied compared to nusinersen. The indirect comparison suggested that OA is at least associated with comparable effects on overall survival and has possibly more effect on event-free survival (survival without permanent assisted ventilation) compared with nusinersen at 18 months of time on study. For the mobility outcome CHOP-INTEND score, a statistically significant difference was observed in favour of OA when compared to nusinersen, but clinical relevance has not been conclusively demonstrated. Nusinersen treated patients seem to be more affected at start of treatment, based on differences in CHOP-INTEND and ventilation support at baseline. Follow-up data from the nusinersen studies are much longer than the immature data from the OA studies. A convincing added benefit of OA versus nusinersen cannot (yet) be concluded. Further the robustness of a naïve unanchored comparison is problematic in determining benefit objectively.

All estimated effects of OA on survival, event (ventilation) free survival and the mobility outcomes are substantial and within the standards of clinical relevance. The Beneluxa assessment team considers the beneficial effects of OA to be clinically relevant compared to best supportive care. However, more information on both number of patients and follow-up time is needed to assess the maintenance of the treatment effect.

Presymptomatic patients
None of the OA and nusinersen presymptomatic treated patients experienced an event of permanent ventilation or death so far. Therefore, the effect of both products on this outcome measure seem to be comparable. In addition, the results on the motor milestones and CHOP-INTEND score of OA and nusinersen treated patients point in the same direction. However, the follow-up of the patients in the OA SPR1NT trial is much shorter with median follow-up <15 months of age vs. 35 months in the latest nusinersen data cut. A longer follow-up is needed in order to draw conclusions about milestones that still need to be met. An equal or added benefit of OA versus nusinersen in pre-symptomatic patients cannot be concluded based on these immature presymptomatic trials.

Presymptomatic patients with two copies of SMN2
In the absence of data to determine benefit in presymptomatic patients, it could be the case that the effectiveness of OA in symptomatic patients is at least similar in pre-symptomatic patients with 2 copies of SMN2. The results of the latest, unpublished data cut of June 2020 suggests at least 4-5 of the patients are developing within the normal range of healthy children measured by the standing and walking alone milestones of the WHO. But there are also patients staying behind in development. Three (3) of the 14 treated presymptomatic patients did not develop the motor milestone sitting without support, although they exceeded the upper bound of the normal development window. Only longer term follow-up can conclude whether these children will indeed continue to lag behind healthy children.

Presymptomatic patients with three copies of SMN2
More variation on the course of the disease is seen in patients with three copies of SMN2. A significant proportion of patients who go on to develop SMA type 1 have three copies of the SMN2 gene and, in the ongoing prospective Dutch population-based prevalence cohort, up to 50% of patients with three copies of the SMN2 gene have SMA type 1c or 2a which mean they will suffer from very severe disease. Hence, there is a strong clinical rationale to provide an active therapy in pre-symptomatic patients with three SMN2 copies. Patients with type 2 SMA will never learn to walk and their life expectancy is still limited to 20-40 years. With the introduction of nusinersen in the treatment regime of SMA patients, the prognosis of patients with 3x SMN2 improved. Treatment with nusinersen in patients with 3x SMN2 (both symptomatic and pre-symptomatic treated patients) is effective. Conclusive evidence of the effectiveness of OA in SMA patients with 3 copies of SMN2 has not yet been provided. SPR1NT is ongoing and includes 15 presymptomatic patients with 3 SMN2 copies. The results from the latest unpublished June 2020 data cut suggests most children in this cohort can sit without support within or slightly behind the normal development window. But the data is still immature as more than half of the patients are too young to make conclusions on group level on the development of the milestones walking and standing alone. 8/15 are able to walk and/or stand alone within the normal window of development. The 7/15 patients that did not achieve these milestones are still under the upper age boundary of the normal developmental window. These latest unpublished data cut represent only the effects within a median follow-up age of 15.2 (range: 3.3 – 21.1) months. Nusinersen generated evidence of effectiveness in these patients with a much longer follow-up (median 35 months). The data from the 15 patients with 3 SMN2 copies treated with OA is immature to the extent that no firm conclusions can be drawn regarding efficacy. Longer follow-up data are needed to draw conclusions about the relative effect of OA versus nusinersen in these patients.

Based on the mechanism of action, the more mature data from the symptomatic treated patients is an indication for the longer term efficacy of OA in the presymptomatic patients. It is widely supported in i.e. the EU consensus document that presymptomatic children with SMA will benefit even more from active treatment than patients that already experienced symptoms of the disease.
Together with the arguments that it is not possible to distinguish between presymptomatic patients with 2 or 3 copies of SMN2 based on the data an added benefit of OA versus best supportive care for the pre-symptomatic SMA patients with 2 **and** 3 SMN2 copies is concluded. Although direct evidence is lacking and only long-term follow-up studies can find out what the magnitude of the added benefit is of OA in presymptomatic patients.

Maintenance of the treatment effect
There is evidence of AAV-delivered transgene durability in clinical programs of Parkinson disease, haemophilia B that demonstrate persistence for 5-15 years in nonhuman primates and up to 4 years in humans[34]. The biological hypothesis is that there is no reason for any loss of the inserted gene once it is in place however this should be borne out in the clinical evidence via the outcomes achieved.

In the clinical trial programme thus far, no direct loss of treatment effect in terms of losing developed milestones, is observed after infusion with OA. The studies demonstrate that patients are possibly maintaining or achieving new motor milestones at a follow up to 5.6 years of age and 5.2 years post-dose. The evidence of the life-long expression of SMN protein and associated treatment effects must however result from the long-term follow-up studies.

Safety

From the available safety data it seems that OA will result in more treatment-related adverse events than treatment with nusinersen. Although the number of serious adverse events, whether or not related to the treatment seem to be lower when treated with OA versus nusinersen, the data remains very limited due to the short follow-up. The burden of treatment with OA should however not be underestimated. Available data suggest that treatment with OA is well tolerated by very young children, but children receiving OA should be treated with high doses of prednisone to prevent liver failure.

The long-term follow up of the adverse events of OA are unknown. The adverse events related to the immune response are not likely to have long term safety consequences. However, the long-term safety of gene expression is less clear. Though the carcinogenicity risk is considered low as AAV vectors mainly do not integrate in the host genome as compared to e.g. lentivirus, it can also not be fully excluded. Much about OA and AAV vector use in general is still unknown, particularly regarding long-term side effects. Intensive monitoring of safety is of great importance in children treated with OA. Treated patients will be followed up till 15 years.

4.2 Final conclusion

The Beneluxa assessment team (Zorginstituut Nederland, the Belgian CRM and the Irish NCPE) conclude that onasemnogene abeparvovec (Zolgensma®) is considered established medical science and medical practice in the treatment of symptomatic SMA type 1 patients. The mechanism of action, the wide consensus about the advantages of presymptomatic treatment and the fact that possibly more than half of the patients with 3 copies of SMN2 will develop very severe disease is considered sufficient to conclude established medical science and medical practice for OA in presymptomatic SMA patients with 2 or 3 copies of the SMN2 gene. There is insufficient evidence to draw a conclusion on the comparative benefit of OA compared with nusinersen.

Appendix 1: Search strategy

Search strategy literature

The literature search has been performed in PubMed (15) with the search terms: ((Onasemnogene abeparvovec OR onasemnogene abeparvovec-xioi OR Zolgensma OR AVXS-101) OR nusinersen OR Spinraza OR IONIS-SMN$_{Rx}$ OR ISIS-SMN$_{Rx}$)) AND (spinal muscular atrophy OR SMA) [CLINICAL TRIALS] and the Cochrane Library (42) on the 5th of November 2020 with the search terms: ((Onasemnogene abeparvovec OR onasemnogene abeparvovec-xioi OR Zolgensma OR AVXS-101) OR nusinersen OR Spinraza OR IONIS-SMN)) AND (spinal muscular atrophy)

Appendix 2: Included studies

First author, year of publication	Study design, class of evidence, follow-up	Patient number	Patient characteristics	Intervention and control	Relevant outcome measures	Comments
OA trails						
START (CL-101) Al-Zaidy et al. 2019[32] Mendell et al. 2017[35] Lowes et al. 2019[47]	Phase I, single-centre, open-label, dose escalating study, dose-finding study Follow-up: 2 years post-dose. First patient enrolled: 05 May 2014, last patient completed: 14 Dec 2017.	N=3 (low-dose cohort) N=12 (therapeutic dose cohort)	Symptomatic SMA type 1 genetically defined by bi-allelic SMN1 mutations (deletion/point mutations) 2x SMN2 disease onset <6 months ≤6 months of age at time of treatment	OA one-time intravenous infusion - Cohort 1 received a low dose 6.7×10^{13} vg/kg - Cohort 2 received a therapeutic dose 2.0×10^{14} vg/kg‡	- Safety outcomes - Event-free Survival ¶ Additional: - CHOP-INTEND - development milestones	
STR1VE-EU (CL-302) EPAR[2]	Phase III open-label, single-arm trial Follow-up: 18 months of age	N=33	Symptomatic SMA type 1 genetically defined by bi-allelic SMN1 mutations (deletion or point mutations) 1x / 2x SMN2 ≤6 months of age at time of treatment	OA one-time intravenous infusion 1.1×10^{14} vg/kg	- Milestone development sitting without support Additional: - Survival	Ongoing, data-cut 31 December 2019

First author, year of publication	Study design, class of evidence, follow-up	Patient number	Patient characteristics	Intervention and control	Relevant outcome measures	Comments
STR1VE-US (CL-303) Clinical study report with data cut 22 April 2020	Phase III open-label, single-arm Trial Follow-up: 18 months of age	N=22	Symptomatic SMA type 1 genetically defined by bi-allelic SMN1 mutations (deletion or point mutations) 1x / 2x SMN2 ≤6 months of age at time of treatment	OA one-time intravenous infusion 1.1×10^{14} vg/kg	- Milestone development sitting without support - Survival Additional: - % of subjects maintaining the ability to thrive - % of patients independent of ventilator support	Ongoing, data-cut 22 April 2020
SPR1NT (CL0304) EPAR[2]	Phase III, open-label, single-arm study Follow-up 18 months (cohort 1) 24 months (cohort 2)	N=14 (cohort 1: 2x SMN2 cohort) N=15 (cohort 2: 3x SMN2 cohort)	Presymptomatic SMA type 1 or 2 genetically defined by bi-allelic SMN1 mutations (deletion/point mutations) 2x / 3x SMN2 ≤6 weeks (≤42 days) of age at time of treatment	OA one-time intravenous infusion 1.1×10^{14} vg/kg Age appropriate milestones in healthy population PNCR natural history comparison (SMN2 3x)	• Cohort 1 2x SMN2: % patients achieving milestone independent sitting for at least 30 sec. additional: - Survival - Weight • Cohort 2 3x SMN2: % patients achieving the ability to stand without support for at least 3 sec. additional: - achieving ability to walk alone	Ongoing, data-cut 31 December 2019
LT-001 Al-Zaidy et al. 2019[32]	Long-term (15 years) follow-up of START	3 (Cohort 1 [low-dose]) 10 (Cohort 2 [therapeutic dose])	See START	dosed in START	medical history, physical examinations, clinical laboratory evaluations,	Ongoing

First author, year of publication	Study design, class of evidence, follow-up	Patient number	Patient characteristics	Intervention and control	Relevant outcome measures	Comments
LT-002	Long-term (15 years), safety follow-up study in patients with SMA type 1 who were treated with OA IV or IT in STR1VE EU, STR1VE-US or SPR1NT and other AveXis trial.	Planned: N=~308 IV cohort N=~ 83 IT cohort N=~225	Symptomatic SMA type 1 genetically defined by bi-allelic SMN1 mutations (deletion or point mutations) 1x / 2x / 3x SMN2 ≤6 months of age at time of treatment	OA (Study drug was not administered in LT-001 as patients were IV or IT dosed in the previous AveXis trials)		Ongoing
Nusinersen trials in type 1 SMA						
NURTURE De Vivo et al. 2018 [40] EPAR[46] NICE STA[33] *(ongoing)*	open-label, single-arm trial Phase 2	N=25 N=15 (cohort 1: 2x SMN2) N=10 (cohort 2: 3x SMN2)	Presymptomatic SMA type 1 or 2 genetically defined by bi-allelic SMN1 mutations (deletion/point mutations) 2x / 3x SMN2 ≤6 weeks (≤42 days) of age at time of treatment	Nusinersen intrathecal Administration of 12 mg (2,4 mg/ml) op dag 1, 15, 29, 64, 183 and 302	-% responders on milestone events (HINE-2); -event free-survival -survival Additional: CHOP-INTEND, WHO criteria, grow parameters	Ongoing Study completion: January 2022
ENDEAR Finkel et al. 2017[38] EPAR[46]	Double-blind, sham-controlled RCT phase 3; follow-up ±13 months; range 6-442 d.*; ITT	N=121 (ITT=80:41)	SMA type 1 ; 5q SMA (2x SMN2); age ≤7 mnd; SMA onset ≤6 mnd	Nusinersen intrathecal Administration of 12 mg (2,4 mg/ml) on day 1, 15, 29, 64, 183 and 302 vs. placebo (sham**)	-% responders on milestone events (HINE-2); -event free-survival -survival Additional: CHOP-INTEND; EFS; CMAP	

First author, year of publication	Study design, class of evidence, follow-up	Patient number	Patient characteristics	Intervention and control	Relevant outcome measures	Comments
SHINE Finkel et al. 2018[39] NICE STA[33] *(ongoing)*	Open-label extension of ENDEAR, single-arm trial	N=89	Infantile and later onset SMA (type 1, 2 and 3)	Nusinersen		Ongoing Study completion: August 2022
Historic control studies (not included in search flow-chart)						
PNCR Finkel et al. 2014a[7] EPAR[2]	retrospective and prospective natural history cohort	N=23	SMA type 1; 5q SMA (2x SMN2) SMA onset ≤6 mnd enrolment between May 2005 to April 2009	-	Event-free survival, motor milestones	
NeuroNext Kolb et al. 2017[16] EPAR[2]	Longitudinal, multi-centre, prospective natural history cohort	N=16	SMA onset ≤6 mnd, enrolment between 14 December 2012 and 10 September 2014	-	Survival defined as alive without tracheostomy, CHOP-INTEND, CMAP	

ITT= Intention-to-treat population, defined as all randomized subjects administered at least one dose of study medication; HINE-2=Hammersmith Infant Neurological Exam-Part 2; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder; HFMSE= Hammersmith Functional Motor Scale Expanded; PedsQL= Paediatric Quality of Live Inventory; ULM= Upper Limb Module

§ External datasets from SMA natural history studies (PNCR and NeuroNext) are used to provide an external control comparator.

* Follow-up was 13 months; although nusinersen treatment was only 10 months, the exposure to nusinersen can be considered longer due to the long-half-life of the product. The study was ended prematurely after a planned interim-analysis with positive outcomes on improvement on milestones ('cut-off' was on 15 June 2016, on which 80 patients had reached day 183. The last end date are the safety data on 21 November prior to the last patient visit. Median follow-up was 280 days for nusinersen and 187 days for sham). Of the 80 patients in the nusinersen-arm, 26 completed the study during the follow-up and 39 by the prematurely ending of the study. Of the 41 patients in the sham-control-arm 11 completed the study during the follow-up and 13 by the prematurely ending of the study. These patients were then transferred to an open label study. ** The sham treatment was a fake epidural, in which there was only a superficially placed a needle in the same place as after a real epidural with placing the same patch (plaster).

¶ ¶ Defined as time from birth to either (a) 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 (b) death. This is described as a co-primary endpoint but is treated, statistically, as a secondary endpoint.

Appendix 2: Overview of excluded studies

First auteur, year of publication	**Reason of exclusion**
Montes et al 2019[48]	Other outcome measure. (Post hoc analyses were used to examine changes in 6-minute walk test (6MWT) distance and fatigue in children and adolescents with SMA type II and III who received their first dose of nusinersen in the phase Ib/IIa, open-label CS2 study and were ambulatory during CS2 or the extension study, CS12)
Chiriboga et al. 2016[28]	Other intervention (Risdiplam) (JEWELFISH)
Darras et al. 2019[49]	No clinical trial (biomarker study)
Aragon-Gawinska et al.[50]	Expanded Excess program nusinersen
Mercuri et al. 2018[51]	SMA type 2 and 3 (CHERISCH)
EMBRACE	Symptomatic SMA patients with 3 copies of SMN2, no results published
CS1 Darras et al. 2019a[52]	SMA type 2 and 3
CS2/CS12 Darras et al. 2019b[52]	SMA type 2 and 3
CS10 Darras et al. 2019a[52]	SMA type 2 and 3
Ramos et al. 2019[53]	No intervention
Haché et al. 2016[54]	Other outcome measure (lumbar puncture experience in children with spinal muscular atrophy during a phase 1 open-label study of nusinersen and its extension)
Ohmura et al. 2018[55]	Article in Japanese
Bishop et al. 2018[56]	Examination of the feasibility of assessing motor milestone performance of infants with spinal muscular atrophy (SMA) using the Hammersmith Infant Neurological Exam-Part 2 (HINE-2) in a phase 2 study of nusinersen
Stull et al.[57]	To calculate thresholds of meaningful change on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and Hammersmith Infant Neurological Examination (HINE) motor milestones in patients treated for infantile onset SMA. METHODS: Data from ENDEAR, a phase 3 randomized, double-blind, multicentre, sham-procedure-controlled clinical trial were analysed.

Williams et al. 2019[58]	Identify patients with later-onset SMA who responded to treatment and calculated a threshold of meaningful change in Expanded Hammersmith Functional Motor Scale (HFMSE) scores. Targeted analyses were conducted to estimate MCIDs and responder definitions for the HFMSE for later-onset SMA. METHODS: Data from CHERISH, a phase 3 randomized, double-blind, multicentre, sham procedure-controlled clinical trial of later-onset SMA were analysed.

Appendix 3: Overview of used guidelines

Organisation, ref	Datum	Title
EMA[1]	2020	Summary of Product Characteristics (SmPC) onasemnogene abeparvovec (Zolgensma®)
EMA[2]	2020	European Public Assessment Report (EPAR) onasemnogene abeparvovec (Zolgenma®)
EMA[27]	2017	Summary of Product Characteristics (SmPC) nusinersen (Spinraza®)
EMA[46]	2017	European Public Assessment Report (EPAR) nusinersen (Spinraza®)
Wang et al.[25]	2007	Consensus Statement for Standard of Care in Spinal Muscular Atrophy
Mercuri et al.[26]	2018	Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care
Finkel et al.[39]	2018	Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics
Muscle disease the Netherlands (*Spierziekten Nederland*)[3]	2018	Dutch guideline SMA Type 1
Kirschner et al.[8]	2020	European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy

Appendix 4: Baseline characteristics

Trials in symptomatic SMA type 1 patients with up to 3 copies of SMN2, follow-up studies LT-001 and LT-002 are not taken into account.

Variable	**START/L-001** (CL-101)		**STR1VE-EU** (CL-302) *(ongoing)*	**STR1VE-US** (CL-303) *(ongoing)*	**ENDEAR**		**PNCR**	**NeuroNext**
SMA type	1		1	1	1		1	
SMN2 copies	2		2	2	2		2	2
	Low dose cohort	High dose cohort			Nusinersen	Sham		
N	3	12	33	22	81	41	23	16
Age at symptom onset (months) Mean (SD) Median	1.7	1.4 (1.00) (0-3)	NA	NA	7.9 (2-18) 6.5 weeks	9.6 (1-20) 8 weeks	3.0 (1.6) (range: 0.5-6)	NA
Age at baseline (months) Mean (SD) Median (min, max)	 6.3 5.9 (5.9, 7.2)	 3.4 3.1 (0.9, 7,9)	4.06	 3.7 (1.6) 3.5 (0.5, 5,9)	 5.4 (2.0-7.9)	 5.9	Age at enrolment: 29.0 (41.7) (2-171)	Age at enrolment: 4.1 (1.7) (0-6)
Female, n (%)	2 (66.7)	7 (58)	19 (57.6)	12 (54.6)	43 (54)	24 (59)	12 (52.2)	8 (50.0)
Race, n (%) White Black or African American Asian Other	 3 (100)	 11 (92) 1 (8.3)	NA	 11 (50) 3 (13.6) 2 (9.1) 6 (27.3)	NR	NR	 16 (69.6)	 15 (93.8)
Ethnicity, n (%) Not Hispanic or Latino Hispanic or Latino	 3 (100)	 10 (83.3) 2 (16.7)	NA	 18 (81.8) 4 (18.2)	NA	NA	 3 (13.0%)	 5 (31.3%)
Weight at baseline (kg) Mean (SD) Median (min, max)	 6.6	 5.7	NA	 5.8 (1.1) 5.8 (3.9, 7,5)	NA	NA	NA	NA
Length at baseline (cm) Mean (SD) Median (min, max)	NA	NA	NA	 61.3 (4.3) 61.6 (51,70)	NA	NA	NA	NA

Reported hospitalizations n (%)	NA	NA	NA	17 (77.3)	NA	NA	NA	NA
Reported swallowing thin liquid n (%)	0	4 (33.3)	NA	22 (100)	NA	NA	NA	NA
Reported ventilation support n (%)	3 (100)	2 (16.7)	NA	0 (0)	21/80 (26)	6/41 (15)	12/23 (52.2)	6/16 (37.5)
Ventilation support before 6 months of age.		10/12 (83.3)	NA	NA	NA	NA	21/23 (91.3)	10/16 (62.5)
Reported Nutrition support, n (%)	2/3	5/12 (43%)	NA	NA	NA	NA	18/23 (78.3)	7/16 (43.8)
Use of gastrointestinal tube, n (%)	NA	NA	NA	0	7/80 (9)	5/41 (12)	NA	NA
CHOP-INTEND Mean (SD) Median (min, max)	16.3 (6-27)	28.2 (12-50)	27.5 (14-55) 27.5	32.0 (9.9) 33.5 (17, 52)	26.63 (8.13)	28.43 (7.56)	24.6 (11.6) (5-40)	20.3 (7.3) (10-33)
Head control	NA		NA	2/22	NA	NA	NA	NA

NR: not reported. NA: not available

Baseline characteristics in presymptomatic SMA trials

Variable	**SPR1NT** *(ongoing)*			**NURTURE** *(ongoing)*	
SMA	Presymptomatic			Presymptomatic	
SMN2 copies	2	3	4	2	3
N	14	15	1	15	10
Female				7 (47)	6 (60)
Mean age at study onset (days) Median	20.6	28.7	36	22	
Age at first dose, days, n (%)					
≤14	NA	NA	NA	6 (40)	3 (30)
>14 and ≤28	NA	NA	NA	7 (47)	5 (50)
>28	NA	NA	NA	2 (13)	2 (20)
Median (range)	NA	NA	NA	19.0 (8-41)	23.0 (3-42)
Mean (SD)	NA	NA	NA	19.5 (9.29)	22.3 (12.45)
Female, n (%)	10 (71,4)	9 (60)	0	13 (52)	

Caucasian, n (%)	7 (50)	10 (66.7)	1 (100)	NR	
CHOP-INTEND Mean Median (range)	NA	NA	NA	 48.0 50.0 (25-60)	 53.8 56.0 (40-60)
HINE total motor milestones Mean Median (range)	NA	NA	NA	 2.5 3.0 (0-5)	 4.2 4.0 (2-7)

Appendix 5: Risk of Bias

The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews – Checklist for Case Series is used to determine the Risk of Bias[59].

Inclusion of observational studies/single-arm trials results in default **VERY SERIOUS** Risk of Bias.

Table 18. Risk of Bias

	PNCR	NeuroNext	START	STR1VE-US	ENDEAR/SHINE*
Were there clear criteria for inclusion in the case series?	Yes, but different from the NeuroNext study.	Yes, but different from the PNCR study.	yes	yes	yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	yes	yes	yes	yes	yes
Were valid methods used for identification of the condition for all participants included in the case series?	yes	yes	yes	yes	yes
Did the case series have consecutive inclusion of participants?	Unclear: "Inclusion of the patients ranged from May 2005 to April 2009"	Unclear "Enrolled between 14 December 2012 and 10 September 2014"	yes	yes	yes
Did the case series have complete inclusion of participants?	Unclear	Unclear	yes	yes	yes
Was there clear reporting of the demographics of the participants in the study?	yes	yes	yes	yes	yes
Was there clear reporting of clinical information of the participants?	yes	yes	yes	yes	yes
Were the outcomes or follow up results of cases clearly reported?	yes	yes	yes	yes	yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	yes	yes	yes	yes	yes
Was statistical analysis appropriate?	yes	yes	yes	yes	yes

*Since only the active arm of the ENDEAR/SHINE study is used in the analysis throughout this assessment, risk of bias is assessed with the JBI tool as well.

Appendix 6: GRADE evidence profile

GRADE Evidence profile of the naive indirect comparison between OA and nusinersen in **symptomatic** SMN patients with **two copies of SMN2**

Certainty assessment							Number of patients		Relative effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other	OA	nusinersen	Relative (95% CI)	Absolut (95% CI)		
CHOP-INTENT, mean change from baseline (follow-up: STR1VE-US 18 months after dosing START 24 months ENDEAR/SHINE 19 months)												
2 OA trials 1 nusinersen trial	Single-arm RCT	Very Serious[A]	Not serious	Serious[B]	Serious[C]		STR1VE-US (n=20): +19.3 (9.13) START (n=12): +25.4	ENDEAR/SHINE (n=32) [D] +14.0 (95% CI: 11.0, 17.5)	An SD for the ENDEAR/SHINE results is not applicable. If unknown SD is set as 8, SMD will be: 0.62 (0.05, 1.19)		⊕◯◯◯ VERY LOW	CRUCIAL
Number of patients reaching WHO motor milestone sitting without support (follow-up: START+STR1VE 18 months, 19 months ENDEAR/SHINE 19 months from Casto et al. 2020)												
2 OA trials 1 nusinersen trial	Single-arm RCT	Very Serious[A]	Not serious	Serious[B]	Serious[C]		START+STR1VE-US 20/34 (58.8%)	ENDEAR/SHINE 21/59 (36%)	RR of 1.65 (1.06, 2.58) [F]	2.31 more per 10 (from 0.21 more to 5.62 more)	⊕◯◯◯ VERY LOW	CRUCIAL
Number of patients reached the mortality or ventilator endpoint, median age (follow-up: 18 months)												
2 OA trials 1 nusinersen trial	Single-arm RCT	Very Serious[A]	Not serious	Serious[B]	Not serious		START+STR1VE-US 2/34 (5.9%) NR (7.8 – NR)	ENDEAR/SHINE [E] 40/63 (63.5%)	RR: 0.09 (0.02, 0.36) HR: 0.09 (0.02, 0.37) [G]	5.78 less per 10 (from 6.22 less to 4.06 less)	⊕◯◯◯ VERY LOW	CRUCIAL
Number of patients died, median age (follow-up: 18 months)												
2 OA trials 1 nusinersen trial	Single-arm RCT	Very Serious[A]	Not serious	Serious[B]	Not serious		START+STR1VE-US 1/34 (2.9%)	ENDEAR/SHINE [E] 17/56 (30.4%)	RR: 0.10 (0.01, 0.70) HR: 0.14 (0.02, 1.02) [G]	2.73 less per 10 (from 3.01 less to 0.91 less)	⊕◯◯◯ VERY LOW	CRUCIAL

Certainty assessment							Number of patients		Relative effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other	OA	nusinersen	Relative (95% CI)	Absolut (95% CI)		
Incidence treatment emergent adverse events related to study treatment (follow-up pooled OA: 14.21 (±5.48) months with a range of 1.8-25.7)												
4 OA trials 2 nusinersen trial		Very Serious[A]	Not serious	Serious[B]	Not serious		Pooled OA trials [H, I] 57/100 (57%)	Pooled infantile onset nusinersen trials: 0/100 (0%)	RR: 115 (7.21, 1853.49)	NC	⊕◯◯◯ VERY LOW	
Discontinuation due to treatment emergent adverse events (follow-up pooled OA: 14.21 (±5.48) months with a range of 1.8-25.7)												
4 OA trials 2 nusinersen trial		Very Serious[A]	Not serious	Serious[B]	Serious [J]		Pooled OA trials: 3/100 (3%)	Pooled infantile onset nusinersen trials: 16/100 (16%)	RR: 0.19 (0.06, 0.62)	1.30 less per 10 (from 1.5 less to 0.61 less)	⊕◯◯◯ VERY LOW	

CI: Confidence interval, **HR**: Hazard Ratio, **NA**: not available, **NR**: not reached, **NC**: not calculated, **TEAE:** treatment emergent adverse events
A Because of the observational/Single-arm character of the studies, the risk of bias is default assessed as very serious, see appendix 6 for the risk of bias table which leads to downgrading the certainty of evidence with 2 levels. At baseline, 12/23 (52.2%) in PNCR and 6/16 (37.5%) of patients in the historic cohort studies reported ventilation support. In the START study 2/12 (17%) patients reported ventilation support. In STR1VE-US none of the patients had ventilator support or nutritional support at baseline. In the historic cohorts 78.3% and 43.8% reported nutrition support in PNCR and NeuroNext respectively. This suggests that the patients in the historic control studies were more severely affected, which can result in bias and possible overestimation of the result of OA from this comparison.
B Since single-arm trials are indirectly compared with a historic cohort the evidence is indirect which leads to downgrading the certainty of evidence with 1 level
C Default limit of clinical relevance is exceeded by the CI (SMD of 0.5)
D These outcomes are estimated by the graph provided in the NICE assessment of nusinersen.
E Survival proportions were calculated by the applicant from the Kaplan-Meier curve published in the NICE STA. Proportions are based on number at risk at each time point.
F When only concerning STR1VE-EU vs. ENDEAR/SHINE: Calculated RR: 1.79 (1.12, 2.85)
G HR calculated by the applicant from the naive indirect treatment comparison Kaplan-Meier curves
H Serious TEAE: 48/100 (48%) TEAE resulting in death: 2/100 (97%)
I All patients treated with OA (also cohort one of START with sub-therapeutic OA and patients with >2x SMN2 from SPR1NT)
J Default limit of clinical relevance is exceeded by the CI (RR of 0.75)

GRADE Evidence profile of the naive indirect comparison between OA and natural history cohorts PNCR and NeuroNext in **symptomatic** SMN patients with **two copies of SMN2**

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other	OA	Natural history	Relative (95% CI)	Absolut (95% CI)		
CHOP-INTENT, mean change from baseline (follow-up: START: 24 months, STR1VE-US: 18 months, historic cohort: 14 months)												
2 OA trials 1 historic control	Single-arm Historic cohort	Serious[A]	Not serious	Serious[B]	Not serious		STR1VE-US (n=20)[C, D] START (n=12)	NeuroNext (n=10)	STR1VE-US: +19.3 (9.13) START: +25.4 NeuroNext: -10.7 (NA) [E] increase in the CHOP-INTENT scores in SMA type 1 patients from historic control were never seen	SMD STR1VE-US vs. NeuroNext: 3.61 (2.37, 4.85)	⊕⊕◯◯ LOW	CRUCIAL
Number of patients with CHOP-INTENT ≥40 (follow-up START: 2 year; STR1VE-US: 18 months; historic cohort: all data)												
2 OA trials 1 historic control	Single-arm Historic cohort	Serious[A]	Not serious	Serious[B]	Not serious		START [F]+STR1VE-US 32/34 (94.1%)	PNCR [G] 0/23 (0%)	RR: 44.57 (2.87, 693.27)	NC	⊕⊕◯◯ LOW	CRUCIAL
Number of patients reaching WHO motor milestone sitting without support (18 months, Historic cohort: all data)												
2 OA trials 1 historic control	Single-arm Historic cohort	Serious[A]	Not serious	Serious[B]	Not serious		START [H]+STR1VE-US [I]: 20/34 (58.8%) ST1VE-US (n=14): 12.6 (9.2, 18.6)	PNCR [J] 0/23 (0%)	RR: 28.11 [K] (1.78, 442.83)	NC	⊕⊕◯◯ LOW	CRUCIAL
Number of patients reached the mortality or ventilator endpoint, median age (follow-up: 14 months)												
2 OA trials 1 historic control	Single-arm Historic cohort	Serious[A]	Not serious	Serious[B]	Not serious		START+STR1VE-US [L] 2/34 (5.9%) NR (7.8 – NR)	PNCR 16/23 (69.6%) 9.5 (2.0 - 20.0)	RR: 0.08 [M] (0.02, 0.33)	6.4 less per 10 (from 6.82 less to 4.66 less)	⊕⊕◯◯ LOW	CRUCIAL

Certainty assessment							Number of patients		Effect		Certainty	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other	OA	Natural history	Relative (95% CI)	Absolut (95% CI)		
Number of patients died, median age (follow-up: 14 months)												
2 OA trials 1 historic control	Single-arm Historic cohort	Serious[A]	Not serious	Serious[B]	Not serious		START+STR1VE-US [N] 1/34 (2.9%) NR (7.8 – NR)	PNCR [O] 7/23 (30.4%%) 7.0((3.0 – 12.0)	Pooled calculated RR [P]: 0.10 (0.01, 0.73)	2.74 less per 10 (from 3.01 less to 0.82 less)	⊕⊕◯◯ LOW	CRUCIAL
Incidence treatment emergent adverse events related to study treatment (all data from patients treated with OA at the data cut of 31 December 2019)												
4 OA trials	Single-arm	NA	NA	NA	NA		57/100 (57%) [Q] Serious TEAE: 48/100 (48%) TEAE resulting in death: 2/100 (97%)	NC	NC	NC	NC	NC
Discontinuation due to treatment emergent adverse events (all data from patients treated with OA at the data cut of 31 December 2019)												
4 OA trials	Single-arm	NA	NA	NA	NA		3/100 (3%)	NC	NC	NC	NC	NC

CI: Confidence interval, **HR**: Hazard Ratio, **NA**: not available, **NR**: not reached, **NC**: not calculated, **TEAE:** treatment emergent adverse events
A Because of the observational/Single-arm character of the studies, the risk of bias is default assessed as very serious, which formally leads to downgrading the certainty of evidence with 2 levels. Because of the magnitude of the effects and the consistency of the effects throughout the different trials, it is decided to downgrade only with one level for risk of bias. (See appendix 6 for the risk of bias table). At baseline, 12/23 (52.2%) in PNCR and 6/16 (37.5%) of patients in the historic cohort studies reported ventilation support. In the START study 2/12 (17%) patients reported ventilation support. In STR1VE-US none of the patients had ventilator support or nutritional support at baseline. In the historic cohorts 78.3% and 43.8% reported nutrition support in PNCR and NeuroNext respectively. This suggests that the patients in the historic control studies were more severely affected, which can result in bias and possible overestimation of the result of OA from this comparison.
B Since single-arm trials are indirectly compared with a historic cohort the evidence is indirect which leads to downgrading the certainty of evidence with 1 level
C Pooled OA studies: +19.9 (±8.54) at a follow-up of 12 months after dosing
D STR1VE-EU *ongoing:* +13.3 (6.54) at a median duration of follow-up of 1.4 months (range: 6.9-18.6)
E This represents the mean decline observed between the 6 and 12 months of age. SD was not available so estimated at 5.2 from graph.
F START: 11/12 (91.6%)
G Supplementary control cohort NeuroNext 0/10 (0%) No patients achieved a CHOP-INTEND score >33 at or after the 6-months visit. No patient had an increase in score from baseline
H START: 10/12 (83.3%)
I Pooled OA trial: 34/81 (42%)) at a median age of follow-up of 14.21 months (1.8-25.7)
J Supplementary control cohort NeuroNext 0/10 (0%)
K STR1VE-US + PNCR :Calculated RR: 30.26 (1.91, 478.39)
L Pooled OA studies: 80/83 (96.4%) at a median age of follow-up of 14.21 months (1.8-25.7), STR1VE-EU *ongoing:* 32/32 (97.0%) at a median age of follow-up of 11.9 (1.8-15.4),
M STR1VE-US vs. PNCR gives a RR of 0.13 (0.03, 0.50)
N Pooled OA studies: 81/83 (97.6%) at a median age of follow-up of 14.21 months (range: 1.8-25.7), STR1VE-EU *ongoing:* 32/32 (97.0%) at a median age of follow-up of 11.9 (1.8-15.4)
O NeuroNext: 9/16 (56.3%) 7.0 (4.0 - 13.0)
P STR1VE-US + PNCR: Calculated RR: 0.15 (0.02, 1.12) – NOT STATISCAL SIGNIFICANT
Q All patients treated with OA (also cohort one of START with sub-therapeutic OA and patients with >2x SMN2 from SPR1NT)

Literature

1. EMA. SmPC Zolgensma.
2. CHMP. EPAR Zolgensma. 2020
3. Netherlands *S*-Amt. *Richtlijn spinale musculaire atrofie (SMA) type 1* - Dutch Guideline SMA Type 1 2018.
4. Russman BS, Iannaccone ST and Samaha FJ. A Phase 1 Trial of Riluzole in Spinal Muscular Atrophy. Arch Neurol. 2003; 60: 1601-3.
5. cord NdieabdfditIsmas. Soler-Botija, C. Brain 2002: 1624-34.
6. Bora G, Ayse YK, Can Ebru BK, et al. Recent therapeutic developments in spinal muscular atrophy. Turk J Med Sci 2018; 48: 203-11.
7. Finkel Rea. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology 2014: 810–7.
8. Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Eur J Paediatr Neurol 2020; 28: 38-43.
9. Kolb SJ and Kissel JT. Spinal Muscular Atrophy. Neurol Clin 2015; 33: 831-46.
10. Calucho M, Bernal S, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord 2018; 28: 208-15.
11. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis 2018; 5: 145-58.
12. Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol 2017; 81: 355-68.
13. Fujak A, Raab W, Schuh A, et al. Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. BMC Musculoskeletal Disorders 2013; 14: 283.
14. Wadman RI. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0–4. J Neurol Neurosurg Psychiatry 2017; 0.
15. Mercuri E, Bertini E and Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. The Lancet Neurology 2012; 11: 443-52.
16. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol 2017; 82: 883-91.
17. Cobben J, Lemmink H, Snoeck I, et al. Survival in SMA type I: a prospective analysis of 34 consecutive cases Neuromuscul Disord 2008; 7: 541-4.
18. Kay DM, Stevens CF, Parker A, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genetics in Medicine 2020; 22: 1296-302.
19. Dangouloff T, Burghes A, Tizzano EF, et al. 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, The Netherlands. Neuromuscular Disorders 2020; 30: 93-103.
20. Verhaart I, Robertson A, Leary R, et al. A multi-source approach to determine SMA incidence and research ready population. J neurol 2017; 264: 1465-73.
21. Glascock J, Sampson J, Connolly AM, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis 2020; 7: 97-100.
22. Boemer F, Caberg JH, Dideberg V, et al. Newborn screening for SMA in Southern Belgium. Neuromuscul Disord 2019; 29: 343-9.
23. Netherlands *G*-HCot. Neonatal screening for spinal muscular atrophy the Netherlands - Executive summary. 2019.
24. RIVM. Feasibility study into adding Spinal Muscular Atrophy (SMA) to the newborn blood spot screening. 2020. Accessed on 15 November 2020 via https://www.rivm.nl/publicaties/uitvoeringstoets-toevoeging-sma-aan-hielprik.
25. Wang C, Finkel R, Bertini E, et al. Consensus Statement for Standard of Care in Spinal

Muscular Atrophy. J child neurology 2007; 22: 1027-49.
26. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018; 28: 103-15.
27. EMA. SmPC Spinraza.
28. Chiriboga CA. JEWELFISH: Risdiplam (RG7916) increases SMN protein in non-naïve patients with SMA. 2018.
29. EMA. Briefing Document to the Clinical Trial Readiness in Spinal Muscular Atrophy (SMA) SMA Europe, TREAT-NMD and European Medicines Agency meeting. 2016.
30. Kolb SJ, Coffey CS, Yankey JW, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Annals of Clinical and Translational Neurology 2016; 3: 132-45.
31. WHO. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Pædiatrica 2006: 86-95.
32. Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. Pediatric Pulmonology 2018; 54: 179-85.
33. NICE. Single Technology Appraisal Nusinersen for treating spinal muscular atrophy [ID1069] - Committee Papers 14 August. 2018. Accessed via https://www.nice.org.uk/guidance/ta588/history.
34. Al-Zaidy SA and Mendell JR. From Clinical Trials to Clinical Practice: Practical Considerations for Gene Replacement Therapy in SMA Type 1. Pediatr Neurol 2019; 100: 3-11.
35. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Engl J Med 2017; 377: 1713-22.
36. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. The Lancet 2016; 388: 3017-26.
37. Shieh PB, Ascadi G, Mueller-Felber W, et al. Safety and Efficacy of Nusinersen in Infants/Childeren with SMA: part 1 of the Phase 2 EMBRACE study. Neurology 2018; 90.
38. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med 2017; 377: 1723-32.
39. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord 2018; 28: 197-207.
40. De Vivo DC, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord 2019; 29: 842-56.
41. NovartisGeneTherapies < Data on file > PNCR NeuroNext Report. 2018.
42. NovartisGeneTherapies < Data on file > Clinical Study Report (CSR) v2. STR1VE-US Zolgensma 2020. 2020.
43. Castro D, Finkel R, Farrar M, et al. Nusinersen in Infantile-onset Spinal Muscular Atrophy: Results from Longer-term Treatment from the Open-label SHINE Extension Study (1640). Neurology 2020; 94.
44. NICE. Nusinersen for treating spinal muscular atrophy - Chair's presentation 6 March 2019 - Slides for the public – redacted. 2019.
45. Wijngaarde CA, Stam M, Otto LAM, et al. Muscle strength and motor function in adolescents and adults with spinal muscular atrophy. Neurology 2020; 95: e1988-e98.
46. CHMP. EPAR Spinraza. 2017.
47. Lowes LP, Alfano LN, Arnold WD, et al. Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy. Pediatr Neurol 2019; 98: 39-45.
48. Montes J, Dunaway Young S, Mazzone ES, et al. Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy. Muscle Nerve 2019; 60: 409-14.
49. Darras BT, Crawford TO, Finkel RS, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. Ann Clin Transl Neurol 2019; 6: 932-44.
50. Aragon-Gawinska K, Seferian AM, Daron A, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: A cohort study. Neurology 2018; 91: e1312-e8.

51. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med 2018; 378: 625-35.
52. Darras BT, Chiriboga CA, Iannaccone ST, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. Neurology 2019; 92: e2492-e506.
53. Ramos DM, d'Ydewalle C, Gabbeta V, et al. Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. J Clin Invest 2019; 129: 4817-31.
54. Hache M, Swoboda KJ, Sethna N, et al. Intrathecal Injections in Children With Spinal Muscular Atrophy: Nusinersen Clinical Trial Experience. J Child Neurol 2016; 31: 899-906.
55. Ohmura T, Saeki S, Ogiwara K, et al. Pharmacological and clinical profile of spinal muscular atrophy (SMA) therapeutic drug nusinersen (Spinraza ®). Nihon Yakurigaku Zasshi 2019; 152: 147-59.
56. Bishop K, Montes J and Finkel R. Motor milestone assessment of infants with spinal muscular atrophy using the hammersmith infant neurological Exam—Part 2: Experience from a nusinersen clinical study. Muscle & Nerve 2017; 57: 142-6.
57. Stull D, Williams V and Houghton K. Minimal clinically important differences in motor function in patients with infantile-onset spinal muscular atrophy: results from the phase 3 endear trial. Journal of managed care and specialty pharmacy 2019; 25.
58. Williams V, Stull D, Houghton K, et al. Minimal clinically important differences of the expanded hammersmith functional motor scale in later-onset spinal muscular atrophy: results from the phase 3 cherish trial. Journal of managed care and specialty pharmacy 2019; 25.
59. JBI. Critical Appraisal tools for use in JBI Systematic Reviews – Checklist for Case Series. 2020. Accessed on 15 November 2020

Zorginstituut Nederland

Farmaco-economisch rapport voor onasemnogene abeparvovec (Zolgensma®) bij de behandeling van SMA type 1- samenvatting van review rapport door NCPE

onderdeel van de initiële beoordeling van specialistische geneesmiddelen

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Samenvatting (Dutch summary)

Hoofdpunten

- De kosteneffectiviteit is bepaald voor een subgroep patiënten van de geregistreerde indicatie; symptomatische SMA type 1 patiënten.
- Pre-symptomatische patiënten worden geïncludeerd in een scenario-analyse, als een kosten-minimalisatie analyse.
- De behandeleffecten van onasemnogene abeparvovec (OA) zijn waarschijnlijk overschat door beperkingen van enkel-armige studies en keuzes in het model zoals gemaakt door de registratiehouder. Voornamelijk met betrekking tot lange termijn effecten/voordelen. De meerwaarde van OA ten opzichte van nusinersen kan nog niet bepaald worden gegeven het ontbreken van vergelijkende effectiviteitsdata.
- Gegevens over de kwaliteit van leven ontbreken voor de patiëntengroep; de aannames voor de beste (B status aanname is perfecte gezondheid) en slechtste toestand (D en E status aanname is een utiliteit van 0) zijn erg onzeker en lijken in het voordeel van onasemnogene abeparvovec omdat patiënten in deze behandelarm naar de betere gezondheidstoestanden gaan en de patiënten in de nusinersen behandelarm naar de slechtere toestanden gaan.
- De kosten gerelateerd aan SMA zijn hoog en de keuzes hierin verschillen tussen de landen zonder robuuste rationale; de prijs van nusinersen en de vervolgbehandelingen met nusinersen hebben een grote invloed op de ICER.
- De alternatieve base case schatting van de ICER laat zien dat OA niet kosteneffectief is versus nusinersen of best ondersteunende zorg (BSC); de ICER varieert van €202.001 per QALY voor België, €263.389 per QALY voor Nederland en €298.469 per QALY voor Ierland versus nusinersen. Er is door de registratiehouder onvoldoende onderzoek gedaan naar de onzekerheid rondom de effectiviteitsschattingen.
- De netto budget impact van onasemnogene abeparvovec (Zolgensma®) bedraagt in jaar 3 circa €4,5 miljoen in Ierland, circa €11 miljoen in Nederland en €12,4 miljoen in België. Deze budgetimpact is sterk afhankelijk van de gekozen populatie en de kosten en aannames rondom nusinersen gebruik.

Uitgebreide samenvatting

Het farmaco-economisch rapport is uitgevoerd in het kader van het Beneluxa Initiatief, bestaande uit Zorginstituut Nederland (ZIN), de Belgische Commission Reimbursement of Medicines (CRM) en de Irish National Centre for Pharmacoeconomics (NCPE). Verder in het document worden zij aangeduid als de 'review groep'. De NCPE beschrijft de door de registratiehouder ingediende kosteneffectiviteitsanalyse en budgetimpact analyse van onasemnogene abeparvovec (OA, Zolgensma®) vergeleken met nusinersen, en best ondersteunende zorg (BSC). Omdat nusinersen de standaard behandeling is geworden in alle drie de landen, wordt BSC als secundaire analyse bekeken in het rapport, als een optie wanneer er contra-indicaties bestaan tegen nusinersen. Novartis Gene Therapies vraagt vergoeding aan voor alle symptomatische SMA type 1 patiënten, en pre-symptomatische SMA patiënten met tot 3 kopieën van het SMN2 gen. Dit is een subgroep van de geregistreerde indicatie zoals goedgekeurd door de EMA. De kosteneffectiviteitsanalyse zoals ingediend door de registratiehouder heeft betrekking op een kleinere groep, patiënten met symptomatische type 1 SMA die zijn gediagnosticeerd en behandeld vóór de leeftijd van 6 maanden. Er is een

scenario analyse gedaan voor patiënten met pre-symptomatische SMA. Het gezondheidszorgperspectief is gebruikt voor alle landen. Het maatschappelijk perspectief is gebruikt in de base case analyse voor Nederland en als een scenario voor Ierland.
Een cohort Markov state-transition model werd ontwikkeld rond drie aspecten van de ziekte; functionele motorische mijlpalen, ondersteuning bij beademing en de overleving of tijd tot dood. Het model bevat vijf gezondheidstoestanden, gedefinieerd op basis van motorische status i.e. A status (binnen de range van normale ontwikkeling), B status (lopen zonder hulp), C status (zitten zonder hulp), D status (niet kunnen zitten) en E status (permanente beademing). Alhoewel er vijf stadia in het model zijn geïncludeerd, neemt de base case analyse slechts vier van deze stadia mee (B tot en met E). In het model wordt aangenomen dat het effect van OA aanwezig blijft gedurende het hele leven en dat het effect van nusinersen alleen optreedt voor de duur van de chronische behandeling. Klinische trial data tot ongeveer 36 maanden worden gebruikt voor de initiële kortdurende fase in het model. Input voor de lange termijn in het model is gebaseerd op aannames en extrapolaties van overleving en functionele mijlpalen. Er zijn enkele kritische punten met betrekking tot de modelstructuur: de cyclusduur, incorrecte toepassing van de half-cyclus correctie en de afwezigheid van vervolgbehandelingen na OA of nusinersen.
Behandeleffecten worden gemodelleerd voor ‘sterfte’, ‘permanente beademing’ (E status), en het bereiken van de motorische mijlpalen ‘zitten zonder hulp’ (C status) en ‘lopen’ (B status). Er wordt aangenomen dat het bereiken van de mijlpalen ‘zitten’ en ‘lopen’ geassocieerd zijn met verbeteringen in levensverwachting. Data voor BSC zijn gebaseerd op de natuurlijk beloop studie NeuroNext. OA behandeleffect wordt gebaseerd op de START (n=12) en STR1VE-US (n=22) en voor nusinersen worden de ENDEAR en lange termijn SHINE studies gebruikt voor effectiviteit. Het gebruik van resultaten uit verschillende studies met verschillen in baseline patiëntenkenmerken, verschillende prognoses, en leeftijd bij start van de behandeling zorgt voor onzekerheden in het economische model. De toepassing van de verschillende natuurlijk beloop studies en de methoden om deze in het model te combineren zijn een extra onzekerheid in het model. Verschillen tussen studiepopulaties om de behandeleffecten mee te bepalen zorgen voor bias in de schattingen van relatieve effectiviteit in het economische model. De registratiehouder gebruikt een wegingsmethode om de OA trial data aan te passen voor de vergelijking met nusinersen. Maar deze methode kan niet de verschillen tussen de studies oplossen en de vergelijking met nusinersen is waarschijnlijk nog steeds gebiased.
Aangenomen wordt dat patiënten die stoppen met nusinersen een erg slechte prognose hebben i.e. 90% gaat achteruit binnen een jaar; patiënten in de OA groep verslechteren niet. De review groep vindt dat er veel tekortkomingen zijn in de manier waarop de registratiehouder de behandeleffecten meeneemt in het model. Veel van de gemaakte keuzes hebben enorme invloed op de kosteneffectiviteits-uitkomsten en zijn in het voordeel van OA.
De primaire uitkomstmaat van het model is het aantal voor kwaliteit van leven gecorrigeerde gewonnen levensjaren (QALYs). Er is echter weinig bekend over de gezondheidsgerelateerde kwaliteit van leven (HRQoL) in de betreffende populatie. Er werden geen HRQoL data gemeten in de SMA type 1 klinische trials voor OA of nusinersen. Er worden een aantal HRQoL studies binnen het spectrum van SMA typen beschreven en aangemerkt door de registratiehouder. Deze studies rapporteren een brede range van utiliteiten voor dezelfde gezondheidstoestanden. Verschillen ontstonden door de verschillende HRQoL instrumenten en meetmethoden die gebruikt werden, verschillen in populaties bij wie de utiliteiten werden gemeten (e.g. patiënten, of ouder/arts proxies) en verschillen in de patiënten populatie. In het model doet de registratiehouder extreme aannames voor

de E status en B status utiliteit (nul kwaliteit van leven voor de E status, en kwaliteit van leven gelijk aan de algemene bevolking voor de B status); ouder-proxy resultaten van een SMA Type 1 patiënten cohort uit de UK (n=7, gemiddelde utiliteit = 0,19) wordt gebruikt voor de D status; en een UK klinische expert utiliteitsschatting (0,6) in een algemeen SMA cohort die zonder hulp kunnen zitten wordt gebruikt voor de C status. De aanpak van de registratiehouder om utiliteiten te selecteren is inconsistent. Overall, vindt de review groep dat er veel onzekerheid bestaat over de utiliteiten zoals gebruikt in het model. Dit komt door afwezigheid van data uit de juiste populaties, en door de methodologische uitdagingen van het meten van utiliteiten bij een jonge populatie.
In het model zitten geneesmiddelkosten en toedieningskosten voor OA en nusinersen, en zorgkosten van BSC voor SMA. De apotheek lijstprijs voor OA is €1.945.000. In de base case analyse worden de zorgkosten voor SMA type 2 en type 3 gebruikt als proxies voor de zorgkosten van behandelde patiënten. De review groep heeft hierover de mening van clinici gevraagd en zij gaven aan dat kinderen met SMA type 1 die behandeld waren met OA andere complicaties en onderliggende biologische kenmerken hebben, en later ernstiger kunnen zijn dan onbehandelde patiënten met SMA type 2.
De basis voor de zorgkosten in het model is een UK healthcare resource use study (HCRU study), uitgevoerd door Novartis Gene Therapies. Deze studie werd uitgevoerd om de HCRU kosten gerelateerd aan BSC voor SMA patiënten in de UK te bepalen. Dit werd gevalideerd door clinici, maar hier zijn maar beperkte data van gepresenteerd door de registratiehouder. In België bleken deze kosten veel lager dan in Nederland en Ierland. Er is veel onzekerheid over de in het model gebruikte SMA zorgkosten, door een gebrek aan beschikbare data, onzekerheid in de langetermijn uitkomsten van patiënten behandeld met OA en nusinersen en gebrek aan transparantie in de gebruikte methode om de kosten te schatten door de registratiehouder. De review groep heeft deze kosten aangepast door andere meer toepasselijke bronnen te gebruiken (Klug et al.). De kosten uit de studie van Klug et al. liggen ook meer in de buurt van de kosten die gebruikt worden voor de Belgische base case analyse.
De niet-medische kosten in het model zijn voornamelijk gebaseerd op een studie uit de VS over de indirecte economische impact van SMA op families. Hierin worden verkregen niveaus van onderwijs van SMA patiënten beschreven (en omgezet naar potentieel inkomen gebaseerd op Nederlandse/Ierse inkomens en percentage van beroepsbevolking). Verder wordt in de studie het verloren inkomen van familieleden (direct omgezet van USD naar Nederlandse/Ierse euro's o.b.v. PPP voor 2010) beschreven. Het Nederlandse rapport voor vergoeding van nusinersen werd gebruikt om de directe medische kosten voor nusinersen te bepalen in het model. De kosten in het nusinersen rapport zijn echter veel hoger (vooral voor de C status) dan die beschreven door de registratiehouder. Er bestaat veel onzekerheid over de niet-medische kosten die in het model worden gebruikt; vooral omdat er gebruik wordt gemaakt van data uit de VS om de kosten van Nederland en Ierland te bepalen.
Overeenkomstig de richtlijnen in elk land zijn de disconteringspercentages voor uitkomsten 4% (Ierland) en 1,5% (België en Nederland), en voor kosten 4% (Ierland en Nederland) en 3% (België).
De incrementele analyse van de registratiehouder suggereert dat OA domineert ten opzichte van nusinersen i.e. dat OA minder kost en effectiever is. Dit zorgt voor een besparing tussen €9.943 en €26.881 bij de drie landen voor elke extra QALY. De review groep deed een alternatieve base case analyse waarin verschillende aanpassingen werden gedaan. In deze analyse wordt ervan uitgegaan dat een deel van de patiënten die behandeld worden met OA, daarna ook nog met nusinersen behandeld gaan worden, gebaseerd op data uit de LT-001 studie. Verder wordt in deze analyse gebruik gemaakt van de SMA zorgkosten en niet-medische kosten uit de studie van Krug et al. Deze analyse resulteert in ICERs van €202.001, €263.389,

en €298.469 per gewonnen QALY voor respectievelijk België, Nederland en Ierland. Dus dan is OA niet meer dominant over nusinersen. De ICERs van OA ten opzichte van BSC bedragen €286.413 per QALY voor België, €352.095 per QALY voor Nederland en €387.717 per QALY voor Ierland. De resultaten zijn sterk afhankelijk van de aannames die worden gedaan over vervolgbehandeling met nusinersen na OA.

De registratiehouder presenteert verschillende multiple deterministische one-way en multi-way gevoeligheids- en scenario analyses, waarbij OA dominant blijft ten opzichte van nusinersen. De review groep merkt op dat de gevoeligheidsanalyses te beperkt zijn om inzicht te geven in de onzekerheid van de model inputparameters en hun invloed op de kosteneffectiviteit. Dit komt vooral door de vele kritische aannames die in het model gedaan worden over behandeleffecten, zorgkosten en utiliteiten. Dit wordt niet voldoende zichtbaar gemaakt in one-way/multiway gevoeligheidsanalyses. De probabilistische gevoeligheidsanalyse (PSA) en expected value of perfect information (EVPI) analyse zijn niet bruikbaar, omdat de registratiehouder daarin niet de onzekerheid omtrent de behandeleffecten meeneemt, een key driver van het model.

Het aantal te behandelen patiënten werd verschillend berekend voor België en Nederland en Ierland voor de vergoedingsclaim. De Belgische schatting bevat alle incidente en prevalente type 1 patiënten en voor Ierland en Nederland worden alleen de incidente patiënten meegenomen door de registratiehouder. De review groep includeerde alle patiënten en in België worden de patiënten die voor behandeling in aanmerking komen geschat op circa 13 in jaar 1, in Nederland circa 15 en in Ierland 4 patiënten. Als er gekeken wordt naar de populatie voor de volledige geregistreerde indicatie (dus ook type 2 en 3 patiënten) dan zijn de patiënten aantallen respectievelijk circa 32, 51 en 21. De netto budget impact bij gebruik van de review groep aantallen is dan €20,4m, €22,3m en €7,1m in jaar 1 voor België, Nederland en Ierland voor de vergoedingsclaim. Als de prijs van nusinersen verlaagd wordt en nusinersen vervolgbehandelingen worden meegenomen dan dalen de kosten van nusinersen flink en wordt de budgetimpact groter.

De review groep vindt de kosteneffectiviteitsschattingen erg onzeker. De schattingen zoals berekend door de registratiehouder zijn vaak gebiased in het voordeel van OA en de reviewgroep vindt het bewijs voor de keuzes die worden gemaakt te zwak. Daarom, gebaseerd op de kosteneffectiviteitsschattingen zoals berekend door de review groep, vinden zij OA geen kosteneffectieve behandeling versus BSC of nusinersen.

National Centre for Pharmacoeconomics
NCPE Ireland

NCPE Assessment Report

Drug:	Onasemnogene abeparvovec (Zolgensma®)
Therapeutic indication:	Spinal muscular atrophy
Applicant Company:	Novartis Gene Therapies (formerly AveXis)
Date of completion:	02 April 2021

In collaboration with the Beneluxa Initiative on Pharmaceutical Policy

Beneluxa Initiative on Pharmaceutical Policy

Report content

This report outlines the background to the decision problem, documents the evidence submitted to the Beneluxa Initiative by the Applicant, and presents the outcomes of the NCPE Review Group's assessment of the submission and additional evidence. This report was produced in collaboration with Zorginstituut Nederland and the Belgium CRM, as part of the Beneluxa Initiative.

Results specified by the applicant as "commercial-in-confidence" or "academic in confidence" have been highlighted throughout the report.

Table of Contents

Abbreviations

A&E	Accident and emergency department
AAV	Adeno-associated virus
AAV9	Adeno-associated viral vector serotype 9
ABF	Activity Based Funding
AE	Adverse event
APR-DRG	All Patients Refined Diagnosis-Related Group
BCFI	The Belgian Centre for Pharmacotherapeutic Information
BIM	Budget impact model
BSC	Best supportive care
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence interval
CPI	Consumer price index
CSO	Central Statistics Office
EFS	Event-free survival
EQ-5D	EuroQol-5 Dimensions
ESS	Effective sample size
EU	European Union
EUR	European Monetary Unit
EVPI	Expected value of perfect information
FAS	Full analysis set
FDA	Food and Drug Administration
GBP	British pound sterling
GDP	Gross domestic product
GP	General practitioner
HCC	Half cycle correction
HCRU	Healthcare resource use
HINE	Hammersmith Neurological Examinations
HPO	Healthcare Pricing Office

HRQoL	Health-related quality of life
HSE	Health Service Executive
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
INAMI	Institut National d'Assurance Maladie-Invalidité
ITC	Indirect treatment comparison
IT	Intrathecal
KOL	Key opinion leader
MAIC	Matching-adjusted indirect comparison
NCPE	National Centre for Pharmacoeconomics
NIHDI	National Institute for Health and Disability Insurance
NIV	Non-invasive positive pressure ventilation
OA	Onasemnogene abeparvovec
OECD	Organisation for Economic Co-operation and Development
OS	Overall survival
PAV	Permanent assisted ventilation
PCRS	Primary Care Reimbursement Service
PNCR	Pediatric Neuromuscular Clinical Research
PPP	Purchasing Power Parities
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trials
RIZIV	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering
SD	Standard deviation
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
UK	United Kingdom

US	United States
US ICER	United States Institute for Clinical and Economic Reviews
VAT	Value added tax
WTP	Willingness-to-pay
ZIN	Zorginstituut Nederland

Tables

Key points

- Cost effectiveness has been modelled for a subset of the reimbursement claim; symptomatic SMA type 1 patients.
- Pre-symptomatic patients are included as a scenario however this is mainly included as a cost minimisation analysis.
- Treatment benefits of onasemnogene abeparvovec are likely overestimated due to limitations with single arm studies and choices in modelling made by applicant, in particular in relation to long term benefit. The added benefit of OA over nusinersen is not established given the lack of comparative effectiveness data.
- There is a lack of data on HRQoL in this patient group; the assumptions in relation to the best (B state assumed perfect health) and worst health states (D and E states assumed utility of 0) are extreme and highly uncertain.
- The costs associated with SMA are large and the choices in relation to these differed between countries without robust rationale; the price of nusinersen and the subsequent use of nusinersen all have a large impact on the ICER.
- The alternative base case calculation of ICER indicates that OA is not cost effective when compared to nusinersen or BSC; ICER ranges €202,001 to €298,469 vs nusinersen. There was inadequate exploration by the applicant of uncertainty associated with the key drivers of cost-effectiveness i.e. assumptions underpinning treatment effectiveness.

- The net budget impact in year 1 ranges from €7.0m and €22.1m and is heavily dependent on the population chosen and the costs and assumptions around nusinersen use.

Executive Summary

In this Pharmacoeconomic report undertaken as part of the Beneluxa Initiative, including Zorginstituut Nederland (ZIN: the National Healthcare Institute), the Belgian Commission Reimbursement of Medicines (CRM) and the Irish National Centre for Pharmacoeconomics (NCPE), the NCPE describe the Applicant's submission of evidence on cost effectiveness and budget impact of onasemnogene abeparvovec (OA, Zolgensma®) compared with nusinersen, and with best supportive care (BSC). As nusinersen has become the established standard of care in all three countries, BSC is considered a secondary comparator in the report, likely to be considered an option only if there are clear contraindications to nusinersen. However given the substantial uncertainty associated with the comparative effectiveness with nusinersen it is recognised that the comparison with BSC is an important one.

Novartis Gene Therapies submitted a reimbursement claim for all symptomatic SMA type 1 patients, and pre-symptomatic SMA patients with up to three copies of the SMN2 gene. This is a subset of the licence approved by the EMA. The submission of cost effectiveness evidence was in support of a smaller population than both the targeted population by Novartis Gene Therapies and the EMA licence population: OA for the treatment of patients with symptomatic type 1 SMA who are diagnosed and treated before 6 months of age. A scenario analysis is included for patients with presymptomatic SMA. The perspective is that of the healthcare payer for all countries. The societal perspective is presented as the base case for the Netherlands and is provided as a scenario for Ireland.

A cohort Markov state-transition model was largely constructed around three aspects of the disease; functional motor milestones, ventilation status (need for permanent ventilation) and the survival or time to death. The model incorporates five health states, defined by motor status i.e. A (Within a broad range of normal development), B state (walks unassisted), C state (sits unassisted), D state (not sitting) and E state (permanent assisted ventilation). While five states are included in the model, the base case only incorporates four of these states (B to E). The model assumes for OA that that the benefit is maintained for life whereas the benefit of nusinersen is only for the duration of the chronic treatment. Clinical trial data up to approximately 36 months is used to inform the initial short term phase of the model and inputs for the long term model are informed by assumptions and extrapolations of survival and functional milestones. There are a number of structural limitations to the model including the length of model cycle, inappropriate application of the half cycle correction and lack of sequential treatment options after either OA or nusinersen.

Treatment effects are modelled for death, permanent assisted ventilation (E state), and the attainment of motor milestones of independent sitting (C state) and walking (B state). It is assumed that attainment of sitting and walking are associated with improvements in life expectancy. Data for BSC was informed by natural history studies NeuroNext. OA treatment effectiveness was informed by START (n=12) and STR1VE-US (n=22) and for nusinersen, ENDEAR and the long term SHINE study inform effectiveness. The use of outcomes from separate studies with differences in patient populations at baseline, differing prognoses, and age at treatment initiation introduces considerable uncertainty to the economic model. The applicability of the

various natural history studies and methods of combining these in the model is an additional source of uncertainty. Differences between study populations used to inform treatment effects will likely bias estimates of relative effectiveness from the economic model. The Applicant applies a weighting approach to adjust OA trial data in the comparison with nusinersen. However, this is unlikely to account for differences between studies and the resulting nusinersen comparison is likely still biased. Patients who discontinue from nusinersen are assumed to have a very pessimistic prognosis i.e. 90% regress within one year; no patients on OA disimprove. The review group considers that there are many shortcomings associated with the approaches taken by the Applicant in relation to treatment effectiveness. Many of the choices made heavily influence the outcome of cost effectiveness and are favourable for OA.

The primary health outcome of the model is the quality adjusted life year (QALY). There is a lack of evidence on health-related quality of life (HRQoL) data in the target population. No HRQoL data were measured in the SMA type 1 clinical trials for OA or nusinersen. A number of studies measuring HRQoL across the spectrum of SMA types were identified by the Applicant, reporting a wide range of utilities for the same health states. Variation arose from the HRQoL instruments and measurement methods used, the population from which utilities were drawn (e.g. patients, or parent/clinician proxies) and the target patient population. In the model, the Applicant made extreme assumptions for the E state and B state utility (zero quality of life for the E state, and quality of life of the general population for the B state); used parent-proxy results from an SMA Type 1 patient cohort in the UK (n=7, mean utility 0.19) for the D state; and a UK clinical-expert elicited estimate of utility (0.6) in

a general SMA cohort who can sit unassisted for the C state. The Applicant's approach to selecting utility values was inconsistent. Overall, the Review Group considers that there is significant uncertainty associated with the health state utility values used in the model, due to the scarcity of data in the population of interest, and due to the methodological challenges of utility valuation in young children.

The model included drug acquisition and administration costs for OA and nusinersen, and healthcare costs associated with BSC in SMA. The price to wholesaler/chemist (Ptw/c) for OA is €1,945,000. The model base case uses healthcare resource use costs for SMA type 2 and SMA type 3 patients managed with BSC alone as proxies for pharmacotherapy treated SMA type 1. Clinical opinion obtained by the Review Group indicated that infants with SMA 1 treated with OA would be likely to have different complications and underlying biology, and possibly greater severity, compared with untreated patients with SMA 2.

A UK healthcare resource use study (HCRU study), conducted by Novartis Gene Therapies to determine the HCRU costs associated with BSC for SMA patients in the UK, formed the basis for the healthcare costs used in the model. A validation exercise was conducted with clinicians. Limited details of the validation exercise were provided, though it appears that validation was not strongly received in Belgium given the use of significantly lower costs in the model than the Irish and Dutch costs. There is significant uncertainty associated with SMA healthcare costs in the model, due to a lack of available data on existing patients treated with BSC or nusinersen, uncertainty in the nature of future outcomes for patients treated with OA or nusinersen, and a general lack of transparency in the methods used by the Applicant to calculate costs. The review group adjusted these costs using more

suitable reference sources (Klug et al.). Costs based on the Klug et al study are closely aligned with Belgian base case costs and are significantly lower than Dutch and Irish base case costs.

Societal costs in the model were largely based on a study conducted in the United States on the indirect economic impact of SMA on families, which reported levels of education attainment for patients with SMA (converted to potential income based on Dutch/Irish income levels and employment rate) and lost family income (directly converted from USD to Dutch/Irish euros using the PPP for 2010). Direct medical costs were reportedly adapted from the Dutch reimbursement report for nusinersen for the Dutch model. However, the costs in the nusinersen report are significantly higher, particularly for the C state, than reported by the Applicant. As with the SMA healthcare costs in the model, there is significant uncertainty associated with SMA societal costs in the model, largely due to the Applicant's methods of adapting data from the US to the Netherlands and Ireland. This approach was not justified by the Applicant and is not considered to be an appropriate method of calculating societal costs for these countries.

In line with national guidelines in each country, the discount rates for outcomes were 4% (Ireland) and 1.5% (Belgium and the Netherlands), and the discount rates for costs were 4% (Ireland and the Netherlands) and 3% (Belgium).

Incremental analysis of costs and benefits in the Applicant's base case suggested that OA dominated nusinersen i.e. that OA is less costly and more effective, providing a saving of between €9,943 and €26,881 across the three countries for every additional QALY of benefit. An alternative base-base analysis was conducted by the Review Group, incorporating alternative plausible assumptions to fully explore the

potential cost effectiveness of OA in the modelled population. This analysis included treatment with nusinersen in a proportion of patients after OA, reflecting real-world usage observed in the LT-001 study, and updated healthcare costs based on the study by Klug et al. Contrary to the Applicant's base case, the alternative base case analysis suggested that OA is more costly and more effective than nusinersen, costing €202,001, €263,389, and €298,469 for Belgium, Netherlands and Ireland, respectively, for every additional QALY of benefit. In the comparison with BSC, OA was also more costly and more effective, costing €286,413, €352,095 and €387,717 for Belgium, Netherlands and Ireland, respectively for every additional QALY of benefit.

The Applicant presented multiple deterministic one-way and multi-way sensitivity and scenario analyses, in which OA remained dominant compared with nusinersen. However, the Review Group considers that the Applicant's sensitivity analysis is limited in its ability to meaningfully capture uncertainty in the model inputs and their impact on cost effectiveness. This is largely due to the number of critical assumptions which have been made in the model regarding treatment effectiveness, source of health-state costs and utilities, and the use of proxies, which have not been addressed in one-way/multiway sensitivity analysis. Likewise, the Applicant's probabilistic sensitivity analysis (PSA) and expected value of perfect information (EVPI) analysis are not meaningful, given the exclusion of uncertainty in treatment effects, a key driver of the model.

The number of eligible patients was calculated differently between Belgium and the Netherlands and Ireland for the reimbursement claim. The Belgian estimate correctly included all incident and prevalent type 1 patients whereas for Ireland and

Netherlands only the incident type 1 patients were included. The review group included all and in Belgium the eligible patients for year 1 were 12.53 and in Netherlands 15.10 and in Ireland 3.96. If the full licensed population (including type 2 and 3) was considered the numbers would increase by 31.70, 50.65 and 21.36 respectively. The five year cumulative net drug budget impact associated with the Reimbursement Claim, using the review group's estimates was €74.4m and €26.2m for Netherlands and Ireland respectively. The corresponding three year cumulative net drug budget impact for Belgium was €47.9 million. Costs are highest in years one to two given then number of prevalent patients potentially eligible for treatment. When reduced cost of nusinersen and subsequent nusinersen use is taken into account the cost offsets reduce considerably and the budget impact increases.

The review group considers the estimates of cost effectiveness to be highly uncertain. The estimates calculated by the applicant are, in most cases, biased in favour of OA and the review group considers the evidence used to support many of these choices to be poor. We consider that the case in support of cost effectiveness has not been robustly made.

1. The decision problem and model structure

1.1. Population

The population included within the licence issued by the European Medicines agency includes all patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. Therefore, the population to be modelled should include all patients who fall under this categorisation.

The applicant submitted a reimbursement claim for all symptomatic SMA type 1 patients, and pre-symptomatic SMA patients with up to three copies of the *SMN2* gene. However, the applicant has primarily modelled a subset of this licence; patients who are symptomatic with type 1 SMA who are assumed to be diagnosed and treated before 6 months of age. The model therefore excludes presymptomatic patients with SMA type 1, patients with SMA type 1 who are treated after 6 months of age, and patients with SMA type 2 or SMA type 3 with up to 3 copies of the SMN2 gene. Further patients who are already on nusinersen who may subsequently switch to OA are not included in the model.

A scenario analysis is included for presymptomatic patients. Clinical opinion has indicated that all patients with SMA types covered by the licence would be considered for treatment with OA. There was a clinical preference to initiate treatment in the presymptomatic phase as this was considered to offer the best outcome for children with this severe type of SMA.

Processes for the identification of patients who are eligible for treatment differs between the three countries. Newborn screening is in place in Southern Belgium as a

pilot and will be introduced in the Netherlands in the next two years. Newborn screening is expected to identify patients who are presymptomatic, based on a laboratory test. Routine screening is not in place in Ireland and diagnosis is made firstly on the basis of clinical assessment, followed by confirmatory laboratory testing or via just laboratory test if a sibling has previously been diagnosed with SMA. The complexities of diagnosis and treatment based on a laboratory test were discussed with clinicians and this was also described in the European Consensus Paper which advises that the number of copies of SMN2 is the most important predictor of clinical severity and age of onset (1). "Currently, SMN2 copy number is the best available predictor of disease severity, even if limitations of the predictive value remain". It is noted that some inaccuracies have been observed in the laboratory tests identifying the number of SMN2 gene copies (2). The impact of an inaccurate diagnosis has not been considered in the cost effectiveness model or the budget impact model. From a modelling perspective, if a patient with slightly less severe disease is treated (e.g. type 2) the amount of benefit accrued is less, relative to a more severe patient.

1.2. Intervention

OA is administered as a single-dose intravenous slow infusion over approximately 60 minutes. The dose is a nominal 1.1 x 1014 vg/kg. The total volume is determined by patient body weight. All patients should be screened for antibodies to the viral vector (AAV9) in advance. Where the titre is >50 OA should not be given.

1.3. Comparators

Two comparators are considered in the model: Best supportive care (BSC) and nusinersen.

BSC includes standard respiratory, gastrointestinal, and nutritional care for patients with SMA, delivered via a multidisciplinary team. While the dossier states that BSC is only given in combination with the treatments, the model includes an option for BSC as a stand-alone comparator. As nusinersen has become the established standard of care in SMA type 1, it is likely that BSC will only be considered an option if there are clear contraindications to nusinersen (e.g. severe scoliosis or surgical interventions which would make intrathecal injection difficult or impossible).

Nusinersen is an antisense oligonucleotide, targeting SMN2 so that it creates more functional SMN protein. It is indicated for the treatment of 5q Spinal Muscular Atrophy. It is administered by intrathecal injection as early as possible after diagnosis with four loading doses of 12 mg on Days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter. It is continued as long as benefit is obtained and there are specific start and stop criteria for its use in place in Ireland; formal assessments occur just before dose 7 (year 2 in the model) and every 4 months thereafter for non-sitter, sitter and ambulatory patients with SMA type 1–3. If no improvement can be seen based on different scoring systems (e.g. CHOP-INTEND, HFMSE) during the formal assessment, patients should discontinue treatment. The only stopping rule in place in Belgium is if the child moves to permanent ventilation. While there are no formal stopping rules in the Netherlands permanent assisted ventilation is an informal rule for discontinuing. An annual discontinuation rate of 3% is assumed in the model for nusinersen.

A scenario in which nusinersen is given after OA is not modelled. The Applicant has provided data from long term follow up studies LT-001 (N=13) which indicate that 40-50% of patients who received OA are now on subsequent therapy with

nusinersen (4/10 who received the higher dose in phase I/IIa study and all three patients who received the lower dose in this study are on nusinersen). It is noted that nusinersen was regulatory approved in the US at the time while OA was still an investigational agent. Clinical opinion from Ireland also noted that if a child was to become symptomatic and deteriorate after receiving OA, subsequent treatment with nusinersen would be considered. Clinical opinion from the Netherlands acknowledges that subsequent treatment e.g. nusinersen or risdiplam is likely to be a development over time. However it was also highlighted that there is no clear evidence on an additional effect and that such practices should be confined to clinical trial settings, as also recommended by the Consensus statement published by Kirscher et. al 2020. The assessment team considers that the cost of subsequent treatments should be considered in the cost effectiveness and budget impact estimates, as access to such studies in the future is currently unknown, and it is possible that costs may still be borne by the healthcare payer.

1.4. Model type and structure

The model is based on that of the US Institute for Clinical and Economic Review (US ICER), published in April 2019 which provided an evidence report of OA and nusinersen for SMA (3). However, the US ICER modelled three distinct groups in separate models; infantile-onset (type 1) SMA; later-onset (type 2 and 3) SMA; and presymptomatic SMA as distinct from one group in the applicant's model.

A cohort Markov state-transition model models patients over a lifetime horizon who have SMA type 1 who are symptomatic and <6months old (Figure 1). The model is largely constructed around three aspects of the disease; functional motor milestones, ventilation status (need for permanent assisted ventilation) and the

survival or time to death. Functional motor milestones and survival are correlated and is generally improved while on treatment. However the duration of effect on OA is life-long, but on nusinersen it is for the duration of the chronic therapy.

The model consists of two stages; the first is the short term model incorporating the data from the clinical trials (approx. 36 months) and the second is the long term model which is informed by assumptions and extrapolations of survival and functional milestones.

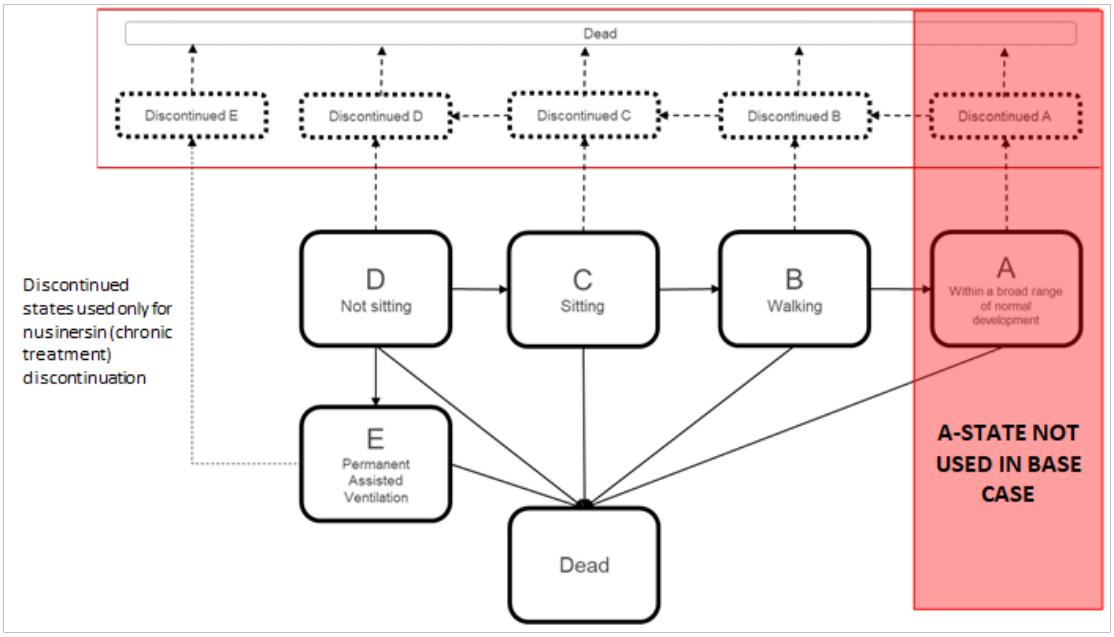

Figure 1: Model Structure.

The model includes four living health states and one absorbing death state (Table 1). Each health state is associated with different costs and utilities, reflecting the severity of the disease. At model baseline, all patients are in the D state (not sitting). At the end of each model cycle patients can transition into a new health state or stay in the same health state. Patients transition to higher health states when they attain motor milestones (sits unassisted or walks unassisted). As patients transition through

the model they accrue costs and utilities depending on the health state occupied. In the base case analysis, it is assumed that the motor 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 nusinersen. The rate of regression, upon discontinuation is assumed to be 90% annually. Backward transitions are not permitted in the OA arm. From each state there is the possibility of discontinuing treatment or dying. The discontinuing states are only a possibility for patients on nusinersen treatment. Patients can improve only as far as state B and only from state D. The applicant indicates that state A is not included in the base case but transitions to state A are investigated in a scenario analysis. Transitions to state E (ventilation) can only occur from state D. Futher details on the transition probabilities applied are provided in section 2.1 (table 2) under treatment effectiveness.

Table 1: Functional Status across health states *(Adapted from Table 54 in the dossier)*

State	Motor features
A	Within broad range of normal development (Not included in the base case).
B	Walks unassisted
C	Sits unassisted
D	Not sitting
E	Permanent assisted ventilation

Note : While the Applicant dossier includes additional features for each of the health states, these additional features are not used anywhere in the model. Therefore the health states are solely informed by the motor milestones.

The model includes 6 monthly cycles for the first three years, followed by 12 monthly cycles thereafter. The review group does not consider these cycles lengths to be

appropriate given the changes in childhood development in this time. While arguments have been put forward by the Applicant in support of this rationale the review group note that the US-ICER model on which this model is based uses monthly cycles. Further clinical opinion indicates that patients are reviewed more frequently and at least on a 4 monthly basis. A half-cycle correction was applied to account for events and transitions that can occur at any point during the cycle; however, this was applied using an inappropriate approach which assumes that cycle lengths, and costs and utilities per cycle, are the same for the time horizon of the model, which is not the case in this model. The life-table method is the accepted method for half-cycle correction and would be the appropriate approach here. Both the cycle length and half-cycle correction error are expected to impact on the cost-effectiveness results of the model, though the magnitude of this impact is unknown.

The applicant states that the model was validated by clinical experts in the UK and the Netherlands (one KOL). While experts from Ireland (2 clinical experts, one involved in the treatment of SMA) and Belgium (one in the South and one in the North) were consulted on the submission, this appears to have been limited to the model inputs and not the model structure.

The review group highlight that the time horizon of the model extends to 99 years. There remain a proportion of persons in the model at this time point however it is small. The average age reached in the model is 22.4 years for OA, 12.5 years for nusinersen and 2.4 years for best supportive care. Approximately 79% of QALY gain for OA is accrued in the period for which we have as yet no direct evidence i.e. after 5 years.

1.5. Perspective

The perspective is that of the payer for all countries. For the Netherlands the societal viewpoint is the base case and provided as a scenario for Ireland.

2. Economic model inputs

2.1. Treatment effectiveness

Treatment effects are modelled for death, permanent assisted ventilation (E state), and the attainment of motor milestones of independent sitting (C state) and walking (B state). Other outcomes measured in OA clinical trials, such as intermediate motor milestones or nutritional support, are not used to inform treatment effects in the economic model. It is assumed that attainment of sitting and walking motor milestones are associated with improvements in life expectancy.

2.1.1. Data sources

The available evidence for OA consists of single-arm non-comparative clinical studies. There is no direct evidence for the effectiveness of OA compared to either BSC or nusinersen. A summary of the studies used to inform health state transitions in the economic model are provided in Table 2 (these have all been fully described in the associated Relative effectiveness report onasemnogene abeparvovec (Zolgensma®) for 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, Zorginstituut Dec 2020).

Table 2: Data sources used to inform treatment effects in Applicant base case

Health state transitions	To BSC	To Onasemnogene abeparvovec	To Nusinersen
at model baseline, all patients are in the D state			
From D to C or B	Not possible for BSC in model	Pooled data from START (n=12 licensed dose cohort) and STR1VE-US (n=22)	Nusinersen arm (n=81) ENDEAR/SHINE
From D to E or Death	NeuroNext (n=16 subset which were identified as having 2 copies SMN2)	Pooled data from START (n=12 licensed dose cohort) and STR1VE-US (n=22); NeuroNext	Nusinersen arm (n=81) ENDEAR/SHINE; NeuroNext
From C or B to E	-	Assumed not possible in model	
From C to Death	-	SMA Type 2 patients Zerres et al 1997	
From B to Death	-	National life tables	
From E to Death	Gregoretti et al 2013 (n=24 patients receiving non-invasive ventilation only, not trachestomy)		

Treatment effects in the model are informed by data on absolute outcomes from separate studies for each treatment considered in the economic model: death, permanent assisted ventilation (E state), sitting (C state), and walking (B state). Extrapolation of survival is also informed by natural history cohort studies.

The use of outcomes from separate studies with differences in patient populations at baseline, differing prognoses, and age at treatment initiation substantially increases uncertainty in the economic model. The applicability of the various natural history studies and methods of combining these in the model is an additional source of uncertainty. The Applicant applies MAIC weights to pooled START/STR1VE-US data to try to make it more comparable to the ENDEAR/SHINE population. This methodology is limited in that it only applies to pairwise comparisons and does not take

comparison with BSC into account. The Applicant presented a naïve comparison with BSC using NeuroNext and pooled START/STR1VE-US without any reweighting. Therefore outcomes (for example life years) for OA in the comparison with BSC (no weighting applied to OA) will not match those in the comparison with nusinersen (MAIC weighting applied to OA). These differences highlight limitations and substantial uncertainty in using non-comparative single armed studies of OA.

2.1.1.1. Onasemnogene abeparvovec

The Applicant uses pooled data from phase I/IIa START and phase III STR1VE-US trials (4-6) to inform treatment outcomes for OA. The European Medicines Agency (EMA) identified differences in the manufacturing process used for OA in these two trials, so it is unclear whether pooling this data is appropriate (7). Follow up in START was up to 24 months post treatment (age 30 months), while follow up in STR1VE-US was up to 18 months of age.

The Applicant used LT-001 to provide selective qualitative support for modelling assumptions, but did not use LT-001 data directly to inform model inputs (8).

Available results from interim analyses of STR1VE-EU were not used to inform the economic model. The inclusion criteria for the STR1VE-US and STR1VE-EU studies were similar. The Applicant stated that they excluded STR1VE-EU as the data was immature (up to median age 15.4 months, December 2019 data cut) and the study was ongoing. In response to request by the review group a further interim datacut (June 2020) for STR1VE-EU was provided by the Applicant, but this data was not incorporated into the economic model. Data being interim is not a sufficient reason to justify exclusion from the economic model. The mean age of patients in STR1VE-EU at the June 2020 datacut was 17.1 months in comparison to planned follow up of

18 months. Given the limited information (small number of patients) available to inform outcomes for OA use of available data from STR1VE-EU would have been preferable.

2.1.1.2. Nusinersen

ENDEAR was a randomised sham controlled phase III study of nusinersen in patients with SMA type 1 with two SMN2 copies (9). SHINE is an open-label extension study of nusinersen for infants and children who previously participated in the nusinersen clinical trial program, including patients in (10) (11).

The Applicant uses a combination of data reported from ENDEAR and SHINE for patients randomized to nusinersen in ENDEAR to inform treatment effect for nusinersen. This includes one patient who although randomized to intervention arm of ENDEAR withdrew prior to treatment and received treatment with nusinersen for the first time as part of the SHINE extension study.

Data used from ENDEAR/SHINE are reported according to time in study. As the economic model is built on age (rather than time since treatment initiation) the Applicant assumes that patients were the median age of 5.4 months at treatment initiation when incorporating outcome for nusinersen into the economic model.

2.1.1.3. Best Supportive Care

Modelling choices for BSC also impact the comparison between nusinersen and OA as the transition probabilities for BSC were used to extrapolate outcomes for active treatments after observed data from respective clinical trials for transitions from D to Death or E state.

Regulatory authorisation (EMA) for OA was informed by naïve comparison with data from two cohort studies of patients not receiving active treatment in the USA (NeuroNext and Paediatric Neuromuscular Clinical Research Network for SMA (PNCR)) (9) (12). Individual-patient level data were available to the Applicant for both these studies. STR1VE-US was compared with PNCR, while START was compared to both PNCR and NeuroNext studies.

Treatment outcomes for BSC in the economic model were only informed by data from NeuroNext in the Applicant base case. Use of PNCR data (n=23) was available as a scenario option only. The Applicant stated that pooling the PNCR and NeuroNext studies was considered inappropriate due to differences in outcomes definitions and database design. However, these differences will also likely impact the comparability with the active treatment trials. A scenario using the sham control arm of ENDEAR nusinersen study (n=41) to inform BSC was also available in the economic model. The model was sensitive to the choice of data for BSC and the Applicant's selection was the most favourable to OA.

2.1.1.4. MAIC weighting applied to onasemnogene abeparvovec

Differences between study populations may bias estimates from naïve comparisons of outcomes between separate clinical trials. The Applicant presented an unanchored matching adjusted indirect comparison (MAIC) with nusinersen as part of their comparative clinical effectiveness evidence to attempt to adjust for some of these differences. Summary estimates of relative effectiveness (relative risks, risk differences, hazard ratios) from unanchored MAIC and ITC analyses used to support comparative clinical effectiveness in the Applicant submission are not used in the

economic model. However, the propensity score weights estimated as part of the MAIC were applied to adjust the pooled START/STR1VE-US data for OA.

The Applicant considered variables for which data were available in both START and STR1VE-US, that were also reported in ENDEAR/SHINE for inclusion in MAIC (Table 3). The Applicant used proportions reported for ENDEAR where information was not available for SHINE, under the assumption that the addition of one patient would not significantly affect the reported proportions. Due to the small number of patients included in the START/STR1VE-US studies the MAIC weights could not be estimated when using all considered factors. Factors were removed from the analysis in a stepwise fashion until it was possible to estimate MAIC weights. The effective sample size (ESS) from the MAIC analysis was 24.6, from an original sample size of 34.

Table 3: Patient characteristics at baseline in START/STR1VE-US and ENDEAR/SHINE

	Onasemnogene abeparvovec START/STR1VE-US	**Nusinersen ENDEAR/SHINE**
Not included in calculation of MAIC weights		
Female	56%	54%
SMN2 copy number	2	2
Age in months at symptom onset	mean 1.7 (range 0 to 4)	median 1.6 (range 0 to 4)
Age in months at treatment initiation	mean 3.6 (range 0.5 to 7.9)	median 5.4 (range 2 to 15)
Respiratory support	6%	26%*
Included in calculation of MAIC weights		
Feeding support	15%	9%*
Chop intend score Mean (range/SD)	30.8 (range 12 to 52)	26.7 (SD=8.1)

*Data for patients that received nusinersen as part of ENDEAR. These figures exclude one infant randomised to nusinersen arm in ENDEAR that first received nusinersen in SHINE.

Weights used in the economic model were estimated based on CHOP-INTEND score and proportion receiving nutritional support at baseline. Clinical opinion identified level of respiratory support as an important prognostic factor for patients. The

proportion receiving respiratory support in ENDEAR/SHINE was four times higher than in START/STR1VE-US. However, respiratory support was not incorporated into the calculation of the MAIC weights. The age at symptom onset was similar between trials, but age at treatment initiation in ENDEAR/SHINE was later and had a wider range than for START/STR1VE-US. Clinical opinion suggests that patients who are treated sooner may be expected to have better outcomes. The Review Group consider the MAIC weights applied in the economic model do not fully account for differences between OA and nusinersen study populations. In addition to the difficulties generating robust MAIC weights, the population is considered much too small to provide a meaningful comparison for a population with such a heterogeneous disease. Therefore, results of the comparison between OA and nusinersen are likely subject to bias and are highly uncertain.

2.1.1.5. Scenario analysis for presymptomatic patients

The applicant did not use data from SPR1NT study of presymptomatic infants (n=14 with 2 copies SMN2 and n=15 with 3 copies SMN2) to inform the economic model as data was immature and the study was ongoing (median age 10.5 months and 9.6 months for SMN2 2 and 3 copies cohorts respectively, December 2019 data cut). The applicant instead used data from NURTURE study of nusinersen (13) to inform a separate scenario analysis of presymptomatic patients. The applicant assumes that at age 5 years half of patients in the B state will transition to the A state. This assumption was not justified by the applicant. This scenario was presented as a cost minimisation analysis, assuming that nusinersen and OA will have equal efficacy.

2.1.2. Transitions between States

2.1.2.1. Transitions from the baseline D state to C and B states

Transitions from the baseline D health state to C and B health states are only possible for active treatments in the economic model. The probability of transitioning to a better health state (D state to C state, or C state to B state) was calculated using the number of patients who newly achieved motor milestones (sitting or walking) before the start of each cycle as the numerator, and the number of patients in the outgoing state (D or C states) in the previous cycle as the denominator. This uses transitions that occur in a cycle time period to calculate transitions occurring in the next cycle; for example the follow up for OA is to age 30 months, but the economic model includes transitions to C and B states up to cycle 6 (up to 36 months). This approach does not appear to be consistent with the approach used for transitions to death or E state.

The available data for OA is incorporated within the short term portion of the model (up to month 36 with cycle lengths of 6 months). Whereas transitions to better health states for nusinersen are incorporated up to cycle 8 (60 months) where cycle length is 12 months. It is unclear why the model switches to a longer cycle while milestone attainment is still occurring for nusinersen; this choice likely disadvantages nusinersen.

Onasemnogene abeparvovec

Transitions into the C and B health states for OA are informed by pooled data on motor milestone attainment: 'sitting unassisted for ≥30 seconds' as per item 26 in the Bayley Scales Gross Motor Subtest; and 'takes independent steps' in Gross Motor Checklist or 'walks independently' in Motor Milestone Development Survey (START), or 'takes at least five steps independently, displaying coordination and balance' in Bayley Scales Gross Motor Subtest per item 43 (STR1VE-US). Patients in STR1VE-US

were assumed to maintain the last obtained milestone (as at 18 months) for the rest of the short term portion of the model, equivalent to a last observation carried forward analysis.

Duration of treatment effect:

The Applicant assumes that motor milestones achieved at end of initial model section will be maintained across a patient's lifetime: the model assumes a lifelong treatment effect for OA, with no treatment effect waning. There is no evidence available to support the assumption of a lifelong treatment benefit for OA. Clinical opinion also considered the long term benefit for OA to be uncertain.

The model uses a lifetime time horizon, but the longest available follow up data for patients treated with OA is up to age 5.6 years in LT-001 study. While a loss of motor milestones has not been recorded in LT-001, 4 out of 10 patients who received the licensed dose in START subsequently received treatment with nusinersen in LT-001. The number of patient who go on to receive subsequent nusinersen could increase with longer follow up. Therefore, the treatment outcomes observed for these patients are confounded, and indicating that model assumptions regarding the long-term maintenance of quality of life with OA are not justified. The Applicant did not present any scenario analyses examining the potential impact of subsequent treatment with nusinersen. Clinical opinion to the NCPE indicated that nusinersen would be considered as a treatment option for patients who had not reached target motor milestones.

The Applicant presents scenario analysis using a cross-sectional study in the Netherlands (Wadman et al 2018) (14) to inform a scenario around a loss of benefit with OA in the longer term of SMA type 2 and 3 patients (as proxies for C and B

states) to approximate rate of subsequent loss of attained milestones. In this scenario the proportion of patients losing independent sitting or walking per year increases linearly from 0 before age 6 years to 25% by 24 years in the C state and 58% by 50 years in B state, respectively. Costs and utilities for the D and C state are applied to those that have lost milestones from the C and B states respectively. Survival is not altered in this scenario. This scenario is substantially more optimistic than the approach used for nusinersen loss of effect after discontinuation.

Nusinersen

Transitions from baseline D state to the C and B health states for nusinersen are informed by ENDEAR/SHINE data on motor milestone attainment: 'stable sit and pivots (rotates)' in the sitting item and 'walking independently' in the walking item of the HINE-2 score scale. It should be noted that the definition of sitting used in ENDEAR/SHINE represents a greater level of control than the Bayley scale definition used for OA; the HINE measure is also considered more fatiguing for fragile infants such as those with SMA. The differences between these outcome measures and definitions likely favour OA.

Data on motor milestones for ENDEAR/SHINE are reported as proportion having achieved milestone of those with data available at that study time point. The Applicant assumes that the proportion of patients achieving sitting or walking reported at each time point applies to all patients who are still alive and event free at that study visit.

Duration of treatment effect:

The Applicant assumes that patients will remain in the health state attained while receiving nusinersen treatment. The discontinuation rate for nusinersen is assumed to be 3% annually in the D and C health states, informed by the proportion of patients who had a 4-point worsening in CHOP-INTEND score in ENDEAR. Patients who discontinue treatment with nusinersen are assumed to move into 'discontinuation' state – whereby they regress and transition back through health states at a rate of 90% annually. A scenario assuming no discontinuation in the first year of treatment and a higher initial discontinuation rate is presented for Ireland. The assumption of 90% rate of backwards transitions is potentially a pessimistic assumption – particularly for patients who have been on nusinersen treatment in the long term. The Applicant could have considered scenarios where regression was modelled from natural history data for SMA patients who achieve motor milestones. The model is sensitive to assumptions regarding nusinersen discontinuation. Patients do not receive nusinersen in the E state in line with clinical stopping rules.

2.1.2.2. Transitions from D state to Death or E state

Transitions to the E state (permanent assisted ventilation) are only possible from the D state in the model. It is assumed patients who achieve motor milestone of sitting will not require permanent assisted ventilation. Transitions into the E state are informed by overall survival (OS) and event free (permanent assisted ventilation or death) survival (EFS) curves. Transitions from D to death are informed by OS curves. The Applicant does not adjust for general population mortality in the D state; incorrectly assuming no possible deaths in some initial model cycles. This is inappropriate; however, given the low rate of general population mortality in this age group this error may not have a substantial impact.

Permanent assisted ventilation was defined as tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event in ENDEAR/SHINE; tracheostomy or the requirement of ≥16 hours of non-invasive ventilatory support for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation in START/STR1VE-US; and intubation in NeuroNext. The EFS outcome defintion in NeuroNext does not align with that used for active treatment in the model. The EFS outcome definitions in either PNCR (requiring at least 16 hours/day of non-invasive ventilation support for at least 14 days in the absence of an acute reversible illness or perioperatively) or ENDEAR sham control arm (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event) were more similar to definitions used in active treatment arms. Therefore, use of these studies are likely to have been more appropriate than NeuroNext.

It is not clear whether the achievement of motor milestones of sitting or walking (which would imply no longer being in the D state) were taken in to account via censoring for the EFS and OS curve calculations for nusinersen.

The Applicant uses Kaplan-Meier data from respective studies to inform transition probabilities initially for each treatment arm. The Applicant censors those who receive permanent assisted ventilation in calculation of the NeuroNext OS curves. For BSC the Applicant uses piecewise parametric survival extrapolation for OS and EFS from NeuroNext inform transitions from D state to Death and E states respectively. The Applicant applies a limit to survival in the D state for BSC, assuming that all patients will be dead at four years.

To extrapolate survival for active treatments in the D state beyond the period where clinical trial OS and EFS data were available the Applicant appends transition probabilities as used for BSC to inform transitions to E or Death states, to both active treatment arms. The Applicant applies these BSC transition probabilities from 36 months (at end of follow up from START trial) for OA, but from 60 months for nusinersen arm. EFS and OS were only available to approximately 143 weeks follow up (age 38 months) for ENDEAR/SHINE. The Applicant assumes that there are no EFS or OS events for nusinersen from end of reported nusinersen OS and EFS data (age 38 months) until BSC data is applied at 60 months. This is not considered appropriate by the Review Group. The use of BSC transition probabilities for extrapolation includes the assumption that all patients remaining in the D state will die by 84 months for OA and 108 months for nusinersen. The application of a survival limit was not well justified by the Applicant, particularly in how it is applied to active treatments.

The applicants approach results in lower OS in the OA arm than for nusinersen. Patients in the D state have low quality of life, but incur high costs, and are at risk of transitioning to the E state (with higher costs again). Transitions to better health states are only possible in the initial period of the model. Therefore, the shorter time spent in the D state improves cost-effectiveness of the intervention. This is not considered plausible by the Review Group. The Review Group considers that a more appropriate assumption is to assume that transitions from the D state are equivalent between treatments, given the lack of evidence on differential efficacy in this health state and the lack of supporting evidence provided by the company that efficacy should differ. The Applicant presents a scenario where OA is assumed to have the

same transition probabilities from D state to Death or E states as nusinersen. An alternative approach would have been to extrapolate OS and EFS data from ENDEAR/SHINE using parametric survival analysis.

2.1.2.3. Transitions from C and B states to Death

Limited data is available to extrapolate survival outcomes for patients in the C and B states. Individuals in the C health state are assumed to have improved survival in line with patients with SMA type 2 (15). Individuals in B health state are assumed to have normal general population life expectancy, based on the assumption that life expectancy for patient with SMA type 3 is normal. Mortality in B state is informed by data from national lifetables for each respective country (16-18).

It is unclear whether SMA type 2 and 3 patients represent an appropriate proxy for SMA type 1 patients who achieve independent sitting or walking. Based on experience with nusinersen, clinical opinion to the NCPE indicated that patients' clinical courses continues to indicate a more severe disease severity than SMA type 2 and that it may not be reasonable to assume that a patient with SMA type 1 who is doing well equates to a patient with SMA type 2. A scenario analysis applying C state survival (in line with patients with SMA type 2) to the B health state was provided by the Applicant in response to a request from the Dutch scientific advisory board (WAR) of Zorginstituut Nederland.

2.1.2.4. Transitions from E state to Death

The Applicant uses OS data on patients receiving non-invasive ventilation from Gregoretti et al (19) to inform transition from E state to death for all treatment arms. The Applicant excludes data for patients with tracheostomy – clinical opinion

indicated that tracheostomy would not be used for these patients. An exponential extrapolation is used – this assumes a constant risk of death over time. The Applicant applies a survival limit of 16 years in the E state. UK clinical opinion sought by the Applicant suggests that, while it is rare, there have been cases of patients with SMA type 1 receiving permanent assisted ventilation in their 20s.

2.1.3. Exploration of uncertainty in treatment effects

Uncertainty in economic models is typically explored using deterministic sensitivity, probabilistic sensitivity, and scenario analyses. Limited scenario analyses varying treatment outcomes for OA were provided by the Applicant. These scenarios did not adequately address uncertainty surrounding treatment outcomes. However, treatment effectiveness inputs from OA and nusinersen trials are not varied in probabilistic sensitivity analyses (PSA) or in deterministic sensitivity analyses (DSA). Parameters in relation to nusinersen discontinuation and corresponding loss of treatment effect are varied by +/-20% in the DSA, but are not varied in the Applicant PSA. Therefore uncertainty associated with treatment effects is not captured, either in the probability of cost effectiveness estimated from PSA or in Expected Value of Information (EVPI) analysis. The Review Group consider excluding treatment effects from the DSA, PSA and EVPI to be inappropriate, especially given the very small number of patients used to inform OA treatment outcomes.

2.2. Identification of health outcomes

The primary health outcome of the model is the quality adjusted life year (QALY). HRQoL parameters in the model include health state utilities associated with each

model health state. Utilities associated with AEs were not included as the Applicant considered that it is difficult to separate utilities due to treatment from the complications associated with SMA, which are already accounted for in the health state utility values. Caregiver disutilities were not included in the base case, as methods for incorporating caregiver burden are still under development. In particular, methodological limitations associated with bereavement and counter-intuitive results were identified. Caregiver disutilities were incorporated into an exploratory analysis. An "on-treatment" utility increments are applied in both treatment arms (OA and nusinersen) in a scenario analysis for achieving interim milestones such as head control, rolling, standing, crawling, etc. No evidence was submitted to justify the inclusion of "on-treatment" utilities, in addition to the health-state utilities already applied, except to state that this approach was taken by the US ICER. The potential for double-counting with existing health-state utilities was not addressed by the Applicant.

2.3. Measurement and valuation of health outcomes

The Applicant conducted an SLR to gather evidence of HRQoL for patients with SMA. No HRQoL data were reported in the SMA type 1 clinical trials for OA, nusinersen or natural history cohorts identified as part of the clinical effectiveness SLR. Measuring robust utility values in babies and young children is exceptionally challenging, even more so in the rare disease setting. The population included in the Applicant's HRQoL SLR was therefore broader than the modelled population, due to the Applicant's approach of using SMA 2 and SMA 3 as proxy populations.

The Applicant inaccurately described the approach to utility valuation as using SMA type 2 as a proxy for patients who sit unassisted (C state) and SMA type 3 as a proxy

for patients who walk unassisted (B state). This is accurate for the calculation of healthcare resource costs in the model, but is not the approach taken for utility valuation. Instead, the Applicant made extreme assumptions for the E state and B/A state utility (zero quality of life for the E state, and quality of life of the general population for the B/A states), used values from an SMA Type 1 patient cohort for the D state, and a general SMA cohort who can sit unassisted for the C state. Assumptions are described in detail below for each of the health states:

2.3.1. E state

A utility value of 0.000 (no quality of life) was assumed for the E state. No justification was provided for the assumption of no quality of life in the E state, apart from clinical opinion which indicated that there should be a differentiation between the E and D states. An elicitation study conducted by Novartis indicated there was no significant difference between permanent-assisted ventilation (PAV, analogous to the E state) and non-sitting (analogous to the D state), though the study calculated utilities which were less than zero (i.e. worse-than-death) for both of these states (20). The US ICER study, on which the Applicant's approach is reportedly based, used a value of 0.19 for both the E and D states.

2.3.2. D state

A mean utility value of 0.19 was adopted from the US ICER assessment. This value was based on 7 patients with Type 1 SMA in the UK (0.19), from a study by Thomson et al. in 2017, which collected parent/proxy–assessed quality of life using the EuroQol-5 Dimensions (EQ-5D) 3-level version in 4 different European countries (21). The authors of the Thompson study concluded that parent-proxy Qol assessment did not provide sufficient detail on patient health to determine with any amount of

certainty an individual's state of health based on the model health states. This is evident from the utilities reported for the 4 countries which ranged from 0.07 (Spain, n=8) to 0.532 (Germany, n=11). No justification was provided for the selection of the UK value, apart from specifying that the model adopted the same approach as the US ICER assessment. However, in the US ICER assessment, the model also used the value of 0.19 for the E state (22). The UK population was deemed by the Applicant to be representative of the populations in Belgium, the Netherlands, and Ireland though no reference was made to the availability of data from other EU countries. Alternative approaches to utility valuation were explored in the Thompson et al study, including physician-rated QoL (generally lower than parent proxy values) and PedsQL data from the CHERISH trial mapped to the EQ-5D youth version, which gave some counterintuitive results (22).

2.3.3. C state

A mean utility value of 0.6 was adopted from the US ICER assessment. This was based on the value for "sits without support" (SMA) used in the NICE assessment of nusinersen, which was elicited from clinical experts who advised the ERG (23).

2.3.4. B state and A state

The utility for the B state (walks unassisted) and A state (within broad range of normal development) are sourced from general population utilities, and applied annually based on age and gender. These values range from 0.9533 at the age of 10 years to 0.7270 at the age of 80 years. Alternative values include 0.85 (stands/walks unaided), used in the NICE assessment of nusinersen, and 0.878 (walks unaided, later-onset SMA), collected in the CHERISH trial using PedsQL mapped to the EQ-5D youth version.

Alternative scenarios

Alternative scenarios explored by the Applicant include the addition of on-treatment utilities and caregiver disutilities. On-treatment utilities were implemented as an additional utility of 0.1 in the D (non-sitting) health state, and 0.05 in the C (sitting) health state, following the approach of the US ICER analysis (22). No evidence was provided to explain the origin or basis for these values. Caregiver disutilities were incorporated into exploratory scenario analysis as follows: -0.08 for caregivers of a child in the E state (permanent assisted ventilation) or a child in the D state (not sitting) and -0.03 for a child in the C state (sits unassisted). The Applicant stated that these values were based on data obtained from a study by Tilford et al, 2005 (24), who compared Quality of Well-Being scale data from the primary caregivers of children spina bifida with a control sample. Results from this study were converted to "spill over" disutility using a method described in a separate study, by Wittenberg et al, 2013 (25), however no details of this method or how the final values were derived were provided. It was not possible for the Review Group to validate the source of the data used in the caregiver disutilities scenario analysis.

Uncertainty in health state utilities

The Applicant's approach to selecting utility values is inconsistent. The approach of the US ICER assessment is followed in some cases (C and D states), and not in others (E state). Likewise, the approach of the NICE assessment of nusinersen is followed for the D state but not the B state. The Applicant has not offered a rationale or justification for the use of the US ICER approach, which itself is inconsistent in its application of utility values from different sources. The Applicant also cited support for the approach from clinical opinion as justification. This clinical opinion was given

in the form of commentary on the available data and no formal elicitation exercise was conducted to try to generate meaningful values.

The Applicant undertook deterministic and probabilistic sensitivity analyses and scenario analyses. For the deterministic sensitivity analyses, inputs were varied by +/-20%. This approach may be reasonable in situations where the exact value is uncertain but may plausibly fall within the defined range. For SMA, it is difficult to define this level of plausibility given the diversity of values reported in different sources. A more appropriate approach to explore the potential impact of utility values on cost effectiveness is to use different sets of values from alternative data sources. An alternative scenario analysis in the Applicant's submission was based on an alternative method explored within the Thompson et al study: using the PEdsQL from CHERISH (nusinersen later-onset SMA clinical trial) mapped to EQ-5D-Y (21). This was not used in the base case as the Applicant identified problems with the mapping approach available, and the implausibility of the results e.g. unlikely that an individual who requires PAV would be considered as being 75% of that on an individual in perfect health. (21) The Applicant conducted a utilities elicitation study using the Time-trade-off method, but considered the results inappropriate to use given the negative value associated with the PAV state (-0.2634) which generated negative total discounted QALYs for the BSC and nusinersen arm of the model.

Overall, the Review Group consider that there is significant uncertainty associated with the health state utility values used in the model, due to the scarcity of data in the population of interest, and due to the methodological challenges of utility valuation in young children.

2.4. Identification of costs

The model included drug acquisition and drug administration costs for OA and nusinersen. Healthcare costs associated with BSC are applied to all treatment arms, and include:

- Consultations with the multidisciplinary healthcare workers responsible for the care of SMA patients (e.g. neuromuscular specialists, respiratory physicians, 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
- Community and social care services (including personal and respite care)

Patient and caregiver out of pocket costs are included in an additional scenario analysis only or in the base case for the Netherlands.

Table 4: Price of intervention and comparator per treatment course or per year

	Drug acquisition costs				Drug administration costs	
	Onasemnogene abeparvovec Price-to-wholesaler/ Chemist	**Nusinersen Price-to-wholesaler/ Chemist**	**Onasemnogene abeparvovec Total reimbursement price per pack†**	**Nusinersen Total reimbursement price per patient per year†**	**Onasemnogene abeparvovec Per administration**	**Nusinersen Per administration**
Belgium	€1,945,000	€83,300	€2,061,700	Year 1: €529,817§ Year 2+: €264,908§	€1,318	€429 (≤5 years) €416 (6-18 years) €324 (≥19 years)
Netherlands	€1,945,000	€83,300	€2,120,050	Year 1: €499,800 Year 2+: €249,900	€3,278	€3,278 (≤5 years) €3,197 (6-18 years) €3,076(≥19 years)
Ireland	€1,945,000	€76,049.89	€2,285,375	CEM: Year 1: €431,203* CEM: Year 2+: €215,601* BIM: Year 1: €536,152* BIM: Year 2+: €268,076*	€7,013	€5,978

PtW/C=price to wholesaler/chemist. CEM=cost-effectiveness model. BIM=Budget impact model.

Table 4: Price of intervention and comparator per treatment course or per year

† The total reimbursement price used in the model includes or excludes Value-added-tax (VAT) depending on country guidelines. Price inclusive of VAT is used in CEM and BIM in Belgium. Price exclusive of VAT is used in CEM and BIM in the Netherlands. Price exclusive of VAT is used in CEM and price inclusive of VAT is used in BIM in Ireland. VAT=6% in Belgium, 9% in Netherlands, 23% in Ireland.

§ Total reimbursement price per pack of nusinersen in Belgium is €88,305.11 when administered in day clinic and €88,298 when patient stays one night in hospital. Applicant assumed 75%:25% split between day-case:hospital.

*Total reimbursement price in Ireland incorporates a 5.5% rebate on the price to wholesaler, applied in all economic evaluations in Ireland.

Belgium drug administration cost assumptions:

Onasemnogene abeparvovec: mean of 1.5 days in 1 of the 7 reference centres for neuromuscular diseases, a neuropaediatrician's consultation and transport cost (€1,110), prednisolone (€7) and lab-monitoring (€201).

Nusinersen: Assuming 75% ambulant setting, 25% inpatient setting at 1 of the 7 neuromuscular disease centers, a radiologist's consultation and echography in 50% of the cases, and an anesthesist's consultation in 12,5% of the cases and Kalinox® administration in 65% of the cases. All patients will also get a neuropaediatrician's consultation and reimbursement of transport costs (50% of the maximum reimbursement). Costs for inpatient lumbar puncture and day case lumbar puncture range from €751.88 to €819.20, and €151.86 to €218.03 respectively, depending on the patient's age.

Netherlands drug administration cost assumptions:

Onasemnogene abeparvovec: ‡‡Including day-care cost for administration (€2,173) and 1-hour infusion cost (€1,105)

Nusinersen: Assuming that inpatient:outpatient:daycase split is 100%:0%:0% for ≤5 years, 80%:10%:10% for 6-18 years, and 50%:25%:25% for ≥19 years. Inpatient costs are as per onasemnogene abeparvovec assumptions, outpatient and day-case lumbar puncture €2,473 and €3,278 respectively.

A model error incorporated Irish pharmacy dispensing fees for nusinersen in the Dutch model. This has minimal impact on cost-effectiveness results.

Ireland drug administration cost assumptions:

Onasemnogene abeparvovec: Weighted average cost of spinal procedures with minor complexities (ADRG:B03C) in day case (€5,295) and inpatient (€7,572) settings. Weightings based on activity.

Nusinersen administration: Weighted average cost of spinal procedures with minor complexities (ADRG:B03C) in day case (70%, €5,295) and inpatient (30%, €7,572) settings (ABF 2019 Price List – Daycases/Inpatients – B03C Spinal Procedure, MINC) from Healthcare Pricing Office: ABF 2019 Admitted Patient Price List. Weightings based on expert opinion.

2.5. Measurement and valuation of intervention and comparator costs

The price to wholesaler/chemist (Ptw/c) for OA is €1,945,000. The total reimbursement price per pack differs depending on the differential application of fees, rebates, and VAT across countries (Table 4). The total reimbursement price per patient per year for nusinersen accounts for six doses in the first year and three doses each subsequent year. The Applicant considered the public list price of nusinersen in the model. In Belgium, nusinersen is subject to a confidential contract between the company and the NHIDI. In Ireland, a confidential patient access scheme is in place for nusinersen. In the Netherlands nusinersen is subject to a confidential price agreement between the manufacturer and the Ministry of Health. The Applicant did not include the cost of AAV9 testing in the model, assuming that this would be funded by Novartis Gene Therapies. All healthcare costs in the model should be assumed to be borne by the healthcare payer, and exclusion of the cost of AAV9 testing in the model is inappropriate. As this cost has minimal impact on the cost-effectiveness results of the model, no changes relating to the cost of AAV9 were made by the Review Group. Administration costs for OA are assumed to include pre-infusion baseline tests, pre-, peri- and post-infusion monitoring. The Applicant did not include the cost of SMN1/SMN2 genetic testing because it is required to confirm diagnosis for all patients, regardless of treatment choice.

2.6. Measurement and valuation of health state and other costs

2.6.1. Healthcare costs

The model base case uses healthcare resource use costs for SMA type 2 and SMA type 3 patients managed with BSC alone as proxies for pharmacotherapy treated SMA type 1.

Patients in the model C state (sits unassisted) are assumed to have healthcare resource use costs of SMA type 2 patients managed with BSC. Patients in the model B state (walks unassisted) are assumed to have healthcare resource use costs of SMA type 3 patients managed with BSC. The Applicant justified this approach as it replicates the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of OA and nusinersen for SMA (22). The Applicant also stated that this was considered appropriate by clinical experts validating the Applicant's model, though this validation was not apparent from the record of clinical opinion submitted. Clinical opinion obtained by the Review Group, in addition to clinical opinion obtained by the Applicant indicated that infants with SMA 1 treated with OA would be likely to have different complications and underlying biology to untreated patients with SMA 2. Specifically, it was noted that the cost of infants treated with OA who achieve the ability to walk (B state) may be higher than for untreated infants with SMA 3 due to the potential differences in complications/comorbidities between these patient cohorts. Based on experience with nusinersen, clinical opinion to the NCPE indicated that patients' clinical courses continues to indicate a more severe disease severity than SMA 2.

Different approaches were followed to obtain the resource use and cost information for each country. A UK healthcare resource use study (HCRU study), conducted by Novartis Gene Therapies to determine the HCRU costs associated with BSC for SMA patients in the UK, formed the basis for the healthcare costs used in the model (26). The Applicant considered that clinical practice and resource use items in the UK are reasonably comparable with Belgium, the Netherlands and Ireland. Resource use from the UK study was reportedly validated by clinical opinion in Belgium and Ireland, but not the Netherlands. The UK HCRU study sought to establish the current management of SMA type 1, type 2 and type

3. The study was conducted between February and April 2019 and included 16 UK clinical experts. In-depth telephone interviews were conducted with each clinical expert. Weighted means of the proportions of patients using specific resources, frequency and (where relevant) duration, of each type of resource used were calculated. The number of patients using a resource and frequency/quantity of that resource were calculated based on responses from clinical experts who were considered the most likely to use or prescribe that type of resource. Using this approach, just 12/16 experts (neurologists/pulmonologists) accounted for the vast majority of healthcare resource use information in the model. Input from nurse/physiotherapist/health visitor experts was limited. The clinical expert sample did not include palliative care or intensive care/high dependency specialists, and only included one expert (health visitor) with expertise of the community and social care setting. The Applicant considered that costs associated with such specialities may not be fully captured and adjusted the HCRU study costs using costs reported by Noyes et al. 2006 (27). The Noyes study reported the results of interviews with 35 patients or their parents, which aimed to calculate resource use and costs involved in supporting ventilator-dependent children and young people at home compared with those in hospital. The Noyes study provides costs associated with ventilator-dependent children in the UK under different healthcare settings including home-based, high-dependency units and intensive care units, including costs regarding ventilation support and social services. Costs for the model E state (permanent assisted ventilation) were entirely derived from the Noyes et al. 2006 study (27) as a permanently assisted ventilation cohort was not captured in the UK HCRU study.

2.6.1.1. Belgium

There is considerable uncertainty associated with the healthcare costs in the Belgian model, as a limited amount of, sometimes contradictory, information was provided in the

submission. Although the Applicant stated that Belgian costs were based on the UK HCRU study, it is not clear to the Review Group that this is the case. Two Belgian clinical experts were requested to confirm or adjust the outcomes of the UK HCRU study. The mean of the survey results from these two clinicians was then presented to a third Belgian expert to validate the initial data collected and quantify missing data. Only the documentation presented to the third clinical expert for validation was provided in the submission. It is therefore not immediately obvious to the Review Group which aspects of the HCRU study were confirmed or adjusted by the first two clinical experts, nor what changes were made by the third expert following the validation exercise. All patients who receive ventilatory support are expected to receive this at home. It is unclear what costs have been assumed for this resource, as no further details of ventilation costs for Belgium are described in the submission or the model. Information on Belgian unit costs was sourced from the NIHDI (RIZIV/INAMI) website (28, 29), the Belgian Centre for Pharmacotherapeutic Information (BCFI) website for the non-reimbursed drugs (30), and APR-DRG-based payments to Belgian hospitals (2018 data converted to 2020 using the health index) (31). Annual SMA-related healthcare costs for the Belgian model are outlined in (Table 5). The healthcare costs associated with the C, D and E states are significantly lower in the Belgian model (by 4-5 fold) than the Dutch and Irish model. The Applicant noted that in Belgium some medical devices such as wheelchairs are the responsibility of the regions, not of the federal/national level which is the perspective of this cost-effectiveness analysis, and that this may introduce an underestimation of the value of this gene therapy innovation from NIHDI's perspective. These differences in service provision are not expected to account for the significant differences observed between country costs in the submission. The healthcare costs assumed for the Belgian model are much more closely aligned with the costs assumed for

the independent analysis conducted by the US Institute for Clinical and Economic Reviews (US ICER), which based healthcare costs on a claims analysis of commercial health plans comprising infantile-onset SMA (n=23), childhood-onset SMA (n=22) and later-onset SMA (n=296) patients, based on the study reported by Shieh et al, with additional costs for permanent ventilation based on the Noyes 2006 study. Healthcare costs for each health state were varied individually in DSA +/-20%.

Table 5: Annual SMA-care related costs used in the base case for Belgium

Cost Category	**SMA type 1 as proxy**		**SMA type 2 as proxy**	**SMA type 3 as proxy**
Health state	E	D	C	B
Drugs	€185	€185	€98	€65
Medical tests	€314	€314	€288	€129
Medical visits (incl. GPs)	€3,793	€3,793	€3,072	€2,596
Hospitalizations	€30,096	€30,096	€8,997	€128
Health materials	€16,698	€11,294	€8,026	€1,228
Respiratory support	*€14,211*	*€8,808*	*€5,999*	*€866*
Nutritional support	*€1,684*	*€1,684*	*€1,059*	*€32*
Orthopaedic devices	*€802*	*€802*	*€967*	*€330*
Social Services (paramedical)*	€1,538	€1,538	€1,538	€1,538
Total	**€52,623**	**€47,219**	**€22,019**	**€5,685**

Source: Resource use from UK HCRU study, validated by Belgian clinical experts, specific unit specific costs Belgium (28, 29) (30) (31).

Abbreviations: SMA, spinal muscular atrophy * Forfeit for the services from the neuromuscular diseases centres to the patient/families.

2.6.1.2. Netherlands

The UK HCRU study was used as a basis for generating resource use and cost values for the Netherlands. Each health state cost was amended by ventilation costs in different healthcare settings and costs of social services using data from the Noyes et al 2006 study.

Resource use from the UK study was not validated by clinical opinion in the Netherlands. The Applicant stated that Dutch health state specific costs were compared with the SMA type specific costs in the Dutch reimbursement report for nusinersen (32). However, the Applicant did not comment on the comparability of the costs in both submissions, failing to note that the costs in the nusinersen submission are significantly lower than those in the OA submission. Specific unit costs for the Netherlands were sourced using official tariffs for health care products and interventions following the guideline for conducting costing research in the Netherlands (33-35). If Dutch cost estimates were not available, costs were converted applying OECD's PPP from UK to the Netherlands (36). All costs were presented as 2020 values, inflated from other years using consumer price index where necessary. Annual SMA-related healthcare costs for the Dutch model are outlined in Table 6.

Table 6: Annual SMA-care related costs used in the base case for the Netherlands

Cost category	**SMA type 1**		**SMA type 2 as proxy**	**SMA type 3 as proxy**
Health state	E	D	C	B
Drugs	€579	€1,061	€857	€1,084
Medical tests	€186	€342	€293	€256
Medical visits	€1,928	€3,531	€1,662	€1,506
Hospitalisations	€534,231	€126,872	€63,894	€1,053
of which ventilation in ITU/HDU	*€511,922.50*	*€86,002.98*	*€57,335.32*	
GP and Emergency	€383	€702	€274	€106
Health material	€2,644	€4,542	€2,357	€679
Social services (home ventilation)	€60,157	€45,479	€30,319	€4,813
Total	€600,109	€182,529	€99,657	€9,496,75

Source: Resource use from UK HCRU study, specific unit specific costs for the Netherlands (33-35), adjusted by ventilation costs from the Noyes et al 2006 study.

Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy.† Transition to the A state is not possible in the base case. In the scenario where the transition from B state to A state is possible, the SMA-care related costs for the A state equal 0 as patients in this state are assumed to be in a condition as general population.

2.6.1.3. Ireland

The UK HCRU study was used as a basis for generating resource use and cost values for Ireland. Each health state cost was amended by ventilation costs in different healthcare settings and costs of social services using data from the Noyes et al 2006 study. UK resource use values were validated with Irish clinical experts to ensure resource use reflects current Irish clinical practice. Irish unit costs were sourced from the Health Pricing Office's ABC 2019 Admitted Patient Price List (37), the PCRS database (38) and private healthcare providers and medical device distributors in Ireland (for resources related to laboratory tests, respiratory tests/evaluations, orthopaedic and respiratory devices sources). Following interviews with two Irish clinicians, costs from the UK study were found to be low compared to their expectations, though only one of the clinicians was directly involved in the regular provision of care to patients with SMA. It should be noted that these costs were direct conversions of UK costs and did not incorporate Irish unit costs. During a second round of interviews with one of the clinicians, a paediatric neurologist with experience of SMA, further validation of costs was conducted resulting in updates to prevalence and frequency of resource use estimates. Following the second validation exercise, most of the SMA-care costs were reported by the Applicant to have increased substantially compared with those first presented. The Applicant did not submit details of which resources were changed in the validation process, and it is not clear to the Review Group where the substantial changes were made as the Irish health-state costs are very similar to the Netherlands health-state costs, to which no adjustments were made apart from the Noyes et al adjustment, which was also made to the Irish data. In two scenario analyses, Irish healthcare costs were based on 1) data directly from the UK HCRU study to which UK unit costs have been applied,

converted to euros; and 2) data directly from the UK HCRU study to which Irish unit costs have been applied. Annual SMA-related healthcare costs for the Irish model are outlined in Table 7 .

Table 7: Annual SMA-care related costs used in the base case for Ireland

Cost category	**SMA type 1**		**SMA type 2 as proxy**	**SMA type 3 as proxy**	**SMA related costs**
Health state	**E**	**D**	**C**	**B**	**A**
Drugs	€8,789	€16,102	€389	€426	€0
Medical tests	€606	€1,109	€770	€596	€0
Medical visits	€1,974	€3,617	€1,661	€1,230	€0
Hospitalisations	€537,486	€120,899	€65,565	€742	€0
of which ventilation in ITU/HDU	*€519,095.93*	*€87,208.12*	*€58,138.74*		
GP and Emergency	€232	€425	€178	€72	€0
Health material	€2,468	€4,244	€2,208	€487	€0
Social services (home ventilation)	€61,324	€46,361	€30,907	€4,906	€0
Total	€612,879	€192,756	€101,678	€8,458	€0

Source: Resource use from UK HCRU study, specific unit specific costs for Ireland, adjusted by ventilation costs from the Noyes et al 2006 study.
Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy.

2.6.1.4. Costs of ventilation in the Netherlands and Ireland

Costs associated with ventilation in the Irish and Dutch models are shown in Table 6 and Table 7

Table 7: Annual SMA-care related costs used in the base case for Ireland

Cost category	**SMA type 1**		**SMA type 2 as proxy**	**SMA type 3 as proxy**	**SMA related costs**
Health state	**E**	**D**	**C**	**B**	**A**
Drugs	€8,789	€16,102	€389	€426	€0
Medical tests	€606	€1,109	€770	€596	€0

Table 7: Annual SMA-care related costs used in the base case for Ireland

Cost category	SMA type 1		SMA type 2 as proxy	SMA type 3 as proxy	SMA related costs
Health state	**E**	**D**	**C**	**B**	**A**
Medical visits	€1,974	€3,617	€1,661	€1,230	€0
Hospitalisations	€537,486	€120,899	€65,565	€742	€0
of which ventilation in ITU/HDU	*€519,095.93*	*€87,208.12*	*€58,138.74*		
GP and Emergency	€232	€425	€178	€72	€0
Health material	€2,468	€4,244	€2,208	€487	€0
Social services (home ventilation)	€61,324	€46,361	€30,907	€4,906	€0
Total	€612,879	€192,756	€101,678	€8,458	€0

Source: Resource use from UK HCRU study, specific unit specific costs for Ireland, adjusted by ventilation costs from the Noyes et al 2006 study.
Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy.

in the rows labelled "*of which ventilation in ITU/HDU*" and "Social services (home ventilation)". Ventilation costs account for a significant proportion of costs in the C (89%-90%), D (68%-72%) and E (96%-97%) health states.

In the Irish and Dutch models, each health state cost was amended by ventilation costs in different healthcare settings, basing the prevalence of ventilation on results of the UK HCRU study, the setting of ventilation on UK clinical opinion, and the costs of ventilation and social services on results of the Noyes et al 2006 study.

All patients in the E state were assumed to require NIV>16 hours per day. A proportion of patients in the B, C and D health states were assumed to require NIV<16 hours per day based on the prevalence of using non-invasive ventilatory aids (bi-level positive airway pressure [BiPAP] NIPPY, Breas) as reported in the UK HCRU study:

- D state (SMA type 1 proxy): 16% non-ventilated; 84% NIV <16 hours/day
- C state (SMA type 2 proxy): 44% non-ventilated; 56% NIV <16 hours/day

- B state (SMA type 3 proxy): 80% non-ventilated; 20% NIV <16 hours/day

As discussed earlier, based on experience with nusinersen, clinical opinion to the NCPE indicated that patients' clinical courses continues to indicate a more severe disease severity than SMA Type 2 and that it may not be reasonable to assume that a patient with SMA Type 1 who is doing well equates to a patient with SMA Type 2 etc. A proportion of patients in every health state were assumed to receive ventilatory support in either a home-based, high-dependency and intensive care setting, based on UK clinical opinion (39). In the C and D states, patients are assumed to receive NIV<16 hours per day in either the paediatric intensive care setting (5%), high-dependency unit (5%), or at home (90%). In the B state, all ventilatory support is assumed to be provided at home. All patients in the E state are assumed to receive NIV >16 hours/day. 25% of patients are assumed to receive NIV >16 hours/day in the paediatric ICU, and in the high-dependency unit settings, while the remaining 50% of patients are assumed to receive NIV >16 hours/day at home. The proportion of patients receiving ventilatory support in each of the C, D and E states was reported to be based on a UK advisory board conducted by the Applicant, though the proportion of patients receiving ventilatory support at home in the E state was higher in the study (70%) than used in the model (50%). This adjustment was based on clinical opinion in Ireland which indicated that there are less patients receiving NIV>16 hours per day at home than in the UK. Assumptions for the B state were made by the Applicant. Tracheostomy was not included in the model, as per clinical opinion to the Applicant.

Costs for permanent assisted ventilation (NIV>16 hours per days) in the E state and NIV<16 hours per day in the B, C and D health states were derived from the Noyes et al. 2006 study (27). The Noyes study provides detailed costs associated with ventilator-dependent children

in the UK under different healthcare settings including home-based, high-dependency units and intensive care units (including costs regarding ventilation support and social services). Total cost per 12 months across three hospital-settings ranged from £155,158 to £630,388 (UK GBP 2002). These costs were based on seven hospitalised children, only two of whom had a "congenital anomaly" (the remainder had a spinal/brain injury), and all of whom were receiving positive pressure ventilation by tracheostomy for 20-24 hours per day. The total cost per 12 months across three home care settings ranged from £161,174 to £239,855 (UK GBP 2002). Cost components included nursing and person care, equipment, hospital services, community health services, pharmacy, disposably equipment and supplies, social services and education. The Applicant did not present any details of how the data from the Noyes study was used to derive the ventilation costs for the various health states in the model, or which cost components were included/excluded. It is not clear to the Review Group how representative the Noyes study population is of the model SMA population, as the majority of hospitalised children had a spinal/brain injury, and were ventilated using tracheostomy, a practice which is not standard in Belgium, the Netherlands of Ireland. There is a lack of transparency in the Applicant's methods of incorporating data from the Noyes et al study in healthcare resource use cost calculations.

Table 8: Ventilation costs per year in different settings in the Irish and Dutch models

	Netherlands	Ireland
High dependency unit	€691,033	€681,484
Intensive care unit	€1,385,350	€1,366,206
Home E state	€122,649	€120,314
Home D state (assumed to be 50% of E state cost)*	€61,324.28	€60,157.00
Home C state (assumed to be 50% of E state cost)*	€61,324.28	€60,157.00
Home B state (assumed to be 20% of E state cost)*	€24,529.71	€24,062.80

*Source: Based on Noyes et al. *Applicant assumption*

The healthcare costs assumed for the Irish and Dutch models are much higher than the costs assumed for the independent analysis conducted by the US Institute for Clinical and Economic Reviews (US ICER), which based healthcare costs on a claims analysis of commercial health plans comprising infantile-onset SMA (n=23), childhood-onset SMA (n=22) and later-onset SMA (n=296) patients, based on the study reported by Shieh et al. The ICER analysis also adjusted healthcare costs with additional costs for permanent ventilation based on the Noyes 2006 study, though these costs were calculated as $2,701 per month including only the costs of equipment and disposable equipment and supplies associated with ventilation dependent children living at home.

Uncertainty in SMA healthcare costs

There is significant uncertainty associated with SMA healthcare costs in the model, due to a lack of available data on existing patients treated with BSC or nusinersen, uncertainty in the nature of future outcomes for patients treatment with OA or nusinersen, and a general lack of transparency in the methods used by the Applicant to calculate costs. This lack of transparency is particularly important in relation to the costs of ventilation, which account for the vast majority of costs in the C, D and E health states. Significant differences between the Belgian SMA costs and Irish/Dutch costs are insufficiently justified. Significant differences between the Dutch costs in the OA submission and the nusinersen submission (which align very closely with the Belgian costs in the OA submission) are also not identified or discussed.

The Applicant did not sufficiently justify the use of the UK HCRU study as the basis for costs in the OA submission. This study was based on resource-use estimated by clinicians, not patients or their families, and required supplementation with ventilation costs from a US

study whose representativeness is also not justified by the Applicant. The Applicant undertook deterministic and probabilistic sensitivity analyses and scenario analyses. For the deterministic sensivity analyses, inputs were varied by +/-20%. This approach may be reasonable in situations were the exact value is uncertain but may plausibly fall within the defined range. For SMA, it is difficult to define this level of plausibility given the diversity of values reported in different sources. A more appropriate approach to explore the potential impact of costs on cost effectiveness is to use different sets of values from alternative data sources. In the Belgian model, a scenario considering the medical cost of SMA derived from a German study by Klug et al (40) was applied. These costs are very closely aligned with the Belgian base case costs. The Klug et al study formed the basis for the costs included in the Dutch reimbursement report for nusinersen. The study estimated the cost of illness among 189 patients with SMA types 1 to 3 aged <1 to 73 years, using standardised questionnaires developed with input from clinicians, health-economists and patient representatives. Patients with genetically confirmed SMA were identified via the German SMA patient registry. The study included 20 patients with SMA 1, 115 patients with SMA 2 and 130 patients with SMA 3, and included direct medical costs associated with inpatient and outpatient visits, rehabilitation, drug treatment, artificial nutrition, medical aids and respiratory management. In the Dutch model, a scenario including the medical cost of SMA from the Dutch nusinersen reimbursement report (also based on Klug et al) was used, according to the Applicant, however the costs used in this scenario are significantly higher than those used in the nusinersen report. The Applicant didn't explain why the scenario was described as corresponding to the nusinersen report, while actually including costs that are much higher.

Given the limitations identified with the use of the HCRU study and the Noyes et al study, and the previous use of the Klug et al study for the Dutch nusinersen reimbursement report, the Review Group considers that costs from the Klug et al study may represent a more appropriate source of data in the base case for all country models. The use of data from the Klug et al study maintains the Applicant's assumption that SMA Type 2 and Type 3 proxies can be used for treated SMA Type 1. This assumption has already been identified by the Review Group as problematic, and may potentially underestimate costs. Nevertheless, the Review Group consider this to be a more appropriate approach to SMA costing for this submission. Costs for Belgium and Ireland were calculated by applying OECD PPP conversion from Germany to the respective countries and inflating from €2013 to €2020. Costs for the Netherlands were taken directly from the nusinersen reimbursement report, inflated from €2013 to €2020. Costs based on the Klug et al study are closely aligned with Belgian base-case costs and are significantly lower than Dutch and Irish base case costs (Table 9).

Table 9: Health state costs based on Klug et al

	SMA Type 1 (proxy E&D health states)	SMA Type 2 (proxy C health state)	SMA Type 3 (proxy B health state)
Belgium*	€60,541	€17,253	€10,286
The Netherlands†	€65,277	€18,538	€11,003
Ireland*	€63,833	€18,191	€10,845

*Source: *Belgium/Ireland:Klug et al, converted to local €2020 using OECD PPP, and CPI for inflation. †Netherlands: Klug et al, from Dutch nusinersen reimbursement report, converted to €2020. PPP conversion rates: Ireland 1.0801, Belgium 1.0244. Inflation values for Belgium/Ireland conversion provided by the Applicant.*

2.6.2. Societal and other costs

2.6.2.1. Patients' potential income

Societal costs were included in the base case for the Netherlands, and in scenario analysis for Ireland. The Belgian submission did not include societal costs. Dutch guidelines for

conducting pharmacoeconomic studies (41) require that a societal perspective should be applied to include non-health care costs (e.g. transport, out of pocket expenses) and other indirect costs such as productivity losses (33). The Dutch model base-case (and Irish scenario analysis) therefore includes patients' potential income if patients could participate in the workforce in the future, lost family income due to SMA-specific care provided by family, and direct non-medical costs.

Patients' potential income in the Netherlands and Ireland was estimated using potential levels of education achievement reported from a 2012 survey of households in the United States (US) who have one or more member diagnosed with SMA (42), median annual Dutch/Irish income by educational achievement (43) (44, 45), and expected employment rate(46) (47) (48). The survey was conducted by the Lewin Group for the Muscular Dystrophy Association in the US in 2012, in order to estimate the non-medical costs and indirect economic impact of various neuromuscular diseases on families. The sample consisted of 279 respondents with SMA, 59 of whom self-reported as having SMA 1 and 220 of whom self-reported as having SMA 2, 3 or 4. Results were analysed according to age of onset i.e. SMA Early Onset (age 3 and younger) and SMA other. Information on education attainment was only obtained for persons who were aged 18 or above, and therefore excluded all SMA Early Onset. The Applicant assumed that the "SMA Other" group i.e. those with SMA onset at age >3 years, is representative of patients in the B and C state in the model and applied results from this group to those health states. The Applicant assumed that the level of education gained by the general US population (based on the US Census Bureau, Current Population Survey, 2017) is representative of the A state in the model, though no justification for this assumption was provided. The level of education attainment

for the "SMA Other" group in the survey were higher than for that of the general US population 2017 (19% vs 11.4%). No explanation or validation of this finding was provided.

Combining the information from the US education attainment survey, and Dutch/Irish sources of income and employment rates, the Applicant calculated the average income per patient per year in the A state (Netherlands: €50,349, Ireland: €35,650), B state (Netherlands: €40,386, Ireland: €24,753) and C state (Netherlands: €24,330, Ireland: €11,524) state. These values were inputted into the model between the ages of 25 and 68. The Applicant did not discuss the suitability of the selected data sources for use in the model, nor the availability of alternative sources of information. This is not the standard method of calculating societal costs in the Netherlands, which recommends the friction cost approach.

2.6.2.2. Lost family income

Lost family income was based on the level of care required per day. The Applicant stated that health state specific level of care information for patients with SMA was assumed based on data from the SMA UK Patient and Caregiver survey (March 2019) (49) and compared with estimates included for the economic analysis for nusinersen in the Netherlands. However, the Review Group could not identify any information in the reference provided for the SMA UK Patient and Caregiver survey to support the data used in the model. The submitted model indicates that the level of care required was actually based on KOL advice. All patients in health states D and E were assumed to require care for 16-24 hrs/day. Patients under the age of 60 months (5 years) in health-states B, C D and E were

also assumed to require care for 16-24 hrs/day. In health-states C and D, over the age of 5 years patients were assumed to require 8-15 hrs/day, decreasing to 1-8 hrs/day from the age of 22 years in the C state and no SMA-specific care needed from the age of 22 years in the B state. No further validation of these estimates was provided by the Applicant. The Review Group considered that some of the estimates were not aligned with other assumptions in the model relating to quality of life, particularly for patients in the B state (for whom 16-24 hrs/day care is assumed until the age of 5) who are assumed to have the same utility as the general population.

The lost income by level of care required was obtained from the Lewin Group survey described above, and converted to Dutch/Irish euros using the PPP for 2010 (50). The Lewin Group data appears to aggregate income loss across three disease areas including SMA, DMD and ALS. The Review Group considers that income lost by families in the US may not be representative of losses to families in the Netherlands and Ireland due to significant differences in both healthcare provision, and income. The Applicant did not discuss the suitability of using this data to represent income loss of families in the Netherlands and Ireland, nor the availability of alternative sources of information. The lost family income (Eur 2012) in the model for different levels of care are outlined in Table 10.

Table 10: Lost family income per family per year

Level of care required	Netherlands	Ireland
16-24 hrs/day	32,789	27,501
8-15 hrs/day	11,117	9,324
1-8 hrs/day	4170*	5,310
SMA-specific care not needed	0	0

Source: Lewin Group Survey from the US, converted to EUR 2020

**should be €6,331 but the model omitted to convert US costs to euros for this parameter*

2.6.2.3. Direct non-medical costs

Direct non-medical costs for early onset SMA were used as a proxy for the E and D health states. Costs for late-onset SMA was used as a proxy for the B health state, and the cost of the C health state was assumed to be the mid-point between early and late-onset SMA. Costs for early and late onset SMA patients were adapted from the Dutch reimbursement report for nusinersen for the Dutch model (32). For the Irish model, direct non-medical costs estimated for early and late-onset SMA patients were based on the Lewin Group Survey from the US, converted to EUR 2020. Significant differences exist between the Irish and US healthcare systems. No evidence was submitted to support the use of direct non-medical US costs from the Lewin Group Survey as a proxy for non-medical costs in Ireland. The vast majority of the direct non-medical costs for the D and E health states in the Irish model are accounted for by professional caregiving, based on the US survey. The Applicant already attributed a sizeable healthcare cost to the provision of ventilatory support at home and the Review Group considers that the potential for double-counting/ overlap with a non-medical cost for professional caregiving is significant.

Table 11: Annualised direct non-medical costs for the Netherlands

Health state	Caregiving (16–24 hrs/day)	Other non-medical (food, travel, dietary supplements, home, transport)	Total
E	€47,255	€21,777	€69,032
D	€28,353	€17,422	€45,774
C	€21,908	€17,444	€39,352
B	€15,463	€17,467	€32,930
A	€0	€0	€0

Source: Dutch reimbursement report for nusinersen (32)

Table 12: Annualised direct non-medical costs for Ireland (US$ converted to EUR)

Health state	Caregiving (16–24 hrs/day)	Move/modify home	Buy/modify vehicle	Other non-medical (food, travel, dietary supplements)	Total
Annualised direct non-medical costs - EUR (2020)					
E	€64,355	€4,692	€2,310	€2,682	€74,039
D	€64,355	€4,692	€2,310	€2,682	€74,039
C	€35,518	€4,504	€2,614	€4,436	€47,071
B	€6,681	€4,315	€2,918	€6,190	€20,104
A	€0	€0	€0	€0	€0

Source: Lewin Group Survey from the US

Uncertainty in SMA societal costs

As with the SMA healthcare costs in the model, there is significant uncertainty associated with SMA societal costs in the model, largely due to the Applicant's methods of adapting data from the US to the Netherlands and Ireland. This approach was not justified by the Applicant and is not considered to be an appropriate method of calculating costs for these countries. The Applicant conducted a scenario analysis incorporating unrelated medical costs from a healthcare a societal perspective based on the PAID application (51, 52), which resulted in minimal change to cost effectiveness. No further details of this data source or analysis were provided. Other than this, the Applicant did not undertake any further sensitivity analysis to explore the impact of uncertainty in societal costs on the cost effectiveness results. The Review Group incorporated non-healthcare costs from the Dutch nusinersen reimbursement report in the alternative base case analysis (Table 13). These costs are significantly higher than those used in the OA model and have a significant impact

on the cost effectiveness results. As is the case for healthcare costs, the Dutch nusinersen reimbursement report maintains the Applicant's assumption that SMA Type 2 and Type 3 proxies can be used for treated SMA Type 1. This assumption has already been identified by the Review Group as problematic, and may potentially underestimate costs.

Table 13: Non-healthcare (societal) costs for the Netherlands based on the Dutch nusinersen reimbursement report

	SMA Type 1 (proxy E&D health states)	SMA Type 2 (proxy C health state)	SMA Type 3 (proxy B health state)
Transport	€2,492	€2,457	€4,124
Informal care	€37,994	€34,415	€15,541
Other out of pocket	€15,018	€35,001	€13,430
Lost productivity	€16,814	€43,424	€30,235
Total costs	€72,319	€115,297	€63,331

Source: Dutch nusinersen reimbursement report inflated to €2020.

3. Results of incremental cost effectiveness analysis

3.1. Incremental analysis of costs and benefits

3.1.1. Applicant base-case analysis

The Applicant's base case cost-effectiveness results for OA versus nusinersen for each country are presented in Table 14. Results in Table 14 only refer to the subgroup of the licensed population addressed by the Applicant i.e. patients who are symptomatic with type 1 SMA who are assumed to be diagnosed and treated before 6 months of age. Importantly this is also a smaller population than the applicant submitted in their reimbursement claim. Cost-effectiveness results for the remaining licensed population were not included by the Applicant in the base case i.e. presymptomatic patients with SMA Type 1, patients with SMA Type 1 who are treated after 6 months of age, patients with SMA Type 2 or SMA Type 3 with up to 3 copies of the SMN2 gene, and patients who are already on nusinersen who may subsequently switch to OA. The Applicant presented an additional analysis exploring the cost effectiveness of OA versus BSC, based on an unadjusted naïve comparison of treatment effectiveness with NeuroNext natural history cohort (Table 15). Absolute outcomes e.g LYs for OA in this comparison will not match those of nusinersen comparison due to the application of MAIC weights in the latter case.

Base case results only refer to list prices of OA and nusinersen. Confidential price agreements or patient access schemes are in place for nusinersen in all three countries. The impact of potential nusinersen price discounts is explored in scenario analyses.

Table 14: Applicant base case cost-effectiveness results of onasemnogene abeparvovec versus nusinersen for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment at age ≤6 months

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
costs (€)				
Nusinersen	€2,470,038	€3,620,011	€3,468,533	€3,932,460
Onasemnogene abeparvovec	€2,420,277	€3,485,570	€3,426,522	€3,799,155
Incremental costs (€)	-€49,761	-€134,441	-€42,011	-€133,304
Life years				
Nusinersen	10.29	10.28	7.94	10.28
Onasemnogene abeparvovec	17.16	17.15	12.05	17.15
Incremental life years	6.87	6.87	4.11	6.87
QALYs				
Nusinersen	4.44	4.44	3.15	4.44
Onasemnogene abeparvovec	9.44	9.44	6.31	9.44
Incremental QALYs	5.00	5.00	3.16	5.00
ICER (€/QALY)	-€9,943	-€26,881	-€13,300	-€26,654

Onasemnogene abeparvovec dominates nusinersen i.e. it is less costly and more effective, providing a saving of between €9,943 and €26,881 across the three countries for every additional QALY of benefit.

Table 15: Applicant cost-effectiveness results of onasemnogene abeparvovec versus BSC for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment at age ≤6 months

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
BSC	€108,591	€809,053	€833,248	€962,865
Onasemnogene abeparvovec	€2,428,358	€3,461,432	€3,400,218	€3,812,772
Incremental costs	€2,319,767	€2,652,370	€2,566,970	€2,849,907
Life years				
BSC	2.28	2.28	2.11	2.28
Onasemnogene abeparvovec	19.98	19.95	13.45	19.95
Incremental life years	17.70	17.66	11.33	17.66
QALYs				
BSC	0.21	0.21	0.21	0.21
Onasemnogene abeparvovec	12.02	12.00	7.64	12.00
Incremental QALYs	11.81	11.79	7.43	11.79
ICER (€/QALY)	€196,444	€225,038	€345,554	€241,798

Results versus BSC are presented using unanchored naïve comparison (no MAIC weighting applied to OA).
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

3.1.2. Alternative base-case analysis conducted by the Review Group

An alternative base-base analysis was conducted by the Review Group, incorporating alternative plausible assumptions to fully explore the potential cost effectiveness of OA in the modelled population. The results of the alternative base case for OA compared with nusinersen and BSC, are presented in Table 16 and Table 17, respectively.

The alternative analysis differs from the Applicant's model through the inclusion of the following assumptions:

1) Treatment with nusinersen is received after OA in a proportion of patients, reflecting real-world usage observed in the LT-001 study, under the following assumptions:
    - nusinersen started at age 2 (cycle 5 onwards), assuming that clinicians will wait at least 18 months (post dose at or younger than 6 months) to initiate a second treatment.
    - uptake by patients in C and D state only. This is reflected in the current modelling approach for nusinersen which assumes 100% discontinuation in the E state and 0% discontinuation in the B state.
    - 40% uptake by patients in C and D state.
    - nusinersen cost reduced by base-case discontinuation probability in each state.
2) SMA healthcare health-state costs based on Klug et al.
3) Societal costs in the Dutch model based on Dutch nusinersen reimbursement report.

Table 16: Alternative base-case cost-effectiveness results of onasemnogene abeparvovec versus nusinersen for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment at age ≤6 months

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
Nusinersen	€2,487,257	€2,262,237	€2,059,909	€2,811,870
Onasemnogene abeparvovec	€3,498,244	€3,204,438	€3,002,671	€4,129,150
Incremental costs	€1,010,987	€942,201	€942,762	€1,317,280
Life years				
Nusinersen	10.29	10.28	7.94	10.28
Onasemnogene abeparvovec	17.16	17.15	12.05	17.15
Incremental life years	6.87	6.87	4.11	6.87
QALYs				
Nusinersen	4.44	4.44	3.15	4.44
Onasemnogene abeparvovec	9.44	9.44	6.31	9.44
Incremental QALYs	5.00	5.00	3.16	5.00
ICER (€/QALY)	€202,001	€188,392	€298,469	€263,389
	Onasemnogene abeparvovec is more costly and more effective than nusinersen, costing between €188,392 and €298,469 across the three countries for every QALY of benefit.			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Table 17: Alternative base-case cost-effectiveness results of onasemnogene abeparvovec versus BSC for Belgium, the Netherlands, and Ireland, in patients with SMA type 1, with 2 copies of SMN2, with onset of symptoms and treatment at age ≤6 months

	Healthcare payer perspective			Societal perspective
	Belgium	**The Netherlands**	**Ireland**	**The Netherlands**
Costs (€)				
BSC	€3,514,024	€137,976	€134,924	€255,112
Onasemnogene abeparvovec	€131,837	€3,402,982	€3,015,103	€4,404,935
Incremental costs	€3,382,188	€3,265,006	€2,880,179	€4,149,822
Life years				
BSC	2.28	2.28	2.11	2.28
Onasemnogene abeparvovec	19.98	19.95	13.45	19.95
Incremental life years	17.70	17.66	11.33	17.66
QALYs				
BSC	0.21	0.21	0.21	0.21
Onasemnogene abeparvovec	12.02	12.00	7.64	12.00
Incremental QALYs	11.81	11.79	7.43	11.79
ICER (€/QALY)	€286,413	€277,022	€387,717	€352,095

Results versus BSC are presented using unanchored naïve comparison (no MAIC weighting applied to OA).
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

3.2. Analysis of Uncertainty

Sensitivity and scenario analysis results are presented for the comparison versus nusinersen. To allow comparison between sensitivity and scenario analysis results in the Applicant's analysis, net monetary benefit (NMB) is presented in addition to ICERs.

**Note on the interpretation of negative ICERs and NMB in scenario analysis:*
It is not possible to compare relative cost effectiveness of scenarios based on negative ICERs as changes in the negative numerator (incremental costs) or positive denominator (incremental QALYs) in the ICER formula will cause the ICER to change in the opposite direction. By converting incremental costs and QALYs to incremental NMB, the scenarios associated with the greatest and least cost effectiveness can be clearly distinguished. If the NMB for the intervention increases following a scenario analysis, this means that the intervention is more cost-effective than it was in the base case analysis. Conversely, if the NMB falls, then the intervention is less cost-effective. Finally, if the NMB remains unchanged, then the strategy is equally as cost-effective as it was in the base case analysis.

3.2.1. Applicant's one-way/multi-way sensitivity analysis

Parameters included in the Applicant's one-way sensitivity of the cost-effectiveness analysis were varied +/-20% (or natural limits if these were within the +/- 20% range). However not all parameters were varied in the analysis, and the Review Group considers that the key drivers of cost-effectiveness i.e. assumptions underpinning treatment effectiveness, are not captured in this analysis. A key driver of the incremental cost-effectiveness ratio (ICER) is the price of both

treatments, in all country models. The proportion of patients who discontinue nusinersen also has a significant impact. The cost of ventilation (hospitalisations and social services) in the C and E states has a significant impact on the Irish and Dutch models. Other variables have limited influence on the ICER estimates. With the exception of drug price changes, OA remained dominant (or highly cost-effective with ICERs <€10,000/QALY) versus nusinersen all other scenarios in the one-way sensitivity analyses. The Applicant presented multi-way sensitivity analysis in which the three variables with the largest impact on the results (excluding drug treatment costs) in the one-way sensitivity analysis were varied simultaneously. These changes did not result in ICERs going beyond €13,000/QALY in any case. One-way/multiway deterministic sensitivity analysis based on arbitrary +/-20% limits is limited in its ability to meaningfully capture uncertainty in the model inputs and their impact on cost effectiveness. This is largely due to the number of critical assumptions which have been made in the model regarding treatment effectiveness, source of health-state costs and utilities, and the use of proxies, which have not been addressed in one-way/multiway sensitivity analysis. For these reasons, tornado diagrams of the Applicant's one-way sensitivity analysis have not been presented here.

3.2.2. Applicant's probabilistic sensitivity analysis

As discussed in Section 2.3, treatment effectiveness inputs from OA and nusinersen studies are not varied in PSA and uncertainty associated with treatment effects is therefore not captured. The Review Group considers the exclusion of treatment effects from the PSA to be inappropriate, particularly given the very small number of patients used to inform OA treatment

outcomes. The Applicant declined requests at to update the PSA to include treatment effectiveness inputs from OA and nusinersen trials. The results of the Applicant's PSA are presented here for completeness, but given the exclusion of uncertainty in treatment effects, a key driver of the model, the Review Group considers that PSA results are not meaningful. The Applicant's PSA, based on 1000 simulations, suggested that OA has a 100% probability of cost-effectiveness versus nusinersen in Belgium, based on a willingness-to-pay (WTP) threshold of €146,126 per QALY i.e. three times the Belgian GDP/inhabitant). The probability of cost effectiveness in the Netherlands, based on a WTP threshold of €80,000/QALY (chosen following calculation of 0.92 (95% CI: 0.92-0.93) for the burden of disease, using the proportional shortfall method) was calculated at 82.2%. In Ireland, at the WTP thresholds of €20,000 and €45,000 per QALY, OA has 64.7% and 76.2% probability of cost-effectiveness, compared with nusinersen. As outlined, the PSA does not capture uncertainty in treatment effects and therefore the results have limited validity. For this reason, scatterplots and CEACs of the Applicant's PSA have not been presented here.

3.2.3. Applicant's expected value of perfect information (EVPI) analysis

The results of the Applicant's EVPI analysis are presented here for completeness but, as discussed in section 5.2 above, given the exclusion of uncertainty in treatment effects, a key driver of the model, the Review Group considers that EVPI results are not meaningful. For the estimation of the population EVPI, the Applicant aligned the cohort size with the number of expected eligible patients for OA in Belgium in each year i.e. 10 in Belgium, 9 in the Netherlands and 2 in Ireland. In Belgium, at the WTP of €146,126 per QALY, both the overall EVPI (per patient) and the population EVPI are estimated to be €0. In the Netherlands, at the WTP of

€20,000, €50,000 and €80,000 per QALY, the overall EVPI is estimated to be €120,776 and €55,623 and €14,575 per patient, respectively, while the estimated population EVPI is €18,941,982, €8,723,708 and €2,285,794, respectively. In Ireland, at the WTP of €20,000 and €45,000 per QALY, the overall EVPI is estimated to be €47,504 and €24,097 per patient, respectively, while the estimated population EVPI is €1,342,848 and €681,183, respectively. As outlined, the EVPI analysis does not capture uncertainty in treatment effects and therefore the results have limited validity.

3.2.4. Other sensitivity and scenario analyses

In addition to the sensitivity analyses above, the results of the cost-effectiveness model have been subject to various scenario analyses. The scenarios included variation in the discount rates, source of utility values, source of treatment effectiveness (milestones and survival), source of SMA costs, caregiver disutilities (Dutch model), societal costs (Irish model). Not all of these scenarios were considered relevant or informative by the Review Group and a selection have been presented below (Table 18). Additional scenario analyses provided by the Applicant in response to requests from the WAR are provided in Appendix 2. These changes were not provided in the Excel models therefore we were unable to fully critically assess these scenarios. Of note a scenario assuming survival in the B state is the same as in C state (i.e. in line with SMA Type 2 patients as opposed to general population) was provided. Due to the small number of patients who achieve walking changing assumptions around mortality in the B state has limited impact on cost-effectiveness in this model.

The Applicant presented scenarios varying attainment of sitting and standing separately for OA. The review group considers that an arbitrary variation of 20% is unlikely to appropriately capture uncertainty in the proportion attaining milestones, considering the small number of patients informing these proportions and concerns about the validity of pooling START and STR1VE-US data. It would have been more appropriate to vary proportions obtaining sitting and walking simultaneously as these are likely related. Additionally, scenarios exploring uncertainty in OA and nusinersen outcomes simultaneously would have been more appropriate to explore uncertainty in relative effectiveness. These scenarios were repeated by the Review Group using the alternative base case, in addition, to a scenario exploring variation in the price of nusinersen including a range of potential discounts from 25% to 75% of the PtW (Table 19).

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Belgium				
Base case results	€2,420,277 9.44	€2,470,038 4.44	-€9,943.00	€274,761
DISCOUNT RATES				
Costs and effects at 0%	€2,597,239 12.77	€3,452,143 5.74	-€121,660.00	€1,171,254
Costs and effects at 5%	€2,355,507 5.51	€2,102,632 2.8	€93,456	-€130,925
UTILITY VALUES				
Applying on-treatment utilities from US ICER for both treatments (0.10 for D state; 0.05 for C state)	€2,420,277 10.33	€2,470,038 4.92	-€9,205	€293,211
Using CHERISH values	€2,420,277 13.2	€2,470,038 7.84	-€9,277	€290,961
Caregiver disutility scores included	€2,420,277 8.83	€2,470,038 3.95	-€10,207	€269,361
TREATMENT EFFECTIVENESS (MILESTONES AND SURVIVAL)				
Use of MAIC POOLED dataset, but with 20% less sitters by 36 months of age compared to empirical data	€2,390,318 7.88	€2,470,038 4.44	-€23,182	€234,520

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Use of MAIC POOLED dataset but with 20% more sitters by 36 months of age compared to empirical data	€2,450,235 11.01	€2,470,038 4.44	-€3,013,71	€315,453
Use of MAIC POOLED dataset, but with no walkers by 36 months of age	€2,425,838 8.79	€2,470,038 4.44	-€10,163	€239,950
Survival of onasemnogene abeparvovec equal - nusinersen's survival	€2,345,853 5.5	€2,470,038 4.44	-€117,444	€171,885
NATURAL HISTORY DATA				
Loss of independent ambulation and independent sitting after 6 years of age	€2,454,516 8.62	€2,470,038 4.44	-€3,714	€203,622
Use of Novartis Gene Therapies external PNCR control dataset for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€2,444,643 9.46	€2,477,428 4.44	-€6,531	€258,685
Use of Finkel et al. 2017a (ENDEAR sham control) for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€2,433,389 9.44	€2,472,742 4.44	-€7,862	€264,353
EXPLORATORY SCENARIO				
Proxy analysis for pre-symptomatic patient population	€2,283,469	€8,014,978	N/A (Cost-minimization of OA)	€5,731,509
The Netherlands (Societal)				
Base case results	€3,799,155	€3,932,458	-€26,654	€358,360

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
	9.44	4.44		
DISCOUNT RATES				
Costs and effects at 0%	€4,959,485 12.75	€5,686,114 5.73	-€103,595	€1,042,264
UTILITY VALUES				
Applying on-treatment utilities from US ICER for both treatments (0.10 for D state; 0.05 for C state)	€3,814,777 10.32	€3,937,366 4.92	-€22,693	€365,685
Using CHERISH values	€3,814,777 13.19	€3,937,366 7.83	-€22,876	€363,738
Caregiver disutility scores included	€3,814,777 8.82	€3,937,366 3.95	-€25,164	€341,811
TREATMENT EFFECTIVENESS (MILESTONES AND SURVIVAL)				
Use of MAIC POOLED dataset, but with 20% less sitters by 36 months of age compared to empirical data	€3,724,733 7.87	€3,937,366 4.44	-€61,896	€367,221
Use of MAIC POOLED dataset but with 20% more sitters by 36 months of age compared to empirical data	€3,904,821 11.00	€3,937,366 4.44	-€4,956	€328,074
Use of MAIC POOLED dataset, but with no walkers by 36 months of age	€3,843,039 8.79	€3,937,366 4.44	-€21,675	€290,165
	€3,852,324	€3,937,366	-€80,502	€132,579

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Survival of onasemnogene abeparvovec equal - nusinersen's survival	5.49	4.44		
NATURAL HISTORY DATA				
Loss of independent ambulation and independent sitting after 6 years of age	€3,907,276 8.61	€3,937,366 4.44	-€7,205	€218,023
Use of Novartis Gene Therapies external PNCR control dataset for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€4,083,385 9.45	€3,987,426 4.44	€19,130	€129,762
Use of Finkel et al. 2017a (ENDEAR sham control) for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,973,019 9.44	€3,956,665 4.44	€3,269	€208,737
EXPLORATORY SCENARIO				
Proxy analysis for pre-symptomatic patient population	€2,825,866	€7,045,637	N/A (Cost-minimization of OA)	€4,219,771
Ireland				
Base case results	€3,426,522 6.31	€3,468,533 3.15	-€13,300	€184,151
DISCOUNT RATES				
Costs and effects at 0%	€4,426,299 12.75	€5,023,530 3.24	-€85,161	€912,813

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Costs and effects at 10%	€2,854,662 5.73	€2,460,755 1.76	€265,536	-€327,152
UTILITY VALUES				
Applying on-treatment utilities from US ICER for both treatments (0.10 for D state; 0.05 for C state)	€3,426,522 9.24	€3,468,533 3.54	-€12,268	€196,119
Using CHERISH values	€3,426,522 9.24	€3,468,533 6.03	-€13,084	€186,502
Caregiver disutility scores included	€3,426,522 8.79	€3,468,533 5.63	-€13,583	€181,194
TREATMENT EFFECTIVENESS (MILESTONES AND SURVIVAL)				
Use of MAIC POOLED dataset, but with 20% less sitters by 36 months of age compared to empirical data	€3,347,308 5.26	€3,468,533 3.15	-€57,278	€216,466
Use of MAIC POOLED dataset but with 20% more sitters by 36 months of age compared to empirical data	€3,505,735 7.35	€3,468,533 3.15	€8,856	€151,836
Use of MAIC POOLED dataset, but with no walkers by 36 months of age	€3,459,767 6.03	€3,468,533 3.15	-€3,405	€138,329
Survival of onasemnogene abeparvovec equal nusinersen's survival	€3,484,615 3.69	€3,468,533 3.15	€29,531	€8,424

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Initially higher discontinuation rate of nusinersen decreasing gradually in the first four years after treatment initiation (i.e. years 2-5 in the model) and flattening at 3% in subsequent years in the D, C and B states	€3,426,522 6.31	€3,386,309 2.80	€11,475	€117,484
NATURAL HISTORY DATA				
Use of Novartis Gene Therapies external PNCR control dataset for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,663,769 6.32	€3,512,932 3.15	€47,556	-€8,108
Use of Finkel et al. 2017a (ENDEAR sham control) for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,567,124 €6.31	€3,485,690 3.15	€25,776	€60,737
EXPLORATORY SCENARIO				
Proxy analysis for pre-symptomatic patient population	€2,539,235 18.75	€6,237,750 18.75	NA (cost minimisation)	€3,698,515
SOCIETAL COSTS				
Societal costs included: direct non-medical costs, lost family income and potential patient income	€4,199,822 6.31	€4,068,041 3.15	€41,720	€10,359
COST ASSUMPTIONS				

Table 18: Applicant's scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Replacing the base case health state costs with health state costs based on UK resource use (i.e. original resource use data from the UK HCRU study) and Irish unit costs where available	€3,386,463 6.31	€3,426,657 3.15	-€12,725	€182,334

Note: Values are reported per the economic model, discrepancies are due to rounding

Abbreviations: ICER, incremental cost effectiveness ratio; N/A, not applicable; OA, onasemnogene abeparvovec; OS, overall survival; PNCR, Paediatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; UK, United Kingdom; US, United States; vs. versus; EFS, event-free survival; ITC, indirect treatment comparison; MAIC, matching-adjusted treatment comparison; US ICER, United States Institute of Clinical and Economic Review.

* If scenario NMB>base case NMB, OA is more cost effective in the scenario than in the base case, and vice versa. Negative NMB indicates intervention is not cost-effective at the €45,000/QALY threshold

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Belgium				
Base case results	€3,498,244 9.44	€2,487,257 4.44	€202,001	-€785,768
DISCOUNT RATES				
Costs and effects at 0%	€4,399,992 12.77	€3,463,175 5.74	€133,317	-€620,602
Costs and effects at 5%	€3,171,938 5.51	€2,122,158 2.80	€387,972	-€928,019
UTILITY VALUES				
Applying on-treatment utilities from US ICER for both treatments (0.10 for D state; 0.05 for C state)	€3,498,244 13.20	€2,487,257 4.92	€187,022	-€767,730
Using CHERISH values	€3,498,244 13.20	€2,487,257 7.84	€188,472	-€769,602
Caregiver disutility scores included	€3,498,244 12.61	€2,487,257 7.36	€192,662	-€774,852
Use of MAIC POOLED dataset, but with 20% less sitters by 36 months of age compared to empirical data	€3,288,352 7.88	€2,487,257 4.44	€232,954	-€646,346
Use of MAIC POOLED dataset but with 20% more sitters by 36 months of age compared to empirical data	€3,708,137 11.01	€2,487,257 4.44	€185,802	-€925,191

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Use of MAIC POOLED dataset, but with no walkers by 36 months of age	€3,542,940 8.79	€2,487,257 4.44	€242,730	-€859,969
Survival of onasemnogene abeparvovec equal - nusinersen's survival (D state)	€2,974,475 5.50	€2,487,257 4.44	€460,773	-€439,636
NATURAL HISTORY DATA				
Loss of milestones with OA in the longer term using Wadman at al data on SMA type 2 and 3 patients (as proxies for C and B states)	€3,553,238 8.62	€2,487,257 4.44	€255,050	-€877,903
Use of Novartis Gene Therapies external PNCR control dataset for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,534,956 9.46	€2,495,316 4.44	€207,117	-€813,759
Use of Finkel et al. 2017a (ENDEAR sham control) for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,513,799 9.44	€2,490,197 4.44	€204,493	-€798,351
EXPLORATORY SCENARIO				
Proxy analysis for pre-symptomatic patient population	€2,701,919	€8,065,905	N/A (Cost-minimization of OA)	€5,363,986
COST ASSUMPTIONS				
Nusinersen discount 25% of PtW	€3,226,135	€1,943,726	€256,233	-€1,057,191
Nusinersen discount 50% of PtW	€2,954,027	€1,400,194	€310,464	-€1,328,613
Nusinersen discount 75% of PtW	€2,681,918	€856,663	€364,696	-€1,600,036

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
The Netherlands (Societal perspective)				
Base case results	€4,129,150 9.44	€2,811,870 4.44	€263,389	-€1,092,223
DISCOUNT RATES				
Costs and effects at 0%	€6,175,579 0.22	€4,358,641 5.73	€259,040	-€1,501,303
UTILITY VALUES				
Applying on-treatment utilities from US ICER for both treatments (0.10 for D state; 0.05 for C state)	€4,315,053 13.19	€2,811,870 4.92	€278,258	-€1,260,088
Using CHERISH values	€4,315,053 13.19	€2,811,870 7.83	€280,506	-€1,262,036
Caregiver disutility scores included	€4,315,053 12.60	€2,811,870 7.36	€286,656	-€1,267,210
TREATMENT EFFECTIVENESS (MILESTONES AND SURVIVAL)				
Use of MAIC POOLED dataset, but with 20% less sitters by 36 months of age compared to empirical data	€3,973,593 7.87	€2,811,870 4.44	€338,176	-€1,007,137
Use of MAIC POOLED dataset but with 20% more sitters by 36 months of age compared to empirical data	€4,656,513 11.00	€2,811,870 4.44	€280,884	-€1,549,116
Use of MAIC POOLED dataset, but with no walkers by 36 months of age	€4,362,523 8.79	€2,811,870 4.44	€356,309	-€1,354,814

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Survival of onasemnogene abeparvovec equal - nusinersen's survival	€3,480,983 5.49	€2,811,870 4.44	€633,406	-€621,577
NATURAL HISTORY DATA				
Loss of independent ambulation and independent sitting after 6 years of age	€4,362,032 8.61	€2,811,870 4.44	€371,183	-€1,362,230
Use of Novartis Gene Therapies external PNCR control dataset for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€4,378,465 9.45	€2,823,858 4.44	309,931	-1,328,889
Use of Finkel et al. 2017a (ENDEAR sham control) for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€4,344,584 9.44	€2,816,293 4.44	€305,538	-€1,303,202
EXPLORATORY SCENARIO				
Proxy analysis for pre-symptomatic patient population	€3,475,437 35.16	€7,323,482 35.16	N/A (Cost-minimization of OA)	€3,848,045
COST ASSUMPTIONS				
Nusinersen discount 25% of PtW	€3,907,845	€2,341,832	€313,123	-€1,340,956
Nusinersen discount 50% of PtW	€3,686,540	€1,871,794	€362,857	-€1,589,689
Nusinersen discount 75% of PtW	€3,465,234	€1,401,756	€412,591	-€1,838,421
Ireland				
Base case results	€3,002,671 6.31	€2,059,909 3.15	€298,469	-€800,622

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
DISCOUNT RATES				
Costs and effects at 0%	€3,986,287 12.75	€3,108,651 5.73	€125,145	-€562,054
Costs and effects at 10%	€2,482,483 3.24	€1,445,821 1.76	€698,823	-€969,907
UTILITY VALUES				
Applying on-treatment utilities from US ICER for both treatments (0.10 for D state; 0.05 for C state)	€3,002,671 6.96	€2,059,909 3.54	€275,291	-€788,655
Using CHERISH values	€3,002,671 9.24	€2,059,909 6.03	€293,612	-€798,271
Caregiver disutility scores included	€3,002,671 8.79	€2,059,909 5.63	€298,194	-€800,491
TREATMENT EFFECTIVENESS (MILESTONES AND SURVIVAL)				
Use of MAIC POOLED dataset, but with 20% less sitters by 36 months of age compared to empirical data	€2,845,412 5.26	€2,059,909 3.15	€371,141	-€690,263
Use of MAIC POOLED dataset but with 20% more sitters by 36 months of age compared to empirical data	€3,159,929 7.35	€2,059,909 3.15	€261,856	-€910,982
Use of MAIC POOLED dataset, but with no walkers by 36 months of age	€3,037,076 6.03	€2,059,909 3.15	€339,392	-€847,605
	€2,599,621	€2,059,909	€991,101	-€515,207

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Survival of onasemnogene abeparvovec equal nusinersen's survival	3.69	3.15		
Initially higher discontinuation rate of nusinersen decreasing gradually in the first four years after treatment initiation (i.e. years 2-5 in the model) and flattening at 3% in subsequent years in the D, C and B states	€3,002,671 6.31	€1,927,357 2.80	€306,850	-€1,105,179
NATURAL HISTORY DATA				
Loss of independent ambulation and independent sitting after 6 years of age	€3,048,545 5.87	€2,059,909 3.15	€363,482	-€866,241
Use of Novartis Gene Therapies external PNCR control dataset for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,037,549 6.32	€2,067,211 3.15	€305,931	-€827,609
Use of Finkel et al. 2017a (ENDEAR sham control) for D state OS and EFS: fitted curve kept as Weibull, survival limit as in base case	€3,017,886 6.31	€2,062,587 3.15	€302,372	-€813,128
EXPLORATORY SCENARIO				
Proxy analysis for pre-symptomatic patient population	€2,380,179 18.75	€5,802,580 18.75	NA (cost minimisation)	€3,422,401
SOCIETAL COSTS				
	€3,002,671	€2,059,909	€353,490	-€974,414

Table 19: Alternative base-case, Review Group scenario analyses results

	Total Costs Total QALYs *Onasemnogene abeparvovec (OA)*	**Total Costs Total QALYs** *Nusinersen*	**ICER (€/QALY) OA vs nusinersen** *In all cases where ICER is negative, OA dominates*	**Net monetary benefit (NMB)*** *Calculated at the €45,000/QALY threshold*
Societal costs included: direct non-medical costs, lost family income and potential patient income	6.31	3.15		
COST ASSUMPTIONS				
Replacing the base case health state costs with health state costs based on UK resource use (i.e. original resource use data from the UK HCRU study) and Irish unit costs where available	€3,002,671 6.31	€2,059,909 3.15	€298,469	-€800,622
Nusinersen discount 25% of PtW	€2,811,739	€1,654,383	€366,408	-€1,189,009
Nusinersen discount 50% of PtW	€2,620,808	€1,248,857	€434,347	-€1,403,604
Nusinersen discount 75% of PtW	€2,429,877	€843,331	€502,285	-€1,618,198

Note: Values are reported per the economic model, discrepancies are due to rounding

Abbreviations: ICER, incremental cost effectiveness ratio; N/A, not applicable; OA, onasemnogene abeparvovec; OS, overall survival; PNCR, Peadiatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; UK, United Kingdom; US, United States; vs. versus; EFS, event-free survival; ITC, indirect treatment comparison; MAIC, matching-adjusted treatment comparison; US ICER, United States Institute of Clinical and Economic Review.

* If scenario NMB>base case NMB, OA is more cost effective in the scenario than in the base case, and vice versa. Negative NMB indicates intervention is not cost-effective at the €45,000/QALY threshold

4. Budget Impact Analysis

4.1. Eligible population and market share

The Applicant's reimbursement claim is for:

- All symptomatic SMA type 1 patients, and
- Pre-symptomatic SMA patients with up to three copies of the SMN2 gene.

The reimbursement claim is narrower than the product's licensed indication which also includes symptomatic SMA patients with up to three copies of the SMN2 gene. The Review Group conducted scenario analysis examining the additional budget impact if OA was reimbursed for the total licensed population.

The term "prevalent patients" is used by the applicant in the dossier to describe two distinct cohorts of patients in the analysis depending on the context. For clarity, we used the term prevalent patients to represent patients currently known to be eligible for treatment. The Applicant's approach to estimating the eligible population and market share differed across the three countries. A unique approach was taken in the Belgian model given a newborn screening program for SMA is in place.

4.1.1. Definition of eligible patients under the Reimbursement Claim

4.1.1.1. Ireland and Netherlands

As for the cost-effectiveness model, the Applicant only modelled patients with SMA type 1 in the initial submission. Presymptomatic patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 were not included despite their inclusion in the

reimbursement claim. The Applicant did not provide justification for their omission and it is expected that clinicians will seek treatment for these patients in clinical practice. A screening program is planned in the Netherlands in the time horizon of the model which will result in the increased identification of these patients in clinical practice. Given the inheritance pattern of SMA, targeted screening of asymptomatic patients in families who have a history of SMA in both countries means that a cohort of patients will present for treatment even without a screening program in place. The Applicant's assumption that no asymptomatic non-type 1 patient will be treated with OA in the Netherlands or Ireland is inappropriate and underestimates the budget impact associated with reimbursement.

The Applicant further narrowed the size of the eligible patient population by excluding the current prevalent cohort of type 1 patients (estimated by the Applicant as five patients in Ireland, not estimated by the Applicant for the Netherlands). The Applicant assumed that patients who have been diagnosed before the launch of OA are not switched from nusinersen. However, as for the Belgian model (described below) it is expected that many patients will switch given the lower burden of administration with OA and possible treatment failures with nusinersen.

4.1.1.2. Belgium

The Applicant's definition of the eligible patient population was broader in the Belgian model where the Applicant included all pre-symptomatic SMA patients (with up to 3 copies of SMN2) in addition to symptomatic SMA type 1 patients in line with the Applicant's proposed reimbursement claim. The Applicant estimated the incidence of this population by extrapolating

incidence rates derived from the newborn screening program for SMA in Southern Belgium to the total Belgian population. In contrast to the Dutch and Irish models, the Applicant also accounted for the current prevalent cohort of patients with SMA type 1.

4.1.2. Size of the Eligible Population

4.1.2.1. Ireland and Netherlands

The Applicant estimated the incidence of all types of SMA using country specific incidence data derived in one of two papers by Verhaart et al using information reported from genetic testing centres (53). The Review Group is concerned that the incidence rate for Ireland appears low considering the known prevalence of type 1 SMA in Ireland given the high mortality rates associated with the disease. Given the rarity of the condition, random variation could have had a substantial impact on its derivation. Application of the median European rate of 11.9 per 100,000 may be more appropriate. The Applicant estimated that 60% were type 1 using data cited by Verhaart et al in their second paper (54). This is much higher than that reported by the Applicant from the Belgian BNMDR register where the proportion of type 1 is 16% (from type 1-3) or an estimate of 18.4% in Verhaart et al's first paper (53). Patients with SMA type 1 have a shorter life expectancy than patients with SMA type 2 or 3 and thus the percentage of these patients within the total SMA population is significantly underestimated in prevalence-based registries.

4.1.2.2. Belgium

The Applicant extrapolated incident rates of SMA identified from newborn screening in Southern Belgium to the total Belgian population. The Applicant estimated an incidence rate of

SMA of 1 in 7,000 (14.29 per 100,000) and that 66.67% of these would have two or three copies of the SMN gene and therefore be eligible for treatment with OA under the reimbursement claim. Based on the data from the BNMDR register, the Applicant estimated the size of the Type 1 current prevalent cohort as 18 patients which was consistent with estimates derived by the Applicant using literature estimates. The Applicant estimated that five patients in year one, and three patients in year two, would switch from nusinersen to OA.

4.1.2.3. Applicant Parameters

A summary of parameters applied by the Applicant is presented in Table 20.

Table 20 Parameters used by the Applicant to estimate the Eligible Population

Parameter	Ireland		Netherlands		Belgium		Review Group Commentary
	Value	*Reference*	*Value*	*Reference*	*Value*	*Reference*	
SMA Incidence	5.6 per 100,000	Verhaart et al 2017 (53)	10.1 per 100,000	Verhaart et al 2017 (53)	1 in 7000 (14.29 per 100,000)	Belgian Newborn screening program Applicant submission	The incidence rate applied in the Irish study is on the lower bound of estimates in the literature and appears low for a prevalent population of 5 patients with a short life-expectancy. Given the rarity of the condition, random variation could have had an impact on the derivation rate. Application of the median European rate of 11.9 per 100,000 may be more appropriate in the Netherlands and Irish models. (53).
Proportion Type I SMA	60%	Verhaart et al 2017 (54)	60%	Verhaart et al 2017 (54)	16.81% of Type 1 to 3. (Reported but not used by the Applicant in the budget impact model)	BNMDR Registry Applicant Submission	The BNMDR registry represents a robust estimate of the proportion of Type 1 patients from prevalent patients An alternative reference estimates the proportion of Type 1 as 18.4% (53). 60% is reported by Verhaart et al (54) citing Ogino et al (55). The original reference Ogino et al (55) reports prevalence of 57.5% of Type

Table 20 Parameters used by the Applicant to estimate the Eligible Population

Parameter	Ireland		Netherlands		Belgium		Review Group Commentary
	Value	*Reference*	*Value*	*Reference*	*Value*	*Reference*	
							1 which is implied to be from Genetic Data. Patients with SMA type 1 have a shorter life expectancy than patients with SMA type 2 or 3 and thus the percentage of these patients within the total SMA population is significantly underestimated in prevalence-based registries.
Proportion of SMA patients with 2 or 3 SMN2 copies	NE		NE		66.67%	BNMDR Registry Applicant Submission	*Note the Belgian model does not estimate the budget impact exclusively for SMA type 1 patients, it estimates eligible patient numbers based on country-specific newborn screening data for patients with 2 or 3 copies of SMN2.
Number of prevalent patients with SMA Type 1.	5 patients (not included by the Applicant in the eligible population)	Clinical opinion	Not reported. (not included by the Applicant in the eligible population)		18 patients	BNMDR Registry Applicant Submission	Extrapolating SMA Type 1 prevalence from the Belgian to the Dutch population gives an estimated Type 1 prevalence of 27.14 patients.
Proportion of Incident	94.1%	Nusinersen UK EAP	100%	Assumption	100%	Assumption	Given the burden of administration is less for

Table 20 Parameters used by the Applicant to estimate the Eligible Population

Parameter	Ireland		Netherlands		Belgium		Review Group Commentary
	Value	*Reference*	*Value*	*Reference*	*Value*	*Reference*	
population who present for Pharmacotherapy							onasemnogene abeparvovec compared to nusinersen, the proportion who present for pharmacotherapy is likely to be higher than this and approach 100% for the subgroups estimated. This is estimated indirectly in the Belgian model by the inclusion of BSC as a comparator.
Market Share	Year 1 - 33% Year 3:66.7% Year 5: 100%	Applicant Assumption	Year 1, 50% year 3 75% Year 5: 100%	Applicant Assumption	63% in Year 1, 67% in Year 2 75% in Year 3. The applicant also assumed 8 patients (in total) would switch from nusinersen in years 1 and 2.	Applicant Assumption	The market share estimates appear low given the burden of administration of the comparator and the Applicant's projected benefit of the intervention.
Required Level of anti-AAV9 Titre	87.8%				Not accounted for in the model.		

Table 20 Parameters used by the Applicant to estimate the Eligible Population

Parameter	Ireland		Netherlands		Belgium		Review Group Commentary
	Value	*Reference*	*Value*	*Reference*	*Value*	*Reference*	
Mortality Rate	0% Assumption						Assuming a 0% mortality rate for both treatments underestimates the net drug budget impact associated with OA as it leads to an overestimation of the cost-offsets associated with nusinersen treatment. The average annual mortality rate in the nusinersen arm for the first five years of the Applicant's cost effectiveness model is 9.67%.
Nusinersen Discontinuation Rate	3% Assumption						

BNMDR, Belgian neuromuscular disease registry; BSC, Best Supportive Care; OA, onasemnogene abeparvovec; NE, Not estimated.

4.1.2.4. Alternative Reimbursement Claim Scenario

The Review Group adjusted the Applicant's estimates to account for the inclusion of prevalent type 1 patients (in line with the reimbursement claim) and to examine the impact of alternative plausible assumptions. The following adjustments were made:

- Increased incidence of SMA in the Irish and Dutch models to the European average of 11.9 per 100,000.
- Included prevalent type 1 patients in the eligible patient population for the Netherlands and Ireland. (It was already included by the Applicant for Belgium). The Applicant stated the size of Irish type 1 prevalent population was 5 patients. It was assumed Dutch type 1 prevalence was 27.14 patients (equivalent to the size of the Belgian prevalent population after accounting for population size). It was assumed that 25% of prevalent patients are treated in both years one and two.
- Market uptake rates were increased to account for the comparative lower burden of administration compared to nusinersen. The market share for OA was increased to 75% in years one and two, 90% in year three and increasing to 100% in years four and five for the incident population.
- Assume 40% of patients receiving OA start treatment with nusinersen two years after treatment with OA as observed in LT-001.
- The discontinuation rate was increased from 3% to 12.67% as a proxy to reflect an annual average 9.67% mortality rate (as calculated in the first five years of the nusinersen cost-effectiveness model). It was not possible to amend the mortality parameter in the model directly in the time available for the analysis.

- SMA costs were updated in line with costs applied in the alternative base case in the economic model.

The Review Group did not include the treatment of presymptomatic patients with up to 3 copies of the SMN2 gene for the Dutch and Irish models in the alternative reimbursement claim scenario because of a lack of data.

4.1.2.5. Licensed Indication Alternative Scenario

The Review Group also estimated the **additional** budget impact of extending reimbursement to eligible type 2 and 3 patients in line with the licensed indication of OA (patients with up to three copies of the SMN2 gene). This scenario includes incident and prevalent non-type 1 patients in the Irish and Dutch models (regardless of symptom status) and prevalent non-type 1 patients in the Belgian model. Incident presymptomatic patients who are eligible for treatment are already accounted for and included in the Applicants reimbursement claim scenario for Belgium.

The following assumptions were made by the Review Group:

- Total SMA incidence was estimated as 11.9 per 100,000. It was assumed the proportion of eligible (incident) patients is 30.8% of the total SMA population after accounting for the relationship between SMA type and SMN2 copies reported by Calucho et al (56). International data suggests 95% of Type 2 and 54% of Type 3 patients have up to 3 copies of SMN2, and therefore would be eligible for treatment with OA (56).
- Discontinuation rate maintained at 3% (mortality assumed to be 0%).
- 50% market share for OA for the incident population was assumed for all years of the model.

- The size of the Belgian eligible prevalent non-type 1 population was estimated from the numbers reported by the applicant in the BNMDR registry after adjustment for SMN2 copy number. This figure was used to estimate the size of Dutch and Irish prevalent population after adjustment for population size.
- It is assumed that 25% of these start treatment with OA in Year 1 and 25% start in Year 2.
- Two years after treatment with OA, 40% of OA patients subsequently start treatment with nusinersen.

4.1.3. Results

Results under the Applicant's and Alternative reimbursement claim are presented in

Table 21 below. SMA incidence falls under the alternative reimbursement claim in the Dutch and Irish models, but inclusion of the prevalent Type 1 population and increases in the market share increases the number of patients treated in the first years of the model compared to the Applicant's estimate.

The additional patient numbers in a scenario where reimbursement is extended to the total licensed population is presented in Table 22. The additional patient numbers associated with extending reimbursement to the total licensed population is also substantial. It is highest in years 1 and 2 given a proportion of the current eligible population is modelled to receive treatment in these years.

Table 21 Number of Patients receiving OA annually under Applicant and Alternative Reimbursement Claim alternatives.

	Description	Year 1	Year 2	Year 3	Year 4	Year 5
Applicant Reimbursement Claim						
Belgium	All Incident (Eligible Type 1-3) and prevalent Type 1	11.32	9.83	7.69	11.32	9.83
Netherlands	Incident Type 1	4.71	7.15	8.69	9.77	9.89
Ireland	Incident Type 1	0.57	0.84	1.10	1.63	1.61
Alternative Reimbursement Claim						
Belgium	All eligible Incident (up to 3 copies of SMN2) and Prevalent Type 1	12.53	10.65	9.23	NE	NE
Netherlands	Incident and Prevalent Type 1	15.10	15.21	10.24	11.51	11.65
Ireland	Incident and Prevalent Type 1	3.96	3.92	3.15	3.46	3.43

NE, Not Estimated

Table 22 Licensed Indication Alternative Scenario: Additional Patients Numbers

	Description	Year 1	Year 2	Year 3	Year 4	Year 5
Belgium	Prevalent Type 2 or 3 with up to 3 copies of SMN2	31.70	31.70	0	NE	NE
Netherlands	Incident and Prevalent Type 2 or 3 with up to 3 copies of SMN2	50.65	50.68	2.92	2.96	2.99
Ireland	Incident and Prevalent Type 2 or 3 with up to 3 copies of SMN2	21.36	21.35	0.90	0.89	0.88

NE, Not Estimated

4.2. Gross drug budget impact

Drug costs for inclusion in the budget impact model are presented in Table 23. The inclusion and rate of VAT in budget impact estimates is not consistent across countries. The Applicant estimated the budget impact over a three-year time horizon for Belgium and a five-year time horizon for the Irish and Dutch models. Gross drug budget estimates (which represent the drug cost only for OA) projected by the Applicant and the Review Group under the reimbursement claim are presented in Table 24. The additional gross drug budget impact associated with reimbursement to the total licensed population is presented in Table 25.

The budget impact under the alternative reimbursement claim is substantially higher than that projected by the Applicant. The primary driver of this is the omission of the prevalent population in the Irish and Dutch models and the increase in the projected market share.

The additional gross drug budget impact associated with reimbursement to the total licensed population is significant and substantially higher than that of the Type 1 population.

Table 23 Drug Costs applied in the budget impact models *

	Nusinersen	Onasemnogene abeparovec
Belgium (6%) VAT	Year 1: €529,817§ Year 2+: €264,908§	€2,061,700
Netherlands (no VAT)	Year 1: €499,800 Year 2+: €249,900	€1,945,000
Ireland (23% VAT)	Year 1: €536,152 Year 2+: €268,076	€2,285,375

*The Applicant made important errors in estimating nusinersen drug costs in the Irish model and a minor error in the Dutch model. These errors have been corrected by the Review Group.
§ As calculated by the Review Group in Table 9. These costs differ <0.1% than the costs applied by the Applicant in the budget impact model. Budget impact figures based on these figures have not been re-estimated by the Review Group.

Table 24 Gross Drug Budget Impact under the Reimbursement Claim*

Gross drug budget impact	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Applicant Reimbursement Claim						
Belgium	€23,345,001	€20,266,016	€15,854,414	NE	NE	€59,465,431
Netherlands	€9,154,972	€13,906,743	€16,897,234	€19,007,085	€19,239,465	€78,205,498
Ireland	€1,294,800	€1,911,462	€2,510,381	€3,720,527	€3,685,190	€13,122,359
Alternative Reimbursement Claim						
Belgium	€25,828,144	€21,947,319	€19,025,296	NE	NE	€66,800,760
Netherlands	€29,377,313	€29,582,659	€19,908,622	€22,394,486	€22,668,281	€123,931,361
Ireland	€9,047,480	€8,949,503	€7,201,655	€7,906,120	€7,831,028	€40,935,786

*Equivalent to Belgian Level 1 Budget Impact. Irish and Netherlands drug costs were corrected under the Applicant and alternative base case as described in Table 23. NE, Not estimated.

Table 25 Licensed Indication Alternative Scenario: Additional Gross Drug Budget Impact

Gross drug budget impact	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Belgium	€65,355,890	€65,355,890	0	NE	NE	€130,711,780
Ireland	€48,825,968	€48,792,438	€2,053,805	€2,029,237	€2,009,964	€103,711,412
Netherlands	€98,506,059	€98,576,333	€5,677,644	€5,747,918	€5,818,192	€214,326,147

*Equivalent to Belgian Level 1 Budget Impact. Irish and Netherlands drug costs were corrected under the Applicant and alternative base case as described in Table **24**. NE, Not Estimated.

4.3. Net drug budget impact

Net drug budget impact projections which account for cost savings arising from the displacement of alternative drugs are presented in Table 26. These estimates do not account for the individual discounts in place for nusinersen across countries. Given that the Alternative Reimbursement claim scenario assumes that 40% of OA patients go on to receive nusinersen

after two years, the projected cost-offsets arising from displacement of nusinersen are not as great as projected by the Applicant.

Table 26 Net Drug Budget Impact under the Reimbursement Claim*

Net drug budget impact	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Applicant Reimbursement Claim						
Belgium	€18,449,747	€13,859,606	€7,553,415	NE	NE	€39,862,768
Netherlands#	€6,837,738	€9,228,161	€9,701,741	€9,139,116	€6,907,217	€41,813,972
Ireland#	€995,595	€1,320,154	€1,559,822	€2,200,272	€1,743,227	€7,819,070
Alternative Reimbursement Claim						
Belgium	€20,471,460	€15,047,831	€12,418,286	NE	NE	€47,937,577
Netherlands	€22,306,554	€18,927,096	€11,040,984	€12,063,555	€10,102,401	€74,440,590
Ireland	€7,059,394	€5,988,903	€4,490,868	€4,664,607	€3,993,267	€26,197,038

*Equivalent to Belgian Level 2 Budget Impact. Drug costs corrected by the Review Group in Applicant analysis as described in Table 23. NE Not Estimated.

Table 27 Licensed Indication Alternative Scenario: Additional Net Drug Budget Impact

Net drug budget impact	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Belgium	€48,812,526	€40,541,343	-€9,824,248	NE	NE	€79,529,621
Netherlands	€73,572,986	€61,158,935	-€10,576,298	-€6,172,575	-€11,330,100	€106,652,949
Ireland	€37,543,156	€31,875,969	-€5,117,877	-€3,086,287	-€5,432,190	€55,782,770

*Equivalent to Belgian Level 2 Budget Impact. Drug costs corrected by the Review Group in Applicant analysis as described in Table 23. NE Not Estimated.

4.4. Additional costs and cost-offsets

The net health budget impact accounts for the differential costs of drug administration across interventions and other cost-offsets on the health care system associated with reimbursement of OA including SMA care costs. These costs were estimated by the Applicant using the cost-effectiveness model. The cumulative five-year net health budget impact under the

reimbursement claim is presented in Table 28. The net health budget impact is underestimated in the Belgian model given that cost off-sets derived from Type 1 patients are applied to non-Type 1 patients. The additional net health budget impact is not presented under the licensed indication alternative scenario as it is not possible to extrapolate the cost-offsets derived by the Applicant in the CEM to non-Type 1 population.

Table 28 Net Health Budget Impact under the Reimbursement Claim*

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Applicant Reimbursement Claim						
Belgium	€18,462,411	€13,760,967	€7,302,287	NE	NE	€39,525,665
Netherlands	€6,694,354	€8,264,880	€7,426,469	€5,536,233	€2,108,731	€30,030,666
Ireland	€966,370	€1,180,791	€1,247,557	€1,683,318	€1,004,100	€6,082,137
Alternative Reimbursement Claim						
Belgium	€20,498,384	€14,911,272	€12,053,176	NE	NE	€47,462,832
Netherlands	€22,097,363	€18,546,814	€10,688,348	€11,874,674	€10,204,818	€73,412,017
Ireland	€6,954,992	€5,784,358	€4,172,072	€4,227,513	€3,468,118	€24,607,052

*Equivalent to Belgian Level 3 Budget Impact. NE, Not estimated.

4.5. Scenario Analysis

4.5.1. New Born Screening Netherlands

Following a request of the Dutch scientific advisory board (WAR) of Zorginstituut Nederland, a Dutch budget impact analysis scenario was estimated by the Applicant using the newborn screening data available for Belgium in combination with Dutch population numbers. In this scenario, the SMA incidence rate of 1 in 7000 was based on the published Belgian Newborn Screening pilot study by Dangouloff et al, 2020 (57). The percentage of patients diagnosed following newborn screening with 2 or 3 copies of SMN2 was also obtained from the same Belgian study (Dangouloff et al, 2020 (57)). Based on this new born screening pilot study, it was

assumed that 66.67% of the patients would be eligible for treatment with onasemnogene abeparvovec. Other inputs remained the same as in the submitted budget impact analysis.

Table 29Applicant Scenario Anaysis for Newborn screening in the Netherlands

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Number of patient treated with OA	7.40	11.24	13.65	15.36	15.55	63.19
Gross drug budget impact	€14,389,430	€21,858,080	€26,558,418	€29,874,600	€30,239,847	€122,920,374
Net drug budget impact	€10,744,018	€14,496,984	€15,236,454	€14,346,754	€10,833,445	€65,657,655
Net health budget impact	€10,518,667	€12,983,029	€11,660,491	€8,684,232	€3,291,837	€47,138,255

4.5.2. Exploratory analyses

4.5.2.1. Review Group

A confidential price is in place for nusinersen across all countries which is not accounted for in the estimates above. Therefore, the impact of a nusinersen discounted price was considered using discounts of 25%, 50% and 75%. The proportion of patients who will go on to receive nusinersen after treatment with OA is very uncertain and was also varied in scenario analysis. The results of both analyses are presented in Table 30 for the Alternative Reimbursement Claim and the Licensed Indication Alternative Scenario.

Table 30 Scenario Analyses Net Drug Budget Impact*

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Belgium						
NUSINERSEN DISCOUNT						
Alternative Reimbursement Claim						
25%	€21,810,631	€16,772,703	€14,070,038	NE	NE	€52,178,628
50%	€23,149,802	€18,497,575	€15,721,791	NE	NE	€57,369,168
75%	€24,488,973	€20,222,447	€17,373,544	NE	NE	€62,084,964
Licensed Indication Alternative Scenario						
25%	€52,948,367	€46,744,980	-€7,368,186	NE	NE	€92,325,160
50%	€57,084,208	€52,948,616	-€4,912,124	NE	NE	€105,120,700
75%	€61,220,049	€59,152,253	-€2,456,062	NE	NE	€117,916,240
PROPORTION OF PATIENTS WHO RECEIVE NUSINERSEN AFTER OA						
Alternative Reimbursement Claim						
0%	€20,471,460	€15,047,831	€9,763,337	NE	NE	€45,282,628
25%	€20,471,460	€15,047,831	€11,422,680	NE	NE	€46,941,971
50%	€20,471,460	€15,047,831	€13,082,023	NE	NE	€48,601,314
75%	€20,471,460	€15,047,831	€14,741,365	NE	NE	€50,260,656
Licensed Indication Alternative Scenario						
0%	€48,812,526	€40,541,343	-€16,542,365	NE	NE	€72,811,503
25%	€48,812,526	€40,541,343	-€12,343,542	NE	NE	€77,010,326
50%	€48,812,526	€40,541,343	-€8,144,718	NE	NE	€81,209,150
75%	€48,812,526	€40,541,343	-€3,945,895	NE	NE	€85,407,973
Netherlands						
NUSINERSEN DISCOUNT						
Alternative Reimbursement Claim						
25%	€24,074,243	€21,590,987	€13,257,894	€14,646,288	€13,243,871	€86,813,282
50%	€25,841,933	€24,254,877	€15,474,803	€17,229,021	€16,385,341	€99,185,975
75%	€27,609,623	€26,918,768	€17,691,713	€19,811,753	€19,526,811	€111,558,668
Licensed Indication Alternative Scenario						
25%	€79,806,254	€70,513,285	-€6,512,812	-€3,192,451	-€7,043,027	€133,571,248
50%	€86,039,522	€79,867,634	-€2,449,327	-€212,328	-€2,755,954	€160,489,548
75%	€92,272,791	€89,221,984	€1,614,159	€2,767,795	€1,531,119	€187,407,847

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
PROPORTION OF PATIENTS WHO RECEIVE NUSINERSEN AFTER OA						
Alternative Reimbursement Claim						
0%	€22,306,554	€18,927,096	€8,021,389	€7,513,056	€5,025,912	€61,794,006
25%	€22,306,554	€18,927,096	€9,908,636	€10,357,118	€8,198,718	€69,698,121
50%	€22,306,554	€18,927,096	€11,795,883	€13,201,180	€11,371,523	€77,602,235
75%	€22,306,554	€18,927,096	€13,683,130	€16,045,242	€14,544,328	€85,506,350
Licensed Indication Alternative Scenario						
0%	€73,572,986	€61,158,935	-€20,701,404	-€21,367,457	-€22,042,404	€70,620,657
25%	€73,572,986	€61,158,935	-€14,373,212	-€11,870,655	-€15,347,214	€93,140,839
50%	€73,572,986	€61,158,935	-€8,045,021	-€2,373,854	-€8,652,024	€115,661,022
75%	€73,572,986	€61,158,935	-€1,716,830	€7,122,948	-€1,956,835	€138,181,204
Ireland						
NUSINERSEN DISCOUNT						
Alternative Reimbursement Claim						
25%	€7,556,416	€6,729,053	€5,168,564	€5,474,985	€4,952,707	€29,881,725
50%	€8,053,437	€7,469,203	€5,846,261	€6,285,363	€5,912,147	€33,566,412
75%	€8,550,459	€8,209,353	€6,523,958	€7,095,742	€6,871,588	€37,251,099
Licensed Indication Alternative Scenario						
25%	€40,363,859	€36,105,086	-€3,324,957	-€1,807,406	-€3,571,652	€67,764,931
50%	€43,184,562	€40,334,203	-€1,532,036	-€528,525	-€1,711,113	€79,747,091
75%	€46,005,265	€44,563,321	€260,885	€750,356	€149,425	€91,729,252
PROPORTION OF PATIENTS WHO RECEIVE NUSINERSEN AFTER OA						
Alternative Reimbursement Claim						
0%	€7,059,394	€5,988,903	€3,641,848	€3,400,271	€2,473,037	€22,563,453
25%	€7,059,394	€5,988,903	€4,172,485	€4,190,481	€3,423,181	€24,834,443
50%	€7,059,394	€5,988,903	€4,703,123	€4,980,690	€4,373,324	€27,105,434
75%	€7,059,394	€5,988,903	€5,233,760	€5,770,900	€5,323,468	€29,376,425
Licensed Indication Alternative Scenario						
0%	€37,543,156	€31,875,969	-€9,699,730	-€9,955,919	-€10,205,199	€39,558,277
25%	€37,543,156	€31,875,969	-€6,836,072	-€5,662,399	-€7,222,069	€49,698,585
50%	€37,543,156	€31,875,969	-€3,972,414	-€1,368,879	-€4,238,938	€59,838,894

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
75%	€37,543,156	€31,875,969	-€1,108,757	€2,924,641	-€1,255,807	€69,979,202

*Equivalent to Belgian Level 2 Budget Impact. Budget Impact Figures under the licensed indication alternative scenario represent projections in addition to that estimated under the reimbursement claim.
NE, Not Estimated, OA, onasemnogene abeparvovec.

4.5.2.2. Applicant Exploratory Analyis

As part of the response to the Review Group's alternative budget impact analysis, the company conducted an additional exploratory scenario under the reimbursement claim for each country using some of the alternative data suggested by the Review Group. In this scenario, the Belgian cumulative three year net drug budget impact (Belgian Level 2 budget impact) was estimated at €42.6 million. The cumulative five year net drug budget impact for the Netherlands and Ireland was €53 million and €22 million respectively. Details of the amended parameters and full budget impact results are presented in Appendix 2.

5. Conclusion

Novartis Gene therapies submitted a dossier of evidence to support the reimbursement claim for all symptomatic SMA type 1 patients, and pre-symptomatic SMA patients with up to three copies of the SMN2 gene. This is a subpopulation of the licensed indication which includes patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene. The distinction being that the licence could be interpreted to include approximately 95% of type 2 and 54% of type 3 SMA who have the required copies of the SMN2 gene.

For the cost effectiveness model the Applicant has included a smaller population compared to their claim. The model base case only includes symptomatic type 1 SMA patients diagnosed and treated before 6 months. The review group considers this to be an important limitation. The cost effectiveness in asymptomatic/presymptomatic patients was only explored in sensitivity analysis as the OA trial in this population (SPR1NT) is as yet immature. A number of structural limitations to the modelling approach were highlighted by the review group.

The review group considered that the estimation of treatment benefit over a lifetime for OA was considerably more optimistic than the evidence provided by the Applicant could support. A key limitation is the lack of direct comparative evidence to either BSC or nusinersen. The approaches to manage this in the model do not adequately address the uncertainty. In particular, the long term effectiveness of OA is likely to be overestimated as patients remain in

the same health state for their lifetime without any deterioration. The evidence made available by the Applicant from long term studies do not support this claim.

In order to address the lack of utility data on patients in particular health states the Applicant used proxies from type 2 and 3 SMA. Clinical opinion sought by the NCPE consider some uncertainty with this assumption given that due to lack of data it is not clear what the clinical pathway of type 1 patients will be. The assumption that patients on OA who remain in state B (walking unassisted) will lead a 'normal' life similar to that of a patient without SMA is an overestimation of the benefit given the available evidence.

There were some inaccuracies with drug costs corrected by the review group. The costs of SMA were much greater in Irish and Dutch populations than in Belgian populations. This affects cost effectiveness in favour of OA as more patients receiving nusinersen stay in poor, costly health states than OA. The review group used more appropriate cost assumptions for the Irish and Dutch populations for the alternative base case.

The Applicant base case found that OA dominated nusinersen i.e. was more effective and less costly. However, the review group considered that the Applicant base case did not adequately address the uncertainties and contained some errors. The alternative base case estimated by the review group assumed some subsequent nusinersen use and more appropriate cost estimates. Across the three countries the alternative base case ICER of OA vs. nusinersen ranged from €202,001 (BE) to €263,389 (NL) to €298,469 (IRL) for every additional QALY of benefit.

The probabilistic analysis presented by the company and the associated expected value of perfect information were inadequate in addressing the uncertainty associated with the cost effectiveness estimates.

There were differences in methodologies employed for the budget impact between countries. The cumulative net budget impacts for Belgium, Netherlands and Ireland as estimated by the review group for the reimbursement claim were €47.5m, €73.4m and €24.6m respectively. In scenarios where the price of nusinersen is reduced across various ranges to account for potential local pricing discounts the net budget impact increases due to reduced nusinersen offset costs. Assumptions in relation to nusinersen subsequent use also strongly affect the budget impact.

In examining the full body of evidence the review group considers the cost effectiveness estimates to be highly uncertain. The estimates calculated by the Applicant are in most cases biasing the estimates in favour of OA and the review group considers that the evidence used to support many of these choices to be poor. In particular, the claim of life-long benefit is not robustly supported by evidence. Given the extreme uncertainty we do not consider the claim of cost effectiveness to have been adequately made.

References

1. Kirschner J, Butoianu N, Goemans N, Haberlova J, Kostera-Pruszczyk A, Mercuri E, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Eur J Paediatr Neurol. 2020;28:38-43.
2. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1-13.
3. Review. IfCaE. Spinraza and Zolgensma for spinal muscular atrophy: effectiveness and value. Final evidence report . April 3, 2019 (updated May 24, 2019). Accessed) 30 October 2020. 2019.
4. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. The New England journal of medicine. 2017;377(18):1713-22.
5. Novartis Gene Therapies. Data on file. Clinical Study Report (CSR). START (CL-101). 2018.
6. Novartis Gene Therapies. Data on file. Clinical overview onasemnogene abeparvovec [data cut 31 December 2019]. 2020.
7. European Medicines Agency. Zolgensma: EPAR - public assessment report. Available at:https://www.ema.europa.eu/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf. 2020.
8. Novartis Gene Therapies. Data on file. LT-001 Protocol. Version 5.0. 13 Jan 2020. 2020.
9. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014a;83(9):810-7.
10. Castro D, Farrar, M,A., Finkel, R,S., Tulinius, M., Krosschell, K,J., Saito, K., Zhang, Y., Bhan, I., Farwell, W., Reyna, S,P,. Longer-term Assessment of the Safety and Efficacy of Nusinersen for the Treatment of Infantile-Onset Spinal Muscular Atrophy (SMA): An Interim Analysis of the SHINE Study. Poster presented at the American Academy of Neurology, April 21–27, 2018. Los Angeles, California, USA. . 2018.
11. Castro D, Finkel RS, Farrar MA, Tulinius M, Krosschell KJ, Saito K, et al. Nusinersen in Infantile-onset Spinal Muscular Atrophy: Results from Longer-term Treatment from the Open-label SHINE Extension Study (1640). Neurology. 2020;94(15 Supplement):1640.
12. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Natural history of infantile-onset spinal muscular atrophy. Annals of neurology. 2017;82(6):883-91.
13. De Vivo D, Bertini, E., Hwu, W., et al. . Nusinersen in Infants Who Initiative Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Efficacy and Safety Results from the Phase 2 NURTURE Study. Muscular Dystrophy Association (MDA) Clinical Conference. 2018.
14. Wadman RA-O, Wijngaarde CA-O, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. (1468-1331 (Electronic)).
15. Zerres K, Rudnik-Schoneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset

proximal spinal muscular atrophy (type II and III SMA): 569 patients. Journal of the neurological sciences. 1997;146(1):67-72.
16. Central Statistics Office Ireland. Irish Life Tables 2010-2012. Available at: https://www.cso.ie/en/releasesandpublications/er/ilt/irishlifetablesno162010-2012/. 2015.
17. STATBEL. Tables de mortalité et espérance de vie. Available at: https://statbel.fgov.be/fr/themes/population/mortalite-et-esperance-de-vie/tables-de-mortalite-et-esperance-de-vie#figures. 2020.
18. Statistics Netherlands (CBS). Prognose periode-levensverwachting; geslacht en leeftijd, 2017-2060. Available at: https://opendata.cbs.nl/#/CBS/nl/dataset/83795NED/table?ts=1601419550849.
19. Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Ravà L, Bignamini E, et al. Survival of patients with spinal muscular atrophy type 1. Pediatrics. 2013;131(5):e1509-14.
20. Novartis Gene Therapies. Data on file. UK Health State Utilities Elicitation for Spinal Muscular Atrophy - Report. 01 August 2019. 2019. 2019.
21. Thompson R, Vaidya S, Teynor M. The Utility of Different Approachs to Developing Health Utilities Data in Childhood Rare Diseases; A Case Study in Spinal Muscular Atrophy (SMA). Value in Health. 2017;20(9):A725-A6.
22. US Institute for Clinical and Economic Review. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. April 3, 2019. (Updated May 24, 2019). 2019.
23. Tappenden P HJ, Kaltenthaler E, Hock E, Rawdin A, Mukuria C, Clowes M, Simonds A, Childs A. . Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal. School of Health and Related Research (ScHARR). . 2018.
24. Tilford JM, Grosse SD, Robbins JM, Pyne JM, Cleves MA, Hobbs CA. Health state preference scores of children with spina bifida and their caregivers. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2005;14(4):1087-98.
25. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. PharmacoEconomics. 2013;31(6):489-500.
26. Novartis Gene Therapies. Data on file: UK Healthcare Resource Use Study Report. 14 June 2019. 2019.
27. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. Health & Social Care in the Community. 2006;14(6):508-22.
28. INAMI. Médicaments remboursables. Product search page. Available at: https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/fr/Public/ProductSearch.
29. INAMI. Institut national d'assurance maladie-invalidité. Available at: https://www.inami.fgov.be.
30. BCFI. BCFI. Available at: www.bcfi.be.
31. INAMI. Institut National d'Assurance Maladie-Invalidité Technische Cel voor het beheer van de MZG-MFG data. Available at: https://tct.fgov.be/webetct/etct-web/anonymous?lang=fr.
32. Zorginstituut Nederland. Pakketadvies sluisgeneesmiddel nusinersen (Spinraza®) voor de behandeling van spinale musculaire atrofie (SMA). Available at: https://www.zorginstituutnederland.nl/publicaties/adviezen/2018/02/07/pakketadvies-nusinersen-spinraza-voor-de-behandeling-van-spinale-musculaire-atrofie-sma.
33. Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische

evaluaties in de gezondheidszorg. Available at: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn+voor+het+uitvoeren+van+economische+evaluaties+in+de+gezondheidszorg+%28verdiepingsmodules%29.pdf. 2016.
34. OpenDisData. Open data van de Nederlandse Zorgautoriteit. Available at: https://www.opendisdata.nl/.
35. Nederlandse Zorgautoriteit. Nederlandse Zorgautoriteit. Available at: www.nza.nl.
36. Office for National Statistics. Inflation and price indices. Available at: https://www.ons.gov.uk/economy/inflationandpriceindices.
37. Healthcare Pricing Office. ABF 2019 Admitted Patient Price List – DRG Prices for Inpatients and Daycases 2019. Available at: http://www.hpo.ie/abf/ABF2019AdmittedPatientPriceList.pdf. 2019.
38. Health Service Executive. PCRS online services database. Available at: https://www.hse.ie/eng/staff/pcrs/online-services/.
39. Novartis Gene Therapies. Data on file: UK Clinical Advisory Board: Summary Report. 28 May 2019. 2019.
40. Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet journal of rare diseases. 2016;11(1):58.
41. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Available at: https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg.
42. The Lewin Group. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. . 2012.
43. Karthaus J. Modaal en gemiddeld inkomen per leeftijd, opleidingsniveau en branche. Available at: https://bieb.knab.nl/inkomsten-uitgaven/modaal-en-gemiddeld-inkomen-per-leeftijd-opleidingsniveau-en-branche.
44. Central Statistics Office Ireland. NSA09: Mean and median hourly earnings by employment status, sex, level of education, year and statistic, 2009. Available at: https://statbank.cso.ie.
45. Central Statistics Office Ireland. CPA04: Consumer Price Index by selected base reference period and year, CPI for 2018 vs 2009. Available at: https://statbank.cso.ie.
46. Organisation for Economic Co-operation and Development. Educational attainment and labour-force status: Employment, unemployment and inactivity rate of 25-64 year-olds, by educational attainment 2018. Available at: https://stats.oecd.org/Index.aspx?DataSetCode=EAG_NEAC#.
47. Statistics Netherlands (CBS). Met arbeidshandicap vaak niet actief op arbeidsmarkt. Available at: https://www.cbs.nl/nl-nl/nieuws/2016/29/met-arbeidshandicap-vaak-niet-actief-op-arbeidsmarkt.
48. Central Statistics Office Ireland. Population and migration estimates. Available at: https://www.cso.ie/en/releasesandpublications/er/pme/populationandmigrationestimatesapril2019/. 2019.
49. National Institute for Health and Care Excellence. SMA UK Patient and Caregiver Survey – Summary of results – 5 March 2019. 2019.

50. Organisation for Economic Co-operation and Development. Purchasing power parities. Monthly comparative price levels. Available at: https://stats.oecd.org/Index.aspx?DataSetCode=CPL.
51. IMTA. Practical Application to Include Disease Costs (PAID). Available at: https://www.imta.nl/paid/.
52. van Baal PHM, Wong A, Slobbe LCJ, Polder JJ, Brouwer WBF, de Wit GA. Standardizing the Inclusion of Indirect Medical Costs in Economic Evaluations. PharmacoEconomics. 2011;29(3):175-87.
53. Verhaart IEC, Robertson A, Leary R, McMacken G, König K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol. 2017;264(7):1465-73.
54. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review. Orphanet Journal of Rare Diseases. 2017;12(1):124.
55. Ogino S, Wilson RB, Gold B. New insights on the evolution of the SMN1 and SMN2 region: simulation and meta-analysis for allele and haplotype frequency calculations. Eur J Hum Genet. 2004;12(12):1015-23.
56. Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscular Disorders. 2018;28(3):208-15.
57. Dangouloff T, Burghes A, Tizzano EF, Servais L. 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofdorp, The Netherlands. Neuromuscul Disord. 2020;30(1):93-103.

Appendix 1

Table A1 Alternative base case technical changes to the Applicant's cost-effectiveness model

Change	Mode implementation
Use of costs based on Klug et al instead of Applicant base case HCRU costs	Implemented by inputting data from Table 9 into one of the cost categories per state in column X of medicalcostcalculator! e.g. total E state costs in X24. Zero costs in X18:23 etc
Use of societal costs from Dutch nusinersen reimbursement report instead of Applicant's base case approach	Insert total costs from Table 13 into relevant cells in Parameters!E195:G198 and delete contents of the three columns below down to row 221
Assumption of sequential nusinersen use in a proportion of patients post OA	Adjust contents of AVXS-101!AH:AI columns in line with assumptions outlined in Section 3.1.2

Appendix 2

Cost-effectiveness scenarios

Additional scenario analyses as provided by the Applicant in reponse to requests from WAR varying B state survivial, survival limits in E and D states, proportions discontinuing nusinersen, rate of regression after nusinersen discontinuation, and utility value in the E state are presented in Table A2. The Applicant also presented a scenario using a value of 1 for utility in the B health state. As this is more extreme and less plausible than the general population utilty value used in the Applicant base case we do not present those results here.

Table A2: Additional scenario analyses provided by Applicant

	Total Costs Total QALYs *Onasemnogene abeparvovec (OA)*	**Total Costs Total QALYs** *Nusinersen*	**ICER (€/QALY) OA vs nusinersen** *In all cases where ICER is negative, OA dominates*
Belgium			
Base case results	€2,420,277 9.44	€2,470,038 4.44	-€9,943
Using C state survival data for the B state in the model (SMA Type 2 instead of general population survival in B state)	€2,418,762 8.98	€2,439,672 4.24	-€4,415
20% increase in survival limits for E and D states (i.e. cut-offs of 19.2 years and 4.8 years for the E and D state, respectively)	€2,420,876 9.44	€2,471,936 4.44	-€10,202
20% decrease in the survival limits for E and D states (i.e. survival cut-offs of 12.8 years and 3.2 years for the E and D state, respectively)	€2,418,555 9.44	€2,465,613 4.44	-€9,402

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*
20% increase in the proportion discontinuing nusinersen in the E, D and C states (i.e. 100% [base case value] in the E state and 3.6% in the D and C states)	€2,420,277 9.44	€2,354,837 4.13	€12,311
20% decrease in the proportion discontinuing nusinersen in the E, D and C states (i.e. 80% in the E state and 2.4% in the D and C states)	€2,420,277 9.44	€2,623,655 4.79	-€43,687
20% increase in the proportion losing milestone after discontinuing nusinersen (i.e. 100% in the D, C and B states)	€2,420,277 9.44	€2,469,721 4.43	-€9,853
20% decrease in the proportion losing milestone after discontinuing nusinersen (i.e. 72% in the D, C and B states)	€2,420,277 9.44	€2,470,534 4.47	-€10,103
Utility value of 0.1 for the E state (values for D, C and B states remain the same as in the base case)†	€2,420,277 9.49	€ 2,470,038 4.60	-€10,179
The Netherlands			
Base case results	€3,485,569 9.44	€3,620,009 4.44	-€26,881
Using C state survival data for the B state in the model (SMA Type 2 instead of general population survival in B state)	€3,483,945 8.98	€3,600,823 4.24	-€24,675
20% increase in survival limits for E and D states (i.e. cut-offs of 19.2 years and 4.8 years for the E and D state, respectively)	€3,491,347 9.44	€3,638,395 4.44	-€29,402
20% decrease in the survival limits for E and D states (i.e. survival cut-offs of 12.8 years and 3.2 years for the E and D state, respectively)	€3,468,457 9.44	€3,576,022 4.44	-€21,507
20% increase in the proportion discontinuing nusinersen in the E, D and C states (i.e. 100% [base case value] in the E state and 3.6% in the D and C states)	€3,485,569 9.44	€3,525,619 4.13	-€7,539

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY) OA vs nusinersen** *In all cases where ICER is negative, OA dominates*
20% decrease in the proportion discontinuing nusinersen in the E, D and C states (i.e. 80% in the E state and 2.4% in the D and C states)	€3,485,569 9.44	€3,750,376 4.79	-€56,926
20% increase in the proportion losing milestone after discontinuing nusinersen (i.e. 100% in the D, C and B states)	€3,485,569 9.44	€3,622,501 4.42	-€27,307
20% decrease in the proportion losing milestone after discontinuing nusinersen (i.e. 72% in the D, C and B states)	€3,485,569 9.44	€3,614,949 4.47	-€26,027
Utility value of 0.1 for the E state (values for D, C and B states remain the same as in the base case)†	€3,485,569 9.49	€3,620,009 4.60	-€27,520
Ireland			
Base case results	€3,426,522 6.31	€3,468,533 3.15	-€13,300
Using C state survival data for the B state in the model (SMA Type 2 instead of general population survival in B state)	€3,425,075 6.16	€3,451,279 3.09	-€8,534
20% increase in survival limits for E and D states (i.e. cut-offs of 19.2 years and 4.8 years for the E and D state, respectively)	€3,432,422 6.31	€3,487,312 3.15	-€17,378
20% decrease in the survival limits for E and D states (i.e. survival cut-offs of 12.8 years and 3.2 years for the E and D state, respectively)	€3,409,045 6.31	€3,423,610 3.15	-€4,611
20% increase in the proportion discontinuing nusinersen in the E, D and C states (i.e. 100% [base case value] in the E state and 3.6% in the D and C states)	€3,426,522 6.31	€3,383,185 2.96	€12,948
20% decrease in the proportion discontinuing nusinersen in the E, D and C states (i.e. 80% in the E state and 2.4% in the D and C states)	€3,426,522 6.31	€3,586,470 3.36	-€54,218

	Total Costs **Total QALYs** *Onasemnogene abeparvovec (OA)*	**Total Costs** **Total QALYs** *Nusinersen*	**ICER (€/QALY)** **OA vs nusinersen** *In all cases where ICER is negative, OA dominates*
20% increase in the proportion losing milestone after discontinuing nusinersen (i.e. 100% in the D, C and B states)	€3,426,522 6.31	€3,471,014 3.14	-€14,043
20% decrease in the proportion losing milestone after discontinuing nusinersen (i.e. 72% in the D, C and B states)	€3,426,522 6.31	€3,463,453 3.17	-€11,771
Utility value of 0.1 for the E state (values for D, C and B states remain the same as in the base case)†	€3,426,522 6.35	€3,468,533 3.29	-€13,746

Budget Impact scenarios

As part of the response to the Review Group's alternative budget impact analysis, the company conducted a scenario for each country using the same or alternative data of the ones suggested by the Review Group. The company considers these scenarios only exploratory and the budget impact analyses presented in the submission document (section 8) correct for the patient populations included for the three countries.

A summary of the values changed in the company's alternative scenario per country is presented in Table A3. Other inputs in the budget impact analyses remained the same as provided in the Applicant basecase. For the scenario conducted by the company, the number of patients receiving OA and the budget impact results over 5 years per country are presented in Table A4 and Table A5 respectively.

Table A3: Amended values used for the amended BIM scenario per country – company scenario

BIM inputs amended	Values used for		
	Belgium	The Netherlands	Ireland
SMA incidence rate	N/A	11.9 per 100,000 (42)	11.9 per 100,000 (42)
Prevalent SMA type 1 population	N/A	32 prevalent patients are treated with nusinersen (based on the UMCU SMA registry) and of those, 3% discontinue nusinersen (as per cost-effectiveness model) and would receive onasemnogene abeparvovec (i.e. ~1 patient per year) in Y1 and Y2	1 prevalent patient per year would be treated with onasemnogene abeparvovec in Y1 and Y2 (based on information from crowdfunding campaigns and MAP)
Uptake rates for incident patients for onasemnogene abeparvovec	Y1: 50% Y2: 75% Y3: 90%	Values as in original submission (Y1: 50%, Y2: 75%, 3: 90%, Y4: 100%, Y5: 100%)	Y1: 50% Y2: 75% Y3: 90% Y4: 100% Y5: 100%
Annual discontinuation rate for nusinersen (including mortality for nusinersen)	12.67%	12.67%	12.67%
Nusinersen drug cost	N/A	N/A	€89,359*

*Updated price as per feedback from the Review Group and per NCPE guidelines. The estimated price takes into account a 5.5% rebate. In addition, the price used in the budget impact model also includes VAT (23%), as opposed to the price used in the cost-effectiveness model, which does not include VAT. Pharmacy fees are not considered under the Hospital Drug scheme and thus, they are not included.

BIM: budget impact model; N/A: not applicable

Table A4: Number of patients receiving onasemnogene abeparvovec and nusinersen per country – company scenario

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Belgium	10.02*	10.65*	9.23*	N/A	N/A	29.89
The Netherlands	6.55*	9.39*	10.24	11.51	11.65	49.34
Ireland	2.81*	3.67	3.15	3.46	3.43	16.51

*Including prevalent patients on nusinersen switching to onasemnogene abeparvovec

N/A: not applicable.

Table A5: Budget impact results per country – company alternative scenario

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Belgium						
Gross drug budget impact	€20,654,929	€21,947,319	€19,025,296	N/A	N/A	€61,627,545
Net drug budget impact	€16,543,450	€15,670,395	€10,385,902	N/A	N/A	€42,599,748
Net budget impact	€16,554,655	€15,585,301	€10,142,502	N/A	N/A	€42,282,458
The Netherlands						
Gross drug budget impact	€12,732,336	€18,270,518	€19,909,850	€22,395,868	€22,669,680	€95,978,252
Net drug budget impact	€10,133,652	€12,530,356	€11,315,361	€10,772,390	€8,250,552	€53,002,311
Net budget impact	€9,934,252	€11,207,511	€8,300,746	€6,210,676	€2,304,849	€37,958,035
Ireland						
Gross drug budget impact	€6,412,549	€8,378,159	€7,201,655	€7,906,120	€7,831,028	€37,729,512
Net drug budget impact	€5,505,647	€6,049,733	€3,960,155	€3,718,578	€2,791,344	€22,025,457

Net budget impact	€5,386,655	€5,417,730	€2,647,401	€1,906,161	€567,873	€15,925,819

N/A: not applicable.