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2022034854

Onze referentie
2022034854

Datum 27 september 2022
Betreft Pakketadvies sluisgeneesmiddel atidarsagene autotemcel (Libmeldy®)

Geachte heer Kuipers,

Zorginstituut Nederland adviseert u over atidarsagene autotemcel (AA, Libmeldy®) voor de behandeling van metachromatische leukodystrofie (MLD). 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.

AA is een innovatieve, veelbelovende en eenmalige behandeling die aangrijpt op de oorzaak van de ziekte (gentherapie) en voldoet aan de stand van de wetenschap en praktijk voor presymptomatische patiënten. Er zijn echter onzekerheden over de effecten op de langere termijn: of het effect daadwerkelijk levenslang aanhoudt. Verder is de kosteneffectiviteit op basis van de beschikbare data onzeker en vooralsnog ongunstig.

Het Zorginstituut adviseert u AA op te nemen in het verzekerde pakket voor presymptomatische patiënten onder voorwaarde dat een prijsreductie wordt bereikt en pay-for-performance afspraken worden gemaakt. De Adviescommissie Pakket (ACP) is van mening dat een prijs boven de referentiewaarde in dit unieke geval maatschappelijk verantwoord is:

- het betreft jonge kinderen die lijden aan een zeer ernstige aandoening die zonder behandeling veelal jong komen te overlijden;
- het betreft een aandoening die 'ultra zeldzaam' is (maximaal 2-3 patiënten per jaar);
- het betreft een behandeling met een beperkte totale budgetimpact.

Een pay for performance afspraak dient ervoor te zorgen dat het risico op betaling voor patiënten die niet voldoende op de behandeling reageren bij de fabrikant komt te liggen en niet bij de maatschappij. Het Zorginstituut heeft de Universiteit Utrecht opdracht gegeven om de mogelijkheden voor pay for perfomance in het kader van AA, verder uit te werken. Deze uitwerking is beschikbaar voor het Buro Financiële Arrangement van het ministerie van Volksgezondheid Welzijn en Sport. Daarnaast zal het Zorginstituut in overleg met de beroepsgroep en andere relevante partijen een weesgeneesmiddelen arrangement opstellen waarbij ook aandacht besteed zal worden aan de startcriteria. Ook afspraken over de internationale indicatiecommissie, en internationale dataverzameling en –analyse zullen vastgelegd worden in het weesgeneesmiddelen-arrangement.

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Vanuit diverse partijen, waaronder de beroepsgroep hebben ons signalen bereikt dat zij AA graag ook voor enkele specifieke vroegsymptomatische patiënten ter beschikking zouden willen hebben. Voor deze patiënten kan het Zorginstituut op basis van de studiedata niet concluderen dat behandeling behoort tot stand van wetenschap en praktijk (vanwege onvoldoende gegevens).
Voor behandelingen die (nog) niet behoren tot de stand van wetenschap en praktijk, bestaat de Voorwaardelijke Toelating (VT) weesgeneesmiddelen, conditionals en exceptionals. Het Zorginstituut spant zich graag in, samen met alle relevante stakeholders, om te bekijken of dat een geschikte route zou zijn om AA beschikbaar te maken voor een specifieke groep vroegsymptomatische patiënten.

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 AA 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.

Integrale weging pakketcriteria
Metachromatische leukodystrofie (MLD) is een autosomaal recessief overervende lysosomale opslagstoornis die wordt veroorzaakt door mutaties in het ARSA-gen die resulteren in een deficiënte activiteit van het lysosomale enzym arylsulfatase A (ARSA), klinisch onderverdeeld in 3 morbiditeitstypes, afhankelijk van moment van diagnose:

- late-infantile (LI) (≤30 maanden),
- juvenile (met early-juvenile (EJ) 30 maanden -≤ 7 jaar en late-juvenile 7-≤16 jaar) en
- volwassen (leeftijd van begin na 16 jaar).

Dit is een zeer ernstige, erfelijke stofwisselingsziekte waarbij de opslag van bepaalde vetten ervoor zorgt dat myeline, wat de zenuwcellen beschermt, kapot gaat. Hierdoor ontstaat een progressieve ziekte die resulteert in verstandelijke beperking en achteruitgang van de motoriek. De meest ernstig aangedane patiënten overlijden binnen enkele jaren na het ontstaan van symptomen aan de ziekte.

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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 .

Stand van wetenschap en praktijk
Behandeling met AA is bedoeld als eenmalige behandeling die de onderliggende genetische oorzaak van MLD zou moeten aanpakken. De evidence is gebaseerd op 2 enkel-armige studies. Eén studie had een follow-up van 3 jaar en de ander van 1 jaar. Daarnaast loopt er een compassionate use programma (CUP). In totaal zijn er in de studies 12 presymptomatische LI patiënten behandeld, 5 presymptomatische EJ patiënten en 7 symptomatische EJ patiënten. Twee van de 7 symptomatische patiënten zijn overleden. In het CUP werden 7 presymptomatische LI patiënten behandeld (1 is overleden) en 1 presymptomatische EJ patiënt (nog in leven). De GMFM score is de meest gebruikte uitkomstmaat voor het meten van de mobiliteit van MLD patiënten en de IQ-score voor het meten van de cognitieve functie.
Er wordt verwacht dat met AA behandelde presymptomatische kinderen een gelijke motorische en cognitieve vooruitgang hebben als gezonde kinderen, terwijl onbehandelde MLD patiënten enkel achteruitgang van de ziekte zullen doormaken. Uit de data komt naar voren dat het belangrijk is patiënten te behandelen voordat de eerste symptomen van de ziekte zichtbaar zijn (presymptomatisch). Vanwege grote effecten op korte termijn, die in onbehandelde patiënten met MLD niet of nauwelijks gezien worden, concludeert het Beneluxa beoordelingsteam dat AA bij kinderen met LI of EJ vormen, zonder klinische manifestaties van de ziekte voldoet aan de stand van de wetenschap en praktijk. Voor de MLD patiënten die volgens de criteria van de studie zijn aangemerkt als vroeg-symptomatisch zijn onvoldoende gegevens om stand van de wetenschap en praktijk te kunnen concluderen.

Budgetimpact
AA kost €2.875.000 per patiënt. De cumulatieve budget impact over drie jaar voor Nederland is €14.375.000 (gebaseerd op twee patiënten in jaar 1, één patiënt in jaar 2 en twee patiënten in jaar 3). De budgetimpact in het derde jaar is in Nederland € 5.750.000.

Kosteneffectiviteit
De kosteneffectiviteitsanalyses van het model van de registratiehouder zijn methodologisch van voldoende kwaliteit. Wel is er onzekerheid over de langetermijneffecten van AA. De review groep kon zich niet vinden in de aannames die in het model gedaan werden door de registratiehouder en heeft een alternatieve base case analyse gedaan waarbij er wordt aangenomen dat de effectiviteit van de behandeling na 10 jaar afneemt bij een deel van de patiënten. Er wordt dan aangenomen dat na 10 jaar alle volledige en stabiele partiele responders ook verminderd motorisch functioneren ervaren, net als de onstabiele partiele responders. De kosteneffectiviteitsschattingen van de review groep liggen ver boven de voor deze aandoening relevant geachte referentiewaarde en AA is daarom geen kosteneffectieve interventie. Voor de pre-symptomatische LI groep is de ICER: €462,632/QALY en voor de pre-symptomatische EJ groep €225,400/QALY. Bij een referentiewaarde van €80.000 zou de prijs met 85% respectievelijk 60% moeten zakken om kosteneffectief te zijn.

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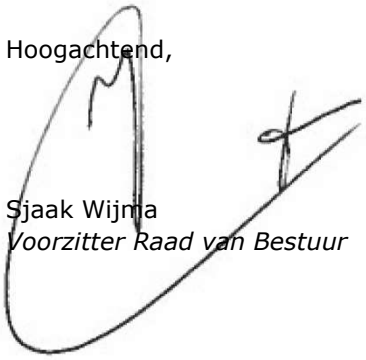
Weesgeneesmiddelenarrangement
Om gepaste inzet van AA te monitoren en te volgen, zal een weesgeneesmiddelenarrangement worden opgezet. Hierin zullen afspraken worden vastgelegd over de startcriteria, een (internationale) indicatiecommissie, dataverzameling en evaluatie. Het bestaande MLDi register kan hiervoor als basis worden gebruikt.

Eindconclusie
Het Zorginstituut adviseert u AA op te nemen in het verzekerde pakket voor presymptomatische patiënten onder voorwaarde dat een prijsreductie wordt bereikt en pay-for-performance afspraken worden gemaakt. De Adviescommissie Pakket (ACP) is van mening dat een prijs boven de referentiewaarde in dit unieke geval maatschappelijk verantwoord is:

- het betreft jonge kinderen die lijden aan een zeer ernstige aandoening die zonder behandeling veelal jong komen te overlijden;
- het betreft een aandoening die 'ultra zeldzaam' is (maximaal 2-3 patiënten per jaar);
- het betreft een behandeling met een beperkte totale budgetimpact.

Een pay for performance afspraak dient ervoor te zorgen dat het risico op betaling voor patiënten die niet voldoende op de behandeling reageren bij de fabrikant komt te liggen en niet bij de maatschappij. Een onderzoek naar pay for perfomance, uitgevoerd door Universiteit Utrecht, kan hier behulpzaam bij zijn. Daarnaast zal het Zorginstituut in overleg met de beroepsgroep en andere relevante partijen een weesgeneesmiddelen arrangement opstellen waarbij ook aandacht besteed zal worden aan de startcriteria. Ook afspraken over de internationale indicatiecommissie, en internationale dataverzameling en –analyse zullen vastgelegd worden in het weesgeneesmiddelen-arrangement.

Hoogachtend,



Sjaak Wijma
Voorzitter Raad van Bestuur

2022033613

ACP advies aan de Raad van Bestuur van het Zorginstituut over atidarsagene autotemcel (Libmeldy®) voor de behandeling van metachromatische leukodystrofie (MLD) gekenmerkt door bi-allelische mutaties in het arylsulfatase A-gen (ARSA-gen), wat leidt tot verminderde enzymatische activiteit van ARSA bij kinderen met laat-infantiele of vroeg-juveniele vormen, zonder klinische manifestaties van de ziekte.

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 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 zogenaamde referentiewaarden voor de kosteneffectiviteit. Deze referentiewaarden moeten worden opgevat als maximale bedragen die we als samenleving per gewonnen levensjaar willen investeren in een behandeling. Gaan we daarboven zitten, dan is er sprake van verdringing. Dat betekent dat voor hetzelfde bedrag meer gezondheidswinst kan worden verkregen door het aan andere behandelingen uit te geven. Er moeten dus hele goede redenen zijn om een kosteneffectiviteit gelijk aan de referentiewaarde of zelfs meer dan de referentiewaarde te accepteren.

De commissie heeft in haar vergadering van 19 augustus 2022 gesproken over de vraag of atidarsagene autotemcel (verder AA) bij de hierboven genoemde indicatie opgenomen dient te worden in de basisverzekering.

Inspraak
Tijdens de vergadering hebben de patiëntenvereniging 'Volwassenen, Kinderen en Stofwisselingszieken (VKS), de beroepsgroep en de fabrikant Orchard Therapeutics gebruik gemaakt van de mogelijkheid om in te spreken. Hieronder volgt een samenvatting van hetgeen zij hebben ingebracht.

"*De patiëntenvereniging licht toe dat behandeling met AA een groot verschil kan maken, onbehandeld gaan deze kinderen onherroepelijk dood. Kinderen die zijn behandeld met AA lijken zich (vrijwel) normaal te ontwikkelen en hebben geen intensieve zorg nodig. Daarnaast wordt de grote impact op het leven van familie en naasten verminderd. Tot slot verzoekt de patiëntenvereniging, vanwege een grijs gebied, de grens tussen presymptomatisch en symptomatisch niet te strikt te hanteren."*

"De beroepsgroep gaat verder in op dat grijze gebied. Met AA is een grote stap voorwaarts gemaakt ten opzichte van hematopoietische stamceltransplantatie, doordat deze behandeling minder complicaties kent en beter werkt. Follow-up van enkele patiënten is inmiddels 10 jaar en de kinderen ontwikkelen zich normaal. De beroepsgroep wil ook graag 'vroegsymptomatische' kinderen (kinderen met minimale neurologische afwijkingen) behandelen met AA. Ondanks dat er bij deze kinderen sprake is van enige 'schade' laat stamceltransplantatie, net als enkele individuele patiënten die met AA zijn behandeld, goede resultaten zien. Europees is er een MLD-initiative opgezet, voor systematische dataverzameling in een onafhankelijk register met als doel verschillende behandelingen voor MLD te kunnen evalueren. Deze internationale overleggroep bespreekt alle nieuwe symptomatische MLD patiënten met de vraag of ze nog in aanmerking komen voor behandeling met stamceltransplantatie dan wel AA. De consensus is dat er geen proefbehandelingen gegeven worden aan alle kinderen vanuit de gedachte ieder kind een kans te geven. Daarvoor zijn de risico's en belasting door de behandeling te groot tegenover een ongunstige uitkomst als de ziekte al te ver gevorderd is. Maar: als de behandeling op tijd is,

zal een kind met behandeling zich nagenoeg normaal kunnen ontwikkelen."

"De fabrikant Orchard Therapeutics is van mening dat de huidige beoordeling door het Zorginstituut geen recht doet aan de positieve impact van AA op het leven van patiënten en hun omgeving. Zeker niet voor de vroeg symptomatische patiënten die nu buiten de boot dreigen te vallen. Een ander punt dat de fabrikant wil maken, is dat zij van mening is dat het alternatieve base case van de kosteneffectiviteit naar haar mening erg conservatief is wat betreft de duur van het effect. Er zijn geen aanwijzingen dat het effect niet zal aanhouden. Inmiddels laten twee kinderen met follow up van 12 jaar nog altijd een normale ontwikkeling zien. De fabrikant wijst erop dat het op de markt brengen en houden van deze gentherapie erg kostbaar is en terugverdiend moet worden bij een zeer kleine groep patiënten. Tot slot geeft de fabrikant aan bereid te zijn tot een pay for performance afspraak, waarbij het risico voor non-respons bij de fabrikant komt te liggen en niet bij de maatschappij."

<u>*Vertrekpunt voor het advies van de commissie:*</u>
- AA betreft een in-vitro (beenmerg) gentherapie die ingrijpt op de onderliggende genetische oorzaak. Het betreft een eenmalige therapie.
- MLD betreft een zeer ernstige progressieve zeldzame aandoening (ziektelast 0,99 op een schaal van 0-1, waarbij 1 gelijk staat aan direct overlijden), waarbij kinderen veelal jong komen te overlijden.
- Behandeling van presymptomatische kinderen voldoet aan de stand van de wetenschap en praktijk. De onderzoeksgegevens zijn beperkt, maar veelbelovend. Door behandeling met AA lijken de meeste kinderen met presymptomatische klachten zich (vrijwel) normaal te ontwikkelen, maar het is nog onbekend of dit effect levenslang aanhoudt.
- Voor aandoeningen met deze ziektelast geldt een referentiewaarde van €80.000 per QALY. Afhankelijk van de subgroep van patiënten ligt de ICER tussen de €225.400 en €462.632 per QALY en is een prijsreductie van tussen de 60-90% nodig om te kunnen spreken van een kosteneffectieve behandeling.
- De kosten voor deze eenmalige behandeling bedraagt bijna 2,9 miljoen euro. Door het geringe aantal patiënten zal de budgetimpact een kleine 6 miljoen euro zijn.

<u>*Gedachtevorming commissie:*</u>
Tijdens de gedachtenvorming in de commissie zijn daarnaast de volgende argumenten ingebracht:
- De commissie beseft dat dit ethisch gezien een complexe casus betreft.
- De commissie is het erover eens dat sprake is van een mooie innovatie.
- De prijs van de behandeling acht de commissie extreem hoog, ook voor een eenmalige behandeling. De commissie heeft uitgebreid gediscussieerd of het uitlegbaar is om een dergelijk hoog bedrag uit te geven voor de behandeling van één patiënt terwijl andere, mogelijk meer kosteneffectieve zorg, verdrongen wordt.
- De commissie is verheugd te vernemen dat de fabrikant open staat voor een pay for performance afspraak en acht een dergelijk afspraak van belang mede omdat lange-termijn effecten nog niet beschikbaar zijn.
- Het betreft een aandoening met een zeer hoge ziektelast, zowel wanneer gekeken wordt naar de proportional shortfall methode (de standaardmethode die het Zorginstituut hanteert bij het bepalen van de ziektelast), als de fair innings methode.
- De commissie begrijpt dat er een grijs gebied bestaat tussen presymptomatisch en symptomatisch. Presymptomatische behandeling met AA voldoet aan de stand van de wetenschap en praktijk. De commissie acht het van belang dat er startcriteria opgesteld worden waarbij de definitie van presymptomatisch enige vrijheid geeft om kinderen die 'vroegsymptomatisch' zijn, indien over behandeling consensus bestaat in de indicatiecommissie, te behandelen. Voorwaarde hiervoor is wel dat er een pay for performance afspraak is overeengekomen om zo het financiële risico voor de maatschappij af te dichten.
- De commissie vindt dat er sprake is van een unieke casus waarbij alle onderstaande argumenten tezamen reden zijn om een bedrag boven de gehanteerde referentiewaarde te

accepteren:
    - het betreft jonge kinderen die lijden aan een zeer ernstige aandoening die zonder behandeling veelal jong komen te overlijden;
    - het gaat vaak om zwaar getroffen gezinnen omdat behandeling alleen in een vroeg stadium mogelijk is, als bij een ouder broertje of zusje de erfelijke ziekte al is geconstateerd, die al ernstig ziek is of overleden;
    - het betreft een innovatie, die mogelijk genezend werkt;
    - het betreft een aandoening die 'ultra zeldzaam' is (2-3 patiënten per jaar);
    - het betreft een behandeling met een beperkte budgetimpact.
- De commissie kan zich voorstellen dat met de huidige methode voor het bepalen van een maatschappelijk verantwoorde prijs een fabrikant geen goed businessmodel heeft doordat het een eenmalige behandeling betreft van een zeer zeldzame aandoening. Echter, het verdringingsvraagstuk mag ook niet uit het oog verloren worden, maar doordat de budgetimpact beperkt is, kent de commissie hieraan relatief minder gewicht toe.
- De vervolgvraag is hoeveel de commissie bereid is om boven de referentiewaarde van €80.000 per QALY te gaan zitten. Na enige discussie concludeert de commissie dat zij dit op dit moment niet nader kan concretiseren en dat dit ook niet los gezien kan worden van de pay for performance afspraak die gemaakt moet gaan worden. De commissie acht een forse prijsreductie wel aangewezen.

Advies

De commissie komt alles afwegende tot een negatief advies, tenzij een prijsreductie in combinatie met een pay for performance afspraak bereikt wordt. De commissie is vanwege de eerder genoemde argumenten van mening dat een prijs boven de referentiewaarde in dit unieke geval maatschappelijk verantwoord is. De commissie acht het echter niet mogelijk te onderbouwen hoe ver boven de referentiewaarde. De commissie adviseert om in overleg met de fabrikant op basis van de ontwikkelkosten en kosten van het op de markt houden van deze gentherapie tot een maatschappelijk aanvaardbare prijs in combinatie met een pay for performance afspraak te komen. De fabrikant heeft aangegeven zowel inzicht te willen geven in de kosten als een pay for performance afspraak te willen maken.

Omdat de commissie niet eerder een dergelijk advies heeft gegeven en ervan wil leren hoe dit uitpakt in de praktijk, verzoekt de commissie of het mogelijk is om op de hoogte te worden gesteld van de gemaakte afspraken en haar te betrekken bij het vaststellen van de prijsreductie.

Tot slot adviseert de commissie een weesgeneesmiddelen-arrangement op te stellen waarbij bij het opstellen van de startcriteria enige vrijheid gegeven wordt aan de behandelaars om kinderen die 'vroegsymptomatisch' zijn, indien over behandeling consensus bestaat in de internationale indicatiecommissie, te behandelen. Een pay for performance afspraak dient ervoor te zorgen dat het risico op nonresponders bij de fabrikant komt te liggen en niet bij de maatschappij. Een onderzoek naar pay for perfomance, uitgevoerd door Universiteit Utrecht, kan hier behulpzaam bij zijn. Ook afspraken over de internationale indicatiecommissie, en internationale dataverzameling en –analyse dienen vastgelegd te worden in het weesgeneesmiddelen-arrangement.

Zorginstituut Nederland

Pharmacotherapeutic report atidarsagene autotemcel (Libmeldy®) for treatment of patients with metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity

Element of the initial assessment of specialty medicines

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Colophon

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Samenvatting (Dutch summary)

In dit farmacotherapeutisch rapport beschrijft het Beneluxa beoordelingsteam, inclusief Zorginstituut Nederland, de Belgische Commissie Vergoeding Geneesmiddelen (CRM) en het Ierse *National Centre for Pharmacoeconomics* (NCPE) de inhoudelijke beoordeling van de waarde van atidarsagene autotemcel (AA, Libmeldy®), hierna afgekort als AA voor de behandeling van patiënten met metachromatische leukodystrofie (MLD) gekenmerkt door bi-allelische mutaties in het arylsulfatase A-gen (ARSA-gen), wat leidt tot verminderde enzymatische activiteit van ARSA:

- bij kinderen met late-infantile of early-juvenile vormen, zonder klinische manifestaties van de ziekte;
- bij kinderen met de early-juvenile vorm, met vroege klinische manifestaties van de ziekte, die nog zelfstandig kunnen lopen en vóór het begin van cognitieve achteruitgang.

Metachromatische leukodystrofie (MLD) is een autosomaal recessief overervende lysosomale opslagstoornis die wordt veroorzaakt door mutaties in het ARSA-gen die resulteren in een deficiënte activiteit van het lysosomale enzym arylsulfatase A (ARSA), klinisch onderverdeeld in 3 morbiditeitstypes, afhankelijk van moment van diagnose:

- late-infantile (LI) (≤30 maanden),
- juvenile (met early-juvenile (EJ) 30 maanden -≤ 7 jaar en late-juvenile 7-≤16 jaar) en
- volwassen (leeftijd van begin na 16 jaar).

Progressieve achteruitgang van de motorische en mentale vermogens zal uiteindelijk leiden tot een vegetatieve toestand, waarbij de dood van de patiënt te verwachten is 1-7 jaar na het begin van de ziekte bij LI patiënten en na 3-15 jaar bij EJ patiënten.

De grootste moeilijkheid bij de behandeling van ziekten van het zenuwstelsel is de slechte doorlaatbaarheid van de BBB (bloed-hersenbarrière), waardoor de toegang van therapeutische stoffen bij systemische toediening wordt beperkt en de doeltreffendheid van veel therapeutische benaderingen gering is. Voor presymptomatische patiënten kan beenmergtransplantatie (BMT) of hematopoëtische stamceltransplantatie (HSCT) van een donor (indien beschikbaar) een therapeutische optie zijn. De meeste patiënten worden echter symptomatisch behandeld met de beste ondersteunende zorg om de kwaliteit van het resterende leven te verbeteren. Er wordt momenteel in Nederland, België en Ierland niet standaard bij de geboorte gescreend voor deze erfelijke aandoening, onder andere omdat er momenteel geen behandeling is. Uitkomsten op overleving, mobiliteit en cognitie worden door de beroepsgroep als cruciaal genoemd bij het beoordelen van de effectiviteit van een nieuwe behandeling voor MLD.

Een aantal studies heeft aangetoond dat BMT leidt tot een stopzetting van de ontwikkeling van neurocognitieve en motorische stoornissen bij patiënten met juvenile vorm van MLD, maar bij deze patiënten blijft de demyelinisatie na BMT in 31% van de gevallen doorgaan, misschien omdat de ziekte progressie blijft vertonen omdat de therapie te laat is begonnen. BMT heeft geen invloed op het natuurlijke beloop van de ziekte bij kinderen met laat infantiele en juvenile vormen van MLD die BMT krijgen na het begin van de ziekteverschijnselen. Bij patiënten met een asymptomatische vorm, die als het meest gunstig wordt beschouwd wat betreft de effectiviteit van de

therapie, blijft de ziekte progressie vertonen na BMT ondanks het normale niveau van het enzym in bloedplasma en urine dat gedurende de observatie blijft bestaan, waarbij de hersen-MRI progressieve afwijkingen laten zien.

Gentherapie met AA wordt gepresenteerd als een nieuwe therapeutische optie voor kinderen met LI of EJ vormen, zonder klinische manifestaties van de ziekte (presymtomatisch: PS), en voor kinderen met de EJ vorm, met vroege klinische manifestaties van de ziekte (vroeg symptomatisch: ES), die nog steeds in staat zijn om zelfstandig te lopen en vóór het begin van cognitieve achteruitgang.

AA is een ex vivo genetisch gemodificeerde autologe CD34+ hematopoietische stam- en progenitorcel (HSPC) gentherapie. Autologe stamcellen worden verzameld uit het beenmerg (BM) van de patiënt of uit gemobiliseerd perifeer bloed (mPB) en getransduceerd met een lentivirale vector (ARSA LVV), die een of meer kopieën van het menselijke ARSA complementaire desoxyribonucleïnezuur (cDNA) in het genoom van de cel inbrengt, zodat de genetisch gemodificeerde cellen in staat worden het functionele ARSA-enzym tot expressie te brengen.

Na een myeloablatief conditioneringsregime worden de genetisch gemodificeerde cellen aan de patiënt toegediend, enten zij en zijn zij in staat het hematopoëtische compartiment opnieuw te bevolken. Een subpopulatie van de geïnfundeerde HSPC's en/of hun myeloïde nakomelingen is in staat om over de bloed-hersenbarrière naar de hersenen, het centraal en perifere zenuwstelsel te migreren en te nestelen. Deze genetisch gemodificeerde cellen kunnen het functionele ARSA-enzym produceren en uitscheiden, dat door de omringende cellen kan worden opgenomen, een proces dat bekend staat als kruiscorrectie, en wordt gebruikt om schadelijke sulfatiden af te breken of de vorming ervan te voorkomen. Na succesvolle en stabiele enting bij de patiënt wordt verwacht dat de effecten van het product blijvend zullen zijn.

De evidence is gebaseerd op 2 enkel-armige trials, de 201222 (3 jaar follow-up) en 205756 (1 jaar follow-up) studie en daarnaast loopt er een *compassionate use* programma (CUP). In totaal zijn er in de studies 12 presymptomatische LI patiënten behandeld, 5 presymptomatische EJ patiënten en 7 symptomatische EJ patiënten. Twee van de 7 symptomatische patiënten zijn overleden. In het CUP werden 7 presymptomatische LI patiënten behandeld (1 is overleden)en 1 presymptomatische EJ patiënt (nog in leven). De GMFM score is de meest gebruikte uitkomstmaat voor het meten van de mobiliteit van MLD patiënten en de IQ-score voor het meten van de cognitieve functie.

In de EPAR en in de publicaties is getracht een vergelijking van met AA behandelde patiënten te maken ten opzichte van enkel symptomatisch behandelde patiënten. In de gematchte analyseset (MAS)-populatie werden de patiënten in de ITT-populatie en alle leeftijds- en MLD-variant-gematchte onbehandelde patiënten uit de TIGET NHx-studie vergeleken. Daarnaast was er ook een *Matched Sibling Analysis Set* welke patiënten uit de ITT-populatie vergeleek met een onbehandelde broer of zus in de TIGET NHx-studie. Alle 19 LI patiënten en alle 12 EJ patiënten in de vergelijkende TIGET NHx-studie waren reeds symptomatisch toen zij werden geïncludeerd in de studie. De registratiehouder heeft geen vergelijking gemaakt met patiënten die werden

behandeld met een HSCT.

Er kan niets worden gezegd over de toegevoegde waarde van AA op gemiddelde of lange termijn mortaliteit, gezien er geen directe statistische vergelijking gemaakt is voor een van de 3 subsets van de met AA behandelde MLD patiënten (LI-PS, EJ-PS en AJ-ES) versus natuurlijk beloop (TIGET NHx referentie cohort of andere literatuur/natuurlijk beloop data) of NHSCT-behandelde vergelijkbare MLD patiënten. Daarnaast is de follow-up voor het grootste deel van de patiënten momenteel te kort om conclusies te kunnen trekken over mortaliteit.

Er zijn grote onzekerheden rondom de toegevoegde waarde van AA op morbiditeit vergeleken met het historische TIGET NHx referentie cohort, door verschillen in patiënt profielen en ontbreken van vergelijkbare natuurlijk beloop data. Daarnaast is er ook geen vergelijking te maken met HSCT behandelde patiënten omdat de data van de effectiviteit en werkzaamheid van HSCT in MLD patiënten zeer gelimiteerd is. Behandeling met AA is bedoeld als eenmalige behandeling die de onderliggende genetische oorzaak van MLD zou moeten aanpakken. Er wordt verwacht dat met AA behandelde kinderen gelijke motorische en cognitieve vooruitgang zouden moeten hebben als gezonde kinderen, terwijl onbehandelde MLD patiënten enkel achteruitgang van de ziekte zullen doormaken. Uit de data komt naar voren dat het belangrijk is patiënten te behandelen voordat de eerste symptomen van de ziekte zichtbaar zijn (presymptomatisch).

Gezien de beperkte gegevens die voor handen zijn kan enkel een voorzichtige schatting van het effect op de morbiditeit worden gegeven:

- presymptomatische late-infantile (LI-PS) patiënten: Wanneer de effecten van AA worden vergeleken door middel van een intra-patiënt vergelijking, kan een toegevoegde waarde van AA worden geconcludeerd op de meest belangrijke motorische en cognitieve klinische uitkomstmaten in de LI-PS MLD-patiënten. 74% van de AA-behandelde LI-PS patiënten behaalde een GMFM verbetering binnen de mediaan±15% van de verwachte normale score voor leeftijd en IQ-score (gebaseerd op de 12 patiënten in de klinische studies en de 19 patiënten van het CUP).

- presymptomatische early juvenile (EJ-PS) patiënten: Wanneer de effecten van AA worden vergeleken door middel van een intra-patiënt vergelijking, kan een toegevoegde waarde van AA worden geconcludeerd op de meest belangrijke motorische (Gross Motor Function Measurements: GMFM) en cognitieve (IQ) klinische uitkomstmaten in de EJ-PS MLD-patiënten. 83% van de AA-behandelde LI-PS patiënten behaalde een GMFM verbetering binnen de mediaan±15% van de verwachte normale score voor leeftijd en IQ-score (gebaseerd op de 5 patiënten in de klinische studies en de 6 patiënten van het CUP).

- vroeg-symptomatische early juvenile (EJ-ES) patiënten: Wanneer de effecten van AA worden vergeleken door middel van een intra-patiënt vergelijking, kan *geen* toegevoegde waarde van AA worden geconcludeerd op de meest belangrijke motorische (Gross Motor Function Measurements: GMFM) en cognitieve (IQ) klinische

uitkomstmaten in de EJ-ES MLD-patiënten. Vergeleken met gezonde kinderen, behaalde geen van de AA-behandelde LI-PS patiënten een GMFM verbetering binnen de mediaan±15% van de verwachte normale score voor leeftijd en IQ-score (gebaseerd op de 7 patiënten in de klinische studies). In EJ-ES patiënten is een mogelijk voordeel van de behandeling met AA op morbiditeit op dit moment niet aangetoond.

Een belangrijk voordeel van AA is de afwezigheid van graft versus host disease (GvHD). Er is geen langdurige immunosuppressieve behandeling nodig. Een mogelijk voordeel op morbiditeit van AA-behandeling versus HSCT in elk van deze 3 patiënten subsets (LI-PS, EJ-PS en AJ-ES) moet worden gewogen tegen het wel of niet beschikbaar zijn van een donor en de variabiliteit in de natuurlijke evolutiedynamiek van MLD in de LI- versus de EJ-fenotypen. Een meerwaarde ten opzichte van HSCT kan op basis van de huidige data niet worden geconcludeerd.

Het Belgische CRM, het Ierse NCPE en Zorginstituut Nederland concluderen dat atidarsagene autotemcel (AA, Libmeldy®) voor de behandeling van patiënten met metachromatische leukodystrofie (MLD) gekenmerkt door bi-allelische mutaties in het arylsulfatase A-gen (ARSA-gen), wat leidt tot verminderde enzymatische activiteit van ARSA:

- bij kinderen met late-infantile of early-juvenile vormen, zonder klinische manifestaties van de ziekte voldoet aan de stand van de wetenschap en praktijk *(BE: een therapeutische meerwaarde heeft)*
- bij kinderen met de early-juvenile vorm, met vroege klinische manifestaties van de ziekte, die nog zelfstandig kunnen lopen en vóór het begin van cognitieve achteruitgang niet voldoet aan de stand van de wetenschap en praktijk *(BE: een therapeutische minderwaarde heeft)*

De bespreking van dit farmacotherapeutisch rapport is door de Wetenschappelijke Adviesraad (WAR-CG) van Zorginstituut Nederland afgerond in haar vergadering van 11 juli 2022 en door de Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) in haar vergadering 12 juli 2022.

Zorginstituut Nederland

Farmaco-economisch rapport voor atidarsagene autotemcel (Libmeldy®) bij de behandeling van MLD

onderdeel van de initiële beoordeling van specialistische geneesmiddelen
Samenvatting van review rapport door NCPE

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5

Uitgebreide samenvatting

Het farmaco-economisch rapport is uitgevoerd in het kader van het Beneluxa Initiatief (verder in het rapport de 'review groep' genoemd), bestaande uit Zorginstituut Nederland, de Belgische Commissie Vergoeding Geneesmiddelen (CRM) en het Ierse National Centre for Pharmacoeconomics (NCPE). Dit rapport beschrijft de inhoudelijke beoordeling van de kosteneffectiviteit en de budgetimpact van atidarsagene autotemcel (AA, Libmeldy®) voor de behandeling van patiënten met metachromatische leukodystrofie (MLD) gekenmerkt door bi-allelische mutaties in het arylsulfatase A-gen (ARSA-gen), wat leidt tot verminderde enzymatische activiteit van ARSA:
- bij kinderen met laat-infantiele (LI) of vroeg-juveniele vormen (EJ), zonder klinische manifestaties van de ziekte (pre-symptomatisch PS);
- bij kinderen met de vroeg-juveniele vorm, met vroege klinische manifestaties van de ziekte, die nog zelfstandig kunnen lopen en vóór het begin van cognitieve achteruitgang (early symptomatisch ES).
De NCPE heeft de door de registratiehouder ingediende kosteneffectiviteitsanalyse en budgetimpact analyse van AA beoordeeld voor de drie landen. De CRM heeft de farmacotherapeutische beoordeling gedaan.

Metachromatische leukodystrofie (MLD) is een autosomaal recessief overervende lysosomale opslagstoornis die wordt veroorzaakt door mutaties in het ARSA-gen die resulteren in een deficiënte activiteit van het lysosomale enzym arylsulfatase A (ARSA), klinisch onderverdeeld in 3 morbiditeitstypes,
- late-infantile (≤ 30 maanden),
- juvenile (met early-juvenile 30 maanden -≤ 7 jaar en late-juvenile 7-≤ 16 jaar) en
- volwassen (leeftijd van diagnose na 16 jaar).
Progressieve achteruitgang van de motorische en cognitieve vermogens zal leiden tot een vegetatieve toestand, waarbij de dood van de patiënt te verwachten is 1-7 jaar na het begin van de ziekte bij late infantiele patiënten en na 3-15 jaar bij early juvenile patiënten.
Er is geen curatieve therapie voorhanden. Behandelingen richten zich vooral op symptoombestrijding of het vertragen van progressie. Een allogene beenmergtransplantatie van een donor met een werkend ARSA enzym kan uitkomst bieden bij vroege MLD. Het voordeel van AA ten opzichte van allo-HSCT is dat er geen donor gevonden hoeft te worden. Hiermee is er ook geen risico op graft versus host disease. Daarmee is het potentieel minder toxisch, ook omdat de noodzaak tot immuun suppressie vervalt na transplantatie. Tot op heden is er geen vergelijkend onderzoek geweest tussen de uitkomsten van gentherapie en allo-HSCT.

AA (Libmeldy®) is een eenmalige ex vivo genetisch gemodificeerde autologe CD34+ hematopoietische stam- en progenitorcel (HSPC) gentherapie.Autologe stamcellen worden verzameld uit het beenmerg (BM) van de patiënt of uit gemobiliseerd perifeer bloed (mPB) en getransduceerd met een lentivirale vector (ARSA LVV), die een of meer kopieën van het menselijke ARSA complementaire desoxyribonucleïnezuur (cDNA) in het genoom van de cel inbrengt, zodat de genetisch gemodificeerde cellen in staat worden het functionele ARSA-enzym tot expressie te brengen. Het werd geregistreerd door de European Medicines Agency (EMA) op 17 december 2020. Het heeft een weesgeneesmiddel status. De geregistreerde indicatie betreft de volgende patiënten: PS LI, PS EJ en ES EJ (zie de patiëntengroepen zoals beschreven aan het begin van deze samenvatting).

De vergelijkende behandeling voor alle landen is best-ondersteunende zorg (BSC). MLD is een aandoening die veel lichaamsfuncties aantast en daarom bestaat BSC uit een breed spectrum van behandelingen voor symptoom bestrijding. Met als doel de kwaliteit van leven (KvL) van de patiënt te verbeteren. Volgens Nederlandse klinische experts is allogene stamceltransplantatie (HSCT) bij sommige patiënten ook een behandeloptie , echter kan er op basis van de data die er nu is geen uitspraak worden gedaan over de relatieve (kosten)effectiviteit. Aangenomen is verder nog dat AA wordt toegevoegd aan BSC.

De populatie zoals meegenomen in het farmaco-economische model is een combinatie van de volgende drie subgroepen patiënten: PS LI ; PS EJ; en ES EJ. De groepen worden afzonderlijk gemodelleerd en gecombineerd voor de hele groep gebruik makend van een gewogen gemiddelde op basis van de verdeling over de subgroepen per land.

Het model betreft een kosten-utiliteitsanalyse met acht gezondheidstoestanden: zeven toestanden op basis van het motorisch functioneren gedefinieerd als GMFC-MLD score en een toestand 'overlijden'. Patiënten kunnen in het model alleen verplaatsen naar slechtere toestanden, aangezien een verslechtering van functioneren bij deze aandoening onomkeerbaar is. De registratiehouder doet de aanname dat veranderingen in motorisch functioneren opeenvolgend plaatsvinden. Cognitieve sub-toestanden binnen elke toestand van motorisch functioneren worden ook gemodelleerd voor de EJ patiënten om zo ook verslechtering van cognitief functioneren mee te nemen per categorie van motorisch functioneren. De registratiehouder doet de aanname dat MLD gerelateerde mortaliteit zich alleen voordoet in de slechtste toestand van motorisch functioneren. Verder is er een levenslange tijdshorizon gebruikt.

De data die zijn gebruikt in het model voor de effectiviteit van BSC behandeling zijn gebaseerd op de historische cohort studie (OSR-TIGET NHx) (N=31; LI n=19, EJ n=12). De effectiviteit van AA is gebaseerd op een subset van patiënten uit de single-arm klinische registratie studie (Study 201222 (N=16 March 2018 data cut) en data van expanded access programma's, waarvan twee compassionate use (CUP207394 (N=1) en CUP206258 (N=5)) en van een ziekenhuis vrijstelling (HE205029 (N=3)). De registratiehouder maakt voor de kosteneffectiviteitsanalyse geen gebruik van beschikbare data van Study 205756 (betreffende de AA commerciële cryopreserved formulering).
De overgangen tussen de verschillende gezondheidstoestanden zijn gebaseerd op de hiervoor beschreven data. Voor patiënten behandeld met AA wordt aangenomen dat ze enkel verbeterde uitkomsten hebben; de mogelijkheid van non-response is niet meegenomen. Responders zijn volledige responder of partiele responder. Partiele responders worden vervolgens onderverdeeld in stabiele en onstabiele responders. De aannames met betrekking tot de classificatie van response zijn te optimistisch bijv. patiënten die verslechtering laten zien in klinische uitkomsten worden alsnog geclassificeerd als 'full' of 'stable partial' responder. In het model neemt de registratiehouder aan dat full responders levenslang niet verslechteren door MLD. De review groep beargumenteert dat de data deze aannames niet onderbouwen. De data laten zien dat drie patiënten die als volledige of partiele responder worden gemodelleerd en die AA kregen, verslechtering in verschillende klinische uitkomsten lieten zien.

De review groep kan zich niet vinden in de manier waarop de registratiehouder enkele aspecten rondom de behandeleffecten meeneemt in het model. De post hoc aanpak van responder classificatie is erg subjectief en gezien het kleine aantal patiënten dat geïncludeerd wordt, zal dit een significante invloed hebben op de

modelresultaten. De registratiehouder doet de aanname dat volledige responders of stabiele partiele responders zullen genezen, wat niet wordt ondersteund door robuust bewijs. Andere biases betreffen de aanpak voor het schatten van de gemiddelde tijd tot de volgende GMFC toestand wat van invloed is op de overgangskansen en de relatieve behandeleffecten zoals gebruikt in het model. Het gebrek aan beschikbare data voor EJ patiënten is ook problematisch omdat het ziekteverloop zo variabel is.

De utiliteiten per gezondheidstoestand zijn vooral gebaseerd op een UK studie uitgevoerd door de registratiehouder. Daarin is gebruik gemaakt van vignetten en de time trade off benadering om de utiliteiten te berekenen. De studie voorspelde een groot aantal 'erger dan dood' utiliteiten en dat is niet echt plausibel volgens clinici. Er bestaat ook inconsistentie in de waardering van deze utiliteiten, omdat betere toestanden lager gewaardeerd worden dan slechtere toestanden. Er zijn ook grote verschillen in de waarden voor LI en EJ groepen, wat volgens de review groep niet mogelijk is. De registratiehouder herberekende de utiliteitsdata uit de studie, zodat de minimum en maximum utiliteitswaarden worden begrensd door het EQ-5D-5L tarief voor het betreffende land. Dit werd gedaan om het aantal erger dan de dood toestanden te verminderen. Er wordt aangenomen dat cognitieve en motorische achteruitgang evenveel voorkomt voor LI patiënten als voor juveniele patiënten na 4-jarige leeftijd. Dit impliceert dat het ziektebeloop verschillend is afhankelijk van de startleeftijd.

De review groep heeft haar bedenkingen over de plausibiliteit van de utiliteiten zoals gebruikt in het model. Deze zorgen zie je terug in de voorspelde uitkomsten van het model, waar negatieve QALY uitkomsten resulteren voor patiënten die behandeld zijn met BSC. De resultaten suggereren dat BSC (meer dan geen behandeling) de kwaliteit van leven zal verminderen en negatieve waarden zal bereiken wat betekent dat het kwaad zal doen; de review groep vindt dat face validiteit hier ontbreekt. Er worden geen alternatieve plausibele waarden geïdentificeerd door literatuuronderzoek. Terwijl de Review Groep verschillende scenario analyses heeft uitgevoerd, blijkt dat alternatieve benaderingen geen significante invloed hebben op de kosteneffectiviteitsschattingen. Die worden vooral gedreven door de modellering van de effectiviteitsdata van de behandelingen

De AIP van AA is €2.875.000. Toedieningskosten van AA en BSC worden ook meegenomen, evenals de kosten voor de lange termijn behandeling met BSC. Klinische input is gezocht om de kosten te valideren. De schatting van de toedieningskosten van AA en de follow-up van deze patiënten is lastig omdat voor zowel Ierland als België, de patiënten de behandeling zullen krijgen binnen andere jurisdicties. Alhoewel de kosten inputs van het model omgeven zijn door onzekerheid, hebben ze weinig invloed op de kosteneffectiviteitsschattingen. Want de meeste invloed komt door de modellering van de behandeleffecten.

De registratiehouder schatte ICERs voor AA versus BSC voor vier groepen.
De gecombineerde gewogen gemiddelde ICER van AA versus BSC was: België €118.234/QALY; Nederland €107.777/QALY en voor Ierland €146.642/QALY.
Voor de presymptomatische LI groep was de ICER: België €112,676/QALY ; Nederland €99,035/QALY en Ierland €144,078/QALY. .
Voor de presymptomatische EJ groep voor België: €92,374/QALY ; Nederland €70,299/QALY en voor Ierland €120,207/QALY .
Voor de early symptomatische EJ groep: België €172,761/QALY ; voor Nederland €166,671/QALY en voor Ierland €216,567/QALY .

De review groep heeft de belangrijkste onzekerheden in het model onderzocht en ze

heeft op basis daarvan enkele aanpassingen gedaan waarvan ze denkt dat die invloed hebben op de uitkomsten. Het uitdoven van het behandeleffect is een aannemelijk scenario, wat meegenomen zou moeten worden gezien het gebrek aan lange termijn data over response op dit moment.

De Review Group heeft de ICERs herberekend als rekening wordt gehouden met een afnemend behandel effect, waarbij na 10 jaar alle volledige en stabiele partiele responders ook verminderd motorisch functioneren ervaren, net als de onstabiele partiele responders.
De aangepaste gecombineerde gewogen gemiddelde ICER voor AA versus BSC is: België €369,048/QALY ; Nederland €327,423/QALY en voor Ierland €382,069/QALY .
Voor de pre-symptomatische LI groep is de ICER: België €484,711/QALY ; Nederland €462,632/QALY en Ierland €438,495/QALY .
Voor de Pre-symptomatische EJ groep voor België: €269,672/QALY ; Nederland €225,400/QALY en voor Ierland €260,467/QALY.
Voor de early symptomatische EJ groep: België €408,461/QALY voor Nederland €396,882/QALY en voor Ierland €392,864/QALY. .
De registratiehouder voerde zowel deterministische als probabilistische gevoeligheidsanalyses uit.De review groep vindt de aanpak van variatie rondom de parameters niet transparant, er is onvoldoende uitleg gegeven over de gemaakte keuzes. Een proportional shortfall berekening is uitgevoerd voor Nederland met een resulterende referentiewaarde van €80,000/QALY. De Review Groep rapporteert de relatie tussen de prijs van AA en de kosteneffectiviteit. De prijs die vereist is voor de relevant geachte referentiewaarden is significant lager dan die voorgesteld door de registratiehouder.

De budget impact voor België voor drie jaar is €6.095.000 (gebaseerd op een patiënt in jaar 1 en 3). Voor Nederland is de cumulatieve budget impact voor drie jaar €14.375.000 (gebaseerd op twee patiënten in jaar 1, een patiënt in jaar 2 en twee patiënten in jaar 3). De budgetimpact in het derde jaar is in Nederland € 5.750.000. en voor Ierland is dit €9,940,314 (drie patiënten in 5 jaar). De netto budget impact is hetzelfde omdat er geen substitutiekosten zijn van vergelijkende behandelingen. Een scenario analyse wordt gedaan voor België waarbij 100% van de geboren early onset patiënten behandeld worden. Dan neemt de drie jaar cumulatieve netto budget impact toe naar €23,529,274. .

Hoofdpunten

- De model structuur geeft een adequate weergave van de aandoening en het behandelpad, echter zijn de keuzes die worden gemaakt over hoe de patiënten vooruitgaan in het model veel te optimistisch voor de interventie die wordt onderzocht en beoordeeld.

- De data die zijn gebruikt in het model voor de behandeleffecten zijn niet de meest recente data die beschikbaar zijn en verschillen daarom van de data die worden gegeven in het FT-rapport.

- De aannames met betrekking tot de effectiviteit van de behandeling hebben een significante invloed op het model; vooral de classificatie van responders en de aannames over genezing. Patienten behandeld met AA worden geclassificeerd als 'full responders', 'stable partial reponders' or 'unstable partial responders'. De classificatie van response is gebaseerd op GMFC-MLD stadium, samen met andere criteria. Echter is het niet duidelijk op basis van welke gewichten de verschillende criteria aan elkaar gerelateed zijn en hoe de verschillende klinische relevantiegrenzen werden bepaald.

- Omdat er geen kwaliteit van leven data verzameld zijn in de klinische trials, werd er een studie opgezet door de registratiehouder om input voor het model te krijgen. Deze studie en de daaropvolgende analyse is volgens de review groep niet robuust.

- De kosten van de behandelingen zijn meegenomen voor de afzonderlijke landen, echter omdat de aangewezen behandelcentra niet in elk land aanwezig zijn kan de toewijzing van de kosten over de landen wijzigen. Omdat er momenteel weinig behandelmogelijkheden zijn voor deze patiënten, zijn de substitutiekosten van andere behandelingen geen belangrijke factor.

- De review groep presenteert een voorstel voor een alternatieve kosteneffectiviteit base case waarbij er wordt aangenomen dat de effectiviteit van de behandeling na 10 jaar afneemt bij een deel van de patiënten. Dit heeft een significante invloed op de ICERs, deze nemen enorm toe bij alle patiëntengroepen.

- De budget impact is op correcte wijze geschat door alleen incidente patiënten mee te nemen. De cumulatieve impact in België over drie jaar varieert van €6,1 tot €23,6 miljoen afhankelijk van aannames omtrent aantal geboren baby's en neonatale screening; voor Nederland is de cumulatieve budget impact voor drie jaar €14,4 miljoen waarvan €5,8 miljoen in het derde jaar. Voor Ierland is de cumulatieve budget impact voor vijf jaar geschat op €9,8 miljoen.

- De kosteneffectiviteitsschattingen liggen allemaal boven de referentiewaarden van de drie landen en AA is daarom geen kosteneffectieve interventie.

De bespreking van dit farmaco-economisch rapport is door de Wetenschappelijke Adviesraad (WAR-CG) van Zorginstituut Nederland afgerond in haar vergadering van 11 juli 2022 en door de Belgische Commissie Tegemoetkoming Geneesmiddelen (CTG) in haar vergadering van 13 juli 2022

RIJKSINSTITUUT VOOR ZIEKTE-EN INVALIDITEITSVERZEKERING

Openbare instelling opgericht bij de wet van 9 augustus 1963
Galileelaan 5/01 - 1210 Brussel

Dienst Geneeskundige Verzorging

COMMISSIE TEGEMOETKOMING GENEESMIDDELEN

Nota CTG 2022 // 0154332801 / R90

BETREFT:
Dossier N°: 0154332801
Naam van de specialiteit :
Libmeldy || 2-10 × 10^6 cellen/ml
1 zak 50 mL dispersie voor infusie, 210106 cellen/µL
Document op agenda : Definitief Beoordelingsrapport

PROCEDURE : K.B. 01.02.2018

OPDRACHT VAN DE COMMISSIE TEGEMOETKOMING GENEESMIDDELEN :

De Commissie wordt verzocht het beoordelingsrapport goed te keuren.

TREFWOORDEN
Geneeskundige verstrekkingen – Farmaceutisch product – Farmaceutische specialiteit

EVALUATIERAPPORT DAG 90

Dossier : 0154332801

LIBMELDY || 2-10 × 10^6 CELLEN/ML

1 ZAK 50 ML DISPERSIE VOOR INFUSIE, 210106 CELLEN/µL

Atidarsagene autotemcel
N07: buiten forfait
infusie - intraveneus

1. ONDERWERP VAN DE AANVRAAG

De firma Orchard Therapeutics B.V. heeft een dossier ingediend met een aanvraag tot vergoeding voor het weesgeneesmiddel Libmeldy® (Atidarsagene autotemcel), een gentherapie die een autologe CD34+ celverrijkte populatie (2-10 x10^6 cellen/ml gesuspendeerd in cryopreservatieve oplossing) met hematopoëtische stam- en voorlopercellen (HSPC), die ex vivo werden getransduceerd met behulp van een lentivirale vector die codeert voor het humane arylsulfatase A (ARSA)-gen.

Het is een Advanced Therapy Medicinal Product (gentherapie), met een weesgeneesmiddelstatuut dd. 13-04-2007 en een Europese vergunning voor het in de handel brengen dd. 17-12-2020.

De therapeutische indicatie van Libmeldy is: behandeling van metachromatische leukodystrofie (MLD) gekenmerkt door bi-allelische mutaties in het arylsulfatase A-gen (ARSA-gen) wat leidt tot verminderde enzymatische activiteit van ARSA:

- bij kinderen met laat-infantiele of vroeg-juveniele vormen, zonder klinische manifestaties van de ziekte;

- bij kinderen met de vroeg-juveniele vorm, met vroege klinische manifestaties van de ziekte, die nog zelfstandig kunnen lopen en vóór het begin van cognitieve achteruitgang.

Deze evaluatie maakt deel uit van een gemeenschappelijke beoordeling in het kader van het BeNeLuxA-project. Het Farmacotherapeutisch rapport werd opgesteld door het RIZIV, het Farmaco-economisch rapport evenals de Budget Impact Analyse werden opgesteld door het NCPE.

U zal in dit dossier dus niet de gebruikelijke indeling terugvinden. U vindt hieronder achtereenvolgens het gemeenschappelijk Farmacotherapeutisch rapport, het gemeenschappelijk Farmaco-economisch rapport en de gemeenschappelijke Budget Impact Analyse, opgesteld in het Engels.

2. WETENSCHAPPELIJKE BIJSLUITER

ORCHARD THERAPEUTICS BV
Prins Bernhardplein, 200
1097 JB Amsterdam
Nederland

Therapeutische indicaties

Libmeldy is geïndiceerd voor de behandeling van metachromatische leukodystrofie (MLD) gekenmerkt door bi-allelische mutaties in het arylsulfatase A-gen (ARSA-gen), wat leidt tot verminderde enzymatische activiteit van ARSA:

- bij kinderen met laat-infantiele of vroeg-juveniele vormen, zonder klinische manifestaties van de ziekte;
- bij kinderen met de vroeg-juveniele vorm, met vroege klinische manifestaties van de ziekte, die nog zelfstandig kunnen lopen en vóór het begin van cognitieve achteruitgang (zie rubriek 5.1).

Dosering en wijze van toediening

Libmeldy moet worden toegediend in een gekwalificeerde behandelinstelling met ervaring in hematopoëtische stamceltransplantatie (HSCT).

Van de patiënten wordt verwacht dat zij deelnemen en worden gevolgd in een langetermijnvervolgonderzoek om een beter inzicht te krijgen in de langetermijnveiligheid en -werkzaamheid van Libmeldy.

Dosering

De toe te dienen dosis Libmeldy wordt bepaald op basis van het gewicht van de patiënt op het moment van de infusie.
De minimale aanbevolen dosis Libmeldy is 3 × 106 CD34+-cellen/kg. In klinische onderzoeken zijn doses tot 30 × 106 CD34+-cellen/kg toegediend.
Het maximale toe te dienen volume Libmeldy dient < 20% van het geschatte plasmavolume van de patiënt te blijven (zie rubriek 4.4 en rubriek 6.6).

Libmeldy is bedoeld voor autoloog gebruik (zie rubriek 4.4) en mag slechts eenmaal worden toegediend.

Beenmergafname of mobilisatie van perifeer bloed en aferese
De autologe CD34+-cellen worden geïsoleerd uit afgenomen beenmerg (BM) of gemobiliseerd perifeer bloed (mPB). Indien CD34+-cellen uit mPB worden geïsoleerd, vinden een of meer afereseprocedures plaats na mobilisatie van perifeer bloed. De beslissing om BM of mPB te gebruiken als het bronmateriaal voor isolatie van CD34+-cellen is aan de behandelend arts, daarbij rekening houdend met de leeftijd en het gewicht van de patiënt, zijn/haar klinische toestand en de toegankelijkheid van de aderen.
Over het algemeen heeft mPB de voorkeur als celbron voor de bereiding van Libmeldy, omdat dit minder invasief is voor de patiënt.
Niettemin is BM de celbron van keuze voor zuigelingen en kinderen met een lichaamsgewicht van minder dan 7 kg in het geval van een contra-indicatie om groeifactoren/mobilisatiemiddelen te gebruiken, en wanneer de toegankelijkheid van de aderen ongeschikt wordt geacht voor het aanbrengen van een katheter voor aferese.
Afhankelijk van het cellulaire bronmateriaal moet de patiënt minimaal 8-10 × 106 CD34+-cellen/kg kunnen doneren, wat nodig is om Libmeldy te kunnen bereiden (zie tabel 1).

Als de CD34+-cellen zo mogelijk uit BM worden geïsoleerd, moet de minimale hoeveelheid CD34+-cellen in één BM-afnameprocedure worden verzameld. Voorafgaand aan deze procedure wordt doorgaans met een eerste beenmergaspiraat een testceltelling uitgevoerd om een schatting te kunnen maken van het totale volume BM dat nodig is voor een voldoende aantal cellen voor geneesmiddelbereiding (zie rubriek 5.1).
Als de CD34+-cellen uit mPB worden geïsoleerd, kan de minimale hoeveelheid CD34+-cellen uit een of meer aferesecycli worden gehaald.

Tabel 1 **Benodigde hoeveelheid CD34+-cellen voor de bereiding van Libmeldy, naar gelang van de celbron (aantal cellen uitgedrukt als 106 CD34+-cellen/kg)**

Celbron	Minimaal aantal	Optimaal bereik
BM	10	20-40
mPB	8	20-30

Als na geneesmiddelbereiding de minimale dosis Libmeldy van 3 × 106 CD34+-cellen/kg niet wordt gehaald, kan de patiënt nog een tweede beenmergafname of een verder mobilisatieprotocol met een of meer aferesecycli ondergaan, om meer cellen voor aanvullende bereiding te verkrijgen (zie *Mobilisatie en aferese* in rubriek 5.1).

Het is ook nodig te zorgen voor een reserveverzameling van HSPC die ten minste 2 × 106 CD34+-cellen/kg bevat voor gebruik als noodbehandeling indien de kwaliteit van Libmeldy is aangetast na initiatie van myeloablatieve conditionering en voorafgaand aan Libmeldy-infusie, falen van primair aanslaan (*engraftment*) of langdurige beenmergaplasie na behandeling met Libmeldy (zie rubriek 4.4).
Deze cellen moeten op het moment van de BM-afname of mPB-aferese van de patiënt worden verzameld en overeenkomstig de ter plekke geldende procedures worden gecryopreserveerd voorafgaand aan de myeloablatieve conditionering.

Mobilisatie perifeer bloed
Wanneer wordt besloten mPB als bronmateriaal te gebruiken, moeten patiënten een HSPC-mobilisatie ondergaan met granulocytkoloniestimulerende factor (G-CSF) met of zonder plerixafor gevolgd door aferese om CD34+-stamcellen te verkrijgen voor geneesmiddelbereiding (zie rubriek 5.1 voor een beschrijving van het in klinische onderzoeken toegepaste mobilisatieregime).

Aanbevolen conditionering vóór behandeling
De behandelend arts dient te bevestigen dat toediening van autologe HSPC-gentherapie klinisch passend is voor de patiënt alvorens te starten met myeloablatieve conditionering (zie rubriek 4.4).

Een myeloablatieve conditionering is noodzakelijk voorafgaand aan infusie met Libmeldy ter bevordering van efficiënte *engraftment* van de genetisch gemodificeerde autologe CD34+-cellen (zie rubriek 5.1 voor een beschrijving van het myeloablatieve regime dat in klinische onderzoeken wordt gebruikt).
Busulfan is het aanbevolen conditionerende geneesmiddel.
Er mag pas worden begonnen met myeloablatieve conditionering als de volledige set met infuuszak(ken) met de dosis Libmeldy is ontvangen en bewaard in de gekwalificeerde behandelinstelling, en de beschikbaarheid van de reserveverzameling is bevestigd.
Gelijktijdig met het conditioneringsregime en voorafgaand aan behandeling met Libmeldy wordt het aangeraden dat patiënten profylaxe krijgen voor veno-occlusieve ziekte (VOD) en daarmee samenhangende complicaties in verband met beschadigd endotheel, d.w.z. met transplantatie-geassocieerde trombotische microangiopathie (TA-TMA) of atypisch hemolytisch-uremisch syndroom (aHUS), overeenkomstig de lokale voorschriften.
Afhankelijk van het toegediende myeloablatieve conditioneringsregime dient ook profylaxe voor epileptische aanvallen te worden overwogen. Fenytoïne wordt niet aanbevolen omdat het de klaring van busulfan kan verhogen.
Profylactisch en empirisch gebruik van anti-infectiemiddelen (bacterieel, schimmel, viraal) moet worden overwogen voor de preventie en behandeling van infecties, in het bijzonder tijdens de neutropene periode na conditionering. Overeenkomstig de plaatselijke richtlijnen wordt routinematige controle op de meest voorkomende virussen die opnieuw worden geactiveerd, aanbevolen. Tijdens de ziekenhuisopname dienen maatregelen voor infectiebestrijding en isolatieprocedures te worden toegepast volgens de lokale normen.

Premedicatie
Aanbevolen wordt premedicatie met intraveneus chloorfeniramine (0,25 mg/kg, max. dosis 10 mg) of een gelijkwaardig geneesmiddel toe te dienen 15-30 minuten vóór infusie met Libmeldy om de kans op een allergische reactie op de infusie te verkleinen.

Bijzondere populaties

Ouderen
Libmeldy is niet onderzocht bij patiënten ouder dan 65 jaar.

Verminderde nierfunctie
Libmeldy is niet onderzocht bij patiënten met een verminderde nierfunctie. Patiënten moeten worden beoordeeld op een verminderde nierfunctie om te verzekeren dat toediening van autologe HSPC-gentherapie aangewezen is. Er is geen dosisaanpassing nodig.

Verminderde leverfunctie
Libmeldy is niet onderzocht bij patiënten met een verminderde leverfunctie. Patiënten moeten worden beoordeeld op een verminderde leverfunctie om te verzekeren dat toediening van autologe HSPC-gentherapie aangewezen is. Er is geen dosisaanpassing nodig.

Pediatrische patiënten
De veiligheid en werkzaamheid van Libmeldy zijn niet vastgesteld bij patiënten met de laat-juveniele vorm van de ziekte (d.w.z. waarbij de ziekte typisch aanvangt bij personen ouder dan 7 jaar). Er zijn geen gegevens beschikbaar.

Wijze van toediening

Libmeldy is uitsluitend bedoeld voor intraveneuze infusie (zie rubriek 6.6 voor alle details van het toedieningsproces).

Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel
Dit geneesmiddel bevat genetisch gemodificeerde humane cellen. Beroepsbeoefenaren in de gezondheidszorg moeten daarom passende voorzorgsmaatregelen nemen (dragen van handschoenen en een bril) om mogelijke overdracht van infectieziekten tijdens het hanteren van het product te voorkomen.
Voor instructies over bereiding, accidentele blootstelling en verwijdering van Libmeldy, zie rubriek 6.6.

Voorbereiding voor infusie
Voordat infusie met Libmeldy plaatsvindt, moet worden bevestigd dat de identiteit van de patiënt overeenkomt met de essentiële unieke informatie van de patiënt op de etiketten op de infuuszak(ken) en het bijbehorende partijinformatieblad. Het tijdstip van ontdooiing en van infusie met Libmeldy moet op elkaar worden afgestemd. De begintijd van de infusie moet vooraf worden bevestigd en gecorrigeerd te worden voor ontdooiing, zodat Libmeldy beschikbaar is voor infusie wanneer de patiënt gereed is. Voor behoud van de levensvatbaarheid van het product wordt aanbevolen Libmeldy onmiddellijk toe te dienen nadat het volledig ontdooid is. De toediening dient binnen 2 uur na ontdooiing voltooid te zijn.

Toediening
Dien het geneesmiddel toe als een intraveneuze infusie via een centraal-veneuze katheter. Wanneer meer dan één zak met Libmeldy nodig is, mag per uur slechts één zak met geneesmiddel via infusie worden toegediend. Elke zak dient binnen ongeveer 30 minuten via infusie te worden toegediend met een infusiesnelheid van niet meer dan 5 ml/kg/uur. De aanbevolen toedieningsset bestaat uit een bloedtransfusieset voorzien van een filter van 200 µm (zie rubriek 6.6).

3. VRAAG VOOR TERUGBETALING , ZOALS DOOR DE AANVRAGER VOORGESTELD

INSCHRIJVING IN DE VERGOEDBAARHEID

Meerwaardeklasse	**Weesgeneesmiddel**

Farmaceutische specialiteit: Punctuele herziening	
Termijn	Blanco
Evaluatiecriteria	1. therapeutische waarde
	2. prijs en vergoedingsbasis
	3. belang in functie van behoeften
	4. budgettaire weerslag
	5. kosten / therapeutische waarde

Vergoedingsvoorwaarden	Hoofdstuk IV, nieuwe §XXX0000 Code M/V : Neen Code T : - G, C: Niet van toepassing * en ** Tariferingseenheid : per behandeling Tariferingsschijf : Niet van toepassing	
Referentieterugbetaling	Neen	
Biologisch geneesmiddel	Ja	
Weesgeneesmiddel	Ja	
Vergoedingscategorie en –groep	A-NEW	Omschrijving : Nieuw

	Aanvrager		**FOD Economie**
LIBMELDY || 2-10 × 10^6 cellen/ml dispersie voor infusie	Prijs (EURO)	Vergoedingsbasis (EURO)	Prijs (EURO)
Niveau publiek	NVT	NVT	NVT
Niveau prijs buiten bedrijf	2.875.000,00	2.875.000,00	Aangevraagd

Ter informatie : ATC-code N07	**buiten forfait**

Paragraaf XXX0000 (nieuw)	**Paragraaf XXX0000 (nouveau)**
a) De farmaceutische specialiteit op basis van atidarsagen autotemcel komt in aanmerking voor een eenmalige vergoeding indien zij wordt toegediend voor de behandeling van metachromatische leukodystrofie (MLD), gekenmerkt door biallelische mutaties in het gen voor arylsulfatase A (ARSA) die leiden tot een vermindering van de enzymatische activiteit van ARSA bij een rechthebbende:	a) La spécialité pharmaceutique à base d'atidarsagen autotemcel fait l'objet d'un remboursement unique si elle est administrée pour le traitement de la leucodystrophie métachromatique (LDM) caractérisée par des mutations bialléliques du gène de l'arylsulfatase A (ARSA) entraînant une réduction de l'activité enzymatique de l'ARSA chez un bénéficiaire :
- met laat-infantiele of vroeg-juveniele vormen, zonder klinische manifestaties van de ziekte;	- atteints de la forme infantile tardive ou juvénile précoce, sans manifestations cliniques de la maladie ;
- OF met de vroeg-juveniele vorm, met vroege klinische manifestaties van de ziekte, die nog zelfstandig kunnen lopen en vóór het begin van cognitieve achteruitgang.	- OU atteints de la forme juvénile précoce, présentant des manifestations cliniques précoces de la maladie, qui ont conservé la capacité de marcher indépendamment et avant l'apparition du déclin cognitif.
b) De terugbetaling zal worden toegekend na een positief antwoord van de door de houder van de vergunning voor het in de handel brengen, gekwalificeerde behandelingscentra op verzoek van een Belgische geneesheer-specialist.	b) Le remboursement sera accordé après une réponse positive des centres de traitement qualifiés par le titulaire de l'autorisation de mise sur le marché, à une demande d'un médecin spécialiste belge.
c) De vergoeding kan slechts eenmaal worden toegekend als een enkelvoudige behandeling voor éénmalig gebruik en houdt rekening met een aanbevolen dosering die in de Samenvatting van de Kenmerken van het Product (SKP) van de betrokken farmaceutische specialiteit.	c) Le remboursement ne peut être accordé qu'une seule fois et que sous forme d'un seul traitement à usage unique et tient compte de la dose recommandée mentionnée dans le résumé des caractéristiques du produit (RCP) de la spécialité pharmaceutique concernée.
d) Vergoeding kan alleen worden toegekend indien de specialiteit is toegediend in een gekwalificeerd behandelcentrum.	d) Le remboursement ne peut être accordé que si la spécialité a été administrée dans un centre de traitement qualifié.
e) De geïdentificeerde en geauthentificeerde arts-specialist vermeld onder punt b), die aldus	e) Le médecin spécialiste identifié et authentifié via la plateforme e-Health, décrit sous b), qui ainsi
- er zich toe verbindt om voor de adviserende arts een gedetailleerd medisch rapport ter beschikking te houden met daarin een uitgebreid verslag van de klinische toestand van de rechthebbende bij aanvang van de behandeling;	- s'engage à tenir à la disposition du médecin-conseil les éléments de preuve établissant que le bénéficiaire concerné se trouvait bien dans la situation attestée;
- er zich toe verbindt om de aanbevelingen zoals vermeld in de Samenvatting van de Productkarakteristieken (SPK) te respecteren.	- s'engage à respecter les recommandations mentionnées dans le Résumé des Caractéristiques du Produit (RCP).

FARMACOTHERAPEUTIC REPORT

LIBMELDY 2-10*10^6 CELLEN/ML
DISPERSIE VOOR INFUSIE, 1 DOSIS

1. SUBJECT OF THE SUBMISSION

The company Orchard Therapeutics B.V. has submitted, for reimbursement, a dossier on the orphan medicinal product Libmeldy®(**Atidarsagene autotemcel)**, a gene therapy containing an autologous CD34+ cell enriched population (2-10 x10^6 cells/mL suspended in cryopreservative solution) that contains haematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene.

It is an Advanced Therapy Medicinal Product (gene therapy), with an orphan designation dd. 13-04-2007 and a marketing authorization valid through the EU dd. 17-12-2020.

The therapeutic indication of Libmeldy is: treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,

- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

The dossier is submitted within the Beneluxa Pharmaceutical Policy Initiative. For the HTA , RIZIV-INAMI (Belgium) authors the pharmacotherapeutic part and NCPE (Ireland) the pharmaco-economic part and budget impact for the 3 countries.

Contents

2. SUMMARY

Metachromatic leukodystrophy (MLD) is an autosomal recessively inherited lysosomal storage disorder caused by mutations in the ARSA-gene resulting in deficient activity of the lysosomal enzyme arylsulfatase A (ARSA), clinically divided in 3 morbidity types , late-infantile (≤30 months), juvenile (with early juvenile 30 months -≤ 7 years and late juvenile 7-≤16 years) and adult (age of onset after 16 years).
Progressive deterioration of motor and mental capabilities will lead to a vegetative state, with patient death to be expected 1-7 years after onset of disease in Late infantile patients and after 3-15 years in Early Juvenile patients.

The main difficulty in the treatment of diseases affecting the nervous system arises from the poor permeability of the BBB (blood-brain barrier), which restricts access of therapeutic compounds during systemic administration and results in low effectiveness of many therapeutic approaches. Pre- and early symptomatic patients might benefit from treatment with bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT). Most of the patients are managed symptomatically with best supportive care to improve the quality of the remaining life.

Gene therapy using Atidarsagene autotemcel (AA) is presented as a new therapeutic option for children with late infantile or early juvenile forms, without clinical manifestations of the disease, and for children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

It should be noted that in most patients studied, a fresh AA formulation has been used. The commercial AA will be a cryopreserved formulation, which has been used in 4 patients so far.

In response to the HTA report, the company is stating that the cryopreserved formulation of arsa-cel is the commercially available formulation, and that the change to a cryopreserved formulation was made to increase the shelf life of arsa-cel allowing patients to be treated closer to home, and to improve safety as the conditioning regimen will not be initiated until receipt of the modified cryopreserved cells, as opposed to the fresh formulation where this needs to be initiated during arsa-cel manufacture. The development of this formulation was endorsed by the EMA, who considered this an equivalent product to the fresh formulation.

It should be stressed that the cryopreserved formulation was only used in 4 patients (2 LI PS and 2 EJ PS) in study 205756, with data available for a maximum of 1,5 years in only 1 patient, which is a rather small cohort to conclude on overall equivalence.

2.1. THERAPEUTIC VALUE

Libmeldy contains autologous CD34+ cell enriched population of haematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene, intended for the treatment of children affected with metachromatic leukodystrophy, either of the late infantile (LI) / early juvenile (EJ) forms without clinical manifestions of the disease or of the early juvenile (EJ)form with early clinical manifestations of the disease but who still have the ability to walk independently and before the onset of cognitive decline.

2.1.1. Efficacy / Efficiency in practice

It should be noted that all of the 19 LI-MLD patients and all of the 12 EJ MLD patients in the comparative TIGET NHX study were symptomatic at enrolment in the study, which can induce a timing bias in a direct comparison on MLD evolution. The company noted in the CSR that retrospective data analysis was performed, resulting mean age of data in the LI patients of 20,65 months (range 10 – 27,9 months) and 51,98 months (range 20,3 – 74,2 months for the EJ patients) which is comparable to the 201222 study patients.

The primary efficiency outcome parameters measured in the clinical studies included mortality, motor function (GMFM-88) and cognitive development (IQ). These were the key data:

Versie préCTG:

	Study 201222			**Study 205756**		**CUP**	
Form of MLD	LI-PS	EJ-PS	EJ-S	LI-PS	EJ-PS	LI-PS	EJ-PS
Number of patients	9	4	7	3	1	7	1
Patient survival (crucial)	100% @3y	100% @3y	2 pts died (28,6%) 5 pts alive @3y (71,4%)	100% @1y	100% @1y	1 pt died (14,3%) 6 pts alive (85,7%)	100%
GMFM-88 score	Baseline 59,12% 72,5% @2y	Baseline 92,39% 96,7% @2y	Baseline 84,64% 60,7% @2y	Baseline 45,83% 76,66% @1y	Baseline 94,94% NA @1y	Baseline 41,51% NA	Baseline 56,14% NA
GMFM within normal median range (95%CI)	Yes: 4/9 (44,4%) No: 5/9 (55,6%)	Yes: 3/4 (75%) No: 1/4 (25%)	Yes: 0/7 (0%) No: 7/7 (100%)	Yes: 3/3 (100%) No: 0/3 (0%)	Yes: 1/1 (100%) No: 0/1 (0%)	Yes: 7/7 (100%) No: 0/7 (0%)	Yes: 1/1 (100%) No: 0/1 (0%)
Median IQ - verbal	94 @3y	100 @3y	89 @1y (1pt)	NA	NA	NA	
Median IQ - performance	102 @3y	119 @3y	95 @1y (1 pt)	NA	NA	NA	

NA: data not available / GMFM-88 score: Gross Motor Function Measure / median normal IQ 90-109 /IQ normal mean 100±15

	LI-PS	EJ-PS	EJ-S
GMFM within normal median range (95%CI)	Yes: 7/12 (58,3%) No: 5/12 (41,7%)	Yes: 4/5 (80%) No: 1/5 (20%)	Yes: 0/7 (0%) No: 7/7 (100%)
GMFM within normal median range (95%CI) – including CUP	Yes 14/19 (73,7%) No: 5/19 (26,3%)	Yes: 5/6 (83,3%) No: 1/6 (16,7%)	NA

Patient survival:

There were 2 early symptomatic Early Juvenile patients dying in study 201222 due to progressive disease and 1 presymptomatic Early Juvenile patient in the CUP. All other patients were alive at final assessment in the CSR (year 3).

Primary outcome parameters:

Quality of engraftment:

The vector copy number (VCN) using AA-fresh formulation in total PBMCs showed engraftment of transduced cells beginning at 28 days post treatment, with a mean of 0.19 copies/cell [range 0.03 to 0.68], being above the minimum per protocol defined target (≥0.04 copies/cell, equivalent to 4%). The VCN in total remained relatively stable from 3 months post-treatment throughout the course of follow-up of study 201222. Statistically significant correlations between VCN in PBMCs and ARSA activity in PBMCs were observed at 6 months, 1 year, 2 years and 3 years post-treatment.

In presymptomatic Late Infantile (LI) MLD patients, the ARSA activity in PBMC increased in study 201222 from a baseline value below the lower level of quantification (LLOQ) being set at 25,9 nmol/mg/h (95%CI 12,8 – 52,5) to a mean of 223,3

nmol/mg/h (95%CI 107,3 – 464,7) at year 2, an 8,6-fold increase (95%CI 3,9 – 19,2, p<0.001). At year 3 this was a mean of 429,3 nmol/mg/g (95%CI 211,8 – 869,9, p<0,001). Comparable results were observed in the CUP patients. This was also seen in study 205756 using the commercially AA-cryopreserved formulation, with ARSA values within or above the normal range.

In Early Juvenile(EJ) MLD patients, the ARSA activity in PBMC increased in study 201222 from a baseline value of 25,9 nmol/mg/h (95%CI 14,3 – 47,0) to a mean of 188,5 nmol/mg/h (95%CI 97,2 – 365,4) at year 2, a 7,3-fold increase (95%CI 3,6 – 14,9, p<0.001). At year 3 this was 237,8 nmol/mg/h (95%CI 120,8 – 468,3, p<0,001).

Clinical Outcomes:

At year 2 post treatment, the mean total GMFM-88 score was 72.5% compared to 7.4% for the historical TIGET NHx subjects (difference 65.1 points, 95%CI 41.6; 88.6), p<0.001). At year 3 the LS mean difference was still 71,5% (95%CI 46,9 – 96,0%, p<0,001).
This was confirmed in study 205756 in LI MLD patients, with GMFM total score for all 4 patients was within the range of gross motor function observed in a healthy cohort, and remained so at the time of last evaluation (1 year of 1,5 years).
In the CUP, in 2 patients there was an initial slow increase in the GMFM-88 score followed by a large increase at 20 months, and in 2 other LI patients was delayed GMFM development despite normal baseline scores, with subsequent stabilization. The remaining 3 patients showed GMFM improvement over time within the normal range.

For the 4 presymptomatic EJ MLD patients in study 201222 , the adjusted LS mean GMFM-88 total score at year 2 post treatment was 96.7% a difference 52.4% (95% CI 25.1; 79.6, p=0.008) versus the TIGET NHx group at year 2. The evolution of these patients was in line with the expected healthy age comparators, but in 1 patient the GMFM scores were between 97% and 99% during the first 2 years, but than declined to only 71% at year 3. The 1 presymptomatic EJ patient in the CUP died after 1 year of follow-up, with a GMFM of 82,11% at last visit.

For the early symptomatic EJ MLD, the clinical results of the effectiveness of the gene-therapy are less pronounced. The adjusted LS mean GMFM total score at year 2 post treatment was 60.7%, with a non-statistically significant difference from the TIGET NHx group of only 28.7% (95% CI -14.1; 71.5, p=0.35) at year 2. At year 3 the difference remained being not statistically significant at year 3, with a treatment effect difference of 43.9% (59.8% vs. 15.9%; p=0.054). In some of these patients the baseline GMFM scores were initially below the normal range, and these patients experienced either a rapid or a slower decline in GMFM after the gene-therapy. For most of the patients the GMFM score still was above the reference TIGET NHx according to the last measurement, but given the rate of decline this will most likely be comparable rather soon.
For the overall EJ MLD patients group, the LS mean GMFM total score (%) at year 2 was 76.5% for treated patients versus 36.6% in the untreated EJ TIGET NHx reference group, a mean difference of 39.8% (95% CI: 9.6%, 70.1%), exceeding the minimum threshold for efficacy (10%) predefined in the protocol and considered clinically meaningful.

Secondary outcome parameters:

At year 1 post-treatment, the proportion of BM-derived colonies harbouring the LV genome (%LV+) in the overall treated population was 48.4% (range: 20.0% to 90.3%, [n=20]). The proportion of BM-derived colonies harbouring the LV genome (%LV+) at year 5 was 45.0% (range: 18.8% to 90.6% [n=6, 4 LI and 2 EJ]), indicative of stable engraftment over time in the treated population.

More than half of LI MLD patients remained in GFMC level 0 or 1 during the follow-up period, but a stabilisation at level or a regression to level 4 was seen in some of them. Overall a GMFC-MLD score below level 3 was observed in the majority of LI patients throughout the follow-up, which was also seen in study 205756 and the CUP.
In 3 of the 4 presymptomatic EJ patients the GFMC-MLD baseline level 0 did not change, and the 4th patient was deteriorating from level 0 to level 2. In 2 of the 7 early symptomatic EJ patients, the GFMC-MLD declined fast to level 4

or 5. In 2 patients there was only a small decline from level 1 to level 2 and the last patient had a decline from level 1 to level 3, but after a feet surgery returned to level 2 for the rest of the follow-up period. Overall, 3 of the 7 early symptomatic EJ patients (42,8%) had a GMFC-MLD score better than 3 throughout the follow-up period.

Comparable results and individual evolution was seen regarding brain MRI score, NCV Index and ARSA activity in CSF.

All LI patients who could be tested on the appropriate cognitive test for their chronological age (7/9) were above the threshold for severe mental disability (IQ>55) at year 2 (n=7), year 2.5 (n=5), and year 3 (n=5). Similar results were found in study 205756 and the CUP.
The majority of AA-f-treated EJ patients had a total IQ above the severe mental disability threshold (IQ>55) at year 2 (mean: 101, range: 83 to 132, n=8), year 2.5 (mean: 102, range: 79 to 136, n=7), and year 3 (mean: 95.14, range: 64 to 119, n=7) post-treatment. The processing speed scores from the 4 presymptomatic EJ patients tended to be lower at each time point relative to other neuropsychological composite scores, with 2 patients having stable scores in the normal range and 2 patients with a declining score over time below the normal values.

In response to the HTA report, the company would like to stress the fact that for the four treatment failures, levels of engraftment and pharmacodynamic effects post-gene therapy were within the range observed in the non-treatment failure group. No differences were observed between treatment failures and non-treatment failures with respect to percentage LV+ cells, vector copy number (VCN) in bone marrow (BM), VCN in peripheral blood mononuclear cells (PBMCs), or arylsulfatase A (ARSA) activity in peripheral blood (PB) and cerebrospinal fluid (CSF). This shows that whilst arsa-cel still resulted in effective engraftment and constitution of ARSA activity, the level of neurodegeneration already reached by these patients prior to treatment prevented any clinical benefit.

This comment of the company reinforces the remarks made in the HTA report that treatment benefit of AA therapy is most pronounced in pre-symptomatic patients, but the clinical effectiveness is smaller or absent once clinical symptoms have appeared, based on the currently available data.

2.1.2. Adverse effects

The majority of adverse events (AEs) occurring in 2 or more subjects were reported during the 3-month post-treatment and short-term phases. No adverse reactions or suspected unexpected adverse reactions were reported for AA-f during the reported time frame.
As expected following busulfan conditioning, all patients experienced severe neutropenia (ANC<500/µL) at one or more time points prior to day 60.
Within 3 months post-treatment, febrile neutropenia, neutropenia, stomatitis, device-related infection, serum ferritin increase, ataxia, renal tubular acidosis, and epistaxis were more evident in subjects treated with the MAC regimen compared with the SMAC regimen, though these kinds of events were common to both conditioning regimens. Mucosal inflammation was more commonly reported in the SMAC regimen than in the MAC regimen.

2.1.3. Applicability

For patients with a presymptomatic diagnosis of LI or EJ MLD following a newborn screening (in case this is implemented in the future) or in family screening after diagnosis of MLD in an affected sibling.

For patients with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

Only to be used in patients without a previous treatment with haematopoietic stem cells gene therapy or allogeneic stem cell transplantation and without contraindications to the mobilisation and the myeloablative medicinal products must be considered (I.e.busulfan).

2.1.4. Practical use

Autologous CD34+ HSPCs are collected from patient bone marrow (BM) harvest or from mobilised peripheral blood (mPB) and transduced with a lentiviral vector (ARSA LVV), taking about 40 days from cell collection to product availability takes approximately.
A myeloablative conditioning is required before infusion of Libmeldy to promote efficient engraftment of the genetically modified autologous CD34+ cells .
AA will be given via a central venous catheter. When more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour.

2.2. ADDED VALUE VERSUS ALTERNATIVES

MORTALITY – MORBIDITY – QUALITY OF LIFE

Mortality : Nothing can be said about the clinical value of the effect on mortality , given no direct statistical comparison with regards to mortality has been performed by the company for the 3 subsets of AA-treated MLD-patients (LI-PS, EJ-PS and EJ-ES) versus either natural history (TIGET NHx reference cohort or other literature/national cohort data) and HSCT-treated comparable patients, and the follow-up period for the majority of patients at this moment is too short.

Morbidity: There are major uncertainties with respect to a morbidity added-benefit of AA. Comparison with the TIGET NHx historical cohort is complicated due to differences in patient profile and the availability of comparative historical data sets. Comparison with HSCT is difficult because data about the efficacy/effectiveness of HSCT in MLD patients is very limited.
Treatment with AA is intended as a once in a lifetime treatment that should eliminate the underlying genetic cause, providing AA-treated children a similar motor and cognitive evolution as expected in healthy children, whereas untreated MLD patients will be subject to a deteriorating disease evolution. An AA-treatment in presymptomatic MLD children seems to be key.

Given the limited data available, a conditional appreciation of the benefit on morbidity would be:

- For LI-PS patients: comparing intra-patient baseline values, some benefit was observed for clinical outcome parameters (Gross Motor Function Measurements, IQ) in these Presymptomatic Late Infantile MLD-patients. Compared to the evolution pattern in healthy children, 74% of the AA-treated LI-PS patients had a GMFM evolution within the median±15% expected normal score for age and with normal IQ scores (based on 12 patients in clinical studies and on 19 patients including CUP-data).

- For EJ-PS patients: comparing intra-patient baseline values, some benefit was observed for clinical outcome parameters (Gross Motor Function Measurements, IQ) in these Presymptomatic Early Juvenile MLD-patients. Compared to the evolution pattern in healthy children, 83% of the AA-treated EJ-PS patients had a GMFM evolution within the median±15% expected normal score for age and with normal IQ scores (based on 5 patients in clinical studies and on 6 patients including CUP-data).

- For EJ-ES patients: comparing intra-patient baseline values, added value was not demonstrated on key clinical outcome parameters (Gross Motor Function Measurements, IQ) in these Symptomatic Early Juvenile MLD-patients. Compared to the evolution pattern in healthy children, none of the AA-treated EJ-ES patients had a GMFM evolution within the median±15% expected normal score for age and with normal IQ scores (based on 7 patients in clinical studies). In EJ-ES patients, a possible morbidity benefit of an AA-treatment is not demonstrated at this moment.

A possible morbidity benefit of an AA-treatment compared to HSCT for each of these 3 patient subsets has to be weighted in the presence or absence of a suitable donor and the variability in natural evolution dynamics of MLD in LI versus EJ phenotypes. Added value could not be demonstrated compared to HSCT.

Quality of life: No validated QoL assessment was done in AA-treated patients in the clinical studies.

Versie préCTG:

In response to the draft assessment report, the company doesn't agree with the conclusion that added value was not demonstrated in the EJ-ES patients, as compared to age-matched untreated ES-EJ patients, a statistically significant and clinically relevant treatment difference was observed, and that this conclusion does not align with the EMA conclusion.

With regard to a potential clinical benefit of AA versus haematopoietic stem cell transplantation (HSCT), the company agrees with the remark in the HTA report that no direct head-to-head studies compared these 2 therapeutic options, but that literature shows that HSCT in pre-symptomatic patients treated with allogeneic HSCT have demonstrated significant decline in motor function. As a result of the poor outcomes seen, allogeneic HSCT is not recommended for late infantile (LI) patients, and according to the company, clinical experts from the Netherlands, Ireland and Belgium all confirm that allogeneic HSCT is not seen as a comparator to arsa-cel in EJ patients, on the basis of clinical data which indicate that allogeneic HSCT is not an effective treatment for early onset MLD.

The company recognises that the HTA conclusion on the limited long-term effects of arsa-cel may have been influenced by concerns with declines in GMFC-MLD score seen for a small number of patients, but clinical experts have noted that these declines are not indicative of lack of durability of effect or of disease progression, but are as a result of pre-existing peripheral damage that becomes evident as patients have become older. It has also been noted that abnormal baseline neurological findings in some PS patients suggest that underlying onset of disease may have already occurred, despite no functional motor or cognitive impairment being detected. Orchard therefore maintains that clinical evidence and expert opinion support the durability of the effects of arsa-cel beyond 10 years.

The company is questioning if all data submitted was taken into account in the HTA evaluation, and not only the data which was available in the EPAR.

With regard to the mentioning of major uncertainties with respect to morbidity, the company considers this not correct, and assumes sufficient data are available at this moment to conclude for a significant benefit in terms of morbidity, rather than a conditional one, and this for the 3 types of patients (LI-PS, EJ-PS and EJ-ES).

It should be noted that the HTA report repeatedly commented to the different possible bias issue in comparing clinical outcome of treated patients to the clinical evolution of the TIGET NHx historical cohort, and that an AA treatment is intended as a once in a lifetime treatment that should eliminate the underlying genetic cause, providing AA-treated children a similar motor and cognitive evolution as expected in healthy children, whereas untreated MLD patients will be subject to a deteriorating disease evolution.

As is stated in the assessment report, the adjusted LS mean GMFM total score at year 2 post treatment was 60.7%, with a non-statistically significant difference from the TIGET NHx group of only 28.7% (95% CI -14.1; 71.5, p=0.35) at year 2. At year 3 the difference remained being not statistically significant at year 3, with a treatment effect difference of 43.9% (59.8% vs. 15.9%; p=0.054). In some of these patients the baseline GMFM scores were initially below the normal range, and these patients experienced either a rapid or a slower decline in GMFM after the gene-therapy. For most of the patients the GMFM score still was above the reference TIGET NHx according to the last measurement, but given the rate of decline this will most likely be comparable rather soon. For the overall EJ MLD patients group, the LS mean GMFM total score (%) at year 2 was 76.5% for treated patients versus 36.6% in the untreated EJ TIGET NHx reference group, a mean difference of 39.8% (95% CI: 9.6%, 70.1%), exceeding the minimum threshold for efficacy (10%) predefined in the protocol and considered clinically meaningful. This clearly demonstrates the importance of differentiation of EJ PS and EJ ES patients in terms of clinical efficacy of the AA treatment.

It should also be noted that an HTA evaluation in view of a possible reimbursement is not the competence of the EMA, but exclusively of the respective National Competent Authorities, and that an EMA/CHMP MA does not guarantee an equivalent reimbursement status.

Concerning the HTA remark on comparison of AA treatment versus HSCT, and the answer of the company, as stated in the HTA report, this only implies on those MLD patients where HSCT could be a possible alternative with respect to age of onset and dynamics of disease progression.

Given the limited number of patients treated with AA in the 3 different patient groups (LI-PS, EJ-PS and EJ-EJ) and the limited duration of follow-up of the AA gene-therapy treatment on all relevant clinical outcome parameters, the overall HTA conclusions on clinical efficacy and added value have to be maintained, until the moment that substantial clinical evidence will be available.

The HTA evaluation considered all relevant clinical data provided by the company at the moment of introduction of the dossier, for all 3 patients types, which led to the conclusions as were made in the HTA report and were agreed upon by the Beneluxa consortium HTA assessment team.

The clinical experts consulted by ZIN in the Dutch reimbursement procedure don't agree with the assessment conclusion that AA treatment in EJ-S patients does not meet established medical science and medical practice ("stand van de wetenschap en praktijk"). The Review Group states that these patients have similar benefit from hematopoietic stem cell transplantation (HSCT) and AA, based on limited HSCT data. An important advantage of AA is the absence of graft versus host disease (GvHD). No long-term immunosuppressive treatment is required, and patients recover much faster than after allogeneic HSCT, with fewer complications. The conditioning regimens used in allogeneic transplantation, typically busulfan/fludarabine or busulfan/cyclophosphamide, are more toxic compared to the busulfan regimen used in gene therapy. Nonetheless, they share the concerns expressed in the HTA report about the limited available evidence, in particular the limited number of EJ patients as well as the length of follow-up, and they recognize that the therapeutic effect of AA is more unambiguous in pre-symptomatic patients. But in their view, however, there is an evident therapeutic benefit of AA for EJ-S patients. Motor and cognitive function as well as MRI abnormalities, for example, are more favorable in treated patients compared to natural controls. An adequate definition of 'early' in early symptomatic is of course crucial. Subclinical decline occurs over a long period of time and eventually clinical signs will appear. In other words, from pre-symptomatic to symptomatic is a sliding scale, there are no hard delineated groups.

2.3. UNCERTAINTIES AND PROBLEMS

Criteria	Uncertainties	Problems
Clinical evaluation	• Sustainability of treatment effect in patients with an initial positive result • Equal long-term efficiency of cryopreserved formulation • Clinical effectiveness in symptomatic EJ patients	• No long-term data available • Limited patient number and follow-up period • Actual data don't support a medium-term clinical effectiveness in this patient group
Place and role in medical practice	• Evidence-based patient selection in LI-PS and EJ-PS versus EJ-S • Outcome versus HSCT in eligible patients	• No clear clinical benefit demonstrated in EJ-S patients • No direct comparative data available.
Budget impact	Cfr report of BI-analysis	
Cost-effectiveness	Cfr report of CE-analysis	

3. HEALTH TECHNOLOGY ASSESSMENT

The label of AA states:

Treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,

- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

PICO-table

P	Children with metachromatic leukodystrophy with: • late infantile (LI) or early juvenile (EJ) forms without clinical manifestations of the disease • early juvenile (EJ) form with early clinical manifestations of the disease but who still have the ability to walk independently and before the onset of cognitive decline.
I	Libmeldy (atidarsagene autotemcel): Autologous CD34+ cell enriched population (2-10 x10^6 cells/mL suspended in cryopreservative solution) that contains hematopoietic stem and progenitor cells (HSPC) transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene.
C	• Clinical evolution in non-affected children • Best supportive care/symptomatic treatment of children with MLD • Bone marrow transplantation (BMT) or hematopoietic stem cell (HSC) transplantation of children with MLD.
O	• Cognitive function evolution measured with age-adapted tools IQ (performance and language) [crucial] • Motor function evolution measured with GMFM-88-score [crucial] • Survival [crucial] • ARSA activity in PBMC [important] • Incidence treatment-related serious adverse events (SAEs) [crucial] • Discontinuation due to adverse events [crucial]
Relevant follow-up period	Since in a natural history patients with LI will die 1-7 years after disease onset, and 3-15 years for EJ patients, a follow-up period for at least 5 years for LI-patients and at least 10 years for EJ patients would be needed to determine whether AA establishes a clinically relevant effect.
Study design	In order to support the therapeutic benefit of AA compared to the current treatment of MLD patients, a direct comparative randomized controlled phase 3 trial would give the most reliable evidence. But given the progressive nature of MLD and the rarity of the disease combined with the few patients that are available for bone marrow or stem cell therapy, an indirect comparison can be considered sufficient.

3.1. CLINICAL DOMAIN

The clinical domain is metachromatic leukodystrophy (MLD), with the target population of treatment within this clinical domain restricted to:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,

- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

3.1.1. Disease description (ref 3, 4, 5, 6, 11, 13, 14, 15, 16)

Metachromatic leukodystrophy (MLD) is an autosomal recessively inherited lysosomal storage disorder caused by mutations in the ARSA-gene resulting in deficient activity of the lysosomal enzyme arylsulfatase A (ASA), an enzyme that catalyzes the first step in the degradation of various sulfatides in lysosomes, including 3-O-sulfogalactosylceramide (sulfatide) and 1- (3-O-sulfo-beta-D-galactosyl) sphingosine (lysosulfatide).
The arylsulfatase A gene is located on chromosome 22q13 and is alternatively spliced with 8 or 9 exons combining to produce 3 different mRNA species. These encode two isoforms of the same protein, an aryl sulfatase involved in the lysosomal degradation of sphingolipid cerebroside 3-sulfate ("sulfatide"). In subjects inheriting 2 mutant ARSA genes, ASA deficiency results in an excessive urinary excretion and intralysosomal accumulation of these sulfatides in various tissues (e.g. nervous tissue, gall bladder, kidneys and liver), but especially myelin sheaths of both the central and peripheral nervous system are affected, resulting in progressive demyelination that causes ataxia, initially flaccid and later spastic tetraparesis, mental regression, and other neurological symptoms.
About 261 unique mutations in the ARSA gene (https://databases.lovd.nl/shared/genes/ARSA) and 64 unique mutations in the PSAP gene, (https://databases.lovd.nl/shared/genes/PSAP) leading to the development of MLD, are reported to date.

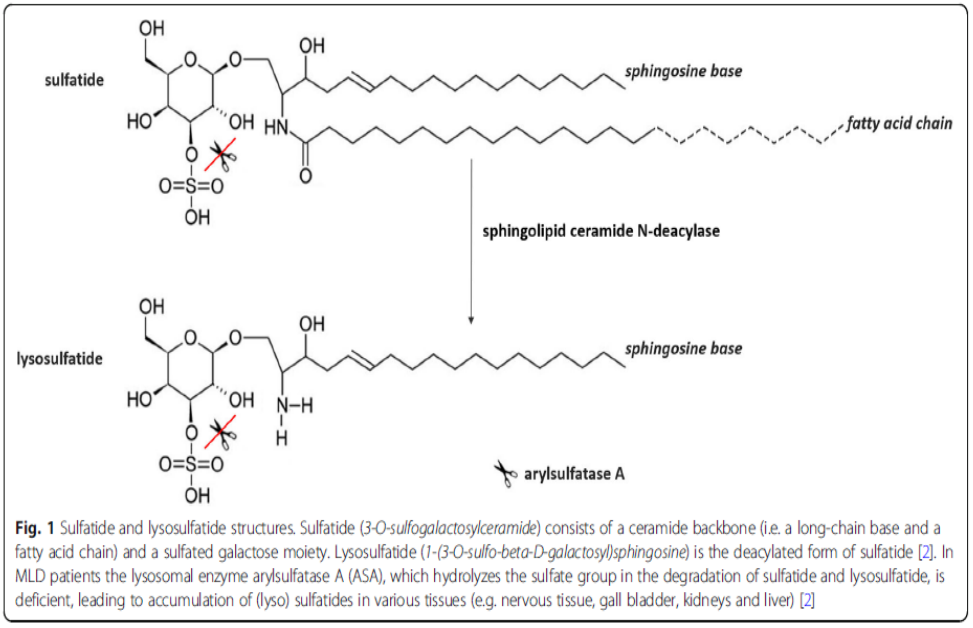


Fig. 1 Sulfatide and lysosulfatide structures. Sulfatide (*3-O-sulfogalactosylceramide*) consists of a ceramide backbone (i.e. a long-chain base and a fatty acid chain) and a sulfated galactose moiety. Lysosulfatide (*1-(3-O-sulfo-beta-D-galactosyl)sphingosine*) is the deacylated form of sulfatide [2]. In MLD patients the lysosomal enzyme arylsulfatase A (ASA), which hydrolyzes the sulfate group in the degradation of sulfatide and lysosulfatide, is deficient, leading to accumulation of (lyso) sulfatides in various tissues (e.g. nervous tissue, gall bladder, kidneys and liver) [2]

Versie préCTG:

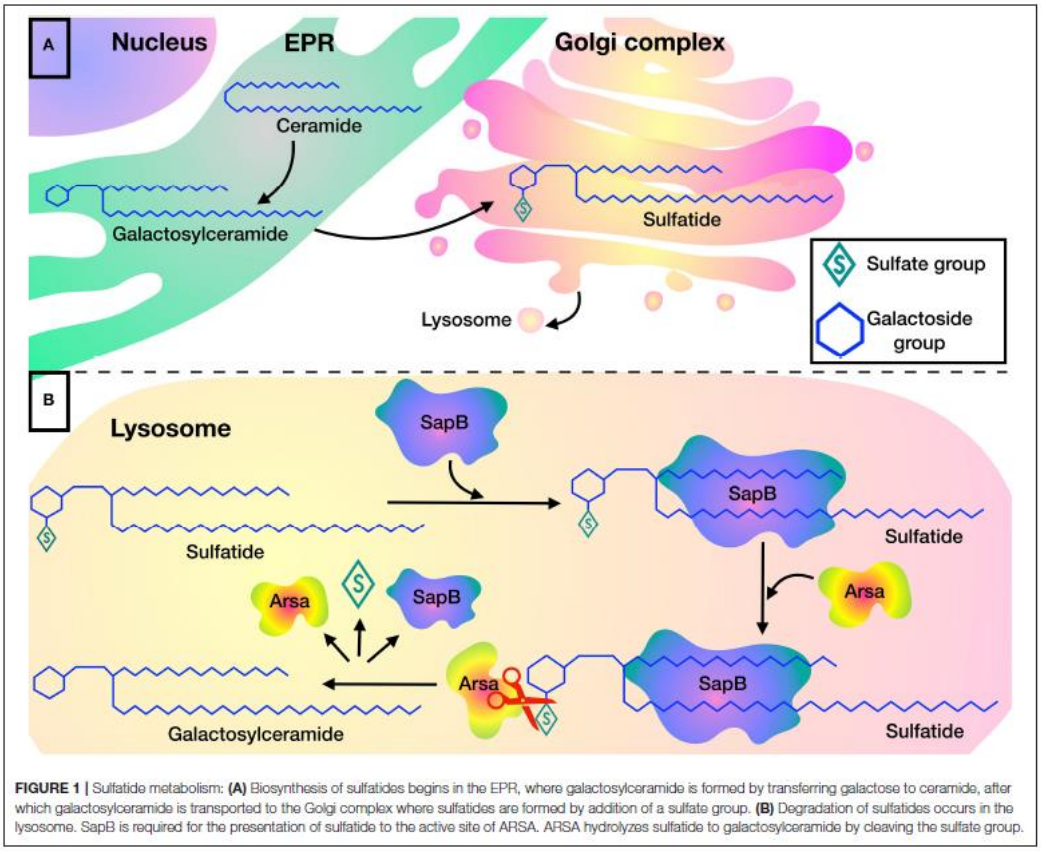


FIGURE 1 | Sulfatide metabolism: **(A)** Biosynthesis of sulfatides begins in the EPR, where galactosylceramide is formed by transferring galactose to ceramide, after which galactosylceramide is transported to the Golgi complex where sulfatides are formed by addition of a sulfate group. **(B)** Degradation of sulfatides occurs in the lysosome. SapB is required for the presentation of sulfatide to the active site of ARSA. ARSA hydrolyzes sulfatide to galactosylceramide by cleaving the sulfate group.

The accumulation of metachromatic material in peripheral nerves consists of Schwann cells and endoneural macrophages that are filled with characteristic lysosomal inclusions of sulfatides, causing a lower cerebroside-sulfatide ratio in myelin composition and a disruption in myelin metabolism, with destruction of Schwann cells and phagocytes die and demyelination of myelin in the PNS and CNS. It should be noted that no correlation between demyelination and the presence of metachromatic material in peripheral nerves has been found, but sulfatide levels in the cerebrospinal fluid (CSF) and sural nerve do reflect the severity of peripheral neuropathy (measured by nerve conduction studies), while they are not proportional to central white matter injury (assessed by the Gross Motor Function Measure 88– items score, somatosensory evoked potentials, and MR spectroscopy).

The lack of a correlation between demyelination and the presence of metachromatic material raises the question whether the pathology of peripheral neuropathy in MLD can be partially explained by a neuroinflammatory scenario, by means of complement activation via the alternative pathway amplifying myelin damage in MLD by inducing or enhancing an immune response against myelin. The neuroinflammatory component in the pathology of MLD is induced by sulfatide accumulation and demyelination in the PNS, able to induce the release of inflammatory cytokines, activate endoneural macrophages and recruit inflammatory myeloid cells and lymphocytes from the periphery.
Significant elevations of MCP-1, IL-1Ra, IL-8, MIP-1b and vascular endothelial growth factor (VEGF) in both CSF and plasma of MLD patients has been found compared to unaffected controls. These inflammatory cytokines are able to disrupt the blood-nerve and blood-brain barrier by downregulating tight junction proteins, causing leakage of noxious substances from the blood into the endoneurium.

Versie préCTG:

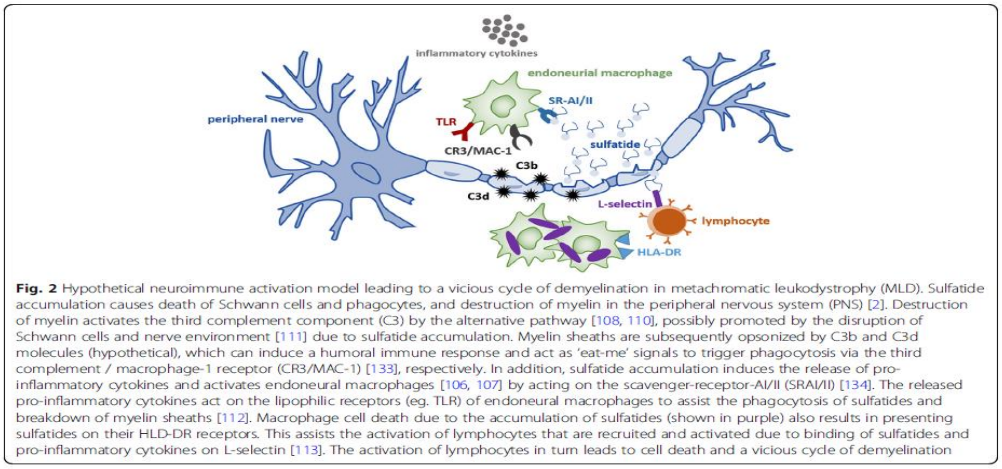


Fig. 2 Hypothetical neuroimmune activation model leading to a vicious cycle of demyelination in metachromatic leukodystrophy (MLD). Sulfatide accumulation causes death of Schwann cells and phagocytes, and destruction of myelin in the peripheral nervous system (PNS) [2]. Destruction of myelin activates the third complement component (C3) by the alternative pathway [108, 110], possibly promoted by the disruption of Schwann cells and nerve environment [111] due to sulfatide accumulation. Myelin sheaths are subsequently opsonized by C3b and C3d molecules (hypothetical), which can induce a humoral immune response and act as 'eat-me' signals to trigger phagocytosis via the third complement / macrophage-1 receptor (CR3/MAC-1) [133], respectively. In addition, sulfatide accumulation induces the release of pro-inflammatory cytokines and activates endoneural macrophages [106, 107] by acting on the scavenger-receptor-AI/II (SRAI/II) [134]. The released pro-inflammatory cytokines act on the lipophilic receptors (eg. TLR) of endoneural macrophages to assist the phagocytosis of sulfatides and breakdown of myelin sheaths [112]. Macrophage cell death due to the accumulation of sulfatides (shown in purple) also results in presenting sulfatides on their HLD-DR receptors. This assists the activation of lymphocytes that are recruited and activated due to binding of sulfatides and pro-inflammatory cytokines on L-selectin [113]. The activation of lymphocytes in turn leads to cell death and a vicious cycle of demyelination

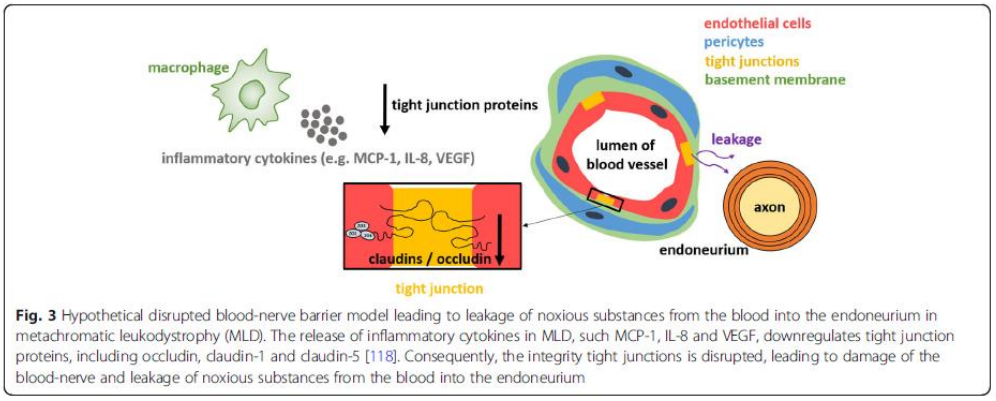


Fig. 3 Hypothetical disrupted blood-nerve barrier model leading to leakage of noxious substances from the blood into the endoneurium in metachromatic leukodystrophy (MLD). The release of inflammatory cytokines in MLD, such MCP-1, IL-8 and VEGF, downregulates tight junction proteins, including occludin, claudin-1 and claudin-5 [118]. Consequently, the integrity tight junctions is disrupted, leading to damage of the blood-nerve and leakage of noxious substances from the blood into the endoneurium

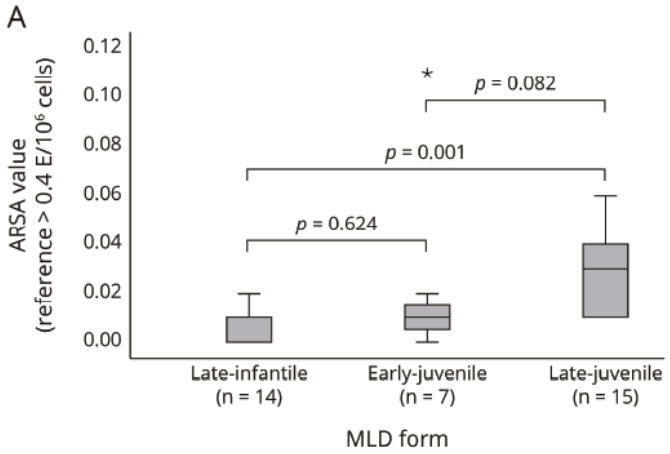
The clinical course can be divided into a presymptomatic stage with normal development, followed by onset of first symptoms and a period of developmental stagnation. This plateau phase with stagnation of initial development is shorter in early onset forms, and longer and more variable in late onset forms. Finally, rapid disease progression evolves with a relatively invariable rapid loss of gross motor function, and a final stabilization at a low functional level. Two types of alleles that cause the development of MLD can be distinguished: null alleles, which encode an inactive enzyme, and R-alleles, which encode an enzyme with residual activity. In late-onset forms of MLD such a stagnation phase of initial development is lacking.

There are 3 main clinical types of MLD, being late-infantile (age of onset before 30 months), juvenile (age of onset between 2.5–16 years, with early juvenile 30 months -≤ 7 years and late juvenile 7-≤16 years) and adult (age of onset after 16 years). Genotype-phenotype correlation revealed that null alleles, which cause hardly any residual ARSA activity, result in an early onset and rapid deterioration of motor and cognitive function characterizing the late-infantile form of MLD with first symptoms occurring before 2.5 years of age. In later onset forms (juvenile MLD with disease onset between 2.5 and 16 years, and adult MLD with disease onset after 16 years of age), the prevalent genotypes were associated with some remaining residual activity of the enzyme (R-alleles).

Levels of residual ASA activity correlate with the type and partly with the severity of symptoms, and the diagnosis of MLD is confirmed by measuring ASA activity in leucocytes, increased urinary sulfatide levels and pathogenic ARSA gene variants. The biological investigations can be completed by typical MRI features, neurophysiological evidence of demyelinating sensorimotor polyneuropathy and neuropsychological evidence of mental regression. Often a brain MRI prompts the diagnosis, consequently the diagnosis is biochemically and genetically confirmed.

Based on the clinical data of 21 patients with late infantile MLD and 38 patients with juvenile MLD in the German LEUKONET survey, Kehrer et al., 2011 found that LI MLD patients all showed a loss of all gross motor function measured (GMFC-MLD scale) until the age of 3 years and 4 months, while patients suffering from juvenile MLD had a more variable and significantly longer motor decline.

Versie préCTG:
An updated publication in 2020, including 97 patients in the LEUKONET survey (Kehrer et al., 2020), of which 35 with EJ MLD, 18 with EJ MLD, 38 with LJ MLD and 6 with adult MLD found that disease onset at an early age was characterized in all patients by motor symptoms alone or in combination with cognitive symptoms, but pure cognitive symptoms were only seen in in older children (youngest 6, 5 years old) and adults. In LI patients, 91% exhibited only motor symptoms and 9% a combination of motor and cognitive symptoms. In EJ patients, this was 61% and 39% respectively. In late-juvenile patients, pure motor symptoms were seen in 13% of the patients, pure cognitive symptoms in 61% and a combination of motor and cognitive symptoms in 26% of the patients.
The ARSA activity was significantly lower in LI patients (mean 0,009±0,007 nmol/mg/h) compared to LJ patients (mean 0,027±0,016 nmol/mg/h, p=0,001)), but not compared to EJ MLD patients (mean 0,023±0,039 nmol/mg/ml, p=0,624) and not between EJ and LJ MLD patients (p=0,082).



The severity of disease progression also differed between the MLD forms (time from disease onset to clinical endpoint in years).

Clinical endpoints		**LI MLD**	**EJ MLD**
GMFC-MLD Level 2	Mean ±SD 95 % CI	0.43±0.09 0.26 – 0.60	1.63±0.32 1.00 – 2.25
GMFC-MLD Level 5	Mean ±SD 95 % CI	1.15±0.12 0.93 – 1.38	2.47±0.50 1.49 – 3.46
Swallowing difficulties	Mean ±SD 95 % CI	1.15±0.12 0.92 – 1.38	2.17±0.50 1.19 – 3.14
Tube feeding	Mean ±SD 95 % CI	3.19±0.69 1.84 – 4.54	3.50±0.74 2.05 – 4.94
Language decline	Mean ±SD 95 % CI	0.87±0.10 0.68 – 1.06	1.37±0.35 0.68 – 2.06
Loss of expressive language	Mean ±SD 95 % CI	1.63±0.35 0.95 – 2.30	2.54±0.45 1.65 – 3.43

The GMFC-MLD classification consists of seven different levels, and can be applied to children aged 18 months and older. These levels cover all stages of gross motor function observed or reported in the 59 participants with MLD. Level 0 in this scale reflects normal walking capabilities normal for age, where level 2 already implies the need of support I order to be able to walk. At level 5 the motor control of the head is still possible, but sitting or other motor functions need external help. At level 6 all motor function has been lost.

Versie préCTG:

Table I: The seven different levels of gross motor function classification in metachromatic leucodystrophy

Level 0	Walking without support with quality of performance normal for age
Level 1	Walking without support but with reduced quality of performance, i.e. instability when standing or walking
Level 2	Walking with support. Walking without support not possible (fewer than five steps)
Level 3	Sitting without support **and** locomotion such as crawling or rolling. Walking with or without support not possible
Level 4	(a) Sitting without support but no locomotion **or** (b) Sitting without support not possible, but locomotion such as crawling or rolling
Level 5	No locomotion nor sitting without support, but head control is possible
Level 6	Loss of any locomotion as well as loss of any head and trunk control

The GMFM-66 or GMFM-88 Gross Motor Ability Estimator Score scoring sheet calculates the % score on 5 dimensions (lying & rolling, sitting, crawling & kneeling, standing and walking, running & jumping). It is a standardized observational instrument designed and validated to measure change in gross motor function over time in children with cerebral palsy.

A brain MRI scoring system measuring T2 hyperintensities of white matter in different cerebral regions can categorize positive brain MR scores into 3 groups: mild disease (score, 1–6), moderate disease (score, 7–15), and severe disease (score, 16–34).

Table 1: Brain MR imaging scoring system for MLD

Brain Areas	Score*			Maximum per Area
Frontal WM	6†			
Periventricular	0	1	2	
Central	0	1	2	
U-fibers	0	1	2	
Parieto-occipital WM	6†			
Periventricular	0	1	2	
Central	0	1	2	
U-fibers	0	1	2	
Temporal WM	6†			
Periventricular	0	1	2	
Central	0	1	2	
U-fibers	0	1	2	
Corpus callosum	4†			
Genu	0	1	2	
Splenium	0	1	2	
Projection fibers	6†			
Internal capsule posterior limb	0	1	2	
Internal capsule anterior limb	0	1	2	
Midline pons	0	1	2	
Cerebral atrophy	0	1	2	2†
Thalamus	0	1		1†
Basal ganglia	0	1	1†	
Cerebellum	2†			
WM	0	1		
Atrophy	0	1		
Total				34†

Note:—MLD indicates metachromatic leukodystrophy; WM, white matter.
* 0 indicates normal; 1, faint hyperintensity; 2, dense hyperintensity.
† XXX.

The nerve conduction velocity (NCV) is affected and slowed down in MLD, and this for both motor and sensory nerves, as is expected for a pathology with demyelinating polyneuropathy.

In late infantile MLD patients, the median age for deteriorating gross motor function (level 1 GMFC-MLD) was 18 months (1,5 years), with a progression to a total loss of gross motor function at a median age of 33,5 months (2,8 years).
In juvenile MLD patients, level 1 GMFC-MLD was observed at a median age of 64,5 months (4,9 years), with an evolution to level 6 at a median age of 116,0 months (9,6 years).
The dynamics at which patients with late infantile MLD progress through the different levels of GMFC-MLD is shorter with each level passed. Which is less pronounced in patients suffering from juvenile MLD.

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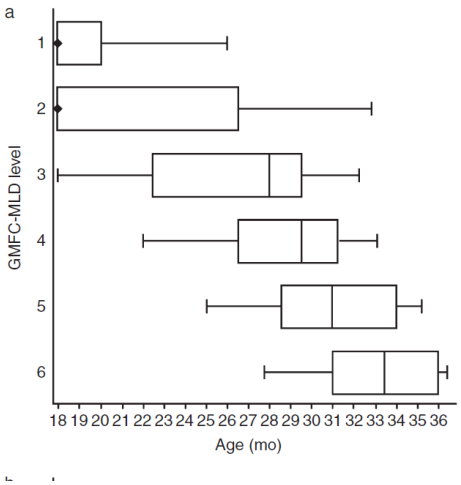

Table I: Medians and quantiles of patients' ages (mo) at entry into the respective level of the Gross Motor Function Classification for metachromatic leukodystrophy (GMFC-MLD) for (a) late-infantile; (b) juvenile forms of the disease

GMFC-MLD	10%	25%	Median	75%	90%
(a)					
Level 1	18.0	18.0	18.0	20.0	26.0
Level 2	18.0	18.0	18.0	26.5	32.8
Level 3	18.0	22.5	28.0	29.5	32.2
Level 4	22.0	26.5	29.5	31.3	33.1
Level 5	25.0	28.5	31.0	34.0	35.2
Level 6	27.7	31.0	33.5	36.0	36.4
(b)					
Level 1	42.0	47.0	64.5	92.0	150.5
Level 2	62.6	72.3	91.0	114.8	166.4
Level 5	63.8	78.0	96.0	157.0	188.4
Level 6	68.0	84.8	116.0	159.0	227.0

Levels 3 and 4 are omitted in (b) owing to the small number of patients. Distributions of age at entry for all levels are higher in patients with the juvenile form than in those with the late-infantile form ($p<0.001$).

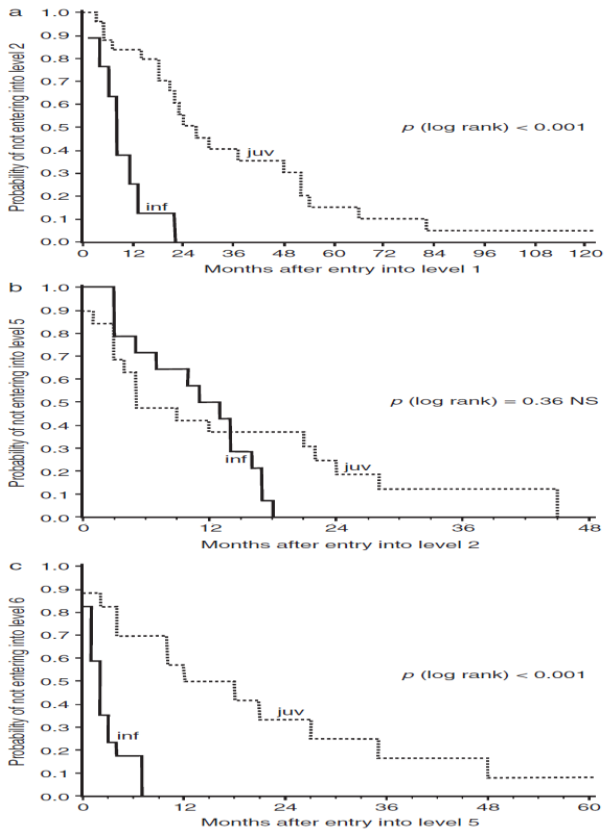

Figure 2: Kaplan–Meier estimates for time interval from (a) entry into level 1 to entry into level 2 (`first period'), from (b) entry into level 2 to entry into level 5 (`second period'), and from (c) entry into level 5 to entry into level 6 (`third period') in patients with the late-infantile (inf) form of metachromatic leukodystrophy compared with those with the juvenile (juv) form (degrees of freedom=1).

<u>Late infantile type:</u>

The most frequent clinical type of MLD is the late infantile type (LI - 50-60% of cases), with an age of onset at 6 months until 2,5 years, which will lead to a severely disabled state with loss of all motor functions and speech, resulting in death within 1-7 years after onset. This form of MLD is considered the most severe, characterized by lack of or minimal residual ARSA activity, which entails rapid neurodegeneration. Typically, the development is normal during the first year of life. In the following period the development will stagnate and then deteriorate. Developmental milestones, such as walking,

standing, or sitting without support, will be lost. Clinically muscle weakness is prominently present. Peripheral neuropathy is observed, which is associated with a decrease in motor and sensory nerve conduction. Subsequently, motor and cognitive abilities will further regress, and spasticity, ataxia, convulsions, visual and hearing impairment occur. (14). The terminal stage is characterized by the development of severe psychomotor retardation and often there is an atrophy of the optic nerve, pseudobulbar and bulbar palsy and, at least, swallowing and breathing alteration. The death of patients with late infantile form occurs in childhood

Juvenile type:

The juvenile type is seen in about 20-30% of cases, with an age of onset between 2,5 and 16 years, but also leading to a severely disabled state with loss of all motor functions and speech, resulting in death within 3-15 years after onset.
It is characterized by a less pronounced clinical manifestation in comparison with the late infantile form. In the juvenile form, cognitive impairment and behavioral changes are often observed, followed by deterioration of central and peripheral motility and epilepsy. The disease manifestation begins with the behavioral problems, psychiatric symptoms, delay in fine motor skills and impaired concentration. Problems with a child's ability to learn are also often observed. As the disease develops, problems with motor function arise, muscle hypertonia, spastic posturing are often observed.
With supportive treatment, including a gastric tube insertion for feeding and antibiotic therapy during infections, patients could survive in a vegetative state for years.

In the document of the company, and additional classification is made in the juvenile form, being early juvenile (EJ, patients between 30 months and 6 years) and late juvenile (LJ, patients between 7 and 16 years, with early juvenile 30 months -≤ 7 years and late juvenile 7-≤16 years).

Given the label of Libmeldy, this is an important parameters, as the current CHMP label of Libmeldy states that is can be used for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity, and this restricted to children with late infantile (LI) or early juvenile forms (EJ) without clinical manifestations of the disease, and in children with the early juvenile (EJ) form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.
This will set the age limit on the maximum age patients can be treated at ≤7 years of age, given the absence of clinical symptoms or with only early clinical manifestations of the disease.

Adult type:

The adult type, observed in about 15-20% of cases has an onset after the age of 16 years, resulting in a severely disabled state with loss of all motor functions and speech and death within 5-35 years after onset.
Adult MLD is the less severe form of the disease. In the adult form, psychoses, cognitive and behavioral impairment, ataxia, polyneuropathy, and epileptic seizures are found. Patients experience depressive disorder and sudden mood swings. Another typical feature is psychotic symptoms, such as hallucinations and illusions, which may be associated with a violation of cortico-cortical and cortico-subcortical connections, especially involving the frontal lobes. Adult MLD is the least common form of MLD, and it is often mistakenly diagnosed as early-onset dementia or schizophrenia because of its slow progression. Slow disease progression with periods of relative stability and regression is typical of an adult MLD. The final stage of the disease is similar to the late infantile and juvenile forms.

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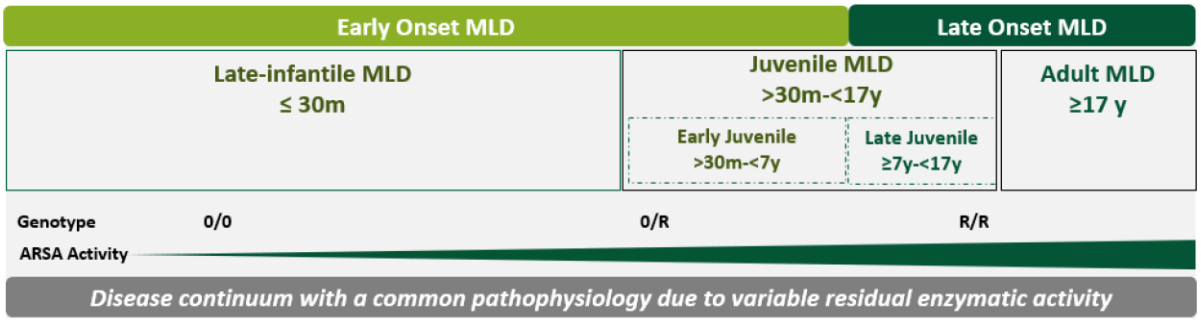
Table S1: Clinical spectrum of metachromatic leukodystrophy (MLD).

	Late-infantile type (48%)	Juvenile type (23%)	Adult type (22%)
Age at onset of symptoms	6 months – 2.5 years	2.5 – 16 years	After 16 years
Initial symptoms	Peripheral neuropathy with clumsiness, muscle weakness, sensory deficits and areflexia, motor regression, ataxia	Deterioration of school performance, behavioral disturbances, less prominent peripheral neuropathy and often combined with a mild pyramidal syndrome and ataxia	Prominent intellectual and behavioral changes often accompanied by other psychiatric symptoms, such as delusions; presentation with peripheral neuropathy also possible
Subsequent symptoms	Mental regression, spastic tetraparesis, visual and auditory impairment, bulbar palsy, seizures (25 – 50% of the cases, mostly grand mal seizures)	Mental regression, spastic tetraparesis, incontinence, optic atrophy, bulbar palsy, seizures (50 – 60% of the cases, mostly complex partial seizures)	Spastic tetraparesis, incontinence, choreiform movements, bulbar palsy, dementia, seizures (2 – 10% of the cases)
End stage	Severely disabled state with loss of all motor functions and speech, and death within 1 – 7 years after onset	Severely disabled state with loss of all motor functions and speech, and death within 3 – 15 years after onset	Severely disabled state with loss of all motor functions and speech, and death within 5 – 35 years after onset

Per MLD type, the most prominent symptoms during natural disease course are reported. The worldwide contribution of MLD types to all MLD cases is displayed between parentheses in the upper row but varies between different populations.

Figure 1: Simplified MLD Genotype-Phenotype Relationship



ARSA= arylsulfatase A; MLD=metachromatic leukodystrophy; O=null allele; R=allele with residual enzyme activity

3.1.2. Epidemiology (ref 5, 6, 7)

MLD is one of the most common leukodystrophies, and has a prevalence rate of 1 in 40,000–160,000 worldwide. Most subjects with MLD are of Caucasian origin (maybe because of underdiagnosis in other ethnicities), but in some isolated populations, the incidence of MLD is much higher. For example, in the group of Habbanite Jews it is estimated at 1 in 75, among the Navajo Indian people at 1 in 2,500, and among the Arab groups of Israel it is estimated at 1 in 8,000. The estimated incidence of MLD ranges from 1.4–1.8/100,000 live births.

Based on the population data from Eurostat for 2020, the Belgian population consist of 11.544.241 inhabitants, the Irish population of 4.985.674 inhabitants and the population of the Netherlands of 17.441.500 inhabitants, with a respective number of live births in 2019 of 117.95, 59.289 and 169.680.

- For Belgium the prevalence would range between 72,2 and 288,6 with an incidence of 1,6 – 2,1.
- For Ireland the prevalence would range between 31,2 and 124,6, with an incidence of 0,8 – 1,1.
- For the Netherlands the prevalence would range between 109,0 and 436,0, with an incidence of 2,4 – 3,1 (generally in the Netherlands an incidence of about 2-2.2 is taken into account).

In the submission file of the company, a prevalence of 0,1-0,9/100.000 and an incidence of 0,6 – 2,5 live births is being used. In the budgetary analysis, the company is only using an incident number, because the nature of the treatment implies that only newly diagnosed patients would benefit.
This would result in 2 to 3 incident patients for Belgium, and in the budget impact model the company assumes a total of 3 MLD patients/year, of which 60% would be LI type and 25% EJ-type based on an expert opinion.
Based on the incidence used by the company, a total of 0 to 1 patient/year is estimated for Ireland, which is also used in the budget impact model (either being 0 or 1 patients per given year).
For the Netherlands, a total of 3 incident patients is calculated by the company.

It should be noted that routine screening of newborn children for MLD is currently not done in Belgium, Ireland and the Netherlands. The detection of presymptomatic patients depends largely on the screening of siblings of an older diagnosed patient. As the diagnosis of MLD is symptom-based, the first patient in a family will most probably be too far progressed in the disease to be able to benefit from the intervention.
This will further reduce the number of eligible patients as calculated based on literature incidence, as newborns of a family without an MLD diagnosed sibling will probably be diagnosed too late to be eligible for treatment with Libmeldy.

3.1.3. Therapeutic options and therapeutic and social needs (ref 2, 6, 10, 12, 17, 22, 23, 24, 25)

The main difficulty in the treatment of diseases affecting the nervous system arises from the poor permeability of the BBB (blood-brain barrier), which restricts access of therapeutic compounds during systemic administration and results in low effectiveness of many therapeutic approaches. In order to prevent MLD progression, it is necessary to ensure the distribution of the drug throughout the nervous system, including the PNS (peripheral nervous system).
The problem of overcoming the BBB could be solved, for example, by direct injection of the recombinant ARSA enzyme or viral vectors encoding the wild-type gene of the missing enzyme into the brain, but such approaches are difficult to apply to humans since they require serious surgical intervention, multiple injections, and yet achieving poor biodistribution of the drug.
Viral vectors, as well as methods of gene-cell therapy are also of interest for the delivery of the missing enzyme in the PNS. However, these approaches also have disadvantages, including possible genotoxicity.
For presymptomatic patients, bone marrow transplantation (BMT) or hematopoietic stem cell (HSC) transplantation may be a therapeutic option, but the therapeutic potential remains controversial because it is still possible that the amount of ARSA secreted by normal cells after the transplantation may not be enough to cross-correct a deficiency, on top of the clinical issues of the morbidity of the procedure and finding a suitable donor.

1. **<u>Bone marrow transplantation (BMT) or hematopoietic stem cell (HSC) transplantation:</u>**

Hematopoietic stem cell transplantation (HSCT) has been used for decades on the basis of providing metabolic cross-correction, in which functional ARSA from donor-derived cells promotes sulfatide degradation. However, reports of transplant outcomes in the medical literature are relatively few and conclusions are mixed.
A number of studies have shown that BMT leads to an increase in the enzyme activity in leukocytes. In early stages of the disease, BMT is able to slow or stabilize disease progression in terms of neurocognitive and motor abilities. There is some evidence that demyelination continues to progress after BMT in 31% of cases.
In patients with an asymptomatic form, which are considered the most promising in terms of the effectiveness of the therapy, the disease continues to progress after BMT despite the normal level of the enzyme activity in blood plasma that persists throughout the observation, with brain MRI showing progressing abnormalities of the white matter in the frontal and occipital regions.

With HSCT it has been reported that siblings with the juvenile form receiving transplantation after the onset of the first symptoms demonstrate significant decrease in psychomotor functions compared to before the onset of the disease, and in patients with an adult MLD, a slowdown in the progression of the disease has also been observed.
In patients who received HSCT before or immediately after the symptom onset, the disease stabilizes and the rate of loss of gross motor and cognitive functions decreases. Stabilization of disease severity observed on MRI by a reduction of CNS demyelination does not implicate a stabilization of peripheral nerve disease too, and the effect of HSCT on peripheral neuropathy remains controversial.

In brain tissue of transplanted patients, metabolically competent donor macrophages expressing aryl-sulfatase A has been found distributed throughout the entire white matter. Compared to non-transplanted patients, these macrophages preferentially expressed markers of alternatively activated, anti-inflammatory cells that may support oligodendrocyte survival and differentiation. Additionally, transplanted patients showed higher numbers of oligodendrocytes and evidence for remyelination.

In the publication of Page et al., 2019, a treatment guideline states that symptomatic patients with LI-MLD are unlikely to derive significant benefit from HSCT. Those transplanted before symptoms will experience some benefit, although most will later develop peripheral neuropathy.
Juvenile and adult MLD patients with early symptoms are appropriate candidates for HSCT. Cognitive function is generally preserved, but motor and expressive language functions are more variable. Peripheral nerve disease appears to be less responsive to HSCT. MRI typically demonstrates increased white matter changes in the first 6 to 12 months post HSCT, followed by stability or even slight improvement. If the disease is too far progressed, HSCT is not considered to be beneficial and might even accelerate disease progression.

Table 7
Guidelines for Determining HSCT Candidacy for Patients with Juvenile and Adult MLD

	Benefit > Risk	Benefit ~ Risk*	Risk > Benefit
General	Pre- or mildly symptomatic	Mild to moderate symptoms	Moderate to severe symptoms and/or rapid progression of symptoms over previous 3 months
Motor function	M0, mildly increased tone or abnormal reflexes	M1-2, mild to moderately increased tone	M3-5, moderate to severely increased tone, abnormal reflexes
Oral motor function/feeding	Normal feeding	Can communicate in complete sentences; reduced quality for age; no signs or symptoms of aspiration	Cannot communicate in complete sentences; signs or symptoms of aspiration
Seizure	None	None	Present
Neuroimaging†	Minimal T2 hyperintensity	Moderate T2 hyperintensity with extension	Extensive T2 hyperintensity with further extension
Neurocognitive testing	IQ ≥ 85	IQ 70-84	IQ < 70
NCS‡	Normal or mildly abnormal	Moderately abnormal	Severely abnormal
EEG	Normal	Normal	Seizure activity or regions of epileptic potential
VEP§	Normal	Normal	Normal or abnormal
BAER¶	Normal or mildly abnormal	Abnormal	Abnormal

* For these patients, it is important to acknowledge that these guidelines are based on clinical experience and, to a lesser degree, published literature.
† Neuroimaging progression and severity well described [112,130]. Mild disease is characterized by T2 hyperintensity of the frontal, periventricular, corpus callosum, or central white matter. Moderate disease is additionally characterized by extension into subcortical white matter (U-fibers) or basal ganglia/thalamic regions. Severe disease is additionally characterized by involvement of projection fibers or cerebellar white matter, with tigroid appearance of white matter common.
‡ NCS were considered abnormal if prolonged distal latency, low amplitude, no evoked response, or prolonged F-wave latency was present [131]. Designation of severity is based on the neurologist interpretation.
§ VEPs are considered abnormal if the P100 wave is absent or delayed [128].
¶ BAERs are considered abnormal if wave I to V interpeak latency is prolonged or if any of the obligate wave forms (I, III, V) are absent [129].

In the publication of Boucher et al., 2015, Forty-three patients underwent HSCT for a reported diagnosis of MLD, of which 4 patients (10 %) had LI-MLD, 27 (67 %) had J-MLD, and 9 (23 %) had adult MLD. Five patients (12 %) underwent reduced-intensity conditioning (RIC) using melphalan, clofarabine, low-dose total-body irradiation (TBI) and alemtuzumab. The remaining 35 (88 %) received myeloablative conditioning that was either busulfan/cyclophosphamide (Bu/Cy) or cyclophosphamide/TBI (Cy/TBI)-based. In 11 (27%) patients related donor marrow was used, in 14 (35%) unrelated-marrow and in 15 (38%) umbilical cord blood.
Twenty-one patients (53 %) are alive at a median post-transplant follow-up of 10 years. For the entire cohort, the Kaplan-Meier (KM) estimate of survival at 5 years is 59 % (95%CI 42 % - 73 %), with a survival at 5 years of 50 % in LI-MLD (95CI 6 % - 84 %), of 59 % in J-MLD (95CI 38 % - 75 %) and of 67 % in A-MLD(95CI 28 % - 88 %). Survival was independent of the conditioning regimen, MLD subtype, and the presence of symptoms at the time of transplantation. A trend toward inferior survival was noted for recipients of unrelated marrow allografts, as compared to those who underwent related-donor or UCB transplantation.
While most J-MLD patients regressed, the aggregate cohort demonstrated superior retention of function compared to published natural history. Relative cognitive sparing was observed despite overall global decline.

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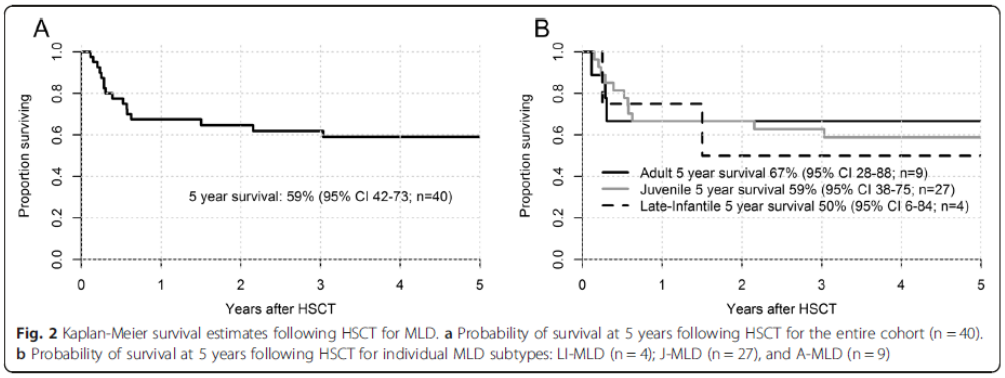


Fig. 2 Kaplan-Meier survival estimates following HSCT for MLD. **a** Probability of survival at 5 years following HSCT for the entire cohort (n = 40). **b** Probability of survival at 5 years following HSCT for individual MLD subtypes: LI-MLD (n = 4); J-MLD (n = 27), and A-MLD (n = 9)

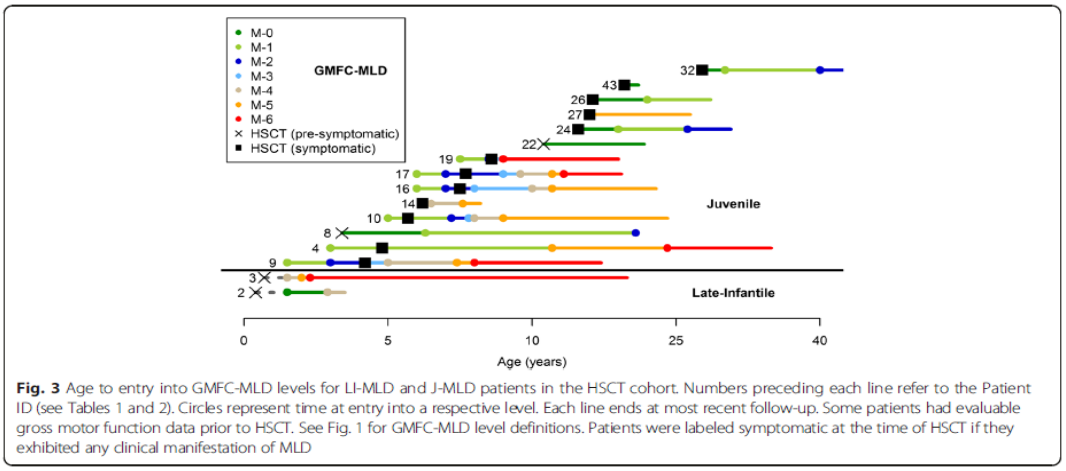


Fig. 3 Age to entry into GMFC-MLD levels for LI-MLD and J-MLD patients in the HSCT cohort. Numbers preceding each line refer to the Patient ID (see Tables 1 and 2). Circles represent time at entry into a respective level. Each line ends at most recent follow-up. Some patients had evaluable gross motor function data prior to HSCT. See Fig. 1 for GMFC-MLD level definitions. Patients were labeled symptomatic at the time of HSCT if they exhibited any clinical manifestation of MLD

In the recent publication of Beshle et al., 2020, the clinical outcome at 24 months following HSCT in 12 children with juvenile MLD was compared to the clinical outcome of 35 non-transplanted children with juvenile MLD, based on motor function (GMFM-88 and GMFM-MLD), cognitive function (FSIQ), peripheral neuropathy (tibial nerve conduction velocity) and cerebral changes (MLD-MR severity score).
Of the 12 transplanted children, 7 remained neurologically stable (loss of no more than 1 level in GMFC-MLD and a loss of ≤30 points in FISQ) while 5 exhibited a rapid disease progression over the first 12 to 18 months after the HSCT, with time from first gross motor symptoms to loss of independent walking being significantly shorter in these 5 patients compared to non-transplanted patients. Positive prognostic factors for outcome after HSCT were good motor function (GMFM=100%, GMFC-MLD=) and a low MR severity score (≤17) at the time of the HSCTprocedure.
As stated by the authors, children who are already suffering from a neuropathology that is causing disturbances in their gross motor function at the time of HSCT are probably more vulnerable to transplant-related (inflammatory/toxic) stress and this might accelerate disease progression.

Table 2 Predictive values for disease progression after HSCT. All *p* values were considered as descriptive

GMFM < 100%	***p* = 0.003**
GMFC.MLD > 0	***p* = 0.013**
FSIQ < 85	*p* = 0.079
MR severity score > 17	***p* = 0.003**
NCV < 40 m/s	*p* = 0.198
Age at onset	*p* = 0.690
Age at HSCT	*p* = 0.530

In the publication of Groeschel et al., 2016, a total of 24 J-MLD patients were transplanted and compared to 41 control J-MLD patients. Among the transplanted patients, 4 children died of transplantation-related mortality, and 2 additional children died of rapid MLD progression 1.5 and 8.6 years after HSCT, resulting in a 5-year survival of 79% (19 of 24). Among

the nontransplanted patients, 5-year survival after disease onset was 100% (41 of 41). However, 11 died of MLD progression, resulting in similar overall survival within the observation period. Nine of the long-term survivors after HSCT had disease progression, while 11 showed stable disease. Compared with the nontransplanted patients, the transplanted patients were less likely to lose their gross motor or language function and demonstrated significantly lower MRI severity scores at the latest examination. Patients after HSCT were more likely to have a stable disease course when undergoing HSCT at an early stage with no or only mild gross motor deficits (Gross Motor Function Classification in MLD level 0 or 1) and an IQ of at least 85, when age at disease onset was older than 4 years, or when MRI severity scores were low (preferably≤17).

HSCT is a viable treatment option for MLD, but has significant limitations. Later-onset phenotypes may benefit most from early, pre-symptomatic transplant. Until superior, novel treatment strategies are demonstrated, MLD patients should be carefully considered for HSCT.

2. Mesenchymal stem cell therapy:

Mesenchymal stem cells (MSCs) have been tested too, as MSCs have a higher level of ARSA expression compared to monocytes from peripheral blood and are also able to migrate and take root in the brain by differentiating into astrocytes. The majority of patients with MLD who previously received successful BMT and then transplanted with allogeneic bone marrow-derived MSCs show an improvement in the nerve conduction velocity.
Currently, MSC treatment has not been proven and does not belong to the 'standard of care'. Indeed, a temporary improvement of NCVs was observed in 4/6 of the patients. However, it is considered to be impossible that MSCs can differentiate into Schwann cells. The explanation for the temporary improvement may therefore be a temporary enzyme presence in the perineural environment.

3. Enzyme Replacement Therapy:

Enzyme replacement therapy (ERT) was one of the first approaches used to increase the level of a normal enzyme, but the BBB prevents direct transfer of the recombinant ARSA enzyme from the bloodstream to the CNS. To overcome this problem the ARSA enzyme should be injected in the CSF, but given the half-life of a recombinant ARSA enzyme, the number of intrathecal injections would be an important point to consider for a chronic treatment.
Previous clinical trials with a recombinant human ARSA enzyme-based drug did not reduced the rate of the loss of motor function and changes in the CSF sulfatides concentration.
The clinical development of a recombinant human arylsulfatase (TAK-611) for intrathecal administration is still continuing.

4. Gene therapy:

4.1 Adenovirus vectors

The direct administration of adeno-associated viral vectors encoding the ARSA gene directly into the brain has been considered as a possible method of MLD therapy, as AAVs can transynaptically transduce neurons over a wide range from the injection site through anterograde neuronal transport, but conflicting results questions the AAV ability to transynaptically transduce neurons. The therapeutic potential of AVV is actively investigated.
The intracerebral delivery of adeno-associated virus (AAV) encoding ARSA can provide a fast arrest of the neurodegenerative process in the MLD patients' brain, since AAVs are one of the safest vectors for clinical use and can efficiently transduce neurons in vivo.
A phase I/II clinical trial with the AAVrh.10 virus (NCT01801709) including 4 children with a presymptomatic or very early symptomatic stage, injected up to 12 injections times 1 × 1012 or 4 × 1012 (depending on age) AAVrh.10-ARSA transducing units into the white matter of the brain. The activity of ARSA in CSF was significantly increased after injection, up to 20–70% of the control values, but in patients with an early symptomatic stage, the symptoms continued to worsen, and in patients with an asymptomatic course, MLD developed, not differing significantly from the natural course of the disease.

4.2 Retroviral vectors

Other therapeutic approaches based on retroviruses, using genetically modified fibroblasts overexpressing ARSA isolated from late infantile MLD patients have been used in vitro to transfer ARSA to defective cells, oligodendrocytes and Schwann cells through transwells.

4.3 Gene-cell therapy

Hematopoietic + stem cells genetically modified with lentivirus (LV) encoding the ARSA gene (7.2 ×106/kg CD34+ HSCs overexpressing the ARSA gene) after a chemotherapeutic destruction of their own hematopoietic stem cells (AA gene therapy) is the subject of the current submission. The clinical outcome of this therapeutic approach will be discussed in detail further in this HTA report.

The method of somatic cell reprogramming into pluripotent cells can make it possible to use the patients own cells as a source of autologous cells for transplantation, e.g. using skin fibroblasts reprogrammed into self-renewing neuroepithelial stem cells, subsequently genetically modified to overexpress ARSA and transplanted into the telencephalon. Currently this has only been investigated in animal MLD models.

Gene-cell MLD therapy seems to be a rather promising approach because, as cells are able to transfer the enzyme to the mutant nervous system cells of the patients having overcome the BBB. Such cross-correction mechanism is based on the fact that a small part of the newly synthesized soluble enzyme is released from the cell in the intercellular space instead of entering the lysosome. Outside the cell the enzyme can enter the neighboring cell by endocytosis and be delivered into the lysosome via M6P receptors

TABLE 2 | Clinical trials of the therapeutic approaches to treat MLD.

Therapeutic agent	Therapeutic regimen	Therapy results
HGT-1110, recombinant human ARSA enzyme	Injection of 10, 30, or 100 mg of HGT-1110 in the CSF for 38 weeks (20 injections in a week)	During therapy with a dose of 100 mg, uncertain improvements in motor function, as well as swallowing function and quality of life improvements were observed
HSCs	Intravenous administration	In patients who received HSCT before the symptom onset or at a very early symptomatic stage, the disease stabilized, the rate of loss of gross motor and cognitive functions and central nervous system demyelination decreased
		A study of brain tissue in two patients with MLD undergone HSCT showed that donor macrophages expressing ARSA distributed throughout the white matter, but cross-correction in resident oligodendrocytes and astrocytes did not occur, or occurred at a very low degree. However, it has been shown that HSCT can provide remyelination.
Allogeneic bone marrow-derived MSCs	Intravenous administration of 2–10 × 10^6 MSCs/kg after BMT	In 4 out of 6 patients with MLD, an improvement in the speed of nerve conduction was observed, but no changes in the mental and physical condition of the patients were noted
	Intravenous administration of 1 × 10^6 MSCs/kg after HSCT	In a clinical case report, stabilization of all the neurological manifestations of the disease was observed in a patient with adult MLD 40 months after the infusion
Genetically modified autologous $CD34^+$ HSCs transduced with LV-ARSA	Intravenous administration of 7,2 × 10^6 $CD34^+$ HSCs/kg	Safety and efficacy have been confirmed. In all 9 patients with pre-symptomatic or with a very early symptomatic stage, the disease did not manifest or progress. However, in one patient out of 9, who already had symptoms of the disease (severe demyelination and motor and cognitive impairment) at the time of initiation of the treatment, motor activity did not improve
AAVrh.10-hARSA	12 injections of AAVrh.10-hARSA with the dose of 10^{12} or 4 × 10^{12} transducing units into the white matter of the brain	In 4 children with a pre-symptomatic or very early symptomatic stage, ARSA activity in CSF, which was not detected before treatment, was significantly increased after injection, reaching 20–70% of the control values at the last assessment. In children with an early symptomatic stage, the symptoms continued to worsen, and in patients with an asymptomatic course, MLD developed, which did not differ significantly from the natural history of the disease course

Versie préCTG:

TABLE 1 | Therapeutic approaches for MLD therapy undergoing *in vivo* animal studies.

Therapeutic agent	Model	Therapeutic regimen	Therapy results
Cell therapy			
MGTA-456 (population of $CD34^+$ $CD90^+$ cells)	Immunodeficient NSG mice	NA	Microglia engraftment efficiency increased by 10 times
ERT			
Recombinant ARSA enzyme	ARSA knockout mice	Continuous administration of the enzyme in the CSF of the right lateral ventricle of the brain for 4 weeks	Sulfatide storage in the infused hemisphere was reduced by 51–56%. Short half-life of the enzyme in the CSF (10 min)
		Intravenous administration of the 20 mg/kg enzyme for 16 weeks	Effective sulfatide removal, if the treatment begins at the pre-symptomatic stage
Chimeric ARSA protein crosslinked with the IgG domain against the human insulin receptor	WT rhesus macaque	Single intravenous administration of 55 μg/kg protein	Rapid penetration into the brain and distribution in the post-vascular parenchyma of all parts of the brain
Chimeric ARSA protein crosslinked with mouse IgG domain of transferrin receptor	ARSA knockout mice	Intraperitoneal or subcutaneous administration of 5 mg/kg protein for 5 weeks three times a week	The safety of recombinant protein was confirmed
Gene therapy			
AAV5-ARSA	ARSA-deficient mice with a mixed genetic background	Injection of the virus with a dose of 3×10^9 vg (the sites of the injections included the cerebellar vermis, and the left and the right internal capsules)	Long-term expression of recombinant ARSA in the brain (for 3–15 months) and prevention of neuropathological and neuromotor disorders
AVV9-ARSA	Newborn ARSA knockout mice	Injection of the drug with a dose of 2×10^{12}vg into the jugular vein of newborn mice	Long-term expression of the enzyme (up to 15 weeks) mainly in the muscles and heart, moderate expression was also found in the CNS. Sulfatide accumulation was significantly reduced in the brain and spinal cord of the treated mice
AAV1-ARSA + AAV1-FGE	ARSA knockout mice	Injection of the virus with a dose of 7.5×10^9 vg into the hippocampus	Co-injection of the two vectors allowed increase in the expression and distribution of ARSA
AAVrh.10-ARSA	ARSA-deficient mice with a mixed genetic background	Intraperitoneal injection (right striatum or right ventral tegmental area)	The correction of the accumulation of certain types of sulfatides in oligodendrocytes
AAVrh.10-ARSA	WT nonhuman primates	12 injections of the vector with the dose of 1.1×10^{11} transducing units per the cerebral hemisphere	Enzyme activity was increased by 14–31% of normal endogenous expression and could be detected at a distance of 12–15 mm from the injection site
AAVrh.10-ARSA, AAV9-ARSA	ARSA knockout mice	Intravenous administration	AAVrh.10-ARSA more effectively infected PNS cells and reduced the sulfatide accumulation in the nervous system of MLD model mice compared to AAV9-ARSA
Gene-cell therapy			
HSCs genetically modified to overexpress ARSA	ARSA knockout mice	BMT	Enzyme level was increased up to 33% of normal in the CNS, up to 100% of normal in the kidneys, and up to 800% of normal in the spleen and bone marrow. The number of sulfatides was reduced, all neurophysiological disorders were normalized
Self-renewing neuroepithelial stem cells genetically modified to overexpress ARSA	Day 1 ARSA knockout mice	Transcranial injection of 100,000 cells 2 μl into the lateral ventricle with a glass capillary	Significant decrease in sulfatide accumulation in the brain
Neural precursors genetically modified to overexpress ARSA	Day 1 ARSA knockout mice and day 60 ARSA knockout mice	Injection of 250,000 cells per 2 μl for postnatal day 60 mice and 200,000 cells per 2 μl in the right hemisphere	The enzyme activity reached 70% of normal expression, the accumulation of sulfatides was lower compared to the control
Symptomatic therapy			
Simvastatin	ARSA knockout mice	20 mg/kg/day orally for 30 days	CNS inflammation, the level of secretion of the pro-inflammatory cytokines MIP-1β and MCP-1, and brain infiltration with T-cells were decreased. 17 months after treatment, demyelination in the treated mice treated was 20% lower in the brain and 42% lower in the spinal cord compared to control animals

5. Symptomatic therapy – Best supportive Care -SOC

Symptomatic therapy includes many different approaches aimed to relieve many clinical symptoms.

For spasticity the intrathecal administration of baclofen can be used, as administration of baclofen to the CNS is preferable, given that only a fraction of orally administered baclofen will cross the BBB. The initial dose of baclofen during intrathecal administration will be 40–100 µg per day and adjusted according to the progressive nature of the disease.

In animal models the anti-inflammatory effect of simvastatin on the neuroinflammation, reducing the rate of demyelination, has been tested successfully. Simvastatin was chosen since it overcomes the BBB better than other statins and inhibits the MAPK signaling pathway through which signals of the pro-inflammatory cytokines MIP-1a, MIP-1b and MCP-1 are transmitted.

The use of IVIG immunotherapy to prevent neuroinflammation has also been suggested, as the effects of IVIG therapy can be mediated by an increase in the level of macrophage colony-stimulating factor (M-CSF) and MCP-1, which has an immunomodulating effect, but most clinical reports are showing no major effect.

Prednisolone is also prescribed for the treatment of neuroinflammation in order to provide short-term functional improvement, but clinical results are conflicting.

Table 1
Common symptoms inherent to many leukodystrophies and recommended treatment goals. Abbreviations: adaptive and augmentative communication (AAC), individualized educational plan (IEP), occupational therapy (OT), speech therapy (SPT).

Symptom	Treatment goals	Comments
Cognitive delay and deterioration	Maximize developmental potential and quality of life	IEPs are appropriate for most patients and should include a focus on life enrichment. OT is appropriate for some patients.
Constipation	Identify and alleviate this under-recognized source of pain and distress	Etiologies include dehydration, improper diet, inactivity, and autonomic dysfunction. Stool softener, fibers, laxative, and/or modified nutrition and hydration should be considered as needed.
Dystonia	Maximize mobility for necessary function with minimal side effects; alleviate pain	Several therapeutic options exist including trihexyphenidyl and tetrabenazine; consider neurology movement disorder consultation.
Hearing impairment	Maintain awareness of auditory function to enable modification of education and communication strategies	Auditory evaluation should be obtained at baseline and as needed thereafter.
Language impairment	Facilitate verbal, non-verbal, and adaptive communication between patients and caregivers	Adequate communication can improve care, reduce distress, and enrich life. SPT is appropriate for many patients; AAC strategies should be considered for non-verbal patients.
Motor milestone delay and deterioration	Maximize mobility and independence; prevent falls	Physical therapy and/or orthotic evaluation are often appropriate.
Scoliosis	Prevent secondary pulmonary, cardiac, and neurologic morbidity	Screening should occur in the form of a brief exam of the spine during routine clinic visits. A pediatric orthopedic consultation should be sought if scoliosis is suspected. Treatment varies depending on the severity and progression of the deformity.
Seizures	Minimize seizure frequency and unnecessary hospitalizations; maximize quality of life and cognitive potential	Establish a clear plan of care for seizure exacerbations with the goal of minimizing unnecessary emergency room visits and radiologic studies. A written plan of care to present at outside ERs may be helpful.
Sialorrhea	Prevent aspiration pneumonia; balance cosmetic/social concerns with risks of medical intervention	Botox injection may offer safety and efficacy profile. Glycopyrrolate should be used with caution; adverse effects may outweigh benefits. Multidisciplinary consult can be helpful when available.
Sleep disturbance	Identify and alleviate an under-recognized source of distress for patients and families; maintain circadian rhythms conducive to social and educational enrichment	Etiologies include pain, improper sleep hygiene, and primary CNS disturbance. If pain and sleep hygiene have been excluded consider a step-wise approach starting with melatonin and other agents that lack the potential for respiratory depression and hypersalivation or are already in the patients' medication regimen (e.g. clobazam for epilepsy or gabapentin for neuropathic pain).
Spasticity	Maximize mobility for necessary function with minimal sedation; alleviate pain	Several therapeutic options exist including baclofen (also administered intrathecally by pump), dorsal rhizotomy, and diazepam.
Visual impairment	Maintain awareness of visual function such that education and communication can be modified accordingly	Ophthalmologic evaluation should be obtained at baseline and on interval basis thereafter. Support services for the visually impaired may be appropriate.

Versie préCTG:

Table 2
Common symptomatic medications. "Start low and go slow" is a good rule of thumb for avoiding overmedication and undesirable off-target effects. All anti-cholinergic agents should be used with caution in patients with autonomic dysfunction as they may exacerbate existing co-morbidities (e.g. constipation, urinary retention). Many anti-epileptics carry a small but important risk of Stevens–Johnson syndrome (SJS), a life-threatening rash.

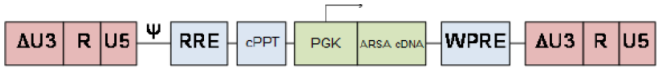
Medication	Indication(s)	Mechanism	Side effects/comments
Amitriptyline	Chronic pain; depression	Anti-cholinergic	Off-target effects can be both helpful (e.g. reduce sialorrhea) and harmful (e.g. exacerbate constipation, urinary retention, hypotension).
Baclofen	Spasticity	GABA-agonist	Off-target effects include sedation, sialorrhea, and constipation. Axial hypotonia may limit dose. Intrathecal administration may reduce systemic side effects but requires implanted hardware which carries some risks.
Botulinum toxin	Spasticity; dystonia; sialorrhea	Enzymatic cleavage of specific vesicular proteins	First-line therapy for focal dystonia. Administered via intramuscular injection every few months. Highly effective with minimal to no systemic side effects if properly administered. Requires an experienced provider.
Carbamazepine and oxcarbazepine	Epilepsy	Sodium channel modulation	May exacerbate some seizure types. Risk of life threatening rash and blood dyscrasias. Risk of hyponatremia with oxcarbazepine.
Clobazam	Epilepsy	Selective GABA-agonist	Expensive in the US, but may result in fewer off-target effects (e.g. sedation, sialorrhea) when compared to other GABA-agonist anti-seizure agents (e.g. phenobarbital).
Diazepam	Spasticity	GABA-agonist	Off-target effects include sedation, increase and/or thickened salivation, and constipation. May have some effect on reducing anxiety.
Gabapentin	Chronic pain/epilepsy	Calcium channel modulation	Minimal drug interaction and low toxicity. The most limiting side effect is usually dose-dependent sedation.
Glycopyrrolate	Sialorrhea	Anti-cholinergic	Anti-cholinergic agent. Thickened secretions are often dose limiting. Off-target effects can be problematic and may outweigh benefits in patients with pre-existing sedation, constipation, cardiovascular instability.
Lamotrigine	Epilepsy	Sodium channel modulation	Effective and non-sedating, but requires unusually slow titration and close observation to mitigate risk of SJS.
Levetiracetam	Epilepsy	Not well-established	Common first line agent. Minimal drug interaction. Risk of psychiatric disturbance (e.g. irritability, depression) requires monitoring, but may be attenuated by pyridoxine supplementation.
Tetrabenazine	Dystonia	Presynaptic dopamine depletion	Sedation, anxiety, insomnia, and sialorrhea are fairly common. All patients should be monitored for depression, suicidality, parkinsonism, liver injury, and QT prolongation.
Trihexyphenidyl	Dystonia	Anti-cholinergic	Peripheral anticholinergic side effects such as constipation can limit dose escalation. Beneficial effect may be delayed for several weeks. Sedation as well as disturbances in memory and concentration may occur with dose escalation, although children may be more tolerant of these cognitive side effects than adults.
Valproic acid	Epilepsy	Multiple mechanisms	Broad efficacy with limited sedation. Mild platelet dysfunction, nausea, weight gain, and tremor may occur. Hepatotoxicity pancreatitis and Stevens–Johnson occur more frequently than with most other anti-seizure medications. Check liver function prior to initiation. Avoid in patients with mitochondrial or liver disease.

3.2. MOLECULAR PHARMACOTHERAPY (REF 2)

International non-proprietary name : Autologous CD34+ cells encoding ARSA gene
Other names : Libmeldy®, atidarsagene autotemcel

Construction of the lentiviral vector (LVV)

ARSA LVV is a recombinant replication-defective third generation pseudotyped self-inactivating (SIN) HIV-1 - based lentiviral vector that has been modified to carry the human ARSA cDNA sequence. The vector is pseudotyped with the Vesicular Stomatitis Virus envelope glycoprotein G (VSV-G), thus wildtype HIV cannot be generated by recombination among the constructs used to make vectors. The vector is designed to integrate the transgene in the target cells (autologous CD34+ cells) with minimal risk of generating Replication Competent Lentivirus (RCL) and maximizing gene transfer efficiency by optimisation of construct design.



ΔU3: HIV-1 long terminal repeat (LTR) unique in 3′ region (origin: HIV-1)
R: HIV-1 LTR region (origin: HIV-1)
U5: HIV-1 long terminal repeat unique in 5′ region (origin: HIV-1)
Ψ: HIV-1 extended encapsidation signal (origin: HIV-1)
RRE: HIV-1 Rev response element (origin: HIV-1)
cPPT: HIV-1 central polypurine tract (origin: HIV-1)
PGK: Human phosphoglycerate kinase promoter (origin: human genome origin)
WPRE: Woodchuck hepatitis virus posttranscriptional regulatory element (origin: Woodchuck hepatitis virus) mutated on nucleotides 1488-1492 at the end of the We1 enhancer (gctga to atcat), to disrupt putative transcriptional element and on nucleotide 1503 (atg to ttg)

Dispersion for infusion

Several different active substance/finished product manufacturing processes are identified. Differences include the starting material (BM or mPB), the CD34+ enrichment procedure, the presence or absence of an additional cryopreservation step for the CD34+ enriched cells, the container closure system, and the final formulation (fresh or cryopreserved). The active substance manufacturing process downstream of the CD34+ enrichment was the same for all clinical batches. It is noted that apart from these changes there were also the changes in the manufacturing of the LVV vector (EPAR).

Libmeldy dispersion for infusion (FP) is composed of 10 – 20 mL of cryoformulation medium (5% DMSO, 7% HSA, and 0.9% saline solution) containing 2-10 x 106 CD34+ enriched cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A (ARSA) gene per ml. The product is presented cryopreserved in EVA bag(s). Each infusion bag contains 10 to 20 mL of Libmeldy. The number of EVA bags depends on the total amount of cells and will vary between individual patients. After thawing, the product is administered by intravenous infusion without further manipulation. Since the total number of cells and concentration of CD34+ cells vary between individual patient batches, the quantitative information regarding strength (total viable cell concentration), volume of dispersion and total number of CD34+ cells per bag and supplied dose of the medicinal product are provided in the Lot Information Sheet. The Lot Information Sheet is included with the cryoshipper used to transport Libmeldy.

Libmeldy was initially formulated as a fresh finished product (i.e. not frozen). In the fresh formulation, the only excipient used was saline. 0.9% w/v Sodium Chloride Infusion is purchased as a medicinal product licensed by a European Union member state. In-house testing performed on the 0.9% w/v Sodium Chloride Infusion has been provided. Endotoxin and sterility are accepted on the supplier's certificate of analysis. Subsequently, Libmeldy has been formulated to produce a cryopreserved finished product. The development of a cryopreserved formulation is endorsed.

The IV administration is performed via a central venous catheter, in one of the five qualified treatment centers which are being planned in Europe, and located in Utrecht (the Netherlands), Manchester (the UK), Paris (France), Tübingen (Germany) and Milan (Italy). This implicates that patients should be transferred to one of these centers for treatment, in accordance with applicable legislation on health insurance coverage.
The treatment process follows the same steps as HSCT for other diseases, with comparable tests/investigations and administration requirements are therefore applicable. The recommended conditioning regimen being busulfan.
It is recommended that patients receive treatment with prophylaxis for veno-occlusive disease (VOD) and related endothelial injury complications i.e. transplant-associated thrombotic microangiopathy (TA-TMA) or atypical hemolytic uremic syndrome (aHUS), in line with local guidelines.

When more than one bag of AA is needed, only one bag of medicinal product should be infused per hour. Each bag should be infused at an infusion rate which does not exceed 5 mL/kg/h, within approximately 30 minutes. The recommended administration set consists of a blood transfusion set equipped with a 200 µm filter. Pre-medication with IV chlorpheniramine (0.25 mg/kg, max. dose 10 mg) or an equivalent drug 15–30 minutes before the infusion of AA is recommended to reduce the possibility of an allergic reaction to the infusion.

Once the eligibility of the patient has been confirmed, the treatment steps begin with cellular source harvest. After blood cells have been collected, the patient can return home while manufacturing and quality control processes take place. The whole process from cell collection to product availability takes approximately 40 days.
Once the drug product has been manufactured, it is cryopreserved until the patient is ready to receive treatment. Approximately 4 days before infusion the patient returns to the treatment center for busulfan conditioning. Patients remain at the treatment center between 4 and 12 weeks from beginning of conditioning to discharge. Standard procedures for patient management after HSPC transplantation should be followed after the infusion.

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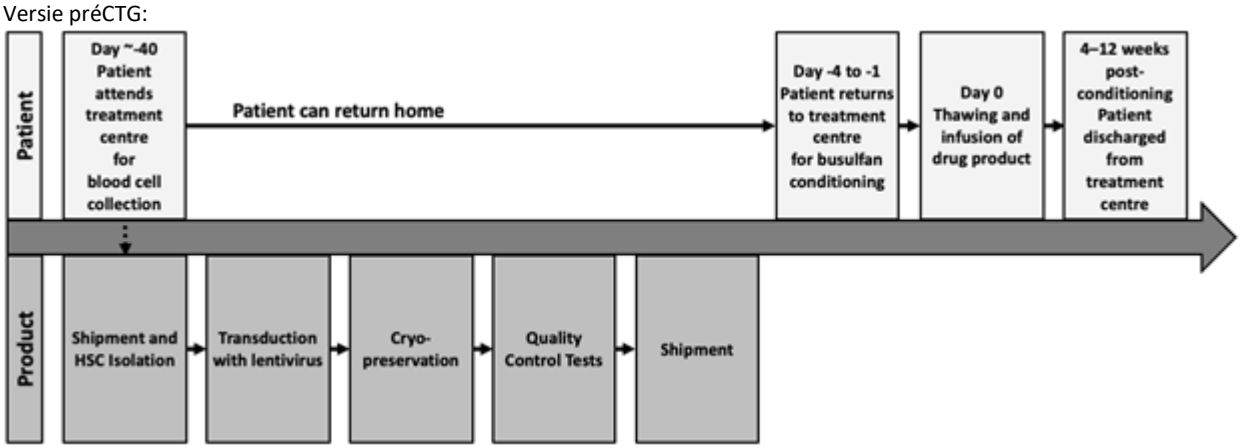
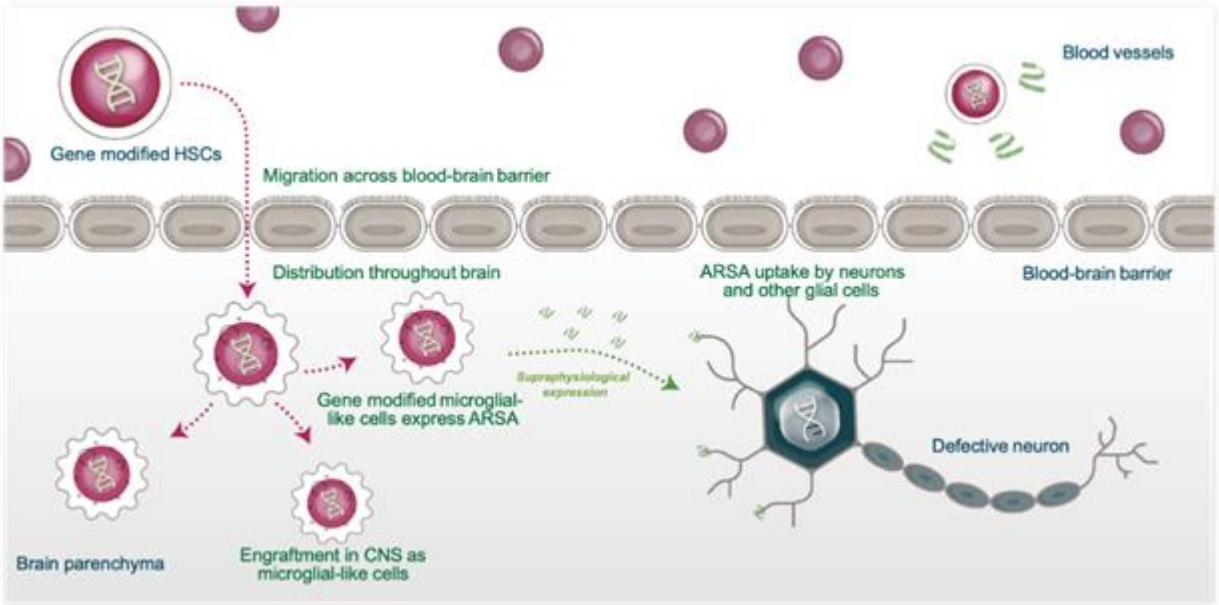


3.2.1. Mechanism of action (ref 2, 8)

Libmeldy is an ex vivo genetically modified autologous CD34+ hematopoietic stem and progenitor cell (HSPC) gene therapy. Autologous CD34+ HSPCs are collected from patient bone marrow (BM) harvest or from mobilized peripheral blood (mPB) and transduced with a lentiviral vector (ARSA LVV), which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome, so that genetically modified cells become capable of expressing the functional ARSA enzyme.

When administered to the patient (a mean (min, max) cell dose of 10.81 x 106 (4.2, 25.9) CD34+ cells/kg as an intravenous infusion) following the administration of a myeloablative conditioning regimen, the genetically modified cells engraft and are able to repopulate the hematopoietic compartment. A subpopulation of the infused HSPCs and/or their myeloid progeny is able to migrate across the blood brain barrier to the brain and engraft as central nervous system (CNS) resident microglia and perivascular CNS macrophages as well as endoneural macrophages in the peripheral nervous system (PNS). These genetically modified cells can produce and secrete the functional ARSA enzyme, which can be taken up by surrounding cells, a process known as cross-correction, and used to break down, or prevent the build-up, of harmful sulfatides. Following successful and stable engraftment in the patient, the effects of the product are expected to be persistent.



3.2.2. Pharmacotherapeutic group (ref 2, 9)

Gene transfer therapy ; ATC code N07.

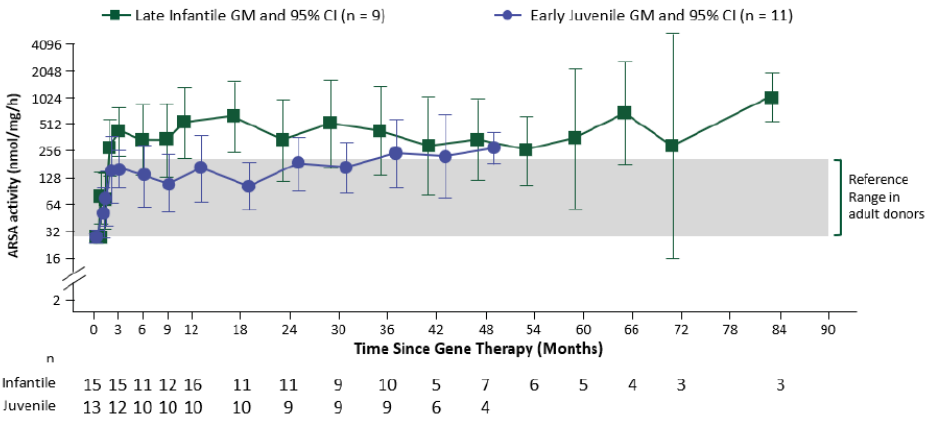
Libmeldy is an ATMP and further classified as a gene therapy medicinal product.

For the EMA, the Committee for Orphan Medicinal products has recommended that Libmeldy, autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA, for treatment of metachromatic leukodystrophy (EU/3/07/446) is not removed from the Community Register of Orphan Medicinal Products. This opinion was adopted on 19-10-2020. The first orphan medicinal product designation was granted by the EC on 13-04-2007.

3.2.3. Pharmacokinetic properties

Durable and stable peripheral engraftment of genetically modified cells was observed from 1-month post Libmeldy administration in all evaluable patients. A persistent vector copy number (VCN) was also observed in CD34+ cells isolated from the bone marrow throughout the follow-up period. These biological findings demonstrate a sustained multilineage engraftment of gene-corrected cells, which is essential for supporting the long-term production of ARSA and resulting long-term clinical benefit. At Year 1 post-treatment, the proportion of BM-derived colonies harboring the LVV genome (%LV+) in the overall treated population was 54.8% (range: 20.0% to 100%, [N=23]). The proportion of BM-derived colonies harboring the LVV genome (%LV+) at Year 5 was 45.0% (range: 18.8% to 90.6% [n=6, 4 Late infantile (LI) and 2 Early Juvenile (EJ)]), indicative of stable engraftment over time in the treated population. Reconstitution of ARSA activity in the hematopoietic system was observed in all MLD patients treated, with a progressive reconstitution of ARSA levels in Peripheral Blood Mononuclear Cells (PBMCs) which reached values within the normal reference range by 3 months post-treatment and remained stable within or above the normal range throughout the duration of the follow-up.
ARSA activity was also measured in cerebrospinal fluid (CSF) as a surrogate compartment of metabolic correction in the brain. The ARSA activity in CSF went from undetectable at Baseline to detectable in all evaluable patients by Month 6 post-treatment and reached reference range levels at Year 1 post-treatment. Thereafter, central reconstitution of ARSA enzymatic activity remained stable within the reference range.

Figure 1 **ARSA activity in PBMCs over time (geometric mean and 95% CIs), by disease subtype (integrated efficacy set; N=29)**



Note: Values < LLQ are imputed at LLQ. LLQ is 25.79 nmol/mg/h. GMs and 95% CIs are presented where there are at least 3 patients with non-missing data. ARSA: arylsulfatase A; CI: confidence interval; GM: geometric mean; LLQ: lower limit of quantification; PBMCs: peripheral blood mononuclear cells.

3.3. ASSESSMENT OF THE THERAPEUTIC VALUE AND ITS IMPORTANCE (REF 2, 18, 19)

Overview of clinical studies:

Study ID	Study Design and population	Libmeldy (OTL-200) formulation; dose; Busulfan conditioning	Objective/ endpoint
201222 (Registrational Study)	Nonrandomised, open-label-, prospective, comparative (non-concurrent control), single centre study 20 subjects; 9 LI, 11 EJ[d]	OTL-200-f; 2-20 x 10^6 $CD34^+$ cells/kg; *SMAC*[a]: Subjects treated prior to Jan 2014 (9 subjects) *MAC*[b]: Subjects treated after Jan 2014 (11 subjects)	**Primary endpoints:** Total GMFM score (2 years) ARSA Activity (total PBMCs, 2 years) **Secondary endpoints:** ARSA activity (BM and CSF), NCV, Brain MRI, GMFC-MLD, Neuropsychological tests, Neurological evaluations, Survival, Engraftment (LV transduced cells, VCN)
CUP **207394**	Single patient CUP (Expanded Access Programmes) 1 subject (EJ)	OTL-200-f; 2-25 x 10^6 $CD34^+$ cells/kg; *SMAC*[a]	
HE **205029**	(Expanded Access Programmes) 3 subjects (LI)	OTL-200-f; 2-20 x 10^6 $CD34^+$ cells/kg; *SMAC*[a]: 1 subject *MAC*[b]: 2 subjects	
CUP **206258**	(Expanded Access Programmes) 5 subjects; 4 LI; 1 EJ	OTL-200-f; 2-30 x 10^6 $CD34^+$ cells/kg; *SMAC*[a]: 2 subjects *MAC*[b]: 3 subjects	
205756	Non-randomised, open-label, single centre 4 subjects; 2 LI, 2 EJ	OTL-200-c; 3-30 x 10^6 $CD34^+$ cells/kg; *MAC* (n=4)[c]	

AA–f: fresh formulation / AA-c: cryopreserved formulation / SMAC: submyeloablative conditioning regimen (busulfan, weight based) / MAC: myeloablative conditioning regimen (busulfan, AUC based).

In the clinical program of the company, a total of 18 LI MLD-patients and 15 EJ MLD –patients were included (n=33 patients), of which 20 (9 LI/11 EJ) in the registration study (201222), 4 in the single-center study (205756) (2LI, 2LI) and 9 patients in expanded access programs (7 LI and EJ).

With respect to the myeloablative conditioning regimens used, there was a difference in dosing within and between the different studies and EAP.

The conditioning regimen initially implemented in the AA-f clinical development program consisted of 14 doses of busulfan (according to subject's weight; submyeloblative conditioning regimen (SMAC)). Subsequently, the conditioning regimen was modified with the goal of reducing the variability of transduced cell engraftment and designed to produce a higher cumulative busulfan AUC. This new conditioning regimen consisted of body surface area-based dosing of busulfan according to the subject's age (myeloablative conditioning regimen (MAC)). In the Integrated Safety Set, 13 subjects (45%) were treated with a SMAC regimen, defined as a target cumulative AUC of 67,200 µg*h/L (target range 58,800 to 78,400 µg*h/L). Sixteen subjects (55%) were administered the MAC regimen, defined as a target cumulative AUC of 85,000 µg*h/L (target range: 76,500 to 93,500 µg*h/L).
Patients who received a SMAC regimen received a lower total dose (mg) and lower total dose per body weight (mg/kg) than subjects who received a MAC regimen. The average exposure to the MAC regimen was 14% higher than the average exposure to the SMAC regimen.

Table 1: Busulfan Conditioning, by Regimen (Integrated Safety Set)

Parameter, Summary Statistic	SMAC Regimen (N=13)	MAC Regimen (N=16)	Total (N=29)
Total Dose (mg), Geometric Mean (95% CI)	146.680 (114.194, 188.407)	204.302 (162.740, 256.479)	176.102 (148.600, 208.694)
Total Dose (mg), Median (Min, Max)	155.300 (72.00, 268.00)	221.150 (108.96, 408.00)	162.500 (72.00, 408.00)
Total Dose (mg), %CVb	43.27	44.70	46.96
Total Dose/kg (mg/kg), Geometric Mean (95% CI)	12.666 (11.425, 14.042)	15.555 (13.261, 18.246)	14.186 (12.816, 15.704)
Total Dose/kg (mg/kg), Median (Min, Max)	13.400 (9.00, 16.20)	15.540 (10.37, 31.75)	14.010 (9.00, 31.75)
Total Dose/kg (mg/kg), %CVb	17.19	30.63	27.19

Table 2: Busulfan Total AUC (Integrated Safety Set)

Summary Statistics (µg*h/L)	SMAC Regimen (N=13)	MAC Regimen (N=16)	Total (N=29)
Geometric Mean (95% CI)	71,923.53 (68,751.04, 75,242.41)	84,043.08 (82,369.52, 85,750.65)	78,376.28 (75,543.86, 81,314.89)
Median (Min, Max)	70,841.00 (63,420.0, 84,305.0)	84,987.00 (78,000.0, 88,310.0)	79,940.00 (63,420.0, 88,310.0)
% CVb	7.5	3.8	9.7

Abbreviation: AUC=area under the curve; CVb=coefficient of variation between subjects; CI=confidence interval; MAC=myeloablative conditioning; max=maximum; min=minimum; SMAC=sub-myeloablative conditioning

3.3.1. Evidence in clinical trials (1, 26,27)

- The registration study (201222) was a non-randomised, open-label, prospective comparative (non-concurrent control) single-centre study, including 20 patients (9 LI and 11 EJ), in which a SMAC regimen was used for 9 patients and a MAC regime for the other 11 patients. The total amount of autologous CD34+ cells encoding ARSA gene infused afterwards ranged from 2-20 * 10^6 CD34+ cells/kg (fresh formulation).

- The second study (205756) was a non-randomized, open-label, single-center study including 4 patients (2LI and 2 EJ), all of them treated with a MAC regimen and an infusion of 3-30 * 10^6 CD34+ cells/kg (cryopreserved formulation).

- 3 expanded access programs (CUP 207394, CUP 206258 and HE 205029) included a total of 9 patients (7 LI and 2 EJ). A SMAC regimen was used in 4 patients and a MAC regimen in 5. All patients received the fresh formulation of AA, differing in dose from 2 to 30 * 10^6 CD34+ cells/kg.

- In all studies and expanded access programs, the primary endpoint was the total GMFM score (gross motor function measure) and the ARSA activity (total PBMC (peripheral blood mononuclear cells)) at 2 years. Secondary endpoints were ARSA activity (in CSF (cerebrospinal fluid) and BM (bone marrow)), NCV (nerve conduction velocity), brain-MRI evolution, GMFC-MLD (gross motor function classification), neurophysiological testing, neurological evaluation, patient survival and engraftment results.

Important note on additional data

The company provided a set of updated tables and figures (ref 20) of study 205756 , without a accompanying report. These updated data will be discussed where possible/appropriate where the data per individual study/patient cohort are available.

An important remark to make is the fact that in the dossier of the company, an updated analysis combining the results of study 201222 and the results of patients included in the CUP programs, which all were treated with the AA fresh formulation (ref. 20), but without updated tables and figures as was done for study 205756.

As discussed in detail per individual trial, it is key in this pathology to evaluate the clinical evolution of each patient on the different clinical outcome parameters, and within comparable morbidity cohorts (i.e. LI, presymptomatic EJ, early symptomatic EJ) in order to assess the effectiveness of the intervention.
Adding to this is the fact patients with negative clinical outcome, deceased patients and patients missing key follow-up assessments will not contribute to the general outcome at later stages, introducing a major bias in favor of the AA therapy at year 2 and year 3, as only patients with a positive effect will contribute, which will overestimate the clinical effectiveness of the intervention.
For example, in the largest cohort of patients studied, the presymptomatic LI patients (15 patients (8/9 of study 201222 and 7 patients from the CUP), for the ARSA activity in PBMC, 14/15 (93,3%) patients have baseline data, 10/15 patients on year 2 (66,6%) and 9/15 at year 3 (60,0%). However, for GMFM there is only data of 10/15 (66,6%) at year 2, 9/15 (60,0%) at year 3, 7/15 (46,6%) at year 4 and 5/15 (33,3%) at year 5.
Given the fact that these additional data do not provide follow-up outcome data on each individual patient included in study 201222 and the CUP, these additional data will not be discussed in detail in this evolution report.

Therefore, the company is invited to deliver the follow-up data of the individual patients of study 201222 and the CUP, in an identical way as was done for study 205756, in order to evaluate the long-term outcome of these patients.

Regarding the historical comparator dataset included in the TIGET NHx cohort, it should be noted that no presymptomatic LI or EJ patients were included in this cohort, as all patients were early-symptomatic LI or EJ (compared to only 6% and 62% in the clinical studies with AA). Especially for LI patients this will cause a bias favoring the relative effectiveness of the current AA treatment.

	ITT set		Natural history cohort	
	Late infantile (n=16)	Early juvenile (n=13)	Late infantile (n=19)	Early juvenile (n=12)
Pre-symptomatic	15 (94%)	5 (38%)	0	0
Early-symptomatic*	1† (6%)	8 (62%)‡	19 (100%)	12 (100%)
Mean age at GT (ITT set) or initial assessment (natural history cohort), months (SD)	12·81 (4·3)	65·86 (33·4)	20·64 (4·7)	51·98 (19·2)
Median follow-up, years (range)	3·04 (0·99–7·51)	3·49 (0·64–6·55)	4·54 (1·80–14·19)	6·79 (2·51–16·10)
Female sex	6 (38%)	7 (54%)	11 (58%)	7 (58%)
Race				
Asian (South-East Asian heritage)	1 (6%)	0	0	0
White (Arabic/North African heritage)	4 (25%)§	0	3 (16%)§	0
White (White/Caucasian European)	11 (69%)§	13 (100%)	16 (84%)§	12 (100%)
MLD variants in matched populations				
Matched analysis set (n)	16	13	17	12
Matched sibling analysis set (n)	8	4	7	4

Data are number (%), mean (SD), or median (range), unless otherwise indicated. GT=gene therapy. ITT=intention-to-treat. MLD=metachromatic leukodystrophy.
*Symptomatic at time of treatment (for atidarsagene autotemcel [arsa-cel]) or at time of enrolment (for natural history). †One patient with late-infantile MLD was pre-symptomatic at time of enrolment but showed disease progression between enrolment and treatment. ‡Two patients with early-symptomatic early-juvenile MLD were enrolled according to the original inclusion criteria, one of them showing disease progression between enrolment and treatment. §Two patients with late-infantile MLD in the ITT set and one patient with late-infantile MLD in the natural history cohort were incorrectly coded as White-White/Caucasian European in the clinical database. After database lock, it was confirmed that these patients are White-Arabic/North African heritage, and the table reflects the correct classification.

Table: **Baseline characteristics in the ITT set and natural history cohort**

- EFFICACY

Element from the EPAR

CHMP conclusion on the efficacy in the benefit/risk assessment (EPAR):

2.7.2. Conclusions on clinical efficacy

Libmeldy shows impressive efficacy in the pre-symptomatic LI MLD and EJ MLD as physical and cognitive performance is within the normal range of healthy subjects for the vast majority of the pre-symptomatically treated subjects for the duration of FU. The median follow-up at time of submission (cut-off date March 2018) for the pivotal study was 5.4 years (range: 2.98 to 7.51 years) and 3.5 years (range: 0.64 to 6.55 years) for LI MLD (n=9) and EJ MLD (n=11), respectively. The effects of the treatment are evident on gross motor function, cognitive function, brain MRI, and survival. As there appears a reduction in cells with high VCN and the ARSA levels seems to decrease over time, it remains to be seen whether the effect of treatment is maintained or whether, in time, progression to symptomatic disease may occur. However, further data can be gathered post marketing to confirm efficacy as the current numbers are limited, and to reassure a maintenance of effect as the follow up will be 15 years.

While deterioration on motor function is observed in all symptomatic EJ subjects, data indicate that for the early symptomatic patients there appears to be a delay in rate of motor function deterioration and the cognitive function is within or above the ranges of heathy subjects form the same age. Also, as there is currently no screening programme for MLD, the majority of subjects will be identified when they are symptomatic. The applicant aimed to identify the "cut-off" points beyond which the window of opportunity for treatment is lost for symptomatic EJ MLD patients. The proposed cut off point is accepted. If more follow up data becomes available, these criteria may need to be adapted. Further identification of prognostic factors for response, i.e. target population, should be part of the Post authorisation safety and efficacy study.

The CAT considered the following measures necessary to ensure the follow-up of efficacy:

In order to further characterise the long-term efficacy and safety of Libmeldy in children with late infantile or early juvenile forms of MLD, the MAH will conduct and submit the results of a prospective study based on data from a registry, according to an agreed protocol.

The CHMP endorse the CAT conclusion on clinical efficacy as described above.

Analysis of the trials on which the efficacy is based on

Before analyzing the clinical efficacy and safety of the different clinical studies and expanded access programs in detail, a general review of the pharmacokinetic and pharmacodynamic data of AA will be given. More detailed information for each individual study will be discussed later in the document:

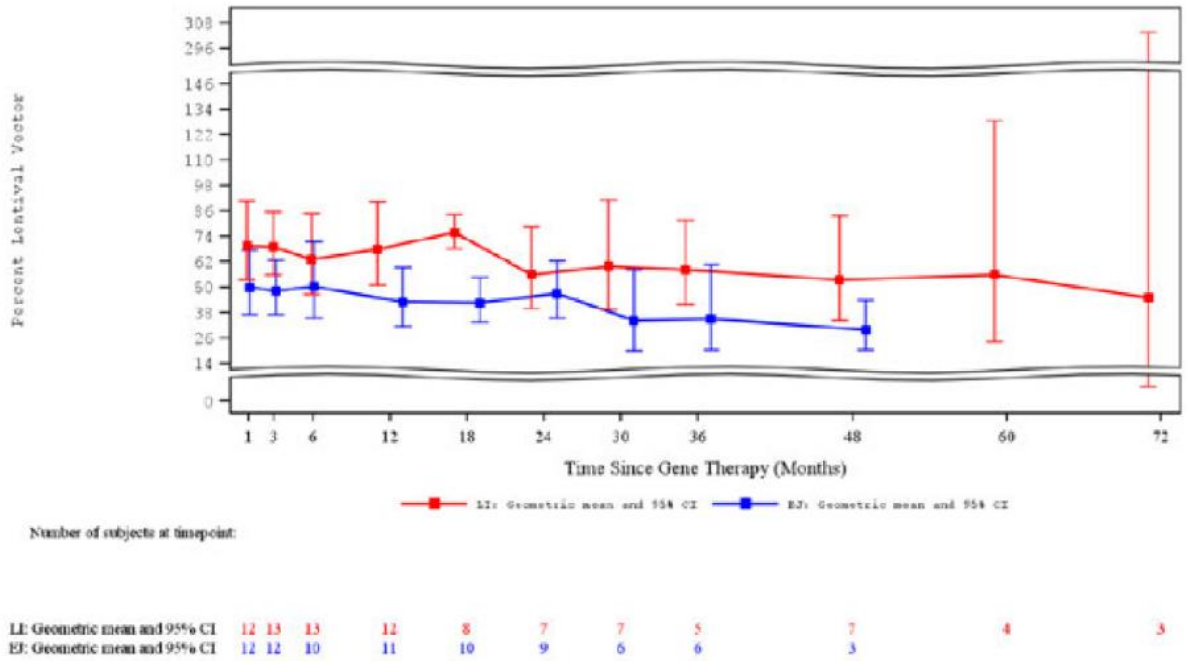
Pharmacokinetic and pharmacodynamic data:

Various pharmacodynamic parameters were measured in all clinical studies, including the engraftment of transduced cells (BM, PBMCs and cell subpopulations) and ARSA activity (in BM, PBMCs and cell subpopulations, and CSF). The Integrated efficacy data set includes data from subjects treated with the fresh AA-f formulation in the registration Study (Study 201222 [n=20]) and patients treated under the Expanded Access Programs (n=9). The 4 patients treated with the cryopreserved formulation are not included.

- The transduced cell engraftment in BM-Derived clonogenic progenitor cells, expressed as the proportion of BM-derived colonies harboring the LV genome (percentage LV+) 1 year after treatment was 54.8% (range 20% to 100% in 23 patients. After 5 years the proportion was 45.0% (range 18.8% to 90.6%), but this included only 6

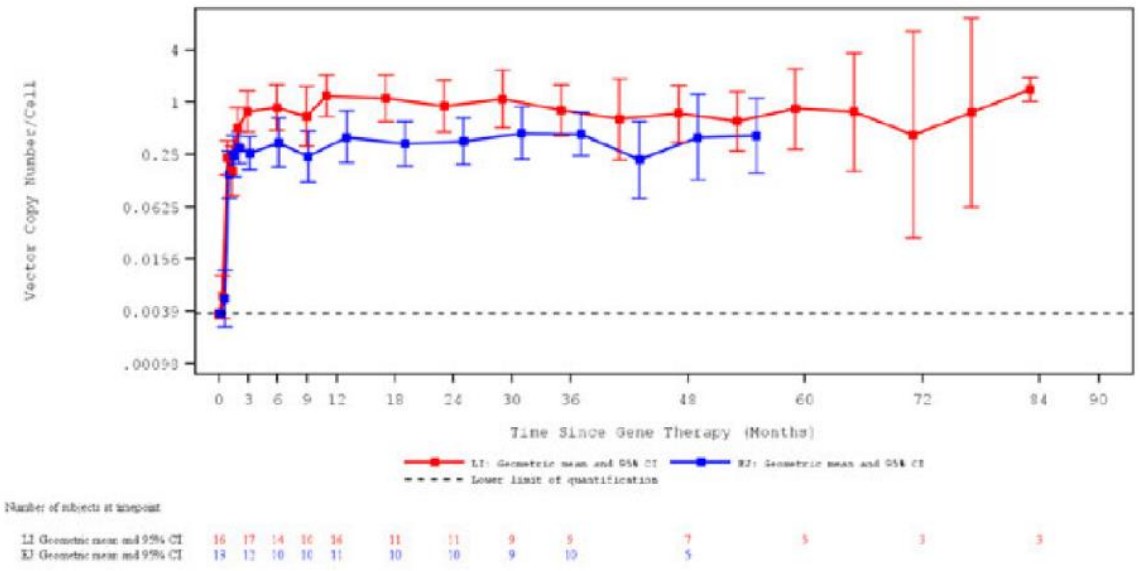
patients. An important finding was the fact that at all time points, the geometric mean LV+ values cells in BM were higher in the LI subgroup compared to the EJ subgroup (but with overlapping 95%CI).

Figure 2: Percentage of Lentiviral Vector Transduced Cells in Bone Marrow Over Time (Geometric Mean and 95% CI), OTL-200-f Treated Subjects by Disease Subtype (Integrated Efficacy Set)



- The vector copy number (VNC) in total PBMCs showed engraftment of transduced cell beginning at 28 days post treatment, with a mean of 0.19 copies/cell [range 0.03 to 0.68] (n=29), being above the minimum per protocol defined target (≥0.04 copies/cell, equivalent to 4%). The VCN in total remained relatively stable from 3 months post-treatment throughout the course of follow-up.

Figure 3: Vector Copy Number in PBMCs Over Time (Geometric Mean and 95% CI), OTL-200-f Treated Subjects by Disease Subtype (Integrated Efficacy Set).



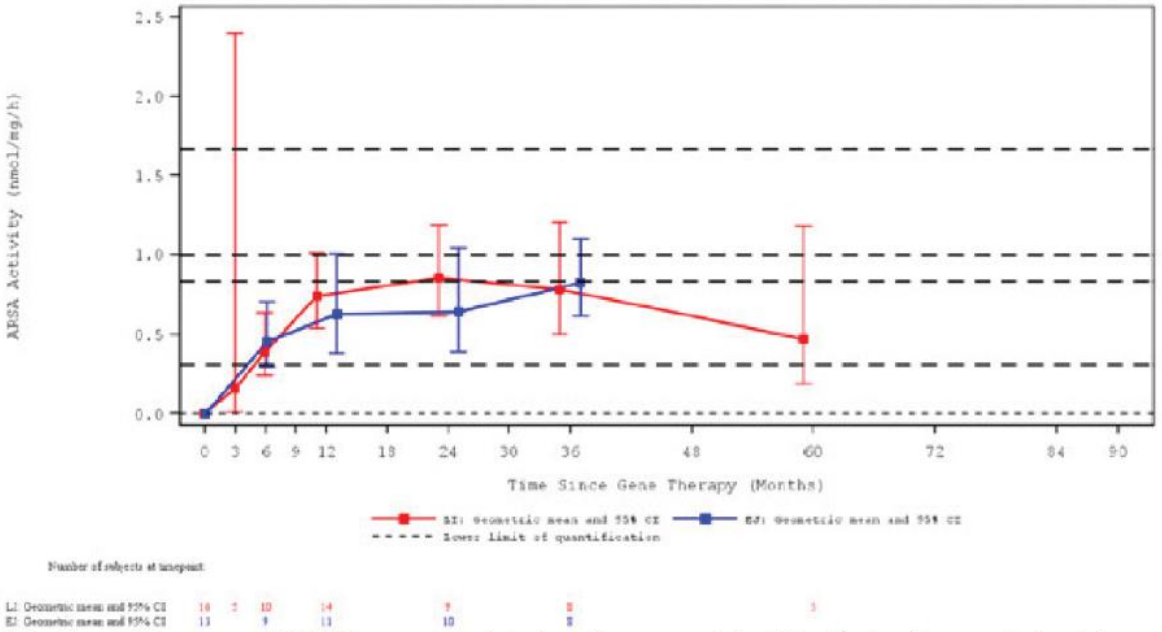
- The ARSA activity in the PBMCs increased within 1 month and at higher levels than reported for healthy subjects at 3 months. After 2 years there was a statistically significant increase in ARSA activity in total PBMCs for the LI

patients (18.7-fold increase; 95%CI: 8.3, 42.2; p<0.001) and for EJ patients (5.7-fold increase; 95 CI: 2.6, 12.4; p<0.001) compared to baseline levels. After 3 years the increase in ARSA activity in total PBMCs remained statistically significant in both LI patients (37.5-fold increase; 95%CI: 17.7, 79.6; p<0.001) and EJ patients (11.2-fold increase; 95% CI: 5.7, 21.9 p<0.001) subgroups compared to baseline.

In BM MNC the ARSA activity increased within 1 month and by month 3 the mean ARSA activity levels in PBMCs were 7.5-fold higher compared to baseline in LI patients and 6.3-fold higher in EJ patients (p<0.001 for all), and remained higher at a comparable level during follow-up.

In the CSF, the ARSA levels were initially below the LLOQ of 0,0032 nmol/mg/g in all patients. At month 6 a mean level of 0,42 nmol/mg/h was observed (range 0,13 – 102). After 1 year, the mean CSF ARSA activity was 0,739 nmol/mg/h in LI patients and 0,473 nmol/mg/h in EJ patients.

Figure 4: ARSA Activity in Cerebrospinal Fluid Over Time (Geometric Mean and 95% CI), by Disease Subtype (Integrated Efficacy Set)



Note: Geometric mean and 95% CI were presented where there were at least 3 subjects with non-missing data.
Note: The reference range represents data from a cohort of paediatric reference donors as per Perugia reference range report.

- The correlation of CD34+/kg dose multiplied by VCN as measure of product potency at month 6 and month 12 showed a statistical significant correlation between the CD34+*VCN product and the VCN in PBMCs of R^2=0,605 (p=0,002) and R^2=0,556 (p=0.003) respectively.

- Statistically significant correlations between VCN in PBMCs and ARSA activity in PBMCs were observed at 6 months, 1 year, 2 years and 3 years post-treatment. As will be discussed in more detail further on, no relevant correlations were observed between levels of ARSA activity in CSF and motor function, cognition or MRI total scores in any of the MLD variant and time points evaluated (2 Years and 3 Years post treatment).

Figure 6: Scatterplot of VCN in PBMCs versus ARSA activity in PBMCs at Months (A), 1 Year (B), 2 Years (C) and 3 Years (D) Post-Treatment (Integrated Efficacy Set)

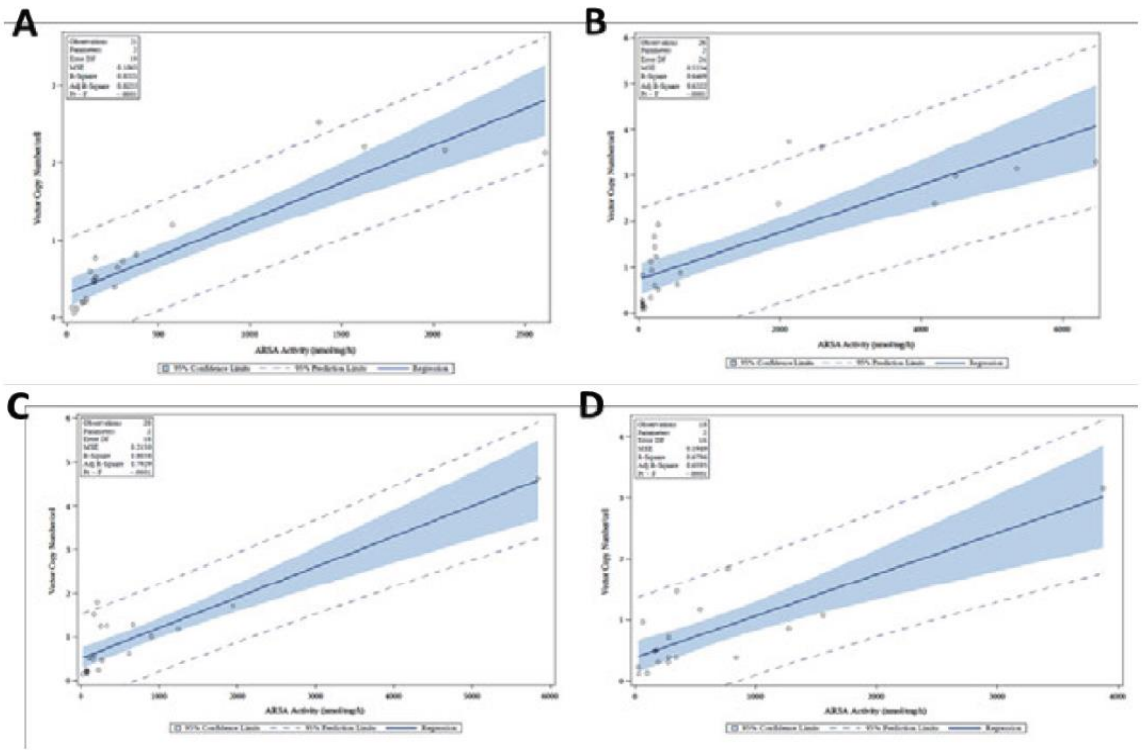


Table 4: Correlations Between ARSA in CSF and Clinical Efficacy Outcomes

	ARSA in CSF					
	Year 2			Year 3		
	Pre-symptomatic Late Infantile	Pre-symptomatic Early Juvenile	Early-symptomatic Early-Juvenile	Pre-symptomatic Late Infantile	Pre-symptomatic Early Juvenile	Early-symptomatic Early-Juvenile
GMFM total score	n=9 p=0.229 corr.=0.446	n=4 p=0.983 corr.=0.017	n=6 p=0.053 corr.=-0.806	n=8 p=0.317 corr.=0.407	n=3 p=0.146 corr.=0.974	n=5 p=0.283 corr.=-0.602
GMFC-MLD	n=9 p=0.262 corr.=-0.419	Not calculable[1]	n=6 p=0.029 corr.=0.858	n=8 p=0.346 corr.=-0.385	Not calculable[1]	n=5 p=0.229 corr.=0.656
DQ	n=9 p=0.936 corr.=0.031	n=4 p=0.871 corr.=0.29	n=6 p=0.027 corr.=-0.863	n=6 p=0.423 corr.=0.407	n=3 p=0.700 corr.=-0.454	n=5 p=0.055 corr.=-0.869
MRI	n=9 p=0.420 corr.=-0.308	n=4 p=0.819 corr.=-0.181	n=6 p=0.139 corr.=0.677	n=8 p=0.523 corr.=-0.266	n=3 p=0.325 corr.=0.873	n=5 p=0.197 corr.=0.690

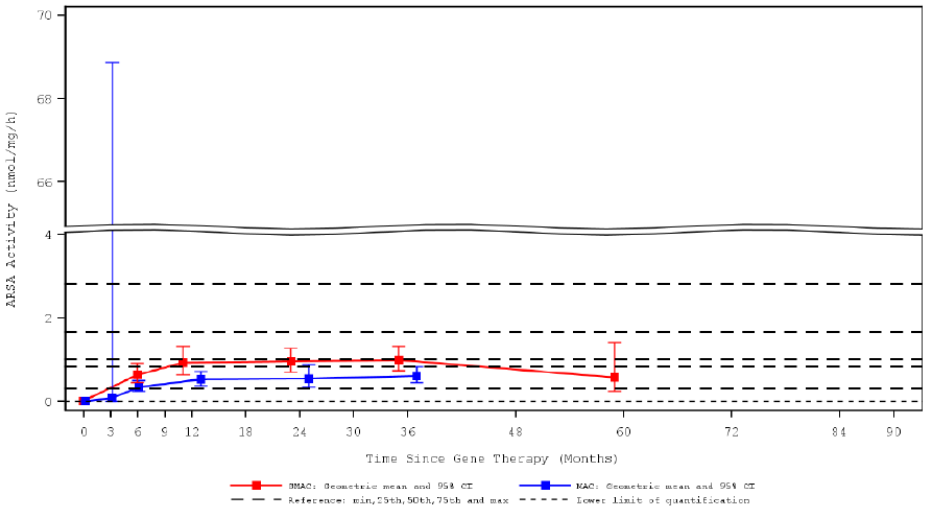
[1] Not calculable due to all pre-symptomatic EJ subjects scoring GMFC-MLD Level 0 with variable levels of ARSA in CSF (Figure 2.7.3.3.2.117)

- The increase in ARSA activity in PBMCs after 2 years was similar in the SMAC group (10.4-fold [range 1.00 to 226.56]) and the MAC group (10.7-fold [range 2.70 to 75.33]). Similar increases were observed in BM-derived

MNCs at Year 2 (SMAC: 6.4-fold [range 1.5 to 21.8]); MAC 11.0-fold [range 4.74 to 63.76]), but in CSF the mean ARSA activity was slightly higher in the SMAC subgroup at Year 2 (geometric mean 0.954 nmol/mg/h [range 0.60 to 1.99 nmol/mg/h]) compared to the MAC subgroup (geometric mean 0.547 nmol/mg/h [range 0.13 to 0.92 nmol/mg/h]). This difference was smaller when the conditioning subgroups were defined as total AUC threshold of ≤76,500 µg*h/L vs. >76,500 µg*h/L (1.5-fold difference between Year 2 geometric means of 0.934 nmol/mg/h [range 0.60 to 1.99] and 0.615 nmol/mg/h [range 0.13 to 1.06 nmol/mg/h] respectively).

Figure 7: ARSA Activity in CSF Over Time (Geometric Mean and 95% CIs), OTL-200-f Treated Subjects by Conditioning Regimen (SMAC vs. MAC [Panel A]; Total AUC Threshold 76,500 µg*h/L [Panel B])

Panel A. SMAC vs. MAC



Comparator(s) and justification of the choice and doses (according to the Belgian context) (ref 18, 19, 20)

Study 201222:

The results obtained with the 22 LI/EJ patients given Libmeldy were compared to a cohort of 31 untreated LI and EJ MLD patients (TIGET NHx study (Telethon Institute for Gene therapy, Natural History Study – Study number 204949)), containing a mixture of cross-sectional and longitudinal data with some patients contributing data at multiple time points while others providing data from a single visit. Matched sibling data was available for 9 subjects treated in study 201222.

The Matched Analysis Set (MAS) population includes subjects in the ITT population and any age and MLD variant-matched untreated subjects from TIGET NHx Study who provided control data for comparison purposes. Matched untreated participants are defined as subjects with LI or EJ MLD or clinical variant of intermediate severity between the classical LI and EJ forms in the TIGET NHx Study who had a study visit where their age (at the study visit) fit within the window of ages for Libmeldy-f-treated subjects in Study 201222. For each MLD subtype (i.e., LI or EJ), at the 2-year and 3-year analysis time points, the lower bound of the age window was based on the lowest age of a treated subject in Study 201222 minus 3 months and the upper bound was the highest age of a treated subject in Study 201222.
The Matched Sibling Analysis Set population includes subjects in the ITT population who had an untreated sibling in the TIGET NHx Study and included the corresponding untreated sibling(s) from the TIGET NHx Study.

No data of HSCT-treated matched patients were used by the company in order to compare the relative clinical effectiveness and safety of HSCT with AA.

Study 205756:

Study 205756 is an open-label, single-arm study in presymptomatic patients with early-onset MLD (i.e. either LI, EJ, or an intermediate variant between LI and EJ), using the intended AA commercial cryopreserved formulation, to evaluate the efficacy and safety of the cryopreserved formulation in comparison to the fresh formulation.

The Matched Analysis Set (MAS) population includes subjects in the ITT population and any age and MLD variant-matched untreated subjects from TIGET NHx Study who provided control data for comparison purposes. Matched untreated participants are defined as subjects with LI or EJ MLD or clinical variant of intermediate severity between the classical LI and EJ forms in the TIGET NHx Study who had a study visit where their age (at the study visit) fit within the window of ages for Libmeldy-f-treated subjects in Study 201222. For each MLD subtype (i.e., LI or EJ), at the 2-year and 3-year analysis time points, the lower bound of the age window was based on the lowest age of a treated subject in Study 201222 minus 3 months and the upper bound was the highest age of a treated subject in Study 201222.
The Matched Sibling Analysis Set population includes subjects in the ITT population who had an untreated sibling in the TIGET NHx Study and included the corresponding untreated sibling(s) from the TIGET NHx Study.

No data of HSCT-treated matched patients were used by the company in order to compare the relative clinical effectiveness and safety of HSCT with AA.

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

A total of 7 presymptomatic LI subjects and 2 presymptomatic EJ subjects were treated in expanded access programmes.

Population studied and target population (ref 18, 19, 20, 21, 22)

Study 201222:

The inclusion criteria were set as either presymptomatic MLD patients with a LI-MLD variant or pre- or early-symptomatic MLD patients with an EJ MLD variant, both with a parental/guardian signed informed consent.

The LI MLD variant was defined as the presence of 2 of 3 criteria: age at onset of symptoms in the older sibling(s) ≤30 months, 2 null (0) mutant ARSA alleles and peripheral neuropathy with a NCV index >2SD normal range.

The EJ MLD variant was defined as the presence of 2 of 3 criteria: age at onset of symptoms in the older sibling(s) between 30 months and 6 years (i.e. not celebrated 7th birthday), 1 null (0) mutant and 1 R mutant ARSA allele(s) and peripheral neuropathy.

For early symptomatic EJ MLD patients the criteria of a baseline IQ≥70 and the ability to walk independently for ≥10 steps had to be fulfilled.

Major exclusion criteria were patients with HIV, HCV, HBV, neoplastic diseases, myelodysplastic syndromes or AML, severe disease with organ dysfunction, allogenic HSCT in previous 6 months or history of HSCT with evidence of residual cells of donor origin.

A total of 22 MLD patients were included, consisting of 9 LI-type MLD and 13 EJ-type MLD patients, all confirmed by ARSA enzymatic activity and genetic analysis. The LI study patients and some of the EJ patients were identified after an older sibling had developed symptoms and received an MLD diagnosis, prompting the testing of other family members.
All 9 LI patients were presymptomatic upon enrolment, defined as subjects without neurological impairment or without symptoms or signs of MLD, however, one subject became symptomatic prior to treatment with AA.

Regarding the 13 EJ MLD patients included in the study, 4 of these patients were presymptomatic and 8 were early-symptomatic, which was defined as either patients identified within 6 months from the first reported symptoms or as being patients with an intelligence quotient (IQ) ≥70 and the ability to walk independently for ≥10 steps.
There was 1 EJ-MLD patient (patient MLD 18) withdrawn by the investigator at the baseline visit because of rapid disease progression and before treatment was administered, leaving a total of 20 patients in the final analysis.

All the patients were treated in the Ospedale San Raffaele – Telethon Institute for Gene Therapy (OSR-TIGET), Milan, Italy.

It should be noted that all of the 19 LI-MLD patients and all of the 12 EJ MLD patients in the comparative TIGET NHX study were symptomatic at enrolment in the study, which can induce a timing bias in a direct comparison on MLD evolution. The company noted in the CSR that retrospective data analysis was performed, resulting mean age of data in the LI patients of 20,65 months (range 10 – 27,9 months) and 51,98 months (range 20,3 – 74,2 months for the EJ patients) which is comparable to the 201222 study patients.

Table 15 Summary of Demographic Characteristics (TIGET NHx Study)

	TIGET NHx Study (N=31)		
	Late Infantile (N=19)	**Early Juvenile (N=12)**	**Total (N=31)**
Sex, n (%)			
N	19	12	31
Female	11 (58)	7 (58)	18 (58)
Male	8 (42)	5 (42)	13 (42)
Age at enrolment (months)[a]			
n	19	12	31
Mean	90.96	120.02	102.21
SD	47.677	46.150	48.496
Median	86.10	106.55	99.00
Min	35.0	59.0	35.0
Max	168.0	214.9	214.9
Ethnicity, n (%)			
n	19	12	31
Hispanic or Latino	2 (11)	0	2 (6)
Not Hispanic or Latino	17 (89)	12 (100)	29 (94)
Race detail, n (%)[b]			
n	19	12	31
White - Arabic/North African heritage	2 (11)	0	2 (6)
White - White/Caucasian European	17 (89)	12 (100)	29 (94)
Symptomatic status at enrolment, n (%)			
n	19	12	31
Pre-symptomatic	0	0	0
Symptomatic	19 (100)	12 (100)	31 (100)

a. Age is presented at the Enrolment visit. Enrolment is the date of the Day 0 visit. As some of the data is retrospective, if the Day 0 visit was missing, then the date of ICF was used as the enrolment date.

Versie préCTG:

Table 13 Summary of Study Populations (All Subjects Population)

Population/ Subgroup	Study 201222 (N=21), n (%)	TIGET NHx Study (N=31), n (%)	Total (N=52)[b], n (%)
All subjects	**21[a]**	**31**	**52[b]**
Disease subtype			
Late infantile	9 (43)	19 (61)	28 (54)
Early juvenile	12 (57)	12 (39)	24 (46)
Conditioning regimen			
SMAC regimen	9 (43)	0	9 (17)
MAC regimen	11 (52)	0	11 (21)
Not applicable	1 (5)	31 (100)	32 (62)
Intent-to-treat	**20**	**NA**	**20**
Disease subtype			
Late infantile	9 (45)		9 (45)
Early juvenile[c]	11 (55)		11 (55)
Conditioning regimen			
SMAC regimen	9 (45)		9 (45)
MAC regimen	11 (55)		11 (55)
Matched analysis set	**20**	**29[f]**	**49**
Disease subtype			
Late infantile	9 (45)	17 (59)	26 (53)
Early juvenile[c]	11 (55)	12 (41)	23 (47)
Conditioning regimen			
SMAC regimen	9 (45)	0	9 (18)
MAC regimen	11 (55)	0	11 (22)
Not applicable	0	29 (100)	28 (59)
Matched sibling analysis set	**11**	**10**	**21**
Disease subtype			
Late infantile	7 (64)	6 (60)	13 (62)
Early juvenile[c]	4 (36)	4 (40)	8 (38)
Conditioning regimen			
SMAC regimen	6 (55)	0	6 (29)
MAC regimen	5 (45)	0	5 (24)
Not applicable	0	10 (100)	10 (48)

Population/ Subgroup	Study 201222 (N=21), n (%)	TIGET NHx Study (N=31), n (%)	Total (N=52)[b], n (%)
Safety	**20**	0	**20**
Disease subtype			
Late infantile	9 (45)	0	9 (45)
Early juvenile[c]	11 (55)	0	11 (55)
Conditioning regimen			
SMAC regimen	9 (45)[d]	0	9 (45)
MAC regimen	11 (55)[e]	0	11 (55)

Note: The total of N=12 for EJ subjects included 1 subject (Subject MLD18) who was withdrawn by the investigator at the Baseline visit (prior to receiving OTL-200-f) due to rapid disease progression.

a. As provided in Section 5.1 and Table 11, 1 EJ subject was withdrawn by the investigator at the Baseline visit (prior to treatment) due to rapid disease progression (Subject MLD18) (Listing 1.07).
b. The All Subjects study population included all subjects enrolled in Study 201222 and subjects enrolled in Study 204949 (TIGET NHx Study) with disease subtype LI or EJ (see Section 4.8.3).
c. Subject MLD09 (Study 201222) and TIGET NHx Study Subject LDM136 (sibling of Subjects MLD09 and LDM128) were considered as an intermediate disease subtype. Subjects classified as EJ for the purpose of analysis; see Section 5.5.3.1 for additional details.
d. Six LI subjects and 3 EJ subjects received SMAC regimen (Listing 1.09).
e. Three LI subjects and 8 EJ subjects received MAC regimen (Listing 1.09).
f. Two TIGET NHx Study subjects (Subjects LDM127 and LDM138) were excluded from the Matched Analysis Set as they did not have study data meeting the age matching criteria.

Source: Table 1.04.

Study 205756:

This study was performed in 4 patients using the cryopreserved formulation, in order to demonstrate equivalence in clinical efficacy between the fresh and cryopreserved formulation.

Based on the previous experience in study 201222, only presymptomatic subjects were included, as stated in the CSR ('*Interim results from Study 201222 showed that AA is effective in modifying the disease course of early-onset MLD subjects across variants, particularly when subjects were treated prior to the onset of overt clinical manifestations of the disease. For this reason, presymptomatic subjects with early onset MLD were particularly considered for participation in this study*').

The clinical outcome of this study using the commercial cryopreserved formulation should therefore be compared to the previous studies.

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

A total of 7 presymptomatic LI subjects and 2 presymptomatic EJ subjects were treated in expanded access programmes.

EAP CUP207394: 1 symptomatic EJ-MLD patient, symptomatic since 8 months / AA fresh formulation (patients 7,65 months at inclusion, exceeding the threshold age of Early Juvenile (≤7 years), so being in fact a late juvenile patient (LJ-MLD).

EAP HE205029: 3 presymptomatic LI-MLD patients / AA fresh formulation

EAP CUP206258: 4 presymptomatic LI-MLD patients and 1 presymptomatic EJ-MLD patients / AA fresh formulation

Criteria of efficacy in the trials

Study 201222:

Clinical efficacy was primary based on the Gross Motor Function Measure score (GMFM), with the score two years after treatment as primary endpoint. The GMFM score consists of 88 items sorted in 5 groups: lying and rolling; sitting; crawling and kneeling; standing; walking, running and jumping.

A delay in progression of 10% in total of the total GMFM score in treated subjects as compared to a non-concurrent historical control group was the aimed effect size. It should be noted that the data variability might be small for the TIGET NHx group since they are likely to be in the advanced stage of the disease. For the treated subjects, if treatment is effective, the scores could be better and show larger variability. Therefore, the variability for treated and for TIGET NHx groups were estimated from the model separately with different parameters.

The co-primary efficacy endpoint was:

- improvement of 10% of the total GMFM-88 score in treated patients, when compared to the GMFM-88 scores in the historical control MLD population, evaluated at year 2 after treatment,
- significant (≥2 standard deviation [SD]) increase of residual ARSA activity as compared to pre-treatment values, measured in PBMC at year 2 after treatment.

The primary safety endpoints were:

- absence of engraftment failure or delayed haematopoietic reconstitution (prolonged aplasia) defined as absolute neutrophil count <500/µL +60 days after transplantation, with no evidence of BM recovery, requiring cellular back-up administration
- absence of conditioning regimen-related toxicity, as determined by surveillance of clinical (NCI ≥ Grade 2) and laboratory (NCI ≥ Grade 3) parameters applied in the short- and long-term follow-up of the treated subjects to assess the degree of morbidity associated with the conditioning regimen
- short-term safety and tolerability of lentiviral-transduced cell infusion, which consisted of the absence of serious adverse reactions within 48 hours from infusion
- Long-term safety of lentiviral-transduced cell administration:
    - o The absence of Replication Competent Lentivirus (RCL)
    - o The absence of Abnormal Clonal Proliferation (ACP)

The secondary efficacy endpoints were:

- NCV Index at year 2 after treatment that is significantly higher than scores observed in age-matched historical control MLD patients (i.e., the difference is ≥2 SD above 0). NCV in individual sensory and motor nerves was also evaluated
- GMFC-MLD levels at different ages in treated patients compared to the historical control MLD population
- brain MRI total score at year 2 after treatment that is significantly lower than scores observed in age-matched historical control MLD subjects (i.e., the difference is ≥2 SD below 0)
- measurement of an IQ above 55 (threshold for severe disability) at neuropsychological testing performed at year 2, year 2.5, and year 3 follow-up
- transduced cell engraftment above 4% in BM-derived clonogenic progenitor cells at Year 1 after the transplant. This is assessed as the percentage of LV-positive colonies determined by quantitative polymerase chain reaction (PCR) on individual colonies from a colony forming cell assay
- evaluation of correlations occurring between transduced cell engraftment levels and busulfan exposure
- age at death in the treated group compared with the NHx subjects

The secondary safety endpoints were:

- absence of immune responses against the transgene (evaluated via immunoassay)
- monitoring of adverse events (AEs) and serious adverse events (SAEs), routine laboratory tests, vital signs, physical examinations, specialist examinations, and diagnostic imaging and instrumental tests (including chest x-ray, electrocardiogram, echocardiogram, and ultrasound of the abdomen and thyroid)

Study 205756:

Clinical efficacy was primary based on the Gross Motor Function Measure score (GMFM), with the score two years after treatment as primary endpoint, comparable to the 201222 study.
Secondary efficacy endpoints included Gross Motor Function Classification (GMFC)-MLD score, neurological examinations, assessment of nerve conduction velocity (NCV), evaluation of brain MRI assessments/parameters (e.g., modified Loes score) and neurocognitive assessments.

The relative efficacy and safety of the ATL-200-c formulation was also evaluated by measuring the pharmacodynamics data (ARSA activity in total peripheral blood mononuclear cells (PBMCs), the ARSA activity in PB CD15+ cells, the ARSA activity in PB CD14+ cells and the ARSA activity in cerebrospinal fluid (CSF)) and safety endpoints (AE reporting, haematological recovery, incidence and titers of anti-ARSA antibodies, absence of malignancy or abnormal clonal proliferation).

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

In the absence of a suitable clinical trial that was open for enrolment, the objective of the EAPs (HE and CUP) was to provide an alternative treatment option to MLD patients with high unmet need, in advance of AA being commercially available.

No primary and secondary endpoints were defined, but the following clinical efficacy data were collected: ARSA activity in PBMC, GMFM, GMFC-MLD, neuropsychological assessment and nerve conduction velocity (NCV).

Adverse event and Serious adverse event reporting was performed.

Results of the main trials

a) Patient characteristics

Study 201222:

Of the 22 patients screened and enrolled, 2 EJ patients were withdrawn before treatment (1 parent withdrawal of consent before baseline assessment and 1 withdrawal because of rapid disease progression), leaving 20 patients to be treated. Of the 9 LI MLD patients, 8 were presymptomatic at the moment of the treatment infusion (with 1 patients developing symptoms just before the treatment). Of the 11 EJ MLD patients, 4 were asymptomatic at treatment.

Baseline characteristics LI patients:

In the LI MLD patient group, the mean age of these 9 patients was 14,10 months, with a normal GMFC-MLD level in 8 patients and GMFC-MLD level 1 in 1 patients. The total GMFM score at baseline ranged from 20,86% to 80, 11%, the NCV Index ranged from -0.16 to -9,79 and the total MRI score from 0 to 2,25.
The ARSA activity in PBMC ranged from 2,98 nmol/mg/h to 16,67 nmol/mg/h. At Baseline, ARSA activity levels in CSF in all LI MLD patients were below the LLOQ (0.0032 nmol/mg/h).
In 6 patients a SMAC busulfan conditioning regimen was used, and a MAC in the remaining 3 patients, with an AUC ranging from 68.914 µg*h/l to 87.940 µg*h/L. The number of transfused CD34+ HSPC ranged from 4,2*10^6/kg to 19,5 *10^6/kg.

Table 7: Late Infantile: Summary of Demographics and Baseline Characteristics of Individuals in the Late Infantile Subgroup in Study 20122

Subject Number	1	2	3	4	5	6	7	8	9	TOTAL***
Demography and MLD diagnosis information										
Gender	male	male	male	Female	female	male	female	female	Male	Female 4 (44); Male 5 (56%)
Age (months)	15	13	7	17	12	16	23	9	8	Mean 14.10; min 7.6; max 23.3
ARSA mutation 1[b]	c.827C>T (p.Thr276Met)	c.736C>T (p.Arg246Cys)	c.449C>G (p.Pro150Arg)	c.465+1G>A (splice donor)	c.465+1G>A (splice donor)	c.465+1G>A (splice donor)	c.1108-2A>G (splice acceptor)	c.736C>T (p.Arg246Cys)	c.937C>T (p.Arg313*)	N/A
ARSA mutation 2[b]	c.827C>T (p.Thr276Met)	c.737G>A (p.Arg246His)	c.449C>G (p.Pro150Arg)	c.980-1G>A (splice acceptor)	c.855-1G>A (splice acceptor)	c.465+1G>A (splice donor)	c.1108-2A>G (splice acceptor)	c.737G>A (p.Arg246His)	c.937C>T (p.Arg313*)	N/A
Genotype	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0/0
Predicted age of onset, months[c]	18	24-27	15	19	15-18	20	26	24-27	24-30	20.6
Sibling , survival, months (status)	61.3 (died)	68.4 (died)	42.4 (died)	51.8 (withdrawn)	74.7 (died)	Not enrolled	75.8 (alive)	68.4 (died)	Not enrolled	N/A
Baseline characteristics										
Symptomatic	No[d]	No	No	No	No[d]	No[d]	No[d]	No	No[d]	8 PS, 1 S
ARSA activity in PBMCs nmol/mg/h[e]	3.27	10.92	3.17	5.13	16.67	NA	9.85	4.23	2.98	min 2.98; max 16.67
Total GMFM score (%)	65.02	75.63	27.33	80.11	74.99	66.09	71.09	50.92	20.86	min 20.86; max
GMFC-MLD level[f]	NA	NA	NA	NA	NA	NA	1	NA	NA	max 1
NCV Index	-9.79	-0.47	-3.38	-0.16	-6.06	-6.02	-3.11	-1.28	-4.86	min -0.16; max-9.79
Total MRI score	0	0	0	0	0	0	2.25	0	0.25	Min 0 max2.25
Intelligence quotient										
Performance	95	115	100	105	95	100	80	95	95	80-115

Versie préCTG:

Subject Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**TOTAL*****
Language	NA	83	112	109	109	94	89	127	106	83-127
Busulfan conditioning										
Regimen	SMAC[g]	SMAC[g]	SMAC	SMAC	SMAC	SMAC	MAC	MAC	MAC	6 SMAC 3 MAC
Exposure – total AUC (µg x h/L)	84,305	78,572	69,225	68,914	70,744	71,551	87,940	78,000	84,990	Min 68,914 Max87,940
CD34+ HSPC dose (x10^6 cells/kg)	11.1	7.0	7.2	4.2	6.2	18.2	13.1	19.5	13.1	Min 4.2, Max 19.5
DP VCN**	2.5	2.5	4.4	1.7	3.1	4.0	4.2	4.3	7.3	2.5 – 7.3

*=stop codon. DP VCN= Drug product vector copy number, PS= pre-symptomatic, S= symptomatic, NA= not assessed, N/A= not applicable
a. Age at administration of Libmeldy-f.
b. Mutations are described according to standard HGVS nomenclature, as described in Listing 2.06.
c. For pre-symptomatic subjects, the predicted age of onset was calculated on the basis of the age at symptom onset in the subject's older sibling(s).
d. Five Subjects (Patient 1,5,6,7 and 9) had abnormal neurological exam findings at Baseline as outlined in Section 5.5.3.
e. LLQ identified post interim study report as 25.79 nmol/mg/h for PBMCs.
f. Note that on a population basis, the GMFC-MLD score cannot be applied before the age of 18 months, as it is based upon the ability to walk. For an individual person who had already started walking before 18 months of age, however, the GMFC-MLD score can be reasonably applied.
g. All subjects except for 2 (Patient 1 and 2)received a total AUC within the acceptable range. These two subjects received a total AUC higher than the acceptable range.
Source: Listing 1.05, Listing 1.06, Listing 1.08, Listing 1.09, Listing 2.03, Listing 2.04, Listing 2.06, Listing 2.39, Listing 2.40, Listing 2.41, Listing 2.42, Listing 2.43, Listing 2.44, Listing 2.45, and Listing 2.51.
**Row added by Assessor
***colum added by assessor. If averages were not reported by the applicant, minimum and maximum values are presented

Baseline characteristics EJ patients:

- Presymptomatic EJ patients:

In the presymptomatic EJ MLD patient group, the age of these 4 patients ranged from 11 to 66 months, with a normal GMFC-MLD level in all 4 (presymptomatic). The total GMFM score at baseline ranged from 77,91% to 97,31%, the NCV Index ranged from -3,14 to -10,75 and the total MRI score from 0 to 4,25.
The ARSA activity in PBMC ranged from 0,69 nmol/mg/h to 17,86 nmol/mg/h. At Baseline, ARSA activity levels in CSF in all presymptomatic MLD patients were below the LLOQ (0.0032 nmol/mg/h).
In 1 patient a SMAC busulfan conditioning regimen was used, and a MAC in the remaining 3 patients, with an AUC ranging from 73.146 µg*h/l to 84.996 µg*h/L. The number of transfused CD34+ HSPC ranged from 6,7*10^6/kg to 16,3 *10^6/kg.

Table 8: Pre-symptomatic Early Juvenile Subgroup: Summary of Demographics and Baseline Characteristics Study 201222

Subject Number	10[a]	11	12	13[b]	TOTAL**
Demography and MLD diagnosis information					
Gender	female	Female	male	male	Female 2, male 2
Age (months)	18	66	48	66	Min 18; Max 66
ARSA mutation 1[c]	c.931G>A (p.Gly311Ser)	c.465+1G>A (splice donor)	c.200C>T (p.Pro67Leu)	c.465+1G>A (splice donor)	N/A
ARSA mutation 2[d]	c.931G>A (p.Gly311Ser)	c.1283C>T (p.Pro428Leu)	c.1283C>T (p.Pro428Leu)	c.1283C>T (p.Pro428Leu)	N/A
Genotype	R / R	0 / R	Not known[e] / R	0 / R	N/A
Predicted age of onset[f], months	24-36	83	61	75	Min 24-36; Max 83
Sibling , survival, months (status)	211 (alive)	147.8 (alive [g])	97 (alive)	104.3 (alive)	N/A
Baseline characteristics					
ARSA activity in PBMCs (nmol/mg/h)[h]	17.86	5.41	4.07	0.69	Min 0.69; max 17.86
Total GMFM score (%)	77.91	97.31	95.73	98.61	Min 77.91; max 97.31
GMFC-MLD level[f]	0	0	0	0	0
Symtomatic	NO	NO	NO	NO	
NCV Index	-10.25	-3.89	-3.07	-3.14	Min 3.14; Max -10.25
Total MRI score	0	3.5	4.25	3.75	Min 0; Max 4.25
Intelligence quotient					
Performance	90	127	124	115	Min 90; Max 127
Language	79	107	130	118	Min 79; Max 130
Busulfan conditioning					
Regimen	SMAC	MAC	MAC	MAC	SMAC 1; MAC 3
Exposure – total AUC (µg x h/L)	73,146	84,988	84,972	84,996	Min 73,146 Max 84,996
CD34+ HSPC dose (x10^6 cells/kg)	16.3	9	9.7	6.7	Min 6.7; Max 16.3
DP VCN**	2.5	3.1	5.6	5.4	Min 2.5; Max 56

a. Classified as an 'Intermediate' clinical variant, not matching the typical LI or EJ forms. Data for this subject have been pooled with EJ dataset for analysis (see Section 5.5.3 for additional details). Note: The current HGVS nomenclature for the homozygous mutation of the subject and his sibling was inadvertently identified as c.925G>A (p.Glu309Lys) in Listing 2.06; the correct HGVS nomenclature is c.931G>A (p.Gly311Ser).
b. Patient 13 had abnormal neurological exam findings at Baseline as outlined in Section 5.5.3.
c. Age at administration of Libmeldy-f.
d. Mutations are described according to standard HGVS nomenclature as described in Listing 2.06.
e. Not known refers to ARSA gene variant where there is insufficient data to assign severity to the allele.
f. For pre-symptomatic subjects, the predicted age of onset was calculated on the basis of the age at symptom onset in the subject's older sibling(s).
g. Symptomatic EJ subject who did not meet the eligibility criteria for Study 201222 and was treated with Libmeldy-f via Compassionate Use (GSK identifier 205029).
h. LLQ identified post interim study report as 25.79 nmol/mg/h for PBMCs.
Source: Listing 1.05, Listing 1.06, Listing 1.08, Listing 1.09, Listing 2.03, Listing 2.04, Listing 2.06, Listing 2.39, Listing 2.40, Listing 2.41, Listing 2.42, Listing 2.43, Listing 2.44, Listing 2.45, and Listing 2.51.
**Row or Colum added by Assessor

- Symptomatic EJ patients:

In the symptomatic EJ MLD patient group, the age of these 7 patients ranged from 35 to 66 months, with a normal GMFC-MLD level 1 in 6 patients and 0 in 1 patient. The total GMFM score at baseline ranged from 73,91% to 99,44%, the NCV Index ranged from -3,17 to -9,51 and the total MRI score from ,50 to 11.

The ARSA activity in PBMC ranged from 3,45 nmol/mg/h to 27,98 nmol/mg/h. At Baseline, ARSA activity levels in CSF in all presymptomatic MLD patients were below the LLOQ (0.0032 nmol/mg/h).

In 2 patients a SMAC busulfan conditioning regimen was used, and a MAC in the remaining 5 patients, with an AUC ranging from 70.506 µg*h/l to 88.310 µg*h/L. The number of transfused CD34+ HSPC ranged from 6,0*10^6/kg to 11,1 *10^6/kg.

Table 9: Early Symptomatic Early Juvenile Subgroup: Summary of Demographics and Baseline Characteristics in Study 201222

Subject Number	14	15	16	17	18	19	20
Demography and MLD diagnosis information							
Gender/Race/Age[a], months	Female/ White/59	Male/White/ 38	Female/White/88	Male/White/ 139	Female/White/84	Female/White/69	Female/White/71
ARSA mutation 1 (protein or splice site alteration[b])	c.383T>G (p.Leu128Arg)	c.1150G>A (p.Glu384Lys)	c.465+1G>A (splice donor)	c.465+1G>A (splice donor)	c.1175G>A (p.Arg392Gln)	c.465+1G>A (splice donor)	c.1283C>T (p.Pro428Leu)
ARSA mutation 2 (protein or splice site alteration[b])	c.1283C>T (p.Pro428Leu)	c.1223_1231del9 (p.Ser408_Thr410del)	c.1283C>T (p.Pro428Leu)	c.1283C>T (p.Pro428Leu)	c.1283C>T (p.Pro428Leu)	c.1283C>T (p.Pro428Leu)	c.929delG (p.Gly310Alafs)
Genotype	0 / R	R / 0	0 / R	0 / R	0 / R	0 / R	R / 0
Age at onset, months	54	35	66	64	56	60	65
Sibling survival, months (status)	NA	NA	NA	127.4 (alive)	NA	NA	NA
Baseline characteristics							
ARSA activity in PBMCs (nmol/mg/h)[c]	5.33	18.39	3.45	14.45	27.98	12.04	8.56
Total GMFM score (%)	73.91	87.06	99.44	86.06	86.76	81.24	78.04
GMFC-MLD level	1	1	0	1	1	1	1
NCV Index	-7.58	-4.73	-9.51	-9.27	-8.86	-7.93	-3.17
Total MRI score	11	0.5	8.75	4	12	10	10
Intelligence quotient							
Performance	50	100	119	115	89	82	87
Language	76	103	110	102	104	102	112
Busulfan conditioning							
Regimen	SMAC	SMAC	MAC	MAC	MAC	MAC	MAC
Exposure – total AUC (µg x h/L)	70,506	70,841	84,080	84,986	85,000	85,404	88,310
$CD34^+$ HSPC dose ($x10^6$ cells/kg)	9.9	7.1	6.6	8.9	10	6	11.1

a.Age at administration of OTL-200-f.

b.Mutations are described according to standard HGVS nomenclature as described in Listing 2.06.
c.LLQ identified post interim study report as 25.79 nmol/mg/h for PBMCs.
Source: Listing 1.05, Listing 1.06, Listing 1.08, Listing 1.09, Listing 2.03, Listing 2.04, Listing 2.06, Listing 2.39, Listing 2.40, Listing 2.41, Listing 2.42, Listing 2.43, Listing 2.44, Listing 2.45, and Listing 2.51.

OTL-220-f dosing information

The dose varied for each subject within the recommended dose range of 2 to 20 × 10^6 CD34+ HSPCs/kg, with a median volume infused of 20ml, with a median of 8,95 × 10^6 CD34+ HSPCs/kg, a median transduction efficiency of 93,0% and an median vector copy number of 3.200 VCN/cell.

Versie préCTG:

Table 23 Summary of Drug Product Characteristics for OTL-200-f from Bone Marrow Harvest (Safety Population)

		Late Infantile (N=9)	Early Juvenile (N=11)	Total (N=20)
Total volume infused (mL)	**N**	**9**	**11**	**20**
	Geometric mean	20.45	23.61	22.13
	%CVb	7.0	27.4	21.6
	95% CIs	19.38, 21.58	19.71, 28.29	20.03, 24.46
	Median	20.00	20.40	20.00
	Min, max	19.6, 24.5	20.0, 40.0	19.6, 40.0
Total nucleated cells ($x10^6$)	**N**	**9**	**11**	**20**
	Geometric mean	121.0	176.9	149.1
	%CVb	52.6	35.1	47.2
	95% CIs	82.7, 176.9	140.8, 222.4	120.9, 184.0
	Median	102.0	198.0	157.0
	Min, max	62, 245	84, 285	62, 285
Number of nucleated cells ($x10^6$/kg)	**N**	**9**	**11**	**20**
	Geometric mean	12.42	9.83	10.92
	%CVb	50.2	41.0	45.8
	95% CIs	8.63, 17.89	7.54, 12.81	8.90, 13.40
	Median	13.60	11.20	11.35
	Min, max	6.9, 23.8	4.2, 18.0	4.2, 23.8
Number of CD34+ HSPCs ($x10^6$/kg)	**N**	**9**	**11**	**20**
	Geometric mean	9.87	8.12	8.86
	%CVb	55.9	39.4	47.1
	95% CIs	6.61, 14.73	6.29, 10.48	7.19, 10.93
	Median	11.10	8.90	8.95
	Min, max	4.2, 19.5	3.8, 16.3	3.8, 19.5
Number of CFU-GM (/10^6 cells)	**N**	**9**	**11**	**20**
	Geometric mean	38,827.0	63530.0	50903.6
	%CVb	64.9	48.2	61.6
	95% CIs	24,615.9, 61,242.2	46720.4, 86387.5	39042.2, 66368.6
	Median	43,000.0	62700.0	57850.0

Study 205756:

This open-label, single-arm study in presymptomatic LI MLD or EJ MLD patients was performed with cryopreserved formulation and submitted in order to substantiate that the clinical efficacy between the fresh and cryopreserved formulation is similar.
According to the EPAR information and the CSR dd.04-10-2019, only 4 presymptomatic patients were included. As stated in the CSR, 6 patients were screened, but one patient was withdrawn as whole genome sequencing revealed that the patients wasn't affected by MLD and another patient was withdrawn because of motor milestones and neurological signs. Only 1 patient reached the year 1 study visit, 2 patients the 6 month study vist,3 the D90 study visit and 4 the D30 study visit, making it difficult to compare clinical efficacy and safety with the results of study 201222.

The mean age at administration of AA-c was 19,09±16,088 months (median 12,78 months, range 7,83 – 42,96), with 2 LI MLD and 2 EJ MLD patients. The baseline GMFM score was only 29,12% in 1 patient, between 52,80% and 55,57% in 2 patients and 94,94% in the 4th patient. The baseline MRI score was 0 in 2 patients, 0.25 in 1 and 0.50 in the 4th one.

A MAC busulfan conditioning regimen was used, with a dose ranging from 11,48 to 14,56 mg/kg and an AUC ranging from 79.965 to 80.058 µg*h/L).
The geometric mean cell dose was 16.68 × 106 CD34+ cells/kg (range 10.45 to 29.59 x 10^6 CD34+ cells/kg) with a geometric mean VCN in the DP of 4.20 VCN/cell (range 3.2 to 5.0 VCN/cell).

Table 5: Subject Disposition

Visit	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Screening	Yes	Yes	Yes	Yes
Baseline	Yes	Yes	Yes	Yes
Treatment	Yes	Yes	Yes	Yes
Day 30	Yes	Yes	Yes	Yes
Day 60	Yes	Yes	Yes	No
Day 90	Yes	Yes	Yes	No
Month 6	Yes	Yes[a]	No	No
Year 1	Yes	No	No	No

[a] Subject MLDCRY03 completed the Month 6 follow-up visit in his home country rather than at the study site. This remote visit was considered to be a protocol deviation; as per Protocol Version 4.0 (dated 24 August 2018), subjects were expected to attend all study follow-up visits at the clinical site for a minimum of 24 months after OTL-200-c administration.

Versie préCTG:

Table 7: Demographic and Baseline Characteristics by Subject

Subject ID	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Demography and MLD Diagnosis Information				
Gender/Race/Age at OTL-200-c Administration (months)	Male/White/13	Male/White/7	Male/White/12	Male/White/42
ARSA Mutation 1 (Protein or Splice Site Alteration[a])	C.370G>A	C.465+1G>A	C.931G>A	C.465+1G>A
ARSA Mutation 2 (Protein or Splice Site Alteration[a])	C.685-1G>A	C.1108-3C>G	C.931G>A	C.869G>A
Genotype	0/Not known[b]	0/0	R/R	0/R
Predicted Age of Onset, months[c]	12-15	13	42	58
Sibling ID	LDM149	Not enrolled	Not enrolled	Not enrolled
Baseline Characteristics				
Symptomatic Status At OTL-200-c Administration	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic
ARSA Activity in PBMCs (nmol/mg/h)	NR[d, e]	25.79[f]	25.79[f]	NR[d]
ARSA Activity in CD15+ Cells (nmol/mg/h)	5.76	34.73	28.18	25.79[f]
ARSA Activity in CD14+ Cells (nmol/mg/h)	26.39	27.18	25.79[f]	25.79[f]
Total GMFM Score (%)	52.80	29.12	55.57	94.94
GMFC-MLD Level[g]	NA	NA	NA	0
Total MRI Score[h]	0	0.50	0.25	0
Intelligence Quotient				
Language	97[i]	115[i]	94[i]	97[j]
Performance	95[i]	115[i]	100[i]	93[j]

[a] Mutations are described according to Human Genome Variation Society nomenclature.
[b] Not known refers to an *ARSA* gene variant for which there are insufficient data to assign severity to the allele. However the older sibling had the same genotype and LI phenotype, therefore this allele can likely be classified as "0".
[c] The predicted age of onset was calculated on the basis of the age at symptom onset in the subject's older sibling(s).

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

A total of 7 presymptomatic LI subjects and 2 presymptomatic EJ subjects were treated in EAP (expanded access programmes), all with the fresh cell formulation.

HE 205029 – CUP 206258

A total of 8 patients have been enrolled in these 2 programmes, with 3 presymptomatic LI-MLD patients in HE 205029 and 4 presymptomatic LI-MLD patients and 1 presymptomatic EJ patient in CUP 206258. All 8 patients passed the year 1 time point, 3 LI patients who completed the 2-year visit and 1 LI patient passed the year-3 visit.
The mean follow-up period was 1,738±0,7348 years (median 1,495 years, range 0,99 – 2,72 year). All the patients had older affected siblings, who were not enrolled in the SR-TIGET NHx study. The age of diagnosis ranged from 8,2 months to 14,2 months. All patients were GMFC-MLD level 0 with a MRI score of 0.

Table 16: Duration of Follow-up

	Late Infantile (N=7)	Early Juvenile (N=1)	Total (N=8)
Total Follow-up (Years)			
n	7	1	8
Mean	1.823	1.140	1.738
SD	0.7496	NC	0.7348
Median	1.500	1.140	1.495
Min	0.99	1.14	0.99
Max	2.72	1.14	2.72
Total Follow-up, n (%)			
n	7	1	8
<1 year	1 (14)[a]	0	1 (13)
1-2 years	3 (43)	1 (100)	4 (50)
2-3 years	3 (43)	0	3 (38)
3-4 years	0	0	0

Source: Table 14.1.1.2
NOTE: Duration of follow-up was defined as the time from administration of OTL-200-f to the last study visit completed prior to the data cut-off date (05 December 2018).
[a] Patient MLDCUP05 completed the 1-year follow-up visit at 0.99 year (Listing 16.2.4.5).
Max=maximum; Min=minimum; NC=not calculable; SD=standard deviation

Table 17: Demographic and baseline Characteristics

Patient ID	MLDHE01	MLDHE02	MLDHE03	MLDCUP01	MLDCUP02	MLDCUP03	MLDCUP04	MLDCUP05
Demography and MLD diagnosis information								
Gender/Race/ Age[a], months	Male/White/ 8.2	Male/White/ 9.6	Female/White /13.4	Female/White/ 14.2	Male/White/ 13.3	Male/Arabic/ 8.7	Male/White/ 11.4	Male/White/ 10.6
ARSA mutation 1 (protein or splice site alteration[b])	c.240dupC [C.234DUPC]	c.240dupC [C.234DUPC]	c.346C>T	c.418_419insC [C.418DUPC]	c.293C>T	c.371G>A	c.1283C>T	c.465+1G>A
ARSA mutation 2 (protein or splice site alteration[b])	c.465+1G>A [C.459+1G>A]	c.465+1G>A [C.459+1G>A]	c.677C>T	c.1210+1G>A	[C.225-20_854+39DELINS411_685-18INV]	c.929G>T	c.1010A>T	c.1108-1G>A
Genotype severity (mutation 1 /mutation 2)	0/0	0/0	0/R	0/0	0/0	UNK/0	R/0	0/0
Predicted age of onset, months[c]	15-18	15-18	18	15-18	15	15	41	15
Sibling ID[d]	MLDHE02 Another older sibling not enrolled in SR-TIGET NHX Study (204949)[e]	MLDHE01 Another older sibling not enrolled in SR-TIGET NHX Study (204949)	Not enrolled in SR-TIGET NHX Study (204949)	LDM148[f]	Not enrolled in SR-TIGET NHX Study (204949) [g]	Not enrolled in SR-TIGET NHX Study (204949) [g]	Not enrolled in SR-TIGET NHX Study (204949)	Not enrolled in SR-TIGET NHX Study (204949)
Subtype	Late infantile	Late infantile	Late infantile	Late infantile	Late infantile	Late infantile	Early juvenile	Late infantile
Patient identified in publications	(Calbi, 2018) referred to as Patient 1	(Calbi, 2018) referred to as Patient 2						

Table 17: Demographic and baseline Characteristics (Continued)

Patient ID	MLDHE01	MLDHE02	MLDHE03	MLDCUP01	MLDCUP02	MLDCUP03	MLDCUP04	MLDCUP05
baseline characteristics								
Symptom status at OTL-200-f administration	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic	Pre-symptomatic
ARSA activity in PBMCs[h] (nmol/mg/h)	25.79	25.79	25.79	25.79	25.79	25.79	53.13	28.34
Total GMFM score (%)	13.41	16.1	61.31	54.93	61.86	29.81	56.14	53.14
GMFC-MLD level[i]	NA	NA	NA	NA	NA	NA	NA	NA
NCV Index[j]	-0.69	0.55	-1.36	-6.01[k]	-5.52	-3.99	1.12[k]	NA[l]
Total MRI score	0	0	0	0	0	0	0	0
Intelligence quotient								
Performance	80	80	110	95	95	100	105	95
Language	103	100	118	127	103	121	94	94

A SMAC regimen was given to 3 patients and 5 patients received a MAC regimen. The geometric mean AUC of busulfan was 67,972.92 h*ng/mL (95% CI: 53,740.27, 85,974.97) for patients who received a SMAC regimen and 82,315.33 (95% CI:

77,833.82, 87,054.88) for patients who received a MAC regimen. Target AUC for SMAC was 67,200 h*ng/mL (target range: 58,800 to 78,400 h*ng/mL) and for MAC was 85,000 h*ng/mL (target range: 76,500 to 93,500 h*ng/mL).

Table 19: Summary of Areas Under the Curve (AUC) for Busulfan

Parameter	Summary Statistics	SMAC Regimen (N=3)	MAC Regimen (N=5)	Total (N=8)
Total AUC (h*ng/mL)	n	3	5	8
	Geometric mean	67972.92	82315.33	76612.82
	95% CI	53740.27, 85974.97	77833.82, 87054.88	69512.18, 84438.78
	SD (logs)	0.095	0.045	0.116
	Arithmetic mean	68179.00	82382.80	77056.38
	95% CI	51799.19, 84558.81	77718.32, 87047.28	69839.14, 84273.61
	SD	6593.760	3756.637	8632.844
	%CVb	9.5	4.5	11.7
	Median	65411.50	79964.00	79632.00
	Min	63420.0	79324.0	63420.0
	Max	75705.5	87741.0	87741.0

Source: Table 14.1.4.2
%CVb=coefficient of variation between patients; AUC=area under the curve; CI=confidence interval; MAC=myeloablative conditioning; max=maximum; min=minimum; SD=standard deviation; SMAC=sub-myeloablative conditioning

The AA dose (fresh formulation) varied for each patient within the recommended dose range of 2 to 20 × 10^6 CD34+ cells/kg for patients in HE 205029 and 2 to 30 × 10^6 CD34+ cells/kg for patients in CUP 206258. A median of 14,20 × 10^6 CD34+ cells/kg were given (range 10,5 – 25,9).
The median transduction efficiency was 97,0% (range 84 -100), with a median vector copy number of 7,30 VCN/cell (range 4,8 – 8,7).

Table 22: Drug Product for Gene Therapy from Peripheral Blood Source (Patient MLDCUP04)

Parameter	Early Juvenile (N=1)
Total volume infused (mL)	24.50
Total nucleated cells (x10^6)	186.0
Number of nucleated cells (x10^6/kg)	17.90
Number of $CD34^+$ HSPCs (x10^6/kg)	17.60
Number of CFU-GM (/10^6 cells)	33700
Transduction efficiency (CFU-C) (%)	81.0
Vector copy number (VCN/cell)	3.40

Source: Table 14.1.3.1
CFU-C=colony-forming units in culture; CFU-GM=colony-forming units in culture-granulocyte, monocyte; HSPCs=hematopoietic stem and progenitor cells; VCN=vector copy number

<u>CUP 207394:</u>

In this compassionate use program 1 patient aged 91,8 months (7,65 years) with early symptomatic EJ MLD was recruited (symptomatic for 8 months), exceeding the protocol inclusion criteria of study 201222 (symptoms ≤6 months for EJ patients).

The patient received a busulfan SMAC regimen of 14 doses, with a busulfan AUC0-t for patient MLD-C02 ranged from 4.802 to 6.114 ng*h/mL, and total AUC was 75.096 ng*h/mL.

A total of 6.7 CD34+ *10^6/kg were infused, with a transduction efficiency of 80% and a vector copy number of 2,3 VCN/cell

b) Primary outcome

Study 201222:

The co-primary endpoint was the ARSA activity in PBMC (with a significant (≥2 SD) increase in residual ARSA activity at two years as compared to pre-treatment values, and an improvement of 10% of the total GMFM-88 score in treated patients compared to the historical cohort at 2 years.

1. Late infantile MLD

Patient survival [crucial]

All treated patients were alive up to 3 years based on the data provided in the CSR.

ARSA activity in PBMC [important]

The ARSA activity in PBMC in the LI-MLD patients increased from a baseline value of 25,9 nmol/mg/h (95%CI 12,8 – 52,5) to a mean of 223,3 nmol/mg/h (95%CI 107,3 – 464,7) at year 2, which is a 8,6-fold increase (95%CI 3,9 – 19,2, p<0.001). At year 3 this was a mean of 429,3 nmol/mg/g (95%CI 211,8 – 869,9, p<0,001).

Table 25 ARSA Analysis in Total Peripheral Mononuclear Blood Cells in Comparison to Baseline (ITT Population)

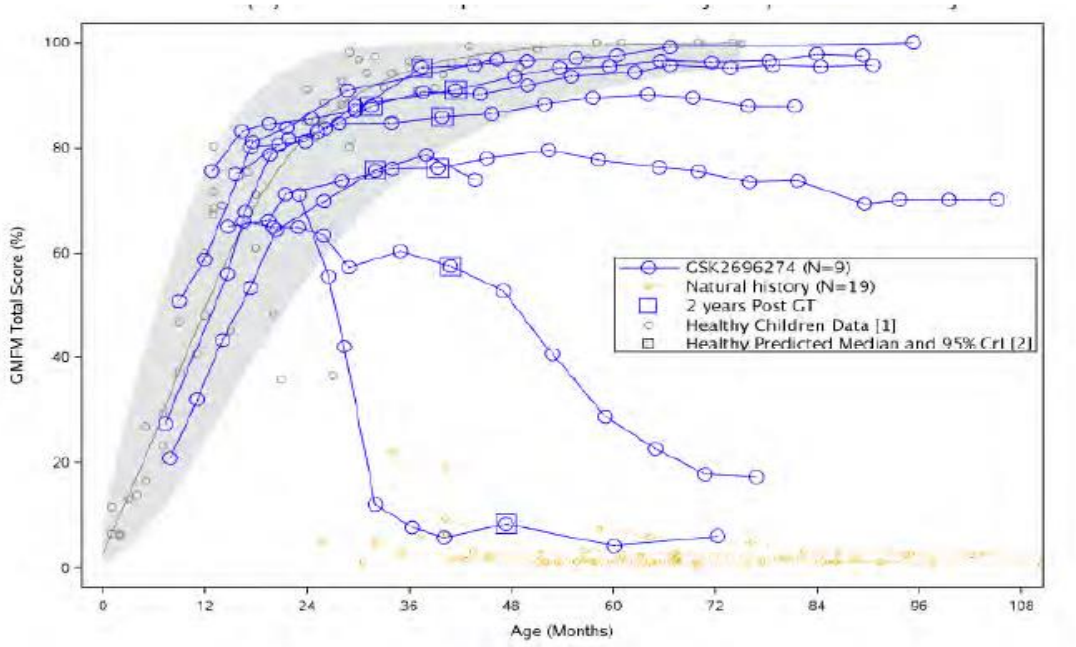
Disease Subtype	Analysis Visit	N	No. Imputed	Adjusted Mean (nmol/mg/h)	95% CI of Adjusted Mean (nmol/mg/h)	Ratio[a]	95% CI of Ratio	P-value
Late infantile (n=9)	**Baseline (derived)**	**8**	**8**	**25.9**	**(12.8, 52.5)**	**NA**	**NA**	**NA**
	Month 3	8	0	264.1	(130.3, 534.9)	10.2	(4.1, 25.2)	<0.001
	Month 6	6	0	274.5	(126.3, 596.8)	10.6	(4.2, 26.5)	<0.001
	Year 1	8	0	248.9	(122.8, 504.3)	9.6	(4.6, 20.1)	<0.001
	Year 1.5	7	0	581.3	(279.0, 1211.3)	22.4	(12.1, 41.5)	<0.001
	Year 2	7	1	223.3	(107.3, 464.7)	8.6	(3.9, 19.2)	<0.001
	Year 2.5	6	0	426.0	(196.4, 924.1)	16.4	(7.4, 36.6)	<0.001
	Year 3	8	1	429.3	(211.8, 869.9)	16.6	(7.9, 34.8)	<0.001
Early juvenile (n=11)	**Baseline (derived)**	**11**	**10**	**25.9**	**(14.3, 47.0)**	**NA**	**NA**	**NA**
	Month 3	11	0	151.4	(83.5, 274.5)	5.8	(2.7, 12.5)	<0.001
	Month 6	9	1	98.8	(51.5, 189.5)	3.8	(1.8, 8.3)	0.001
	Year 1	8	0	110.4	(56.5, 215.6)	4.3	(2.1, 8.5)	<0.001
	Year 1.5	9	1	98.5	(52.2, 185.7)	3.8	(2.2, 6.5)	<0.001
	Year 2	8	0	188.5	(97.2, 365.4)	7.3	(3.6, 14.9)	<0.001
	Year 2.5	8	0	165.3	(84.7, 322.9)	6.4	(3.2, 12.7)	<0.001
	Year 3	8	0	237.8	(120.8, 468.3)	9.2	(4.5, 18.6)	<0.001

a. Ratio in adjusted LS means are shown (Visit/Baseline). The analysis was carried out on the log scale and back transformed.
Note: The analysis method was MMRM adjusted for Visit, Base, Base*Visit, Disease Subtype and Disease Subtype*Visit, and Toeplitz correlation matrix was used.
Note: Errors were identified in the eCRF (personal communication received 01 October 2018) pertaining to ARSA activity. Subject MLD03 ARSA activity in PMBCs at Year 2.5 was noted incorrectly at 107.93 nmol/mg/h; correct value was 1071.93 nmol/mg/h. This error was not noted in the previous Interim CSR 1.
Source: Table 4.14.

GMFM-88 score [crucial]

At year 2 post treatment, mean total GMFM-88 score in the Libmeldy treated LI subjects was 72.5% compared to 7.4% for the NHx subjects (Difference 65.1 points, 95%CI 41.6; 88.6), p<0.001), exceeding the predefined 10% difference. At year 3 the LS mean difference was still 71,5% (95%CI 46,9 – 96,0%, p<0,001).

Figure 12 **Gross Motor Function Measure Total Score (%) Over Time, Late Infantile Subgroup With Comparison to TIGET NHx Data (All Subjects Population)**

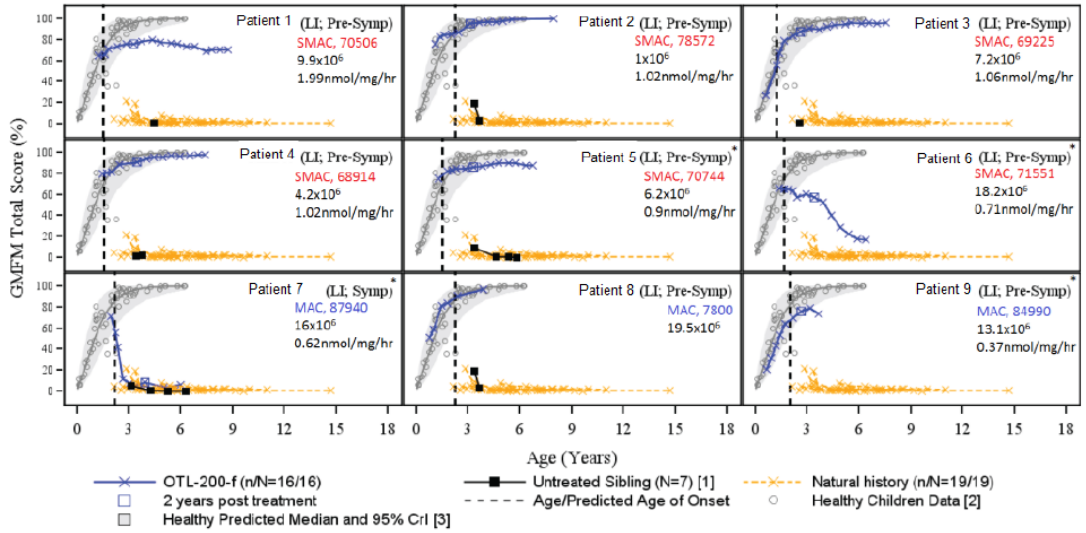


[1] Healthy children data from Dr. Palisano and colleagues, who provided access to the anonymous age and GMFM-88 data on 60 subjects in the "No CP" group as reported in [Palisano, 1997].
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.01.

With the exception of 2 patients with a steep decline, and 3 patients with a suboptimal plateau, the GMFM-88 evolution of the treated LI-MLD patients was within the range of the healthy predicted median (and 95%CI) and well above the evolution of the TIGET NHx reference patients.

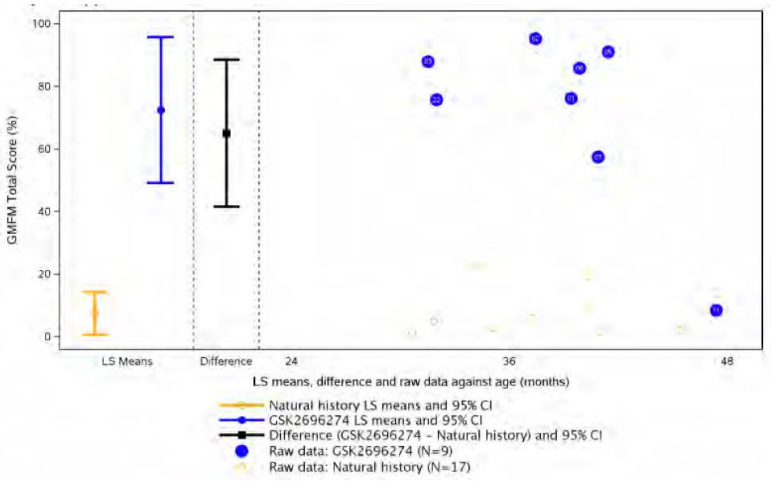
For one of the two patients with a deteriorating GMFM-88 evolution, this patient had initially a 66% score which was normal for age, but showed a gradual deterioration over the course of the study and lost the ability to walk by year 3. At year five the GMFM-88 was about 17% and still higher compared to the reference group. The other patient with a deteriorating evolution was treated just after onset of the MLD disease, and showed a rapidly progressive phase of the disease, with a GMFM score of 71% at baseline dropping to 8% at year 1 and 6% at year 4.

Figure 13: Late Infantile Subgroup: Panel Plot of Gross Motor Function Measure Total Score (%) Over Time Compared to TIGET NHx Data**



[1] Untreated sibling data is a subset of NHx data.
[2] If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects the range given in the eCRF.
[3] Healthy children data from Dr. Palisano and colleagues, who provided access to the anonymous age and GMFM-88 data on 60 subjects in the "No CP" group as reported in (Palisano, 1997).
**figure adapted by Assessor to include:
- Dose (CD 34+ cells/kg)
- ARSA CSF activity levels indicated measured 2 years post treatment (primary endpoint marked by applicant).
*neurological scores hinting at early progression (Patient 1, 5, 6, 9)
- busulfan conditioning: SMAC and MAC treatment indicated with corresponding AUCs.
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to Libmeldy-f.

Figure 14 Gross Motor Function Measure Total Score (%) at Year 2 for Late Infantile Subjects in the Primary Analysis With Comparison to TIGET NHx Data (Matched Analysis Set)



Analysis visit (Year 2) is the visit from the OTL-200-f-treated subjects used in the ANCOVA analysis. TIGET NHx Study participants were age and disease subtype matched to the OTL-200-f-treated subjects.
Note: LS means and difference were from an analysis using an ANCOVA adjusted for age and treatment.
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.05.

2. Asymptomatic EJ MLD

Patient survival [crucial]

All treated patients were alive at 3 year follow-up.

ARSA activity in PBMC [important]

The ARSA activity in PBMC in the EJ-MLD patients increased from a baseline value of 25,9 nmol/mg/h (95%CI 14,3 – 47,0) to a mean of 188,5 nmol/mg/h (95%CI 97,2 – 365,4) at year 2 , which is a 7,3-fold increase (95%CI 3,6 – 14,9, p<0.001). At year 3 this was 237,8 nmol/mg/h (95%CI 120,8 – 468,3, p<0,001). The CSR does not differentiate the data between presymptomatic EJ and early symptomatic EJ patients.

Table 25 ARSA Analysis in Total Peripheral Mononuclear Blood Cells in Comparison to Baseline (ITT Population)

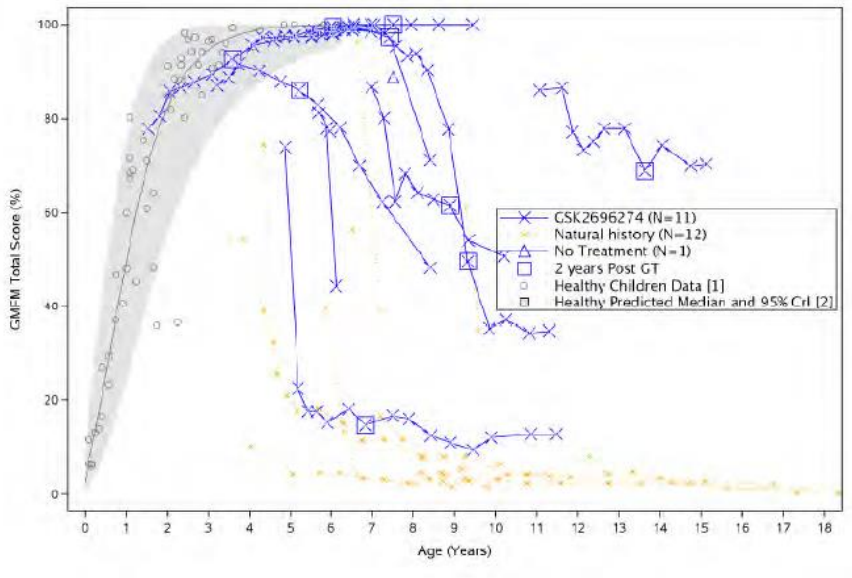
Disease Subtype	Analysis Visit	N	No. Imputed	Adjusted Mean (nmol/mg/h)	95% CI of Adjusted Mean (nmol/mg/h)	Ratio[a]	95% CI of Ratio	P-value
Late infantile (n=9)	**Baseline (derived)**	**8**	**8**	**25.9**	**(12.8, 52.5)**	**NA**	**NA**	**NA**
	Month 3	8	0	264.1	(130.3, 534.9)	10.2	(4.1, 25.2)	<0.001
	Month 6	6	0	274.5	(126.3, 596.8)	10.6	(4.2, 26.5)	<0.001
	Year 1	8	0	248.9	(122.8, 504.3)	9.6	(4.6, 20.1)	<0.001
	Year 1.5	7	0	581.3	(279.0, 1211.3)	22.4	(12.1, 41.5)	<0.001
	Year 2	7	1	223.3	(107.3, 464.7)	8.6	(3.9, 19.2)	<0.001
	Year 2.5	6	0	426.0	(196.4, 924.1)	16.4	(7.4, 36.6)	<0.001
	Year 3	8	1	429.3	(211.8, 869.9)	16.6	(7.9, 34.8)	<0.001
Early juvenile (n=11)	**Baseline (derived)**	**11**	**10**	**25.9**	**(14.3, 47.0)**	**NA**	**NA**	**NA**
	Month 3	11	0	151.4	(83.5, 274.5)	5.8	(2.7, 12.5)	<0.001
	Month 6	9	1	98.8	(51.5, 189.5)	3.8	(1.8, 8.3)	0.001
	Year 1	8	0	110.4	(56.5, 215.6)	4.3	(2.1, 8.5)	<0.001
	Year 1.5	9	1	98.5	(52.2, 185.7)	3.8	(2.2, 6.5)	<0.001
	Year 2	8	0	188.5	(97.2, 365.4)	7.3	(3.6, 14.9)	<0.001
	Year 2.5	8	0	165.3	(84.7, 322.9)	6.4	(3.2, 12.7)	<0.001
	Year 3	8	0	237.8	(120.8, 468.3)	9.2	(4.5, 18.6)	<0.001

a. Ratio in adjusted LS means are shown (Visit/Baseline). The analysis was carried out on the log scale and back transformed.
Note: The analysis method was MMRM adjusted for Visit, Base, Base*Visit, Disease Subtype and Disease Subtype*Visit, and Toeplitz correlation matrix was used.
Note: Errors were identified in the eCRF (personal communication received 01 October 2018) pertaining to ARSA activity. Subject MLD03 ARSA activity in PMBCs at Year 2.5 was noted incorrectly at 107.93 nmol/mg/h; correct value was 1071.93 nmol/mg/h. This error was not noted in the previous Interim CSR 1.
Source: Table 4.14.

GMFM score [crucial]

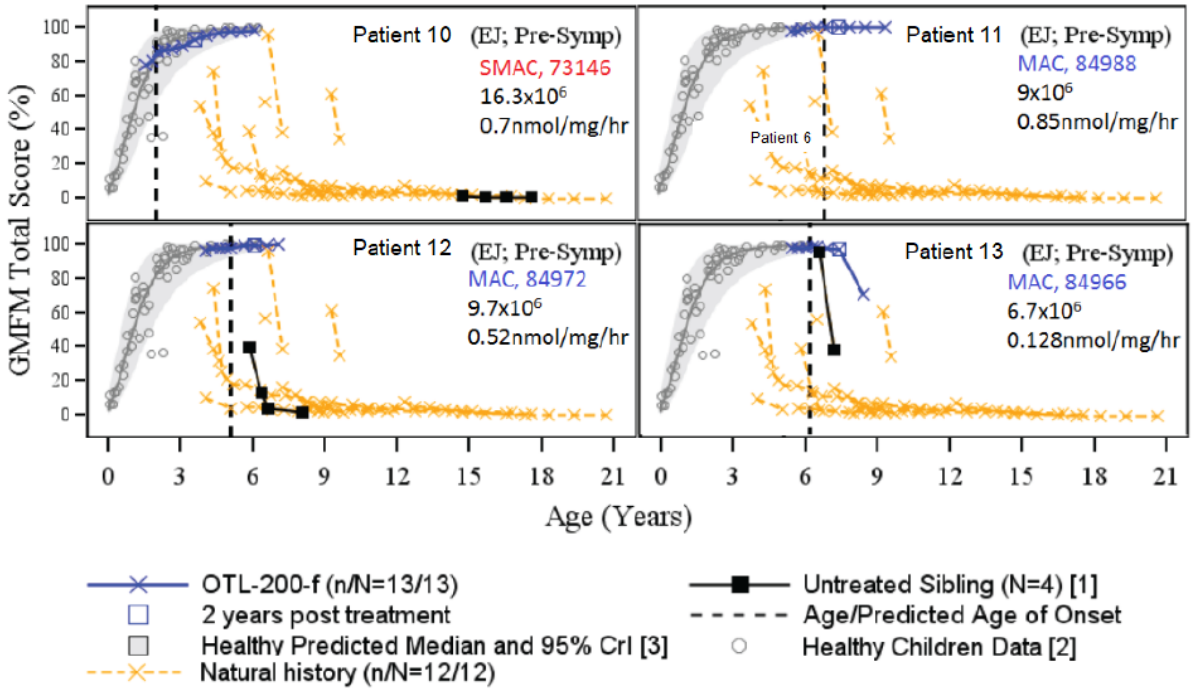
For the 4 presymptomatic EJ MLD, the adjusted LS mean GMFM-88 total score at year 2 post treatment was 96.7%. Difference from the NHx group was 52.4% (95% CI 25.1; 79.6, p=0.008) at year 2. The evolution in 3 of these patients was in line with the expected healthy age comparators, but in 1 patient the GMFM scores were between 97% and 99% during the first 2 years, but than declined to only 71% at year 3.

Figure 16 **Gross Motor Function Measure Total Score (%) Over Time, Early Juvenile Subgroup With Comparison to TIGET NHx Data (All Subjects Population)**



The open blue triangle denotes the Baseline GMFM total score for Subject MLD18, who was withdrawn from the study prior to treatment.
[1] Healthy children data from Dr. Palisano and colleagues, who provided access to the anonymous age and GMFM-88 data on 60 subjects in the "No CP" group as reported in [Palisano, 1997].
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.03.

Figure 14: **Pre-Symptomatic Early Juvenile subgroup: Panel Plot of Gross Motor Function Measure Total Score (%) Over Time Compared to TIGET NHx Data***



[1] Untreated sibling data is a subset of NHx data.
[2] If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects the range given in the eCRF.

3. Early symptomatic EJ MLD

Patient survival [crucial]

During the follow-up period 2 of the 7 patients early symptomatic AA-f treated patients died due to disease progression.

ARSA activity in PBMC [important]

The ARSA activity in PBMC in the EJ-MLD patients increased from a baseline value of 25,9 nmol/mg/h (95%CI 14,3 – 47,0) to a mean of 188,5 nmol/mg/h (95%CI 97,2 – 365,4), which is a 7,3-fold increase (95%CI 3,6 – 14,9, p<0.001). At year 3 this was 237,8 nmol/mg/h (95%CI 120,8 – 468,3, p<0,001).
The CSR does not differentiate the data between presymptomatic EJ and early symptomatic EJ patients.

Table 25 ARSA Analysis in Total Peripheral Mononuclear Blood Cells in Comparison to Baseline (ITT Population)

Disease Subtype	Analysis Visit	N	No. Imputed	Adjusted Mean (nmol/mg/h)	95% CI of Adjusted Mean (nmol/mg/h)	Ratio[a]	95% CI of Ratio	P-value
Late infantile (n=9)	**Baseline (derived)**	**8**	**8**	**25.9**	**(12.8, 52.5)**	**NA**	**NA**	**NA**
	Month 3	8	0	264.1	(130.3, 534.9)	10.2	(4.1, 25.2)	<0.001
	Month 6	6	0	274.5	(126.3, 596.8)	10.6	(4.2, 26.5)	<0.001
	Year 1	8	0	248.9	(122.8, 504.3)	9.6	(4.6, 20.1)	<0.001
	Year 1.5	7	0	581.3	(279.0, 1211.3)	22.4	(12.1, 41.5)	<0.001
	Year 2	7	1	223.3	(107.3, 464.7)	8.6	(3.9, 19.2)	<0.001
	Year 2.5	6	0	426.0	(196.4, 924.1)	16.4	(7.4, 36.6)	<0.001
	Year 3	8	1	429.3	(211.8, 869.9)	16.6	(7.9, 34.8)	<0.001
Early juvenile (n=11)	**Baseline (derived)**	**11**	**10**	**25.9**	**(14.3, 47.0)**	**NA**	**NA**	**NA**
	Month 3	11	0	151.4	(83.5, 274.5)	5.8	(2.7, 12.5)	<0.001
	Month 6	9	1	98.8	(51.5, 189.5)	3.8	(1.8, 8.3)	0.001
	Year 1	8	0	110.4	(56.5, 215.6)	4.3	(2.1, 8.5)	<0.001
	Year 1.5	9	1	98.5	(52.2, 185.7)	3.8	(2.2, 6.5)	<0.001
	Year 2	8	0	188.5	(97.2, 365.4)	7.3	(3.6, 14.9)	<0.001
	Year 2.5	8	0	165.3	(84.7, 322.9)	6.4	(3.2, 12.7)	<0.001
	Year 3	8	0	237.8	(120.8, 468.3)	9.2	(4.5, 18.6)	<0.001

a. Ratio in adjusted LS means are shown (Visit/Baseline). The analysis was carried out on the log scale and back transformed.
Note: The analysis method was MMRM adjusted for Visit, Base, Base*Visit, Disease Subtype and Disease Subtype*Visit, and Toeplitz correlation matrix was used.
Note: Errors were identified in the eCRF (personal communication received 01 October 2018) pertaining to ARSA activity. Subject MLD03 ARSA activity in PMBCs at Year 2.5 was noted incorrectly at 107.93 nmol/mg/h; correct value was 1071.93 nmol/mg/h. This error was not noted in the previous Interim CSR 1.
Source: Table 4.14.

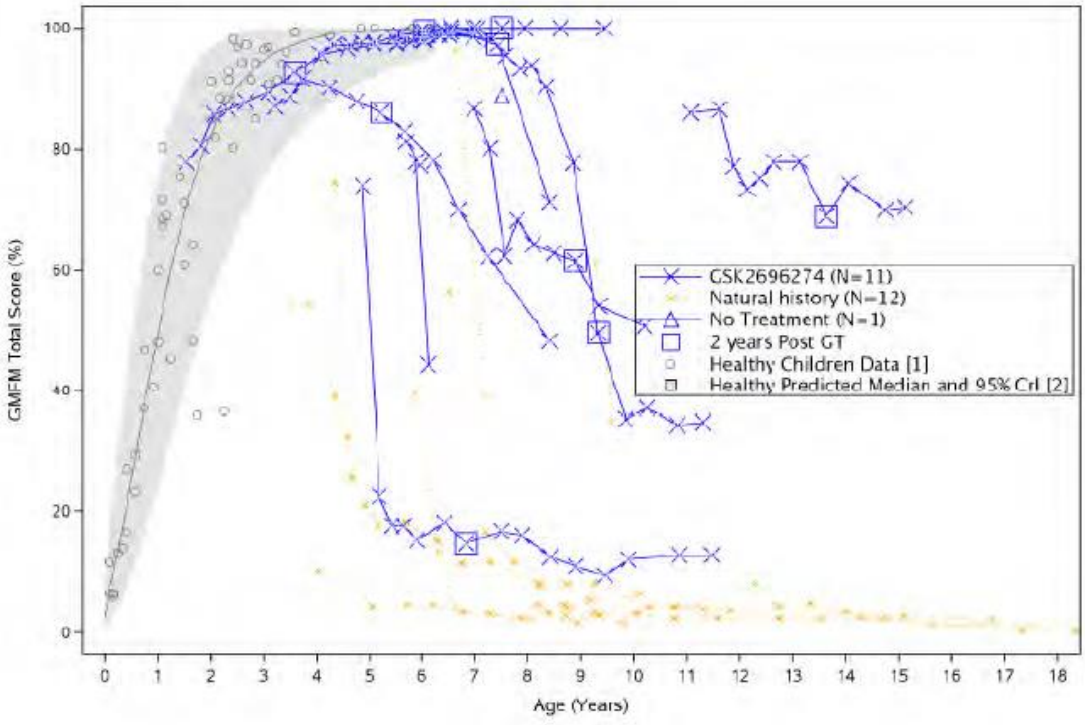
GMFM-88 score [crucial]

For the early symptomatic EJ MLD, the clinical results of the effectiveness of the gene-therapy are less pronounced. The adjusted LS mean GMFM total score at year 2 post treatment was 60.7%, without a statistically significant difference from the NHx group of only 28.7% (95% CI -14.1; 71.5, p=0.35) at year 2. In 5 of these patients the baseline GMFM score were initially below the normal range, and these patients experienced either a rapid or a slower decline in GMFM after the gene-therapy. For most of the patients the GMFM score still was above the reference TIGET NHx according to the last measurement, but given the rate of decline this will most likely be comparable rather soon.

The treatment effect in the early symptomatic EJ MLD patient group remained being not statistically significant at year 3, with a treatment effect difference of 43.9% (59.8% vs. 15.9%; p=0.054).

For the overall EJ MLD patients group, the LS mean GMFM total score (%) at year 2 was 76.5% for treated patients versus 36.6% in the untreated EJ TIGET NHx reference group, a mean difference of 39.8% (95% CI: 9.6%, 70.1%), exceeding the minimum threshold for efficacy (10%) predefined in the protocol and considered clinically meaningful.
The treatment difference (AA-f-treated EJ patients minus untreated EJ TIGET NHx Study patients) of 39.8% was of borderline statistical significance (p=0.026) when tested against the null hypothesis that the difference was ≤10% , at a 1-sided alpha level of 0.025.

Figure 16 Gross Motor Function Measure Total Score (%) Over Time, Early Juvenile Subgroup With Comparison to TIGET NHx Data (All Subjects Population)



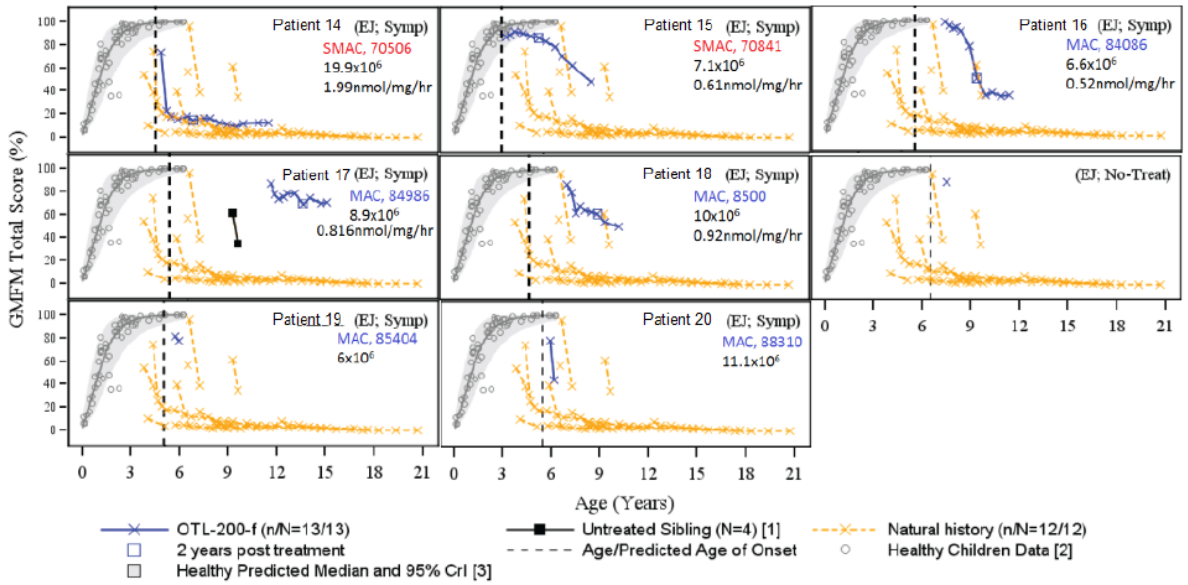
The open blue triangle denotes the Baseline GMFM total score for Subject MLD18, who was withdrawn from the study prior to treatment.

[1] Healthy children data from Dr. Palisano and colleagues, who provided access to the anonymous age and GMFM-88 data on 60 subjects in the "No CP" group as reported in [Palisano, 1997].

Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.

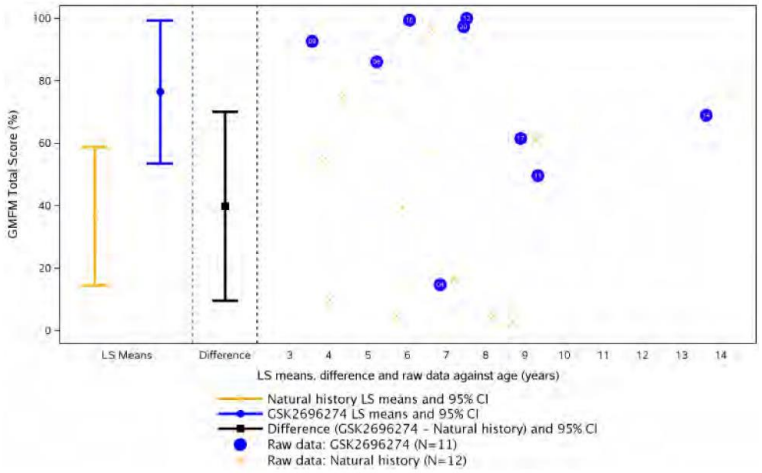
Source: Figure 4.03.

Figure 15: Early-Symptomatic Early Juvenile Subgroup: Panel Plot of Gross Motor Function Measure Total Score (%) Over Time Compared to TIGET NHx Data*



[1] Untreated sibling data is a subset of NHx data.
[2] If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects the range given in the eCRF.
[3] Healthy children data from Dr. Palisano and colleagues, who provided access to the anonymous age and GMFM-88 data on 60 subjects in the "No CP" group as reported in (Palisano, 1997).
The triangle included in all panels represent the baseline value measured for one subject who was not treated due to rapid disease progression.
*figure adapted by Assessor to include:
- Dose (CD 34+ cells/kg)
- ARSA CSF activity levels indicated measured 2 years post treatment (primary endpoint marked by applicant).
- busulfan conditioning: SMAC and MAC treatment indicated with corresponding AUCs
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to Libmeldy-f.

Figure 18 Gross Motor Function Measure Total Score (%) at Year 2 for Early Juvenile Subjects in the Primary Analysis With Comparison to TIGET NHx Data (Matched Analysis Set)



Analysis visit (Year 2) is the visit from the OTL-200-f-treated subjects used in the ANCOVA. TIGET NHx Study participants were age and disease subtype matched to the OTL-200-f-treated subjects.
Note: LS means and difference were from an analysis using an ANCOVA adjusted for age and treatment.
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.05.

Study 205756:

Patient survival [crucial]

All treated patients were alive at 1 year follow-up.

ARSA in PBMC [important]

Post-treatment, all patients with available data had ARSA values within or above the normal range (normal range=30.56-198.02 nmol/mg/h) at month 1 and above the normal range at month 2. Levels above the normal range were maintained at month 3, 6, and year 1 for the only patients with available data.
Due to the very limited number of patient(s) providing data and the short follow-up period, a valid comparison with the previously used fresh formulation is not feasible.

Table 15: ARSA Activity in Total PBMCs (nmol/mg/h)

Assessment	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Baseline	NR[a]	25.79[b]	25.79[b]	25.79[ab]
Month 1	161.73	589.09	157.48	590.8
Month 2	420.47	2768.65	1158.33	NA
Month 3	560.85	3398.47	1119.05	
Month 6	1616.69	2373.02	NA	
Year 1	1930.56	NA		

[a] ARSA activity in total PBMCs was not measured at Baseline for Subjects MLDCRY02 and MLDCRY06 due to insufficient material (protocol deviations). The Screening level for Subject MLDCRY06 was 25.79 nmol/mg/h and is provided in this table as the Baseline value.
[b] Values were imputed at the lower limit of quantification.
Source: Listing 16.2.6.1
Abbreviations: ARSA=arylsulfatase A; h=hour; NA=not assessed (subject had not yet completed this follow-up assessment); NR=not reported; PBMCs=peripheral blood mononuclear cells

The company provided some updated sheets (appendix A) regarding the ARSA activity in PBMCs:

For patient 1 the activity dropped from 1.930,56 nmol/mg/h at year 1 to 1.327,38 nmol/mg/h at 1,5 year.
For patient 2 the activity increased from 2.373,02 nmol/mg/h at month 6 to 3.767,86 nmol/mg/h at 1 year.
For patient 3 the activity increased from 1.119,05 nmol/mg/h at month 3 to 1.529,76 nmol/mg/h at month 6.
For patient 4 the activity increased from 590,8 nmol/mg/h at month 1 to 1.019,84 nmol/mg/h at month 6.

GMFM-88 [crucial]

Preliminary data on GMFM total score showed that gross motor function for all 4 patients was within the range of gross motor function observed in a healthy cohort of children from of similar chronological age (grey shade), and remained so at the time of last evaluation (1 year of 1,5 years).

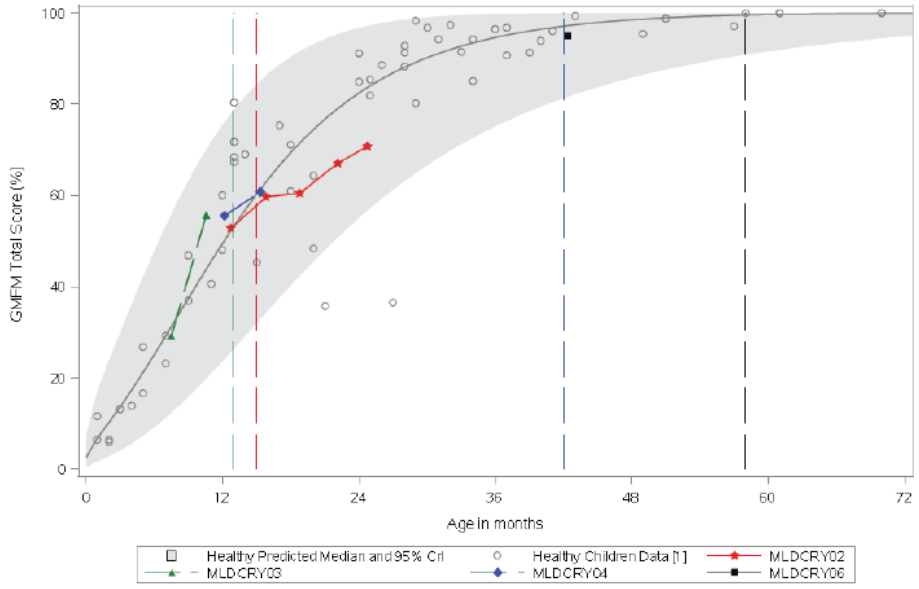
The company provided some updated sheets (appendix A) regarding the GMFM-88 values:

For patient 1 the GMFM-88 score was 52,80 at baseline and increased to 78,34 at 1,5 year.
For patient 2 the GMFM-88 score was 29,12 at baseline and increased to 72,21 at 1 year.
For patient 3 the GMFM-88 score was 55,57 at baseline and increased to 79,44 at 1 year.
For patient 4 the GMFM-88 score was 95,73 at baseline and stayed stable 95,73 at month 9.

In an updated table, we see the reporting on GMFM-88 evolution of all patients starting in the healthy predicted median range, and following this evolution during the observation period of maximum 1,5 years.

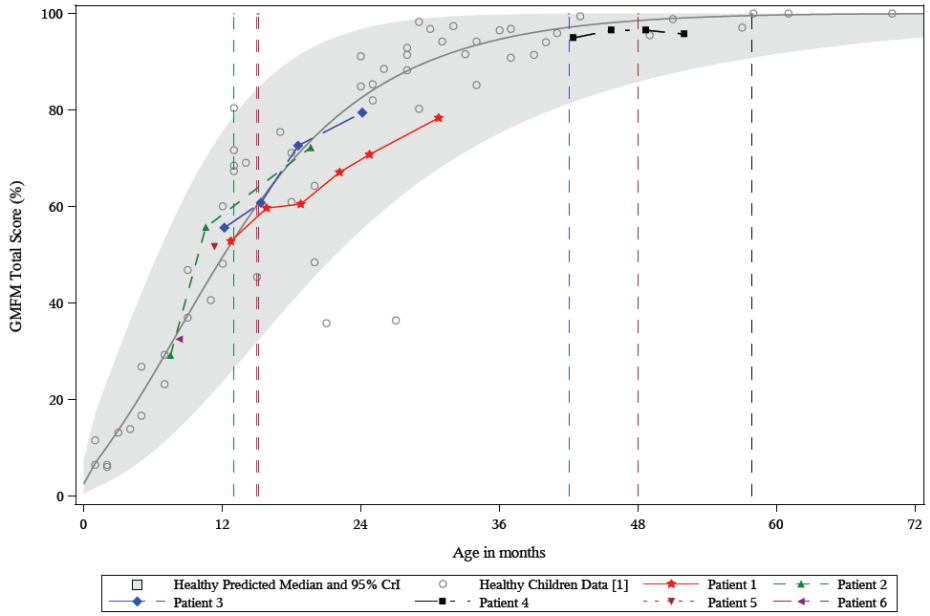
It should be noted that only presymptomatic patients (3 LI and 1 EJ) are included in the analysis of this study, starting at an early age of 12,2 months, 6,5 months, 10,2 months respectively for the LI patients and at the age of 41,5 months for the EJ patient.

Figure 6: Gross Motor Function Measure Total Scores



Source: Figure 14.2.1.1
Abbreviation: GMFM-Gross Motor Function Measure
Note: Vertical dotted lines represent expected age of disease onset.

Figure 1.1.100
Plot of GMFM Total Score (%)



[1] Healthy children data is from Dr. Palisano and colleagues, who provided access to the anonymous age and GMFM88 data on 60 subjects in the 'No CP' group as reported in Palisano et al. (1997) Development and reliability of a system to classify gross motor function in children with celebral palsy.
Data cut-off is 2019-11-15
Vertical lines show predicted age of MLD onset.
Program: neuromet/mld/meta/maccess/tfl/intmain/program/F_GMFM.sas
Output: F_GMFM (2021-01-19 15:51). Source Data: PRGMFMRW PRGMFM

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

HE 205029 – CUP 206258

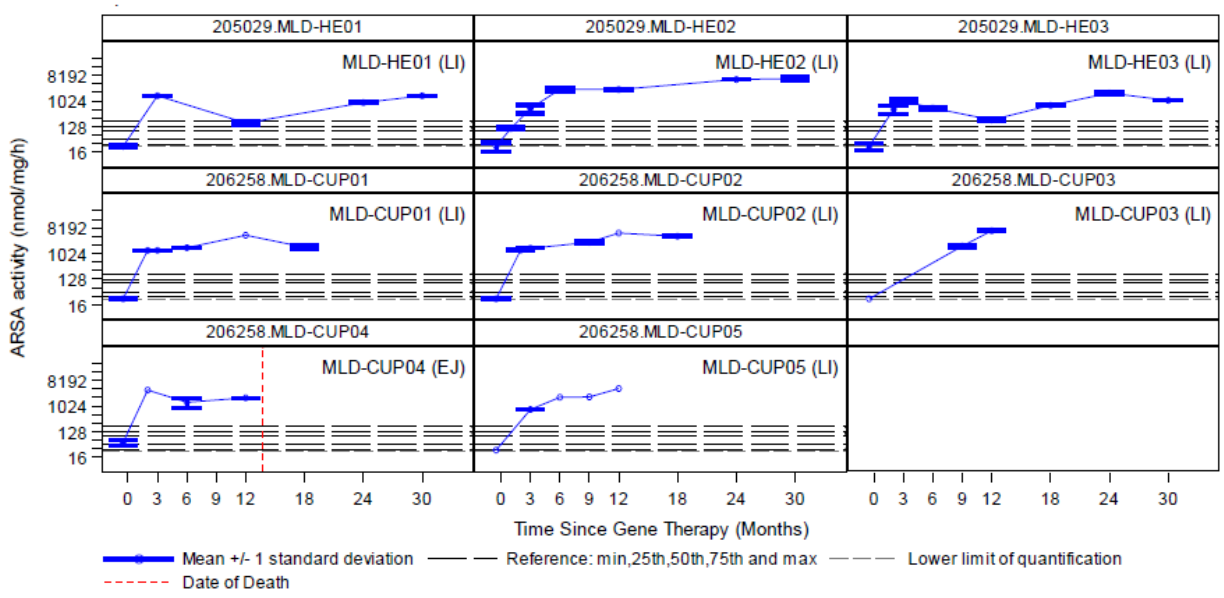
Patient survival [crucial]

One treated patient died and 7 patients were alive at follow-up.

ARSA in PBMC [important]

The mean ARSA activity levels in total PBMCs generally increased after treatment with AA-f, reaching the normal range by 3 months after treatment with AA-f in all patients with available data (mean: 1.057,9 nmol/mg/h at Month 3; n=6) and remaining stable within or above the normal range throughout the follow-up period. At Year 1, a 64-fold increase (95% CI: 19-fold, 214-fold; n=8) in ARSA activity in PBMCs was observed compared with baseline levels.
The mean value at Year 1 (1830.1 nmol/mg/h) was 9.24-fold higher than the upper limit of the ARSA activity normal range (198.02 nmol/mg/h).

Figure 11: Panel Plot of ARSA Activity in Total PBMC



Source: Figure 14.2.2.5
NOTE: Values less than the LLQ were imputed at the LLQ (25.79 nmol/mg/h)
ARSA=arylsulfatase A; EJ=early juvenile; LI=late infantile; LLQ=lower limit of quantitation; max=maximum; min=minimum; PBMC=peripheral blood stem cell

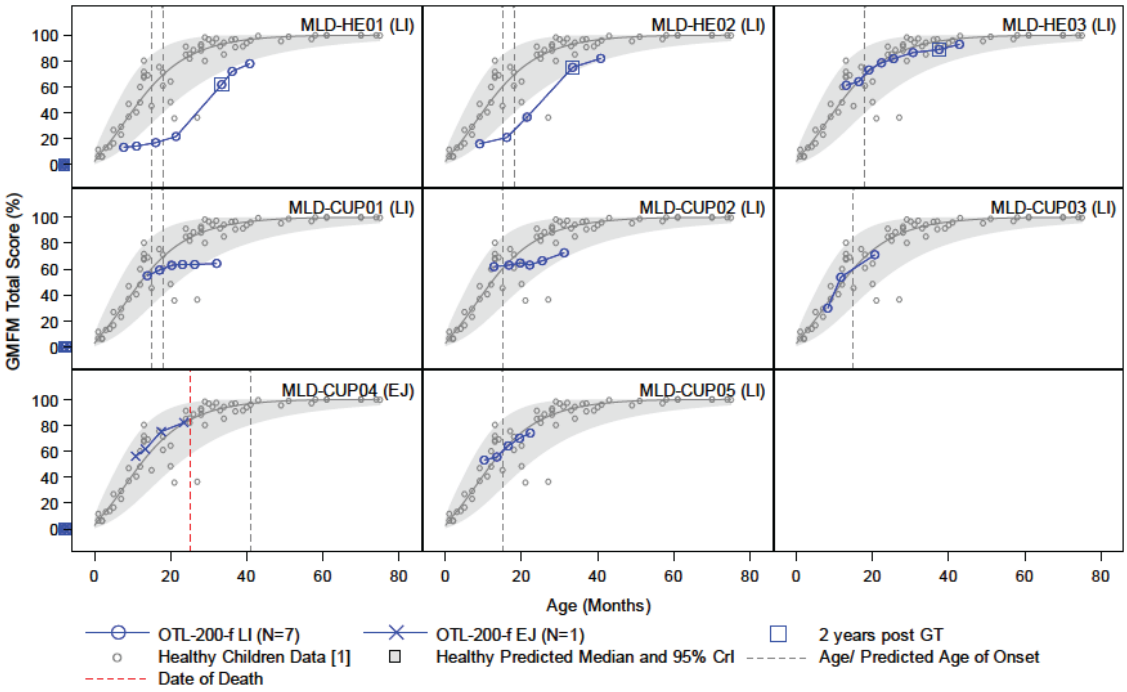
GMFM-88 [crucial]

In 2 twin prematurely born patients with a delayed initial GMFM there was an initial slow increase in the first year after treatment, but at 20 months there was a large increase, from 21,8% at year 1 to 61,79% at year 2 in one patient and from 36,78% at year 1 to 75,19% at year 2 in the other patient.
In 2 other LI patients there an initial delayed GMFM development noted, despite normal baseline scores (55% and 62% respectively), but the further development of these 2 patients stabilized and did not increase according to their chronological age.

In 1 LI patient a GMFM score of 81,9% at year 1 was observed and 88,96% at year 2, consistent with the data in healthy children. 2 other LI patients showed GMFM improvement over time within the normal range.

The 1 presymptomatic EJ patient died after 1 year of follow-up, with a GMFM of 82,11% at that the last visit.

Figure 14: Panel Plot of GMFM Total Score (%) Profiles



Source: Figure 14.2.1.2
NOTE: Healthy children data were from Palisano and colleagues, who provided access to the anonymous age and GMFM88 data on 60 subjects in the "no CP" group as reported in Palisano, 1997.
Two reference lines for 'Predicted Age of Onset' reflect the range of ages provided in the eCRF.
CP=cerebral palsy; CrI=credible interval; eCRF=electronic case report form; EJ=early juvenile; GMFM=gross motor function measure; GT=gene therapy; LI=late infantile

CUP 207394:

Patient survival [crucial]

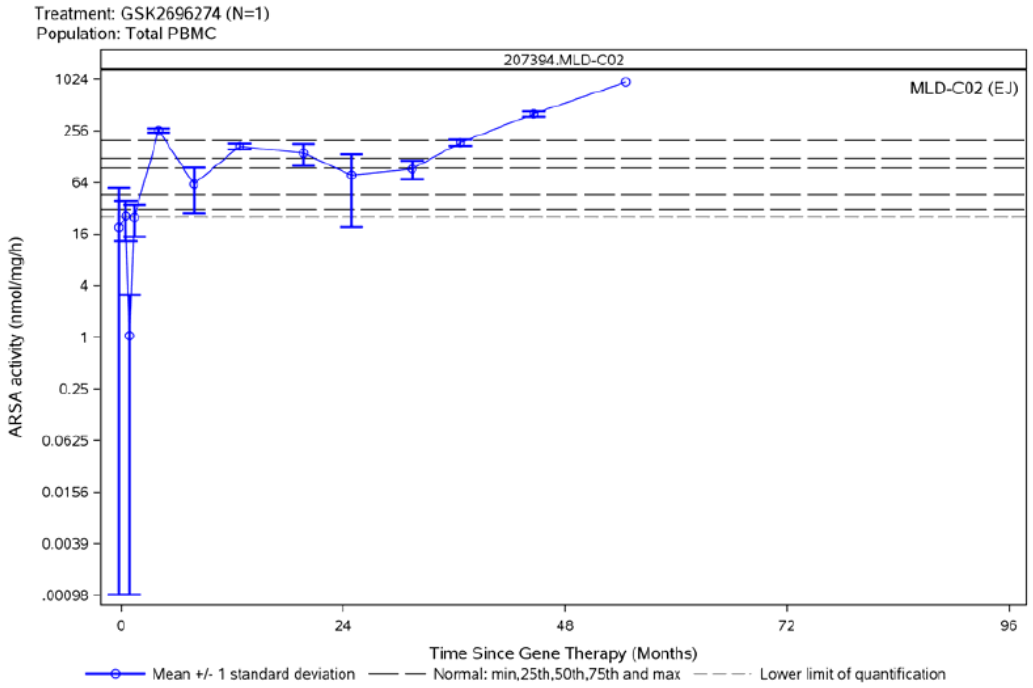
The only treated patient was alive at follow-up.

ARSA in PBMC [important]

At baseline, ARSA activity levels in PBMCs were below the LLOQ of 25.79 nmol/mg/h and beginning at Month 3, ARSA activity levels observed in PBMCs had reached normal levels, which then fluctuated between the 25th and the 75th percentile of the range observed in healthy children through approximately Year 3 post-gene therapy then increased above the reference range.

Versie préCTG:

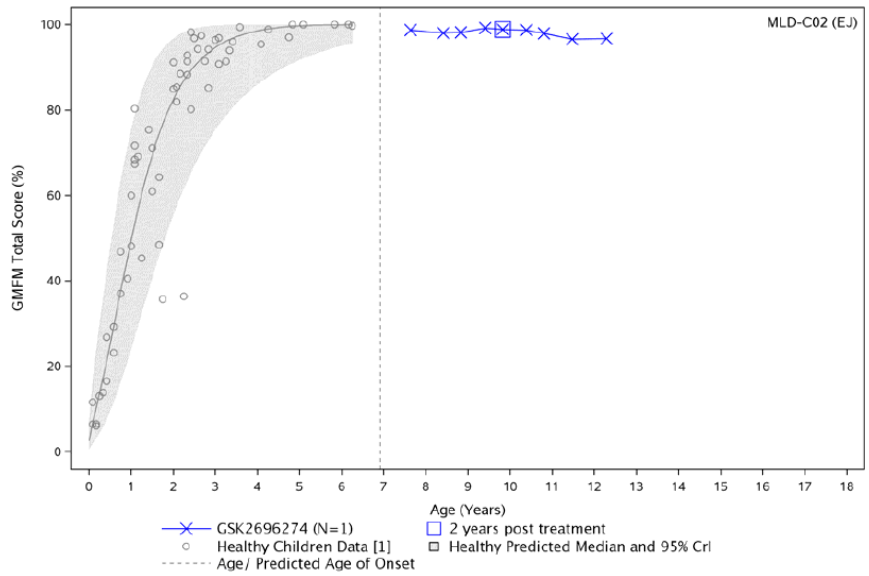
Figure 4 ARSA Activity (nmol/mg/h) in Peripheral Blood Mononuclear Cells Over Time (Mean ± 1 SD)



GMFM [crucial]

The Total GMFM Score remained stable at approximately 98% through Year 3 post-gene therapy and declined slightly in Years 3.5 (96.6%) and 4.5 (96.72%) post-gene therapy when patient MLD-C02 was approximately 12 years of age.

Figure 7 GMFM Total Score (%) Profile over Time



CP=cerebral palsy; CrI=credible interval; EJ=early juvenile; GMFM=Gross Motor Function Measure

[1] Healthy children data from Dr Palisano and colleagues, who provided access to the anonymous age and GMFM88 data on 60 patients in the "No CP" group as reported in " Development and reliability of a system to classify gross motor function in children with cerebral palsy" [Palisano, 1997]

c) Secondary outcomes

Study 201222:

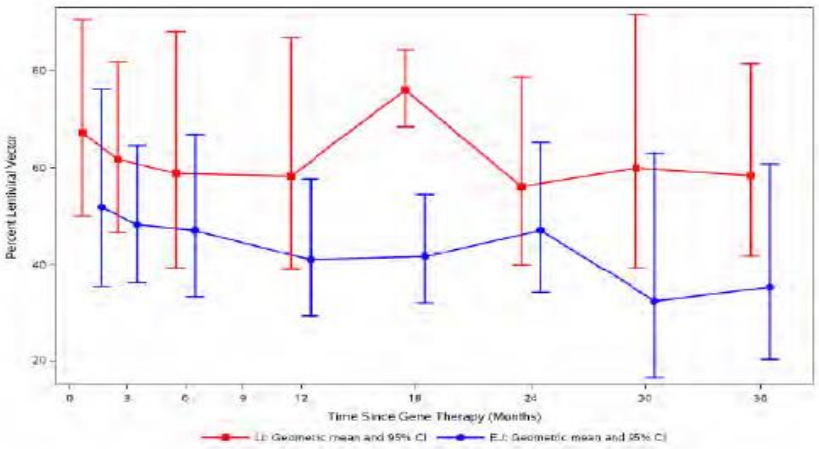
All patients:

Transduced cell engraftment

At year 1 post-treatment, the proportion of BM-derived colonies harbouring the LV genome (%LV+) in the overall treated population was 48.4% (range: 20.0% to 90.3%, [n=20]). The proportion of BM-derived colonies harbouring the LV genome (%LV+) at year 5 was 45.0% (range: 18.8% to 90.6% [n=6, 4 LI and 2 EJ]), indicative of stable engraftment over time in the treated population.
At Year 1 post-treatment in the LI subgroup, the %LV+ was 58.3% (range: 20.3% to 90.3% [n=8]) and in the EJ subgroup was 41.0% (range: 20.0% to 70.3% [n=9]). At Year 5, the %LV+ was 56.0% (range: 29.7% to 90.6% [n=4]) in the LI subgroup and 29.2% (range: 18.8% to 45.3% [n=2]) in the EJ subgroup. This was maintained up to Year 6 post-treatment in the LI subgroup, with the %LV+ at Year 6 being 45.1% (range: 18.8% to 78.1% [n=3]); data was not available for the EJ subgroup at this time point.

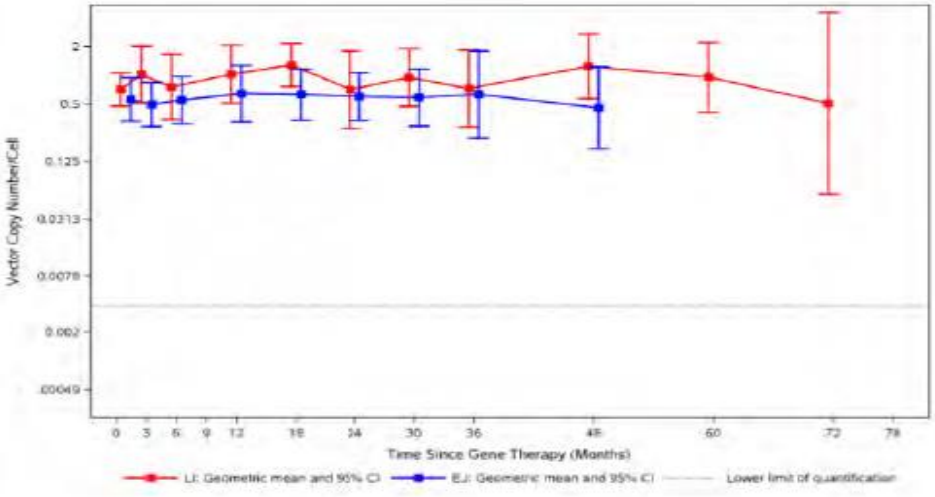
VCN values in CD34+ HSCs isolated from BM indicated stable levels of transduced cell engraftment beginning 1 month post-treatment, that were well above the minimum target defined in the protocol for the overall population as well as the LI and EJ subgroups (defined as VCN/cell ≥0.04 via quantitative PCR; equivalent to 4% assuming a VCN of 1).
At Years 3, 4, and 5 post-treatment, the geometric mean VCN values for the overall population were 0.67 (95% CI: 0.38, 1.19 [n=11]), 0.86 (95% CI: 0.47, 1.57 [n=11]), and 0.92 (95% CI: 0.48, 1.75 [n=6]), respectively. The geometric mean VCN levels in BM-derived CD34+ HSCs at Year 3, 4, and 5 for the LI subgroup were 0.73 (95% CI: 0.29, 1.84 [n=5]), 1.24 (95% CI: 0.57, 2.71 [n=7]), and 0.95 (95% CI: 0.41, 2.22 [n=5]), respectively, and for the EJ subgroup were 0.63 (95% CI: 0.22, 1.80 [n=6]), 0.45 (95% CI: 0.17, 1.22 [n=4]), and 0.77 (n=1), respectively. The geometric mean VCN value for the LI subgroup at Year 6 were 0.510 (n=3), and 1 EJ subject (Subject MLD04) was followed up to Year 6 and had a VCN of 0.74 (n=1), respectively.

Figure 4 **Percentage of Lentiviral Vector Transduced Cells in Bone Marrow Over Time (Geometric Mean and 95% CI), by Disease Subtype (Safety Population; N=20)**



Geometric mean and 95% CI are presented where at least 3 subjects have data.
Source: Figure 6.05.

Figure 5 **Vector Copy Number in BM-derived CD34⁺ Haematopoietic Stem Cells Over Time (Geometric Mean and 95% CI), by Disease Subtype (Safety Population; N=20)**



Note: LLOQ is 0.0037 VCN/cell. Geometric mean and 95% CI are presented where at least 3 subjects have non-imputed data. Values below LLOQ were imputed at LLOQ.
Source: Figure 6.09.

1. Late infantile MLD

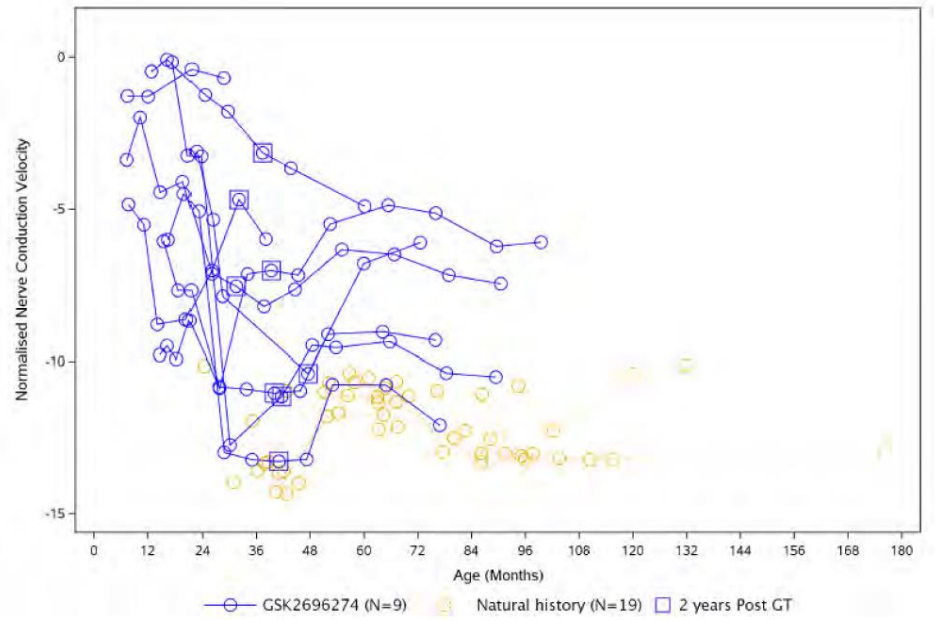
GMFC-MLD

Of the 8 patients asymptomatic LI MLD patients, 5 remained in GFMC level 0 or 1 (62%) during the follow-up period. Regarding the other 3 asymptomatic LI MLD patients, 1 patient remained stable at level 2, another patient was level 2 at the start of the study but declined towards level 4 at year 4 and the last patient of this group was a regression form stage 1 to stage 2. Overall a GMFC-MLD score below level 3 was observed in 87,5% of all LI patients throughout the follow-up period.

NCV index

In 2 patients the NVC index was within the normal range at baseline (0±1), with a marked decrease after treatment in 1 and a gradual decrease in the other.
In 1 patient the NCV was just below the normal range at baseline, but with an increase to normal at the last visit (1,5 year after treatment).
The other 6 patients had a baseline below normal, with 1 increasing and the other 5 decreasing over time. Compared to the untreated reference cohort, the NCV index was higher in 6 LI patients at last follow-up visit.
When adjusting for age and treatment, the model-adjusted LS mean for the NCV Index at year 2 was -8.5 for treated LI patients versus -13.3 in untreated LI TIGET NHx Study participants , a treatment difference of 4.8 (95%CI: 1.9, 7.7; p=0.005).

Figure 22 Nerve Conduction Velocity Index Over Time, Late Infantile Subgroup (All Subjects Population)



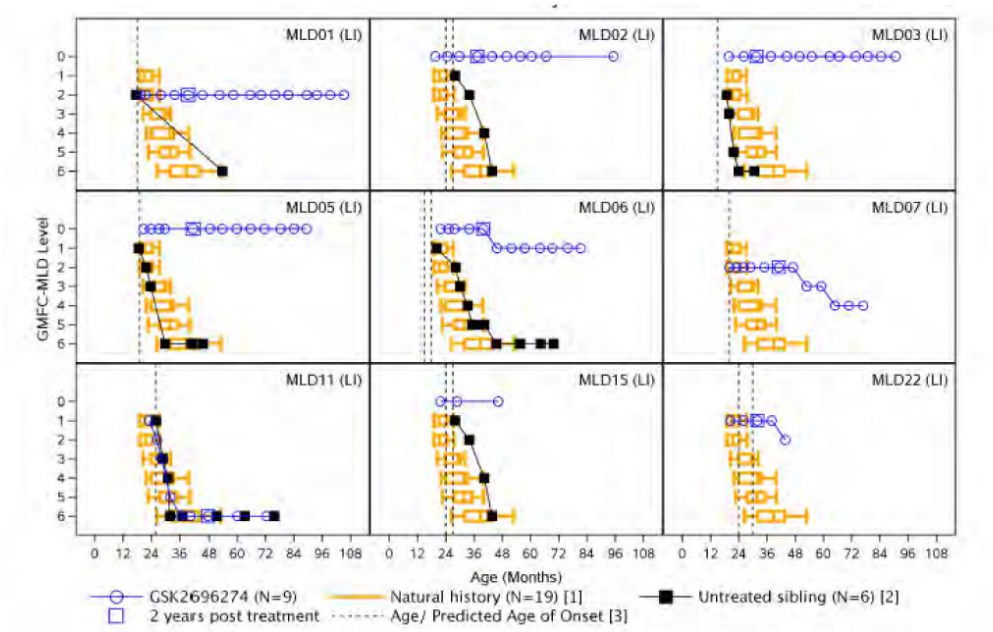
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.34.

Table 27 Subject Listing of Nerve Conduction Velocity Index by Visit in Late Infantile Subjects (ITT Population)

Subject ID	MLD01	MLD02	MLD03	MLD05	MLD06	MLD07	MLD11	MLD15	MLD22
Age at time of GT, months	15.0	13.1	7.6	17.8	15.8	16.8	23.3	9.3	8.2
NCV Index									
Baseline	-9.79	-0.47	-3.38	-0.16	-6.06	-6.02	-3.11	-1.28	-4.86
Month 3	-9.93	-0.08	-1.98	-3.24	-7.68	-4.51	-5.34	-1.30	-5.52
Month 6	-8.67	NP	-4.45	-3.27	-7.69	-5.07	-7.88	NP	-8.80
Year 1	-10.86	-1.24	-4.10	-12.75	-10.82	-12.98	NP	-0.41	-8.64
Year 1.5	-7.15	-1.79	-7.13	NP	-10.90	-13.22	NP	-0.70	-7.03
Year 2	-7.02	-3.15	-7.54	-11.15	-11.04	-13.28	-10.40	NP	-4.69
Year 2.5	-7.18	-3.66	-8.22	-9.48	-10.96	-13.21	NP	NP	-5.99
Year 3	-5.49	NP	-7.65	-9.56	-9.12	-10.76	-6.80	●	●
Year 4	-4.87	-4.92	-6.34	-9.36	-9.04	-10.76	-6.10		
Year 5	-5.14	NP	-6.49	-10.37	-9.31	-12.09	●		
Year 6	-6.24	NP	-7.17	-10.50	●	●			
Year 7	-6.10	NP	-7.46	●					

NP=not performed; ●=subject has not reached this time point; ■=subject has died.
Note: ENG recordings were performed at Day 28 only if the clinical conditions of the subjects were compatible with sedation and execution of them. Therefore, Day 28 NCV Index was recorded for only 1 subject in the LI subgroup (Subject MLD01; Day 28, NCV Index = -9.50).
Source: Listing 1.05 and Listing 2.43.

Figure 20 Panel Plot of Gross Motor Function Classification in MLD Levels by Age for the Late Infantile Subgroup With Comparison to NHx Data (All Subjects Population)

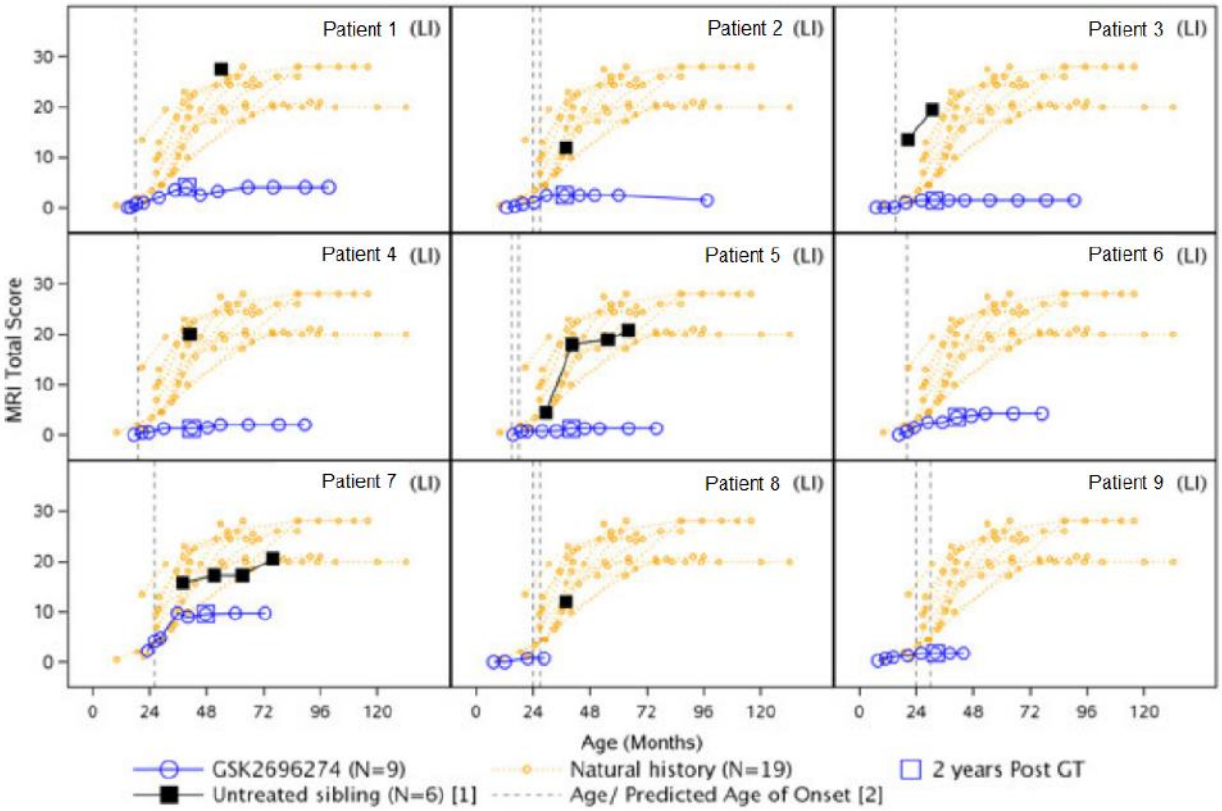


[1] The boxplots display the 10th, 50th, 75th, and 90th percentiles.
[2] Untreated sibling data is a subset of the NHx data.
[3] If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects the range given in the eCRF.
Note: Subjects MLD02 and MLD15 are siblings and, as such, have the same untreated sibling.
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.25.

Brain MRI

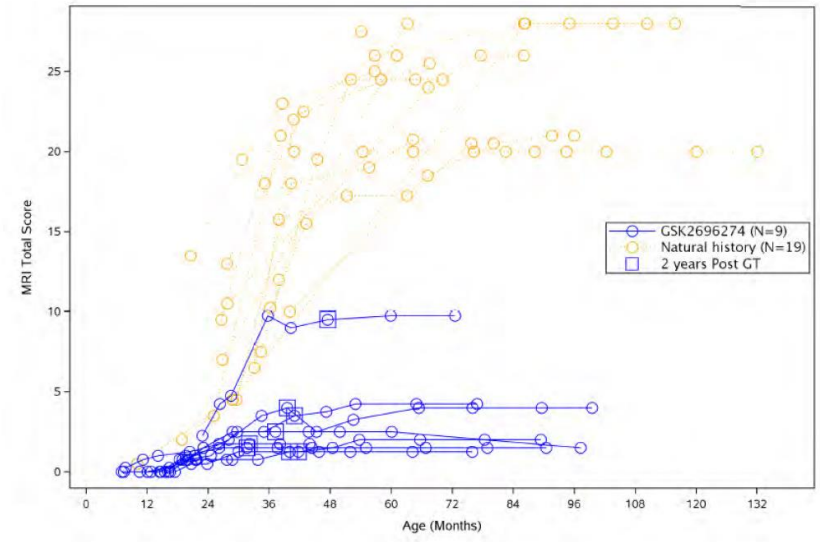
All patients in the LI subgroup had a normal brain MRI at baseline (total score of 0), except 1 patients with mild hyperintensities in the supratentorial white matter and corpus callosum (baseline MRI score 2.5) and 1 patients with very mild atrophy of the corpus callosum (MRI score 0,25). The brain MRI total scores increased in the first 6 months post-treatment for the majority of LI patients, except for 2 who showed evidence of only mild progression in brain MRI total score from Year 1 post-treatment. Stabilisation of brain MRI total score was seen between year 2 and year 3 after treatment in all LI patients except for two, who stabilised later at year 3. The MRI score mean differences between Libmeldy treated LI patients and NHx patients was -11.8 (95%CI -15,4, -8,1, p<0.001).

Figure 16: Late Infantile Subgroup: Panel Plot of Brain Magnetic Resonance Imaging Total Score Over Time Compared to TIGET NHx Data



[1] Untreated sibling data is a subset of NHx data.
[2] If there are 2 reference lines for "Age/Predicted Age on Onset," this reflects the range given in the eCRF.
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to Libmeldy-f. Source: Listing 2.44

Figure 29 Brain Magnetic Resonance Imaging Total Score Over Time, Late Infantile Subgroup With Comparison to TIGET NHx Data (All Subjects Population)



Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.39.

The IQ evolution by means of the Bayley scale for infants and toddler development (Baymey III), the Wehsler preschool and primary scale of intelligence (WPPSI) and the Weshsler intelligence scale for children (WISC) were used in the study depending on the age of the child.

All LI patients who could be tested on the appropriate cognitive test for their chronological age (7/9) were above the threshold for severe mental disability (IQ>55) at year 2 (n=7), year 2.5 (n=5), and year 3 (n=5) with means ranging between 90 and 103 for both the verbal IQ (Language score) and Performance IQ. In 2 LI patients testing was not feasible on the cognitive scale appropriate for their chronological age due to a score below 40 indicating that they already have reached severe mental disability.

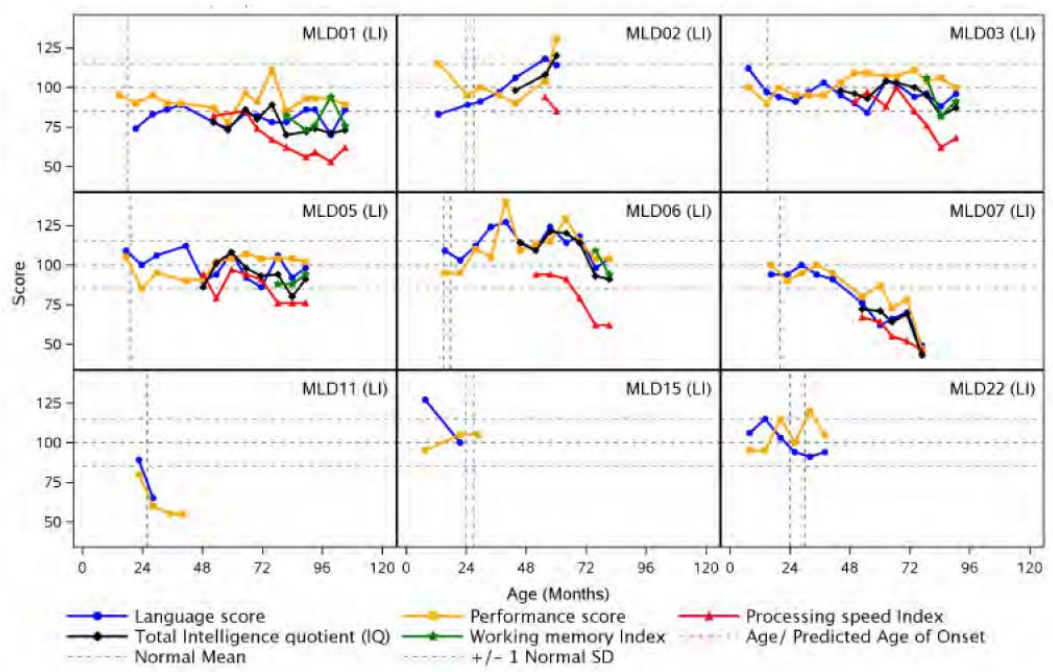
Table 30 Summary of Neuropsychological Tests – Language and Performance Score – Late Infantile Subgoup

	Year 2	Year 2.5	Year 3
Verbal IQ			
n[1]	7	5	5
Mean (SD)	100.57	101.40	90.58
Median	97	103	94
Min, max	89-127	90-114	76-110
Performance IQ			
n[1]	7	5	5
Mean (SD)	103.57	98	97
Median	95	95	102
Min, max	90-140	90-109	80-113

Source: Table 4.42

[1]The number of subjects reflects data available at each time point and from neuropsychological questionnaires appropriate for age. Only data from neuropsychological questionnaires appropriate for the child's age were included in the tabulation.

Figure 37 Panel Plot of Neuropsychological Test Results Over Time by Scale, Late Infantile Subgroup (ITT Population)



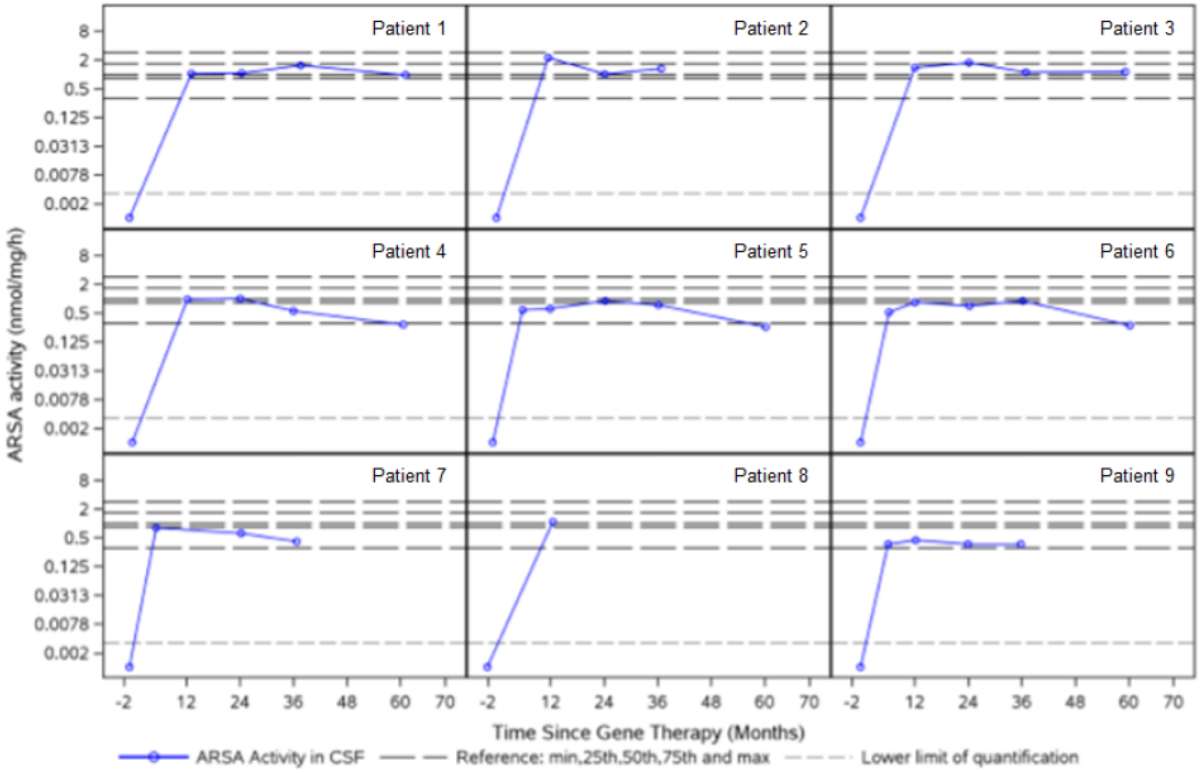
Note: If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects a range of ages provided in the eCRF.

Source: Figure 4.52.

ARSA activity in CSF

At baseline, the ARSA levels were below the LLOQ 0,0032 nmol/mg/h in all patients. Post treatment, ARSA activity levels in the CSF were detectable by Month 6 and levels of 0,9745 nmol/mg/h were reached at 1-year post treatment. The average ARSA activity in the CSF for the LI MLD subjects measured 5 years post treatment was 0,4726 nmol/mg/h.

Figure 10: Late Infantile Subgroup (ITT Population; N=9): Panel Plot of ARSA Activity in Cerebrospinal Fluid Over Time (nmol/mg/h)



Note: Values ≤0/undetectable ARSA activity were imputed at LLOQ. LLOQ was 0.0032 nmol/mg/h.
Note: The reference range represents data from a cohort of paediatric reference donors as per Perugia reference report.

2. Asymptomatic EJ MLD

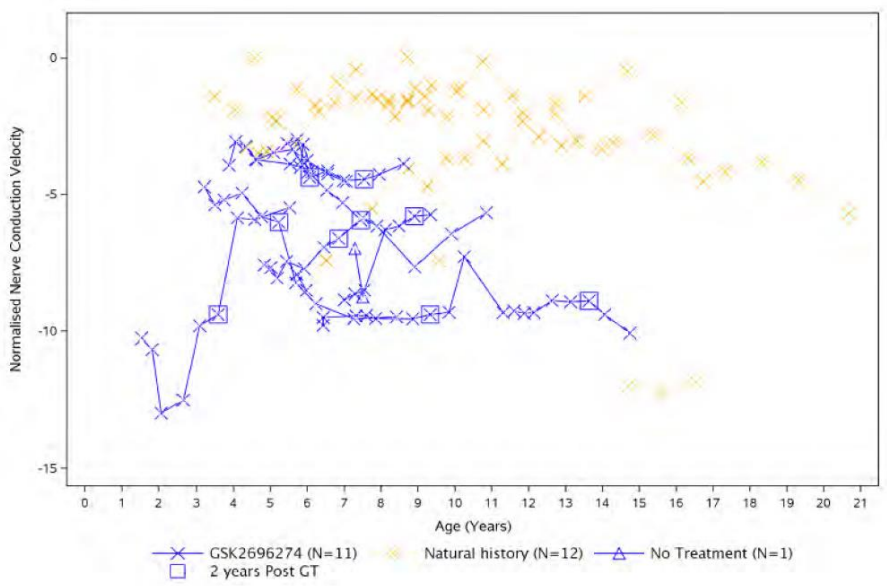
GMFC-MLD

In 3 of the 4 presymptomatic EJ patients the GFMC-MLD was level 0 at baseline and did not change over the course of the follow-up period. The 4th patient had level 0 at baseline deteriorating to level 2 at year 2 trough year 3.

NCV index

Of the 4 patients in the EJ subgroup who were treated prior to the onset of symptoms, the NCV Index remained relatively stable from baseline to the time of the last follow-up visit at year 3 in 1 patient, increased from baseline to the time of the last follow-up at year 4 in another patient, decreased from baseline to the last follow-up at year 3, and the 4th patient experienced a gradual decrease from baseline to the time of the last follow-up at year 2 .

Figure 25 Nerve Conduction Velocity Over Time, Early Juvenile Subgroup (All Subjects Population)



Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.36.

Table 28 Subject Listing of Nerve Conduction Velocity Index by Visit in Early Juvenile Subjects (ITT Population)

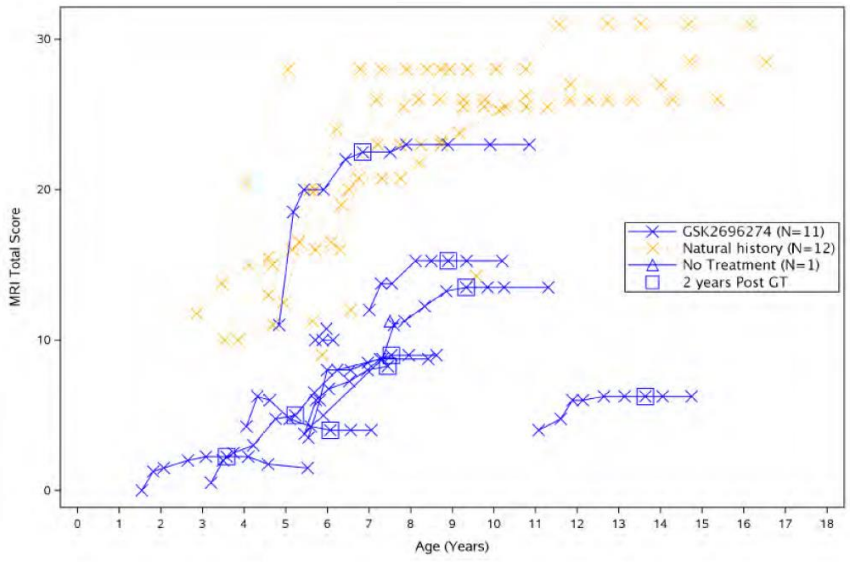
Subject ID	MLD04	MLD08	MLD09a	MLD12	MLD13	MLD14	MLD16	MLD17	MLD19	MLD20	MLD21
Age at time of GT, (months)	59.2	38.8	18.8	66.8	88.2	139.9	48.9	84.6	69.1	66.0	71.2
NCV Index											
Baseline	-7.58	-4.73	-10.25	-3.89	-9.45	-9.27	-3.07	-8.86	-7.93	-3.14	-3.17
Month 3	-8.08	-5.39	-10.64	-4.01	-9.44	-9.36	-3.25	-8.65	-8.52	-3.00	-4.17
Month 6	-7.45	-5.21	-12.98	-3.75	-9.54	-9.34	-3.74	-8.50	NP	-4.18	■
Year 1	-7.73	-4.95	-12.50	-4.25	NP	-8.89	-3.47	-6.29	NP	-4.85	
Year 1.5	-6.94	-5.82	-9.81	-4.50	-9.56	-8.93	-3.36	-6.17	■	-5.30	
Year 2	-6.61	-6.02	-9.40	-4.45	-9.40	-8.90	-4.39	-5.80		-5.95	
Year 2.5	-5.85	-8.24	-5.86	-4.28	-9.32	-9.40	-4.14	-5.75		NP	
Year 3	-6.16	-9.01	-5.92	-3.88	-7.29	-10.09	-4.53	NP		●	
Year 4	-7.65	-9.56	-5.48	●	-9.33	●	●	●			
Year 5	-6.45	-9.49	●		●						
Year 6	-5.67	●									

NP=not performed; ●=subject has not reached this time point; ■=subject has died.
a. Subject MLD09 – classified as an 'Intermediate' clinical variant, not matching the typical LI or EJ forms. Data for this subject have been pooled with EJ dataset for analysis.
Note: ENG recordings were performed at Day 28 only if the clinical conditions of the subjects were compatible with sedation and execution of them. Therefore, Day 28 NCV Index was recorded for only 1 subject in the EJ subgroup (Subject MLD04; Day 28, NCV Index = -7.68).
Note: Subjects MLD09, MLD12, MLD16, and MLD20 were pre-symptomatic at OTL-200-f administration, and Subjects MLD04, MLD08, MLD13, MLD14, MLD17, MLD19, and MLD21 were early-symptomatic at OTL-200-f administration.
Source: Listing 1.05 and Listing 2.43.

Brain MRI

The presymptomatic EJ patients had a baseline MRI score of 0 to 4,25, and these score remained below 9 during follow-up. The difference between the Libmeldy treated patients and the NHx patients was 10,7 (95%CI 7,0 – 14,4, p<0,001).
The model-adjusted LS mean for the brain MRI total score at Year 2 was 9.1 for EJ patients treated with AA-f and 13.2 for untreated EJ TIGET NHx Study participants. The treatment difference (AA-f-treated EJ subjects minus untreated EJ TIGET NHx Study participants) was -4.1 (95% CI: -9.6, 1.3; p=0.123) and was not statistically significant.

Figure 33 Magnetic Resonance Imaging Total Score Over Time, Early Juvenile Subgroup With Comparison to TIGET NHx Data (All Subjects Population)



Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.38.

IQ>55

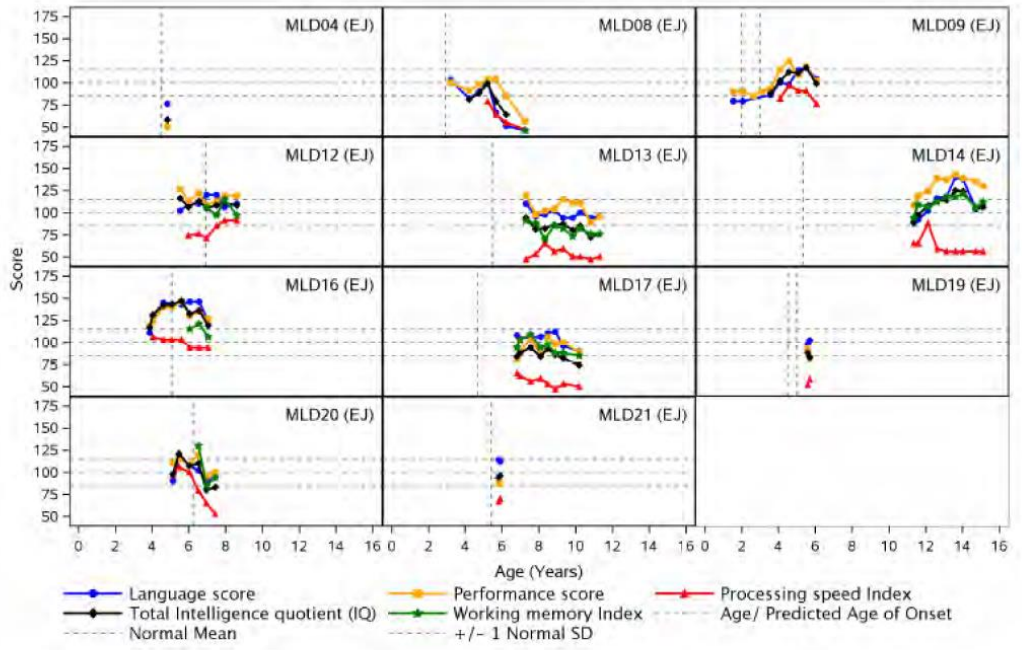
The majority of AA-f-treated patients had a total IQ above the severe mental disability threshold (IQ>55) at year 2 (mean: 101, range: 83 to 132, n=8), year 2.5 (mean: 102, range: 79 to 136, n=7), and year 3 (mean: 95.14, range: 64 to 119, n=7) post-treatment, with the exception of 1 patient who could not be tested due to a score below the evaluable threshold the 2 patients who died because of disease progression and did not reach those time points.
As noted for the LI subgroup, the processing speed scores from the 4 presymptomatic EJ patients tended to be lower at each time point relative to other neuropsychological composite scores, with 2 patients having stable scores in the normal range and 2 patients with a declining score over time below the normal values.

Table 31 Summary of Neuropsychological Tests – Language and Performance Score – Early Juvenile Subgroup

	Year 2	Year 2.5	Year 3
Total IQ			
n[1]	8	7	7
Mean	101.0	102.0	95.14
Median	93.50	102.00	104.00
Min, max	83.0-132.0	79.0-136.0	64.0-119.0
Verbal IQ (Language score)			
n[1]	8	7	7
Mean	111.75	106.57	96.71
Median	107.00	100.00	100.00
Min, max	86.0-146.0	66.0-146.0	51.0-124.0
Performance IQ (Performance score)			
n[1]	8	7	7
Mean	112.00	117.57	112.71
Median	108.50	115.00	119.00
Min, max	93.0-143.0	100.0-139.0	85.0-135.0
Working Memory			
n[1]	6	5	5
Mean	99.00	103.60	95.20
Median	95.50	115.00	97.00
Min, max	82.0-118.0	73.0-121.0	82.0-106.0

Source: Table 4.42
[1]The number of subjects reflects data available at each time point. Only data from neuropsychological questionnaires appropriate for the child's age were included, and as a result, not every subject contributed to the tabulation at each time point.

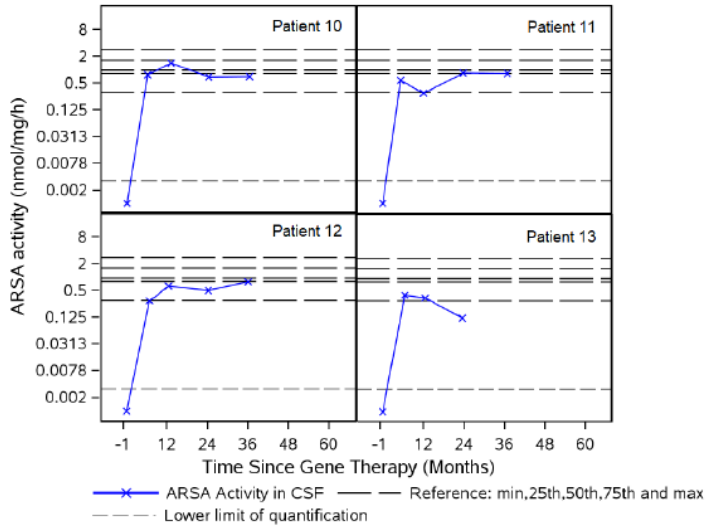
Figure 38 Panel Plot of Neuropsychological Test Profiles by Scale, Early Juvenile Subjects (ITT Population)



Note: If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects a range of ages provided in the eCRF.
Note: Subjects MLD09, MLD12, MLD16, and MLD20 were pre-symptomatic at OTL-200-f administration, and Subjects MLD04, MLD08, MLD13, MLD14, MLD17, MLD19, and MLD21 were early-symptomatic at OTL-200-f administration.
Source: Figure 4.52.

ARSA activity in CSF

The ARSA activity levels in the CSF increased from levels below detection limit to within ranges reported for healthy subjects. The ARSA activity levels in all subjects were detectable by Month 6, with a mean level 0.6352 nmol/mg/h 1-year post treatment. At 5 years post treatment the mean ARSA activity in the CSF was 1.67 nmol/mg/h for the overall EJ group.



Note: Values ≤0 were imputed at LLOQ. LLOQ was 0.0032 nmol/mg/h.
Note: Geometric mean and 95% CI were presented where there were at least 3 subjects with non-missing data.
Note: The reference range represents data from a cohort of paediatric reference donors as per Perugia reference range report.

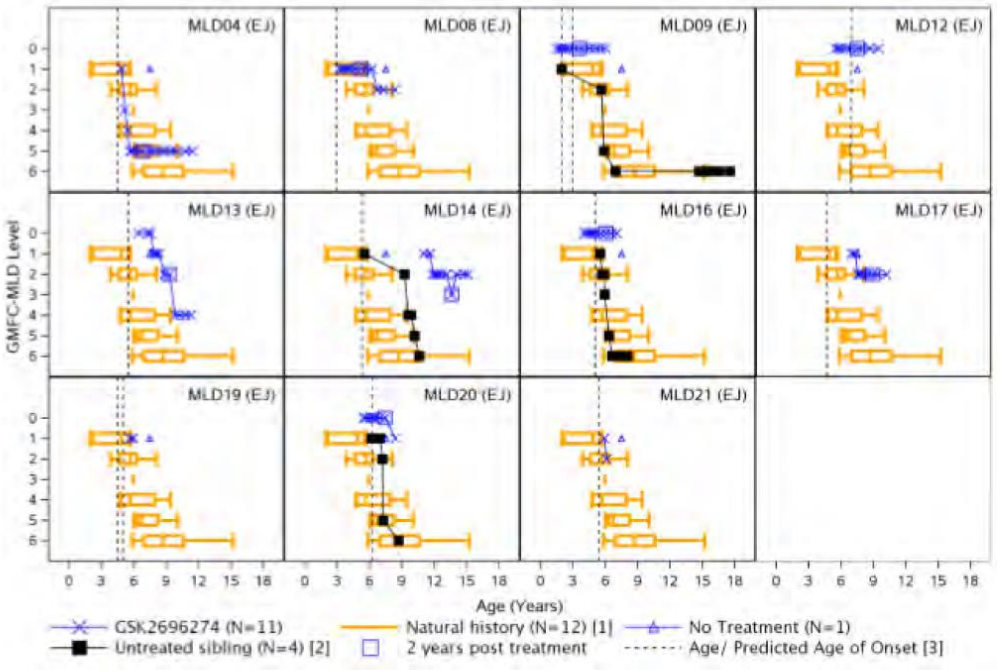
3. Early symptomatic EJ MLD

GMFC-MLD

In 2 of the 7 early symptomatic EJ patients, the GFMC-MLD declined fast, being from level 1 to level 5 over 9 months in one patient and from level 0 to level 4 over a period 30 months in the other patient. In 2 patients there was only a small decline from level 1 to level 2 over the follow-up period. The last patients had a decline from level 1 tot level 3, but after a feet surgery returned to level 2 for the rest of the follow-up period.

Overall, 3 of the 7 early symptomatic EJ patients (42,8%) had a GMFC-MLD score better than 3 throughout the follow-up period.

Figure 21 Panel Plot of Gross Motor Function Classification in MLD Levels by Age for the Early Juvenile Subgroup With Comparison to NHx Data (All Subjects Population)



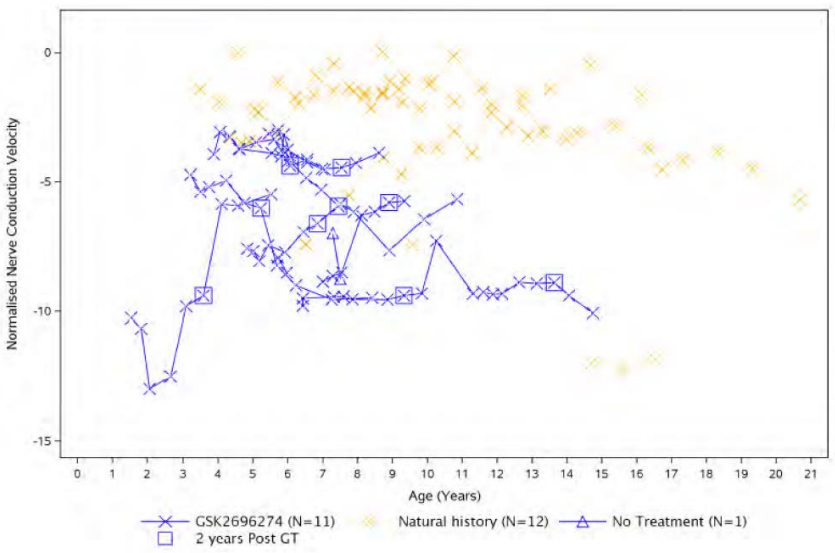
[1] The boxplots display the 10th, 50th, 75th, and 90th percentiles.
[2] Untreated sibling data is a subset of the NHx data.
[3] If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects the range given in the eCRF. The open blue triangle denotes the Baseline GMFC-MLD score for Subject MLD18 who was withdrawn from the study prior to treatment.
Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Note: Subjects MLD09, MLD12, MLD16, and MLD20 were pre-symptomatic at OTL-200-f administration, and Subjects MLD04, MLD08, MLD13, MLD14, MLD17, MLD19, and MLD21 were early-symptomatic at OTL-200-f administration.

NCV index

Of the 7 patients in the EJ subgroup who were treated after the onset of symptoms, the NCV Index data were limited in 2 as they died due to rapid disease progression. In the 5 other patients, the NCV index remained relatively stable from baseline to the time of the last follow-up visit 2 patient, increased from baseline to the time of the last follow-up in 2 patients and decreased from baseline to the last follow-up in 1 patient.

When adjusting for age and treatment, the model-adjusted LS mean for the NCV Index at year 2 was -6.6 for patients in the treated EJ subgroup versus -2.9 in untreated EJ TIGET NHx Study, a treatment difference of -3.7 (95% CI: -6.5, 0.9; p=0.013) that was statistically significant in favour of NHx.

Figure 25 Nerve Conduction Velocity Over Time, Early Juvenile Subgroup (All Subjects Population)



Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.36.

Table 28 Subject Listing of Nerve Conduction Velocity Index by Visit in Early Juvenile Subjects (ITT Population)

Subject ID	MLD04	MLD08	MLD09a	MLD12	MLD13	MLD14	MLD16	MLD17	MLD19	MLD20	MLD21
Age at time of GT, (months)	59.2	38.8	18.8	66.8	88.2	139.9	48.9	84.6	69.1	66.0	71.2
NCV Index											
Baseline	-7.58	-4.73	-10.25	-3.89	-9.45	-9.27	-3.07	-8.86	-7.93	-3.14	-3.17
Month 3	-8.08	-5.39	-10.64	-4.01	-9.44	-9.36	-3.25	-8.65	-8.52	-3.00	-4.17
Month 6	-7.45	-5.21	-12.98	-3.75	-9.54	-9.34	-3.74	-8.50	NP	-4.18	■
Year 1	-7.73	-4.95	-12.50	-4.25	NP	-8.89	-3.47	-6.29	NP	-4.85	
Year 1.5	-6.94	-5.82	-9.81	-4.50	-9.56	-8.93	-3.36	-6.17	■	-5.30	
Year 2	-6.61	-6.02	-9.40	-4.45	-9.40	-8.90	-4.39	-5.80		-5.95	
Year 2.5	-5.85	-8.24	-5.86	-4.28	-9.32	-9.40	-4.14	-5.75		NP	
Year 3	-6.16	-9.01	-5.92	-3.88	-7.29	-10.09	-4.53	NP		●	
Year 4	-7.65	-9.56	-5.48	●	-9.33	●	●	●			
Year 5	-6.45	-9.49	●		●						
Year 6	-5.67	●									

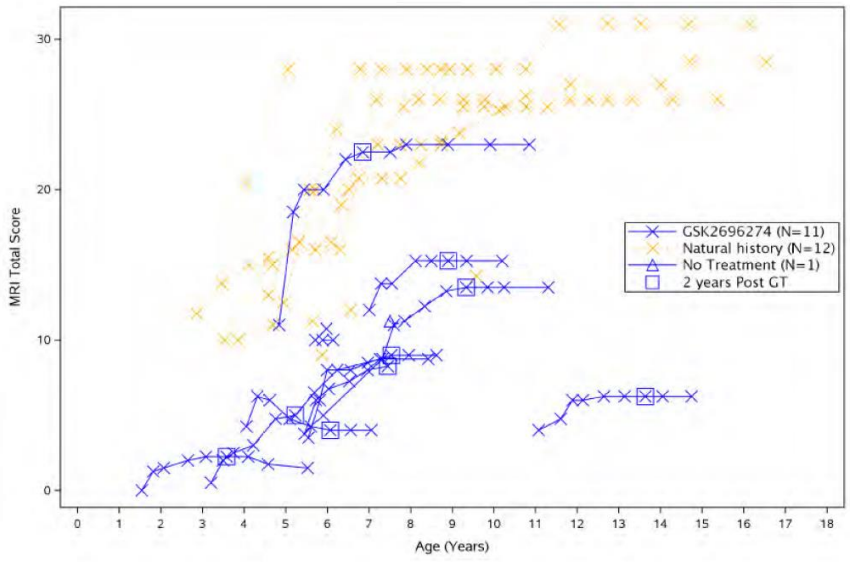
NP=not performed; ●=subject has not reached this time point; ■=subject has died.
a. Subject MLD09 – classified as an 'Intermediate' clinical variant, not matching the typical LI or EJ forms. Data for this subject have been pooled with EJ dataset for analysis.
Note: ENG recordings were performed at Day 28 only if the clinical conditions of the subjects were compatible with sedation and execution of them. Therefore, Day 28 NCV Index was recorded for only 1 subject in the EJ subgroup (Subject MLD04; Day 28, NCV Index = -7.68).
Note: Subjects MLD09, MLD12, MLD16, and MLD20 were pre-symptomatic at OTL-200-f administration, and Subjects MLD04, MLD08, MLD13, MLD14, MLD17, MLD19, and MLD21 were early-symptomatic at OTL-200-f administration.
Source: Listing 1.05 and Listing 2.43.

Brain MRI

The difference between the Libmeldy treated patients and the NHx patients was 5,8 (95%CI -4,0 – 15,5, p=0,21).

The model-adjusted LS mean for the brain MRI total score at Year 2 was 9.1 for EJ patients treated with AA-f and 13.2 for untreated EJ TIGET NHx Study participants. The treatment difference (AA-f-treated EJ subjects minus untreated EJ TIGET NHx Study participants) was -4.1 (95% CI: -9.6, 1.3; p=0.123) and was not statistically significant.

Figure 33 **Magnetic Resonance Imaging Total Score Over Time, Early Juvenile Subgroup With Comparison to TIGET NHx Data (All Subjects Population)**



Note: As of Protocol Amendment 11, the drug product name has been changed from GSK2696274 to OTL-200-f.
Source: Figure 4.38.

IQ>55

The majority of AA-f-treated patients had a total IQ above the severe mental disability threshold (IQ>55) at year 2 (mean: 101, range: 83 to 132, n=8), year 2.5 (mean: 102, range: 79 to 136, n=7), and year 3 (mean: 95.14, range: 64 to 119, n=7) post-treatment, with the exception of 1 patient who could not be tested due to a score below the evaluable threshold the 2 patients who died because of disease progression and did not reach those time points.

Of the early symptomatic patients 4 had multiple neuropsychological tests assessed after baseline, in which 2 patients had scores fluctuating within the normal range, 1 patient with a marked improvement and 1 patient with a significant decline to a score <40.

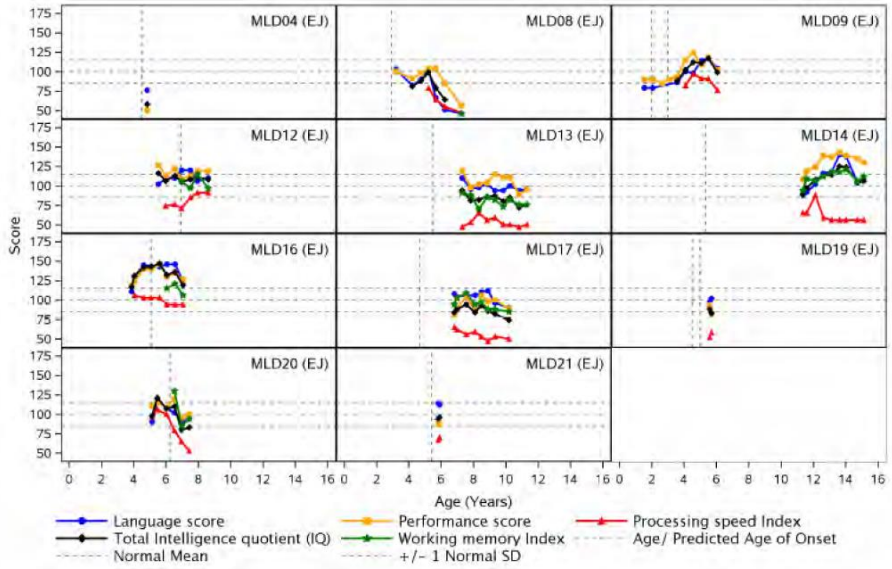
Table 31 Summary of Neuropsychological Tests – Language and Performance Score – Early Juvenile Subgroup

	Year 2	Year 2.5	Year 3
Total IQ			
n[1]	8	7	7
Mean	101.0	102.0	95.14
Median	93.50	102.00	104.00
Min, max	83.0-132.0	79.0-136.0	64.0-119.0
Verbal IQ (Language score)			
n[1]	8	7	7
Mean	111.75	106.57	96.71
Median	107.00	100.00	100.00
Min, max	86.0-146.0	66.0-146.0	51.0-124.0
Performance IQ (Performance score)			
n[1]	8	7	7
Mean	112.00	117.57	112.71
Median	108.50	115.00	119.00
Min, max	93.0-143.0	100.0-139.0	85.0-135.0
Working Memory			
n[1]	6	5	5
Mean	99.00	103.60	95.20
Median	95.50	115.00	97.00
Min, max	82.0-118.0	73.0-121.0	82.0-106.0

Source: Table 4.42

[1]The number of subjects reflects data available at each time point. Only data from neuropsychological questionnaires appropriate for the child's age were included, and as a result, not every subject contributed to the tabulation at each time point.

Figure 38 Panel Plot of Neuropsychological Test Profiles by Scale, Early Juvenile Subjects (ITT Population)



Note: If there are 2 reference lines for "Age/Predicted Age of Onset," this reflects a range of ages provided in the eCRF.

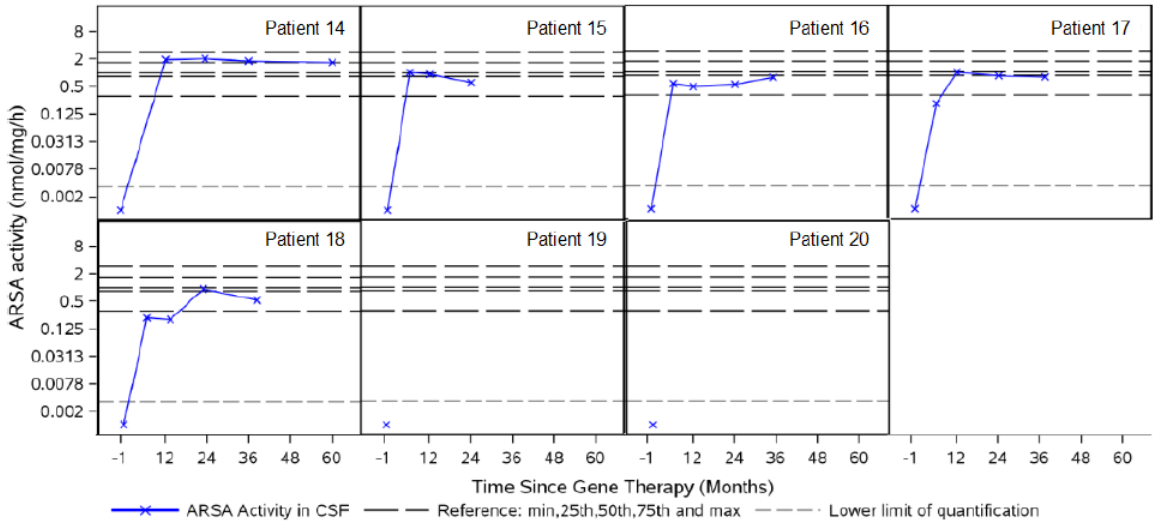
Note: Subjects MLD09, MLD12, MLD16, and MLD20 were pre-symptomatic at OTL-200-f administration, and Subjects MLD04, MLD08, MLD13, MLD14, MLD17, MLD19, and MLD21 were early-symptomatic at OTL-200-f administration.

Source: Figure 4.52.

ARSA activity in CSF

The ARSA activity levels in the CSF increased from levels below detection limit to within ranges reported for healthy subjects. The ARSA activity levels in all subjects were detectable by Month 6, with a mean level of 0.47 nmol/mg/h (95% CI: 0.34, 0.65 and a mean level of 0.6352 nmol/mg/h 1-year post treatment. At 5 years post treatment the mean ARSA activity in the CSF was 1.67 nmol/mg/h for the overall EJ group.

Figure 12: **Early-symptomatic Early Juvenile Subgroup (ITT Population; N=7) Panel Plot of ARSA Activity in Cerebrospinal Fluid Over Time (nmol/mg/h)**



Note: Values ≤0 were imputed at LLOQ. LLOQ was 0.0032 nmol/mg/h.
Note: Geometric mean and 95% CI were presented where there were at least 3 subjects with non-missing data.
Note: The reference range represents data from a cohort of paediatric reference donors as per Perugia reference range report.
Note: Four subjects (Patient 10, 11, 12, 13) were pre-symptomatic at Libmeldy-f administration, and seven subjects (Patient 14, 15, 16, 17, 18, 19, 20) were early-symptomatic at Libmeldy-f administration.

Study 205756:

Transduced cell engraftment

Patients treated with Libmeldy-c showed comparable levels of in the proportion of LV-Positive Colony-Forming Cells in BM: At month 1 post-treatment, all patients tested (n=3) showed high levels of genetically modified cells in BM, with a range between 70.83% LV+ cells and 80.83% LV+ cells. At month 3, data were available for two patients, showing a 89.39% LV+ cells and 80% LV+ cells, respectively, consistent with the level observed at month 1 for one patient.
In general, VCN values in total mononuclear cells (MNC) from BM indicated stable levels of transduced cell engraftment beginning 1 month (Day 30) after administration of AA-c for all patients.

In the updated sheets the company provided following information:

Patient 1: 77,08% lentiviral vector transduced cells at year 1
Patient 2: 86,46% lentiviral vector transduced cells at year 1
Patient 3: 63,95% lentiviral vector transduced cells at year 1
Patient 4: 76,84% lentiviral vector transduced cells at month 6

Table 11: **Percent Lentiviral Vector Transduced Cells after Administration of OTL-200-c**

Assessment	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Month 1	70.83	NR[a]	80.83	75
Month 3	NR[b]	89.39	80	NA
Month 6	56.25	NR[c]	NA	
Year 1	77.08	NA		

[a] Percent lentiviral vector transduced cells was not measured at Month 1 for Subject MLDCRY03 due to low available material (protocol deviation).
[b] Percent lentiviral vector transduced cells was not measured at Month 3 for Subject MLDCRY02 due to technical problems (protocol deviation).
[c] Bone marrow was not collected at Month 6 for Subject MLDCRY03 as this subject was seen remotely in his home country (protocol deviation).
Source: Listing 16.2.6.5
Abbreviations: NA=not assessed (subject had not yet completed this follow-up assessment); NR=not reported.

Table 12: Vector Copy Number in Total MNC in Bone Marrow after Administration of OTL-200-c (VCN/cell)

	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Month 1	1.15	2.67	0.34	0.93
Month 3	2.16	4.21	2.14	NA
Month 6	1.59	NR[a]	NA	
Year 1	2.18	NA		

[a] Bone marrow was not collected at Month 6 for Subject MLDCRY03 as this subject was seen remotely in his home country (protocol deviation).
Source: Listing 16.2.6.4
Abbreviations: MNC=mononuclear cell; NA=not assessed (subject had not yet completed this follow-up assessment); NR=not reported (missed assessment); VCN=vector copy number

ARSA activity in CSF

At Baseline, ARSA activity levels in CSF were undetectable in all 4 patients. After administration of Libmeldy-c, ARSA activity levels were detectable and within the normal range at month 3 in all three patients with available data.

The updated information of CSF ARSA activity at last visit:

Patient 1: 0,365 nmol/mg/h at year 1
Patient 2: 0,518 nmol/mg/h at year 1
Patient 3: 1,28 nmol/mg/h at year 1
Patient 4: 0,245 nmol/mg/h at month 6

Table 17: ARSA Activity in Cerebrospinal Fluid (nmol/mg/h)

Assessment	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Baseline	ND	ND	ND	ND
Month 3	0.429	0.678	0.897	NA
Month 6	0.352	NR[a]	NA	
Year 1	0.365	NA		

[a] CSF was not collected at Month 6 for Subject MLDCRY03 as this subject was seen remotely in his home country (protocol deviation).
Source: Listing 16.2.6.1
Abbreviations: ARSA=arylsulfatase A; h=hour; NA=not assessed (subject had not yet completed this follow-up assessment); ND=not detected; NR=not reported

GMFC-MLD [crucial]

At the moment of data-cut, only 2 patients were old enough to be tested. In 1 patient a baseline score could not be obtained, but this patient had a level 2 at the month 6 and month 9 visit, but ameliorated towards level 1 at year 1 and year 1,5, with independent walking capabilities.

In patient 2 no baseline value was obtained, but at year 1 the patient was in GMFC-MLD level 1.

In patient 3 no baseline value was obtained, but at year 1 the patient was in GMFC-MLD level 0.

In patient 4 evaluated, the baseline GMFC scored level 0, and remained level 0 at month 9.

NCV

The NCV data showed in all patients a further deterioration of the NVC at year 1 (or at month 6 for patients 4).

In the updated information on NCV following data were provided:

Patient 1: Year 1 DPN -10,88 / MN -4,6 / UN -9,02 / SN -14,14
Patient 2: Year 1 DPN -8,88 / MN -2,4 / UN -6,11 / SN -2,3
Patient 3: Year 1 DPN -8,12 / MN -5,45 / UN -7,83 / SN -14,14
Patient 4: Month 6 DPN -5,55 / MN -2,94/ UN -4,2 / SN -3,73

Table 19: Nerve Conduction Velocity Results Z Scores

Time Point		Screening	Month 3	Month 6	Year 1
MLDCRY02	Deep Peroneal Nerve	-8.58	-9.52	-10.73	-10.88
	Median Nerve	-1.53	-2.64	-4.28	-4.6
	Ulnar Nerve	-7.72	-8.57	-9.2	-9.02
	Sural Nerve	NR	NR	NR	-14.14
MLDCRY03	Deep Peroneal Nerve	-6.73	-6.03	NR	NA
	Median Nerve	-2.64	-2.75		
	Ulnar Nerve	-5.63	-6.87		
	Sural Nerve	NR	NR		
MLDCRY04	Deep Peroneal Nerve	-7.88	-10.45	NA	NA
	Median Nerve	-4.75	-5.26		
	Ulnar Nerve	-6.11	-7.07		
	Sural Nerve	NR	NR		
MLDCRY06	Deep Peroneal Nerve	-1.79	NA	NA	NA
	Median Nerve	-1.43			
	Ulnar Nerve	-2.67			
	Sural Nerve	-1.97			

Source: Listing 16.2.6.6
Abbreviations: NA=not assessed, subject has not reached that timepoint; NR=no result

Brain MRI

Given the number of subjects and duration of follow-up, there were limited data available from MRI assessments, but overall MRI scores were low at baseline and during the limited follow-up period (a normal score is 0).

In the updated data sheets, the total scores were:

Patient 1 brain MRI score 0 at baseline and 1,25 at year 1.
Patient 2 brain MRI score 0,5 at baseline and 0,75 at year 1.
Patient 3 brain MRI score 0,25 at baseline and 0,5 at year 1.
Patient 4 brain MRI score 0 at baseline and 0 at month 6.

Table 20: Brain MRI Scores

Assessment	MLDCRY02	MLDCRY03	MLDCRY04	MLDCRY06
Total Score				
Screening	0	0.5	0.25	0
Month 3	0	0.5	0.25	NA
Month 6	1.00	NR[a]	NA	
Year 1	1.25	NA		
Atrophy Score				
Screening	0	0.25	0	0
Month 3	0	0.25	0	NA
Month 6	0.25	NR[a]	NA	
Year 1	0.50	NA		
Demyelination Score				
Screening	0	0.25	0.25	0
Month 3	0	0.25	0.25	NA
Month 6	0.75	NR[a]	NA	
Year 1	0.75	NA		

[a] Brain MRI was not conducted at Month 6 for Subject MLDCRY03 as this subject was seen remotely in his home country (protocol deviation)
Source: Listing 16.2.6.7
Abbreviations: MRI=magnetic resonance imaging; NA=not assessed, subject has not reached that timepoint; NR=no result

Neurological assessment

All patients assessed had neuropsychological test results within the normal range, but the number of evaluations and patients is very limited.

In the additional sheets, the company provided following data at last observation:

Patient 1: Bayley-IIII at baseline P:95 / L: 97 and at year 1 P:95 / L:89
Patient 2: Bayley-IIII at baseline P:115 / L: 115 and at year 1 P:105 / L:103
Patient 3: Bayley-IIII at baseline P:100/ L: 94 and at year 1 P:100 / L:91
Patient 4: WPPS-IIII at baseline P:115/ L: 97 and at month 6 1 P:129 / L:122

Table 22: Neuropsychological Composite Scores – Bayley-III

Assessment	MLDCRY02	MLDCRY03	MLDCRY04
Performance Score			
Screening	95	115	100
Month 6	95	NR[a]	NA
Year 1	95	NA	
Language Score			
Screening	97	115	94
Month 6	91	NR[a]	NA
Year 1	89	NA	

[a] Neuropsychological tests were not administered at Month 6 for Subject MLDCRY03 as this subject was seen remotely in his home country (protocol deviation).
Source: Listing 16.2.6.10
Abbreviations: NA=not assessed, subject had not reached that timepoint; NR=not reported

Table 23: Neuropsychological Composite Scores - WPPSI-III

Assessment	MLDCRY06
Total IQ	
Screening	114
Baseline	95
Performance Score	
Screening	115
Baseline	93
Language Score	
Screening	109
Baseline	97

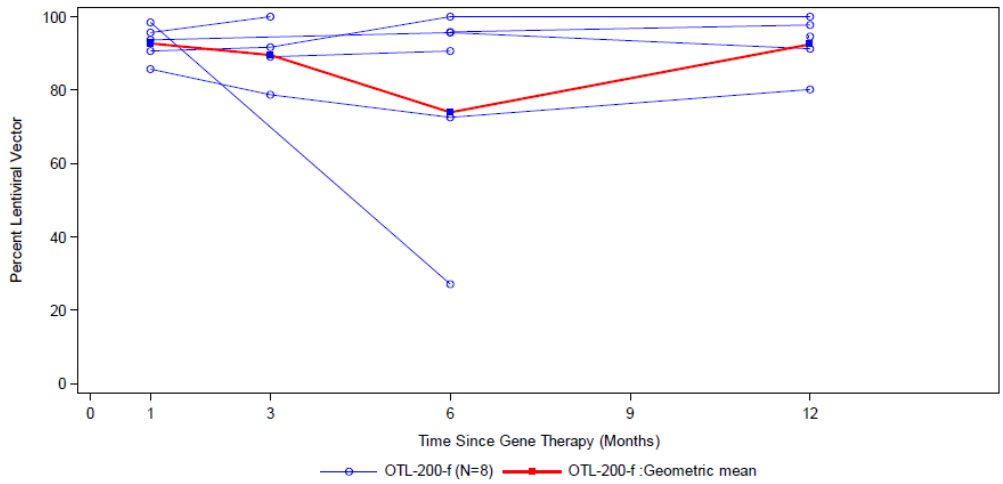
Source: Listing 16.2.6.10

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

HE 205029 – CUP 206258

Beginning 28 days after treatment with AA-f, all tested patients showed a high percentage of %LV+ cells (geometric mean: 92.71%, range: 85.7% to 98.4%; n=5). In 1 patient there was a decrease in %LV+ cells from 98,44% at day 28 to 27,08% at month 6.

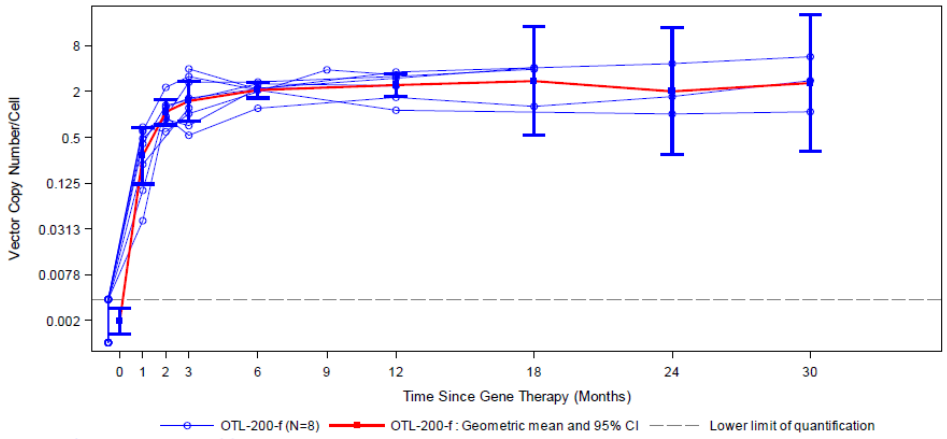
Figure 3: Profiles of Percent Lentiviral Vector Transduced Cells in Bone Marrow, with Geometric Mean



Source: Figure 14.2.9.2, Table 14.2.9.1
The following number of patients contributed data at each time point: Day 28 (n=5); Month 3 (n=4); Month 6 (n=5); Month 9 (n=1); Year 1 (n=5)
NOTE: Geometric means are presented where there are at least 3 patients with data.

Versie préCTG:

Figure 7: Profiles of Vector Copy Number in PBMC

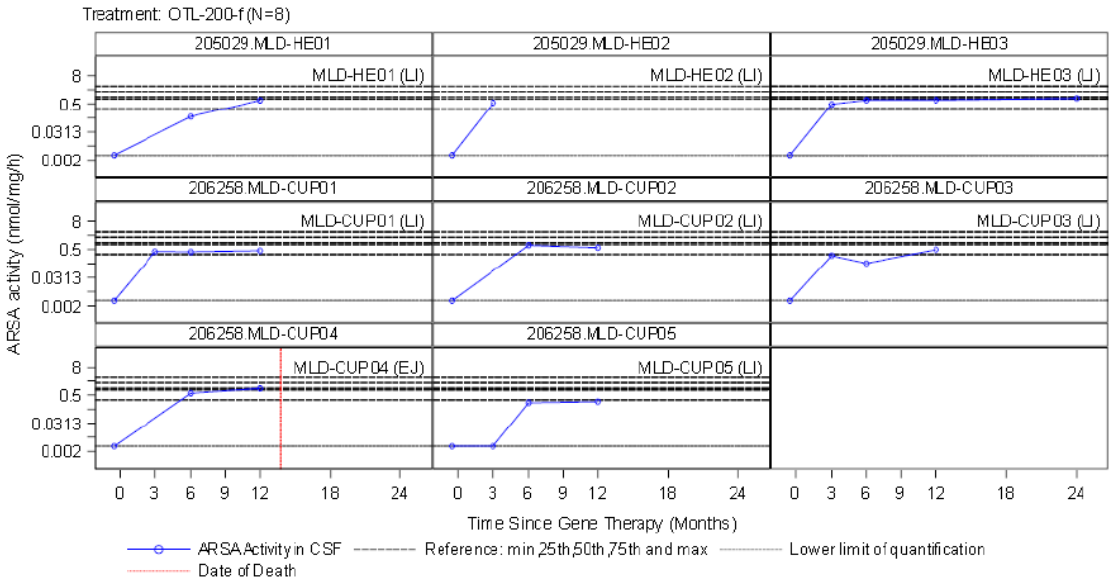


Source: Figure 14.2.8.2, Table 14.2.8.1
The following number of patients contributed data at each time point: baseline (n=8); Day 28 (n=8); Day 60 (n=7); Month 3 (n=7); Month 6 (n=7); Month 9 (n=1); Year 1 (n=8); Year 1.5 (n=3);Year 2 (n=3); Year 2.5 (n=3).
NOTE: LLQ=0.0037 VCN/cell. Values less than the LLQ were imputed as 0.0037 VCN/cell. Geometric means and 95% CIs are presented where there are at least 3 patients with non-imputed data.
CI=confidence interval; LLQ=lower limit of quantitation; PBMC=peripheral blood mononuclear cell; VCN=vector copy number

ARSA in CSF

At baseline, ARSA activity levels in CSF in all patients were undetectable (values at the LLQ (0.0032 nmol/mg/h imputed). After treatment with AA-f the ARSA activity levels in CSF were detectable in 4 of 5 patients with data by Month 3 and in all patients with data (n=7) by Month 6, with a geometric mean activity of 0,3409 nmol/mg/h (95% CI: 0,16968 nmol/mg/h, 0,68502 nmol/mg/h) at Month 6, which is within the reference range. The ARSA activity in CSF remained stable through Year 1 (geometric mean: 0,5599 nmol/mg/h; 95%CI: 0,37958 nmol/mg/h, 0,82591 nmol/mg/h).

Figure 13: Panel Plot of ARSA Activity Profiles in CSF

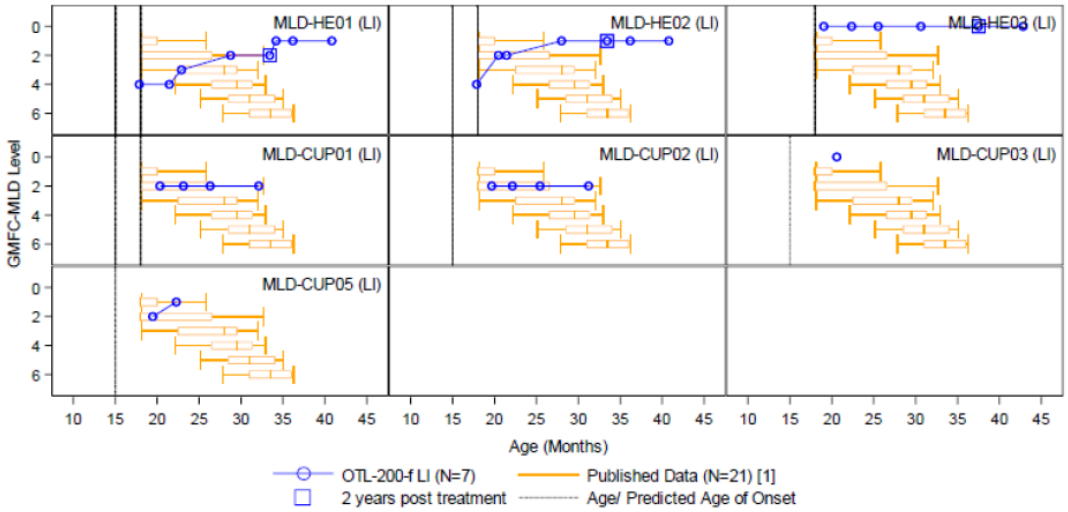


Source: Figure 14.2.4.3
NOTE: Values less than the LLQ were imputed at the LLQ (0.0032 nmol/mg/h).
ARSA=arylsulfatase A; CSF=cerebrospinal fluid; LLQ=lower limit of quantitation

GMFC-MLD

Data from GMFC-MLD is limited for some patients because its utility is only valid after the age of 18 months, and at the last data point 6 patients were at level 0 or level 1, with 2 patients at level 2. All LI patients were able to walk with or without support.

Figure 15: Panel Plot of GMFC-MLD Levels by Age and by Patient (LI)



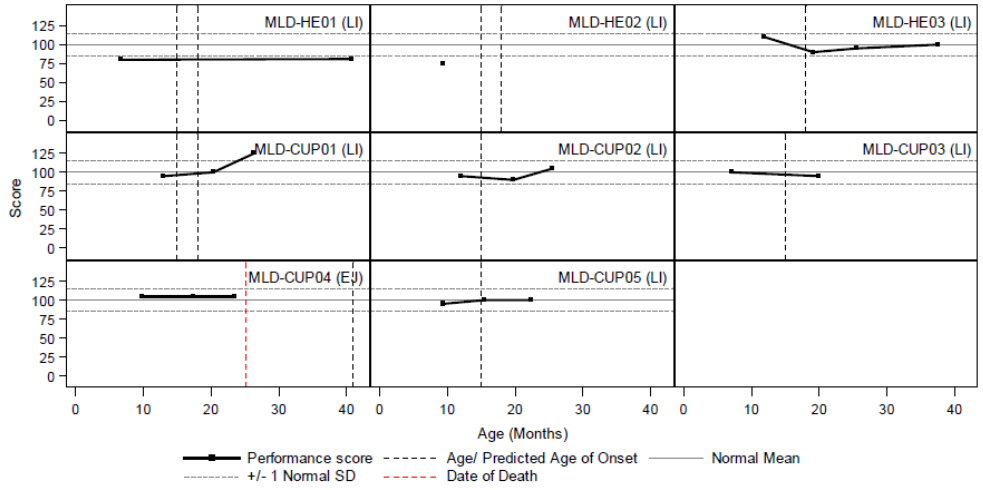
Source: Figure 14.2.1.4, SR-TIGET NHX (Kehrer, 2011b) (for orange box plots showing the natural course of gross motor deterioration in MLD)
NOTE: Two reference lines for 'Age/ Predicted Age of Onset' reflect the range of ages provided in eCRF. Boxplots represent 10th, 25th, median, 75th, and 90th percentiles.
eCRF=electronic case report form; GMFM=gross motor function measure; GT=gene therapy; LI=late infantile; MLD=metachromatic leukodystrophy; NHX=natural history

Neuropsychological results

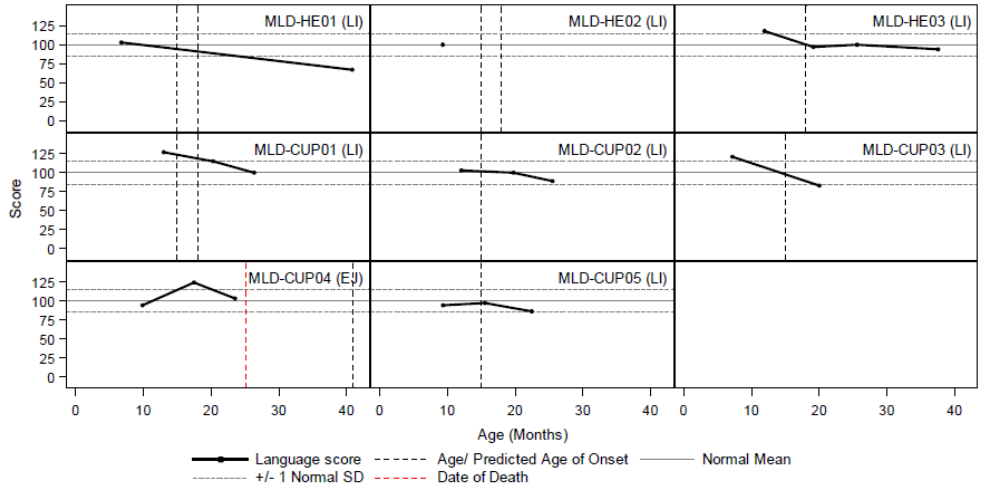
At the time of data cut, all 8 patients were <4 years of age; therefore, only the Bayley-III and WPPSI-III tools were currently employed. Results were generally limited at the time of the data cut, due to limited follow-up in all patients and missing data points in those patients who had the longest post-treatment follow up. All patients had a Performance IQ and a Verbal IQ well above the threshold of severe mental disability (IQ>55).
Overall, the performance scores were stable over time, in contrast to the language scores, which decreased, but styed within the normal range ±1SD in most of the patients.

Figure 17: Panel Plot of Neuropsychological Test Profiles by Component

Performance Score



Language Score

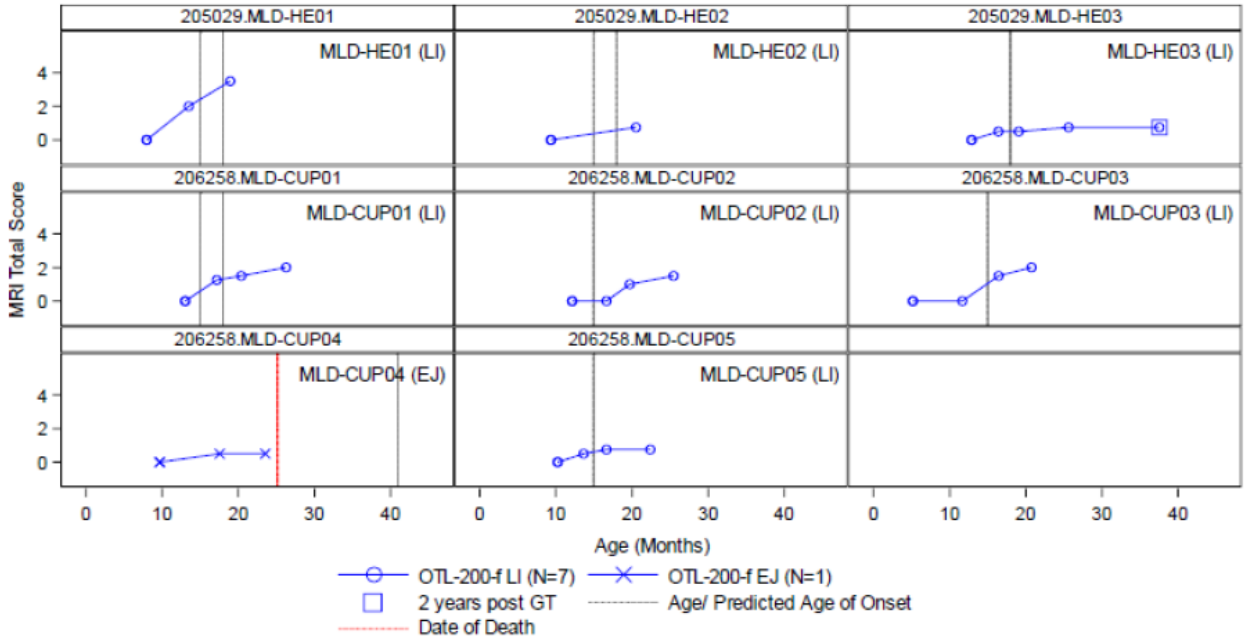


Source: Figure 14.2.7.2
NOTE: If two reference lines are shown for 'Age/Predicted Age of Onset', lines reflect a range of ages that was provided in the eCRF.
eCRF=electronic case report form; EJ=early juvenile; LI=late infantile; SD=standard deviation

MRI score

All patients showed normal MRI total scores (zero) at baseline indicating a lack of brain atrophy/demyelination in all 8 patients at enrollment. The MRI total scores observed over the course of limited follow-up in the treated patients increased slightly to a score of up to 2 in 7 out of the 8 patients. The increase was attributed to a slight increase in the demyelination score.

Figure 18: Panel Plot of MRI Total Score Profiles



Nerve conduction velocity (NCV)

Overall, the NCV was stable in most of the patients, either within or below the normal values for age.

Table 23: Patient Listing of Age-Normalized Nerve Conduction Velocity Index by Visit

Patient ID	MLDHE01	MLDHE02	MLDHE03	MLDCUP01	MLDCUP02	MLDCUP03	MLDCUP04	MLDCUP05
Age at time of treatment, months	8.2	9.6	13.4	14.2	13.3	8.7	11.4	10.6
NCV Index								
Screening	NP	NP	NP[a]	-6.01	NP	NP	1.12	NP
baseline	-0.69	0.55	-1.36	NP	-5.52	-3.99	NP	NP[b]
Month 3	NP	NP	-0.24	NP[c]	-6.25	-5.17	NP	-5.68
Month 6	NP	NP[a]	-0.64	-8.79	-6.77	NP[a]	-0.01	-5.45
Year 1	NP[a]	NP	-1.50	-7.19	-10.14	-4.14	1.19	-6.52
Year 2	NP	NP	0.23	●	●	●	■	●

Source: Listings 16.2.4.1 and 16.2.6.7

[a] Examination performed at local hospital, NCV index could not be calculated.

[b] NCV index could not be calculated – sural nerve missing

[c] NCV index could not be calculated – median nerve missing.

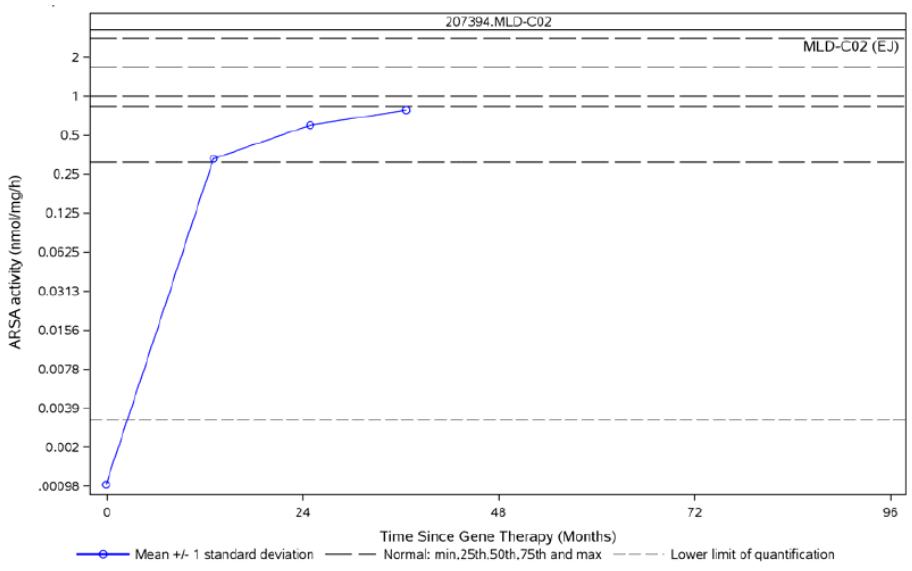
CUP=compassionate use program, HE=hospital exemption; NCV=Nerve conduction velocity; NP=not performed; ●=patient has not reached this time point; ■=patient has died

CUP 207394:

ARSA in CSF

ARSA activity in CSF was within the reference range at Month 12 post-gene therapy (the first time point CSF was tested) and continued to rise until Year 3.

Figure 6 ARSA Activity (nmol/mg/h) in Cerebrospinal Fluid Over Time

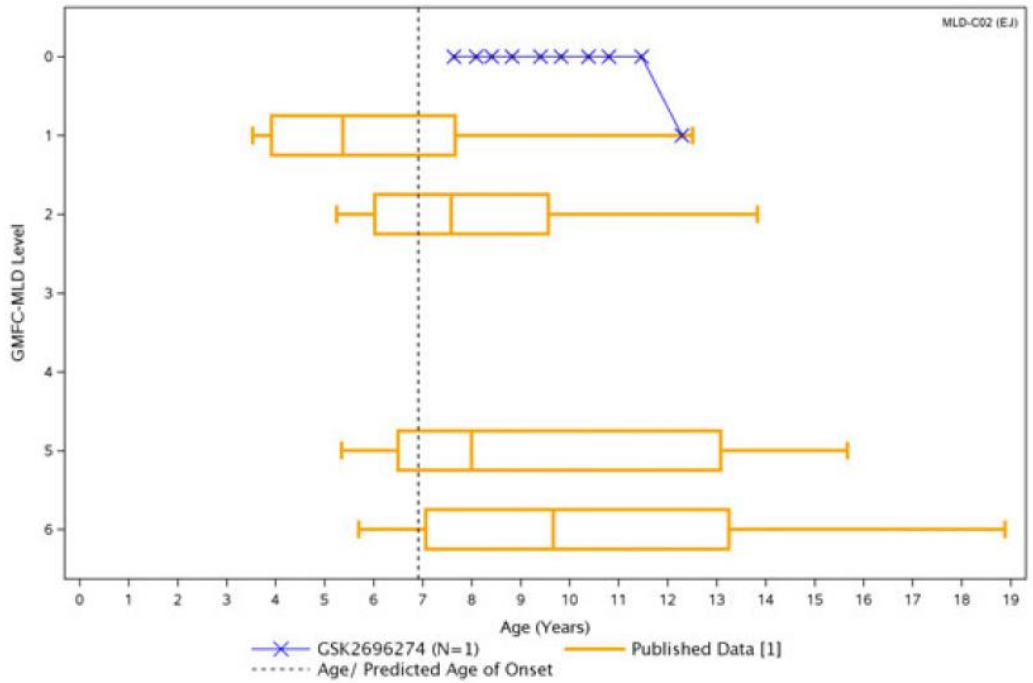


ARSA=arylsulfatase A; EJ=early juvenile; LLOQ=lower limit of quantification
Note: Values ≤0 are imputed as 0.001 to show on the figure. LLOQ is 0.0032 nmol/mg/h.
Normal reference lines at minimum, 25%, median, 75%, and maximum of normal are presented.
Normal range: 0.31 to 2.82 nmol/mg/h.

GMFC-MLD

The patients was at GMFC-MLD Level 0 at baseline and remained at Level 0 through year 3,5 post-gene therapy. At the patient's year 4,5 visit, the patient had moved to GMFC-MLD Level 1 (reduced gait quality).

Figure 9 Panel Plot of GMFC-MLD Levels by Age

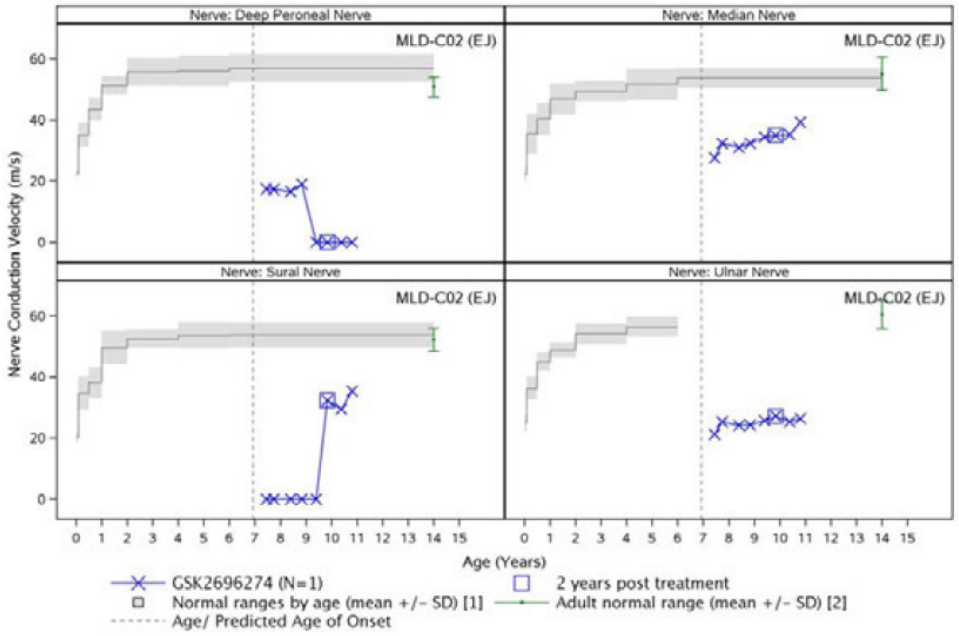


Nerve conduction velocity (NCV)

The upper limb sensory median nerve and motor ulnar NCVs were stable over time. The lower limb sensory sural NCV showed improvement between year 1,5 and 2 post-treatment and remained relatively stable through year 3 (the last assessment time prior to data cut-off). The lower limb motor (deep peroneal) nerve showed a substantial worsening to unrecordable NCVs distal to the tibialis muscle from year 1,5.

The NCV Index increased over time, but it remained markedly abnormal.

Figure 10 Panel Plot of Nerve Conduction Velocity Profiles by Nerve



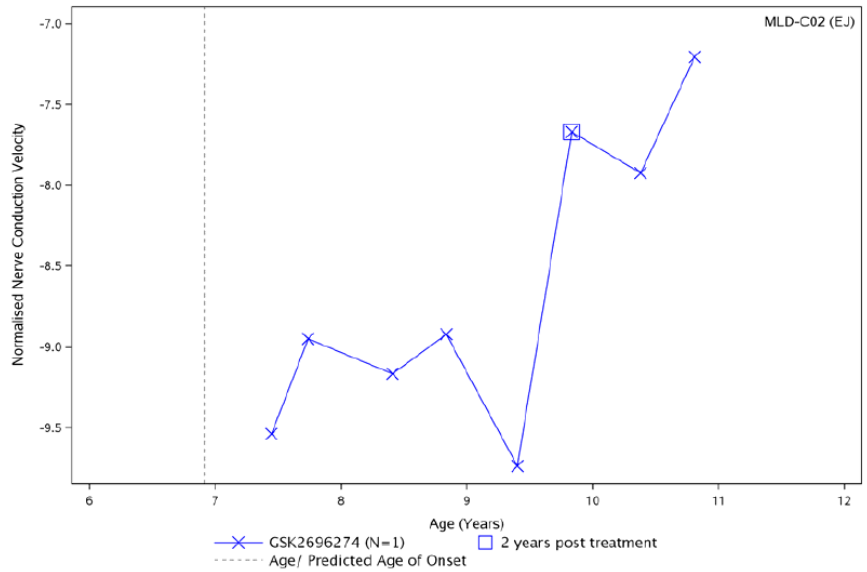
EJ=early juvenile; SD=standard deviation

[1] For deep peroneal, median and sural nerves, data from Parano, 1993: "Electrophysiologic correlates of peripheral nervous system maturation in infancy and childhood." For the ulnar nerve, data from García, 2000: "Peripheral motor and sensory nerve conduction studies in normal infants and children."

[2] Data from Martinenghi, 1997: "Amelioration of nerve conduction velocity following simultaneous kidney/pancreas transplantation is due to the glycaemic control provided by the pancreas."

Source: Figure 2.7

Figure 11 NCV Index

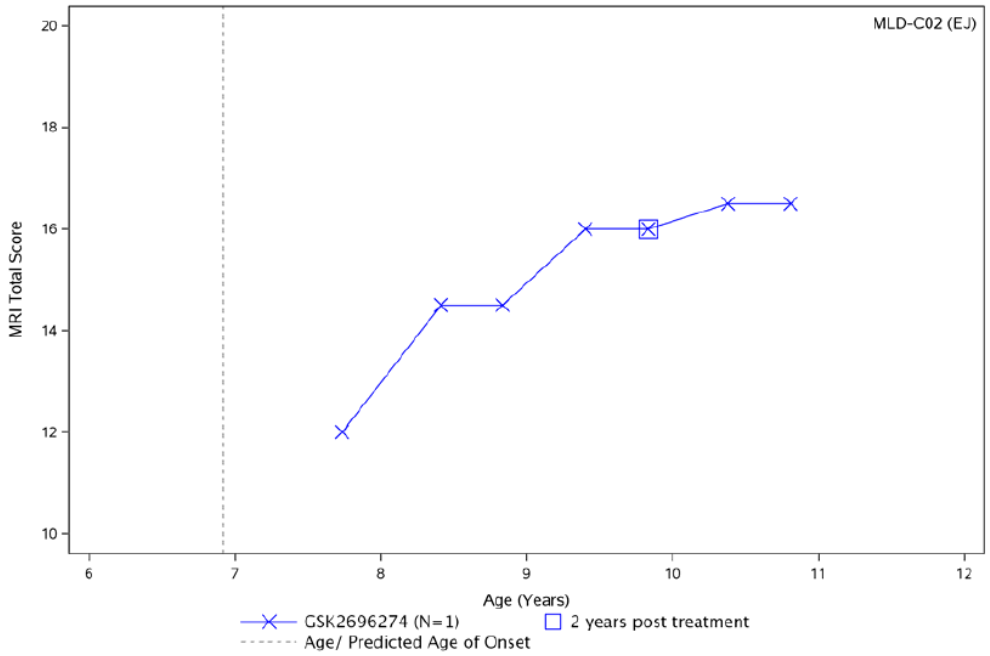


EJ=early juvenile; NCV=nerve conduction velocity

Brain MRI

The baseline MRI total severity score is 12 with demyelination constituting the greater proportion of the total severity score (demyelination score of 10.0 in characteristic regions including the parieto-occipital and frontal lobes, spreading from the peri-ventricular to subcortical regions and the entire corpus callosum with tigroid aspect 0.5), and only a minor degree of atrophy is detected (1.5). Progression in total score is observed during the first 24 months post-treatment, and this is attributed to the worsening of focal and global atrophy, which rises from a score of 1.5 to 5.75. Both MRI total score and the atrophy sub-score stabilised from Year 2 to 3 post-gene therapy.

Figure 12 Panel Plot of MRI Total Score Profiles

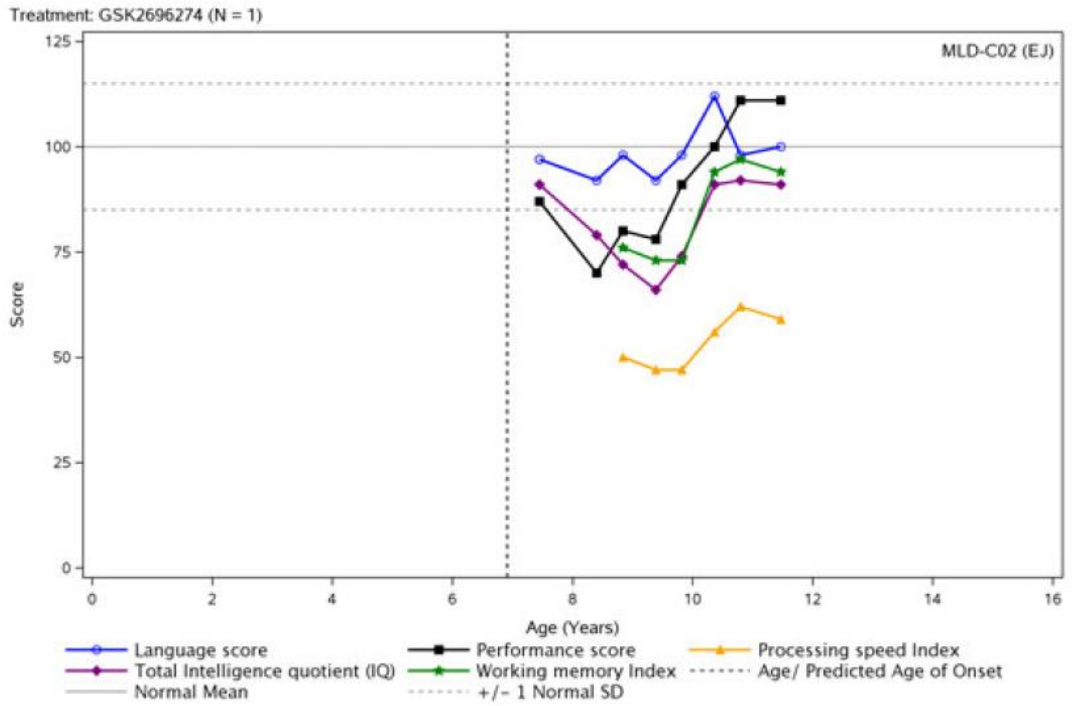


EJ=early juvenile; MRI=magnetic resonance imaging
Source: Figure 2.9

Neuropsychological testing

Neuropsychological test scores (Language, Performance, Full Scale IQ) were in the normal range at pre-treatment and showed a decline in the initial post-treatment period, and this may be related to the conditioning regimen. These scores as well as the Working Memory score began increasing from approximately Year 2 post treatment to within the normal range from Year 2.5 onwards. The exception is the Processing Speed Index, which remains below the normal range throughout the follow-up period.

Figure 14 Panel Plot of Neuropsychological Test Profiles by Component



EJ=early juvenile; SD=standard deviation

d) Exploratory outcomes

Study 201222:

Not applicable

Study 205756:

Not applicable

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

Not applicable

Comparative elements and justification

It should be noted that all of the 19 LI-MLD patients and all of the 12 EJ MLD patients in the comparative TIGET NHX study were symptomatic at enrolment in the study, which can induce a timing bias in a direct comparison on MLD evolution. The company noted in the CSR that retrospective data analysis was performed, resulting mean age of data in the LI patients of 20,65 months (range 10 – 27,9 months) and 51,98 months (range 20,3 – 74,2 months for the EJ patients) which is comparable to the 201222 study patients.

3.3.1.1. ADVERSE EVENTS

EPAR element

Table 12 depicts the most frequently reported adverse events across the treatment phases. The most frequently reported adverse events in the follow-up phase (post gene therapy) were infections and infestations (90% of subjects), blood and lymphatic system disorders (79% of subjects), gastrointestinal disorders (79% of subjects), investigations (79% of subjects), general disorders and administration site conditions (76% of subjects), hepatobiliary disorders (55% of subjects), and nervous system disorders (52% of subjects).

During the Follow-up post-GT phase, in addition to the events of renal tubular acidosis and metabolic acidosis, events associated with MLD included gait disturbance (15 subjects, 52%), motor dysfunction (9 subjects, 31%), muscle spasticity (9 subjects, 31%), aphasia (6 subjects 21%), ataxia (5 subjects, 17%), dysarthria (5 subjects, 17%), cognitive disorder (4 subjects, 14%), dysphagia (4 subjects, 14%), and seizure (2 subjects, 7%).

In Study 205756, there was only one AE classified as associated with MLD, which was gait disturbance in one subject (Patient 30) at Month 6 (age 18.7 months) and Month 9 (age 22.1 months) due to a delay in independent walking.

Versie préCTG:

Table 15: Grade 3 or Higher Adverse Events Reported in 2 or More Subjects (at least 7%) in the Follow-Up Post-GT Phase, by Preferred Term by Study Phase (Integrated Safety Set)

PT	Pre-Tx	Tx	Acute	3 Month Post-GT	Short Term	Long Term	Total Follow-up Post-GT
	(N=29) n (%)	(N=29) n (%)	(N=29) n (%)	(N=29) n (%)	(N=29) n (%)	(N=16) n (%)	(N=29) n (%)
Any Event	7 (24)	8 (28)	0	27 (93)	22 (76)	5 (31)	29 (100)
Febrile Neutropenia	0	0	0	23 (79)	0	0	23 (79)
Gait Disturbance	1 (3)	0	0	5 (17)	9 (31)	1 (6)	15 (52)
Stomatitis	0	0	0	12 (41)	0	0	12 (41)
Motor Dysfunction	0	0	0	2 (7)	7 (24)	0	9 (31)
Muscle Spasticity	0	0	0	1 (3)	6 (21)	2 (13)	9 (31)
Mucosal Inflammation	0	0	0	9 (31)	0	0	9 (31)
Aphasia	0	0	0	1 (3)	4 (14)	1 (6)	6 (21)
Ataxia	0	0	0	2 (7)	3 (10)	0	5 (17)
Device Related Infection	3 (10)	0	0	2 (7)	3 (10)	0	5 (17)
Neutropenia[a]	0	0	0	5 (17)	0	0	5 (17)
Cognitive Disorder	0	0	0	0	3 (10)	1 (6)	4 (14)
Dysarthria	0	0	0	1 (3)	4 (14)	0	5 (17)
Dysphagia	0	0	0	0	3 (10)	1 (6)	4 (14)
Vomiting	0	0	0	3 (10)	0	1 (6)	4 (14)
Enteritis	0	0	0	0	3 (10)	0	3 (10)
Metabolic Acidosis	2 (7)	4 (14)	0	2 (7)	1 (3)	0	3 (10)
Pneumonia	0	0	0	1 (3)	2 (7)	1 (6)	3 (10)
Venooclusive Liver Disease	0	0	0	3 (10)	0	0	3 (10)
Atypical Haemolytic Uraemic Syndrome	0	0	0	2 (7)	0	0	2 (7)
Clostridium Difficile Colitis	0	0	0	2 (7)	0	0	2 (7)
Epistaxis	0	0	0	2 (7)	0	0	2 (7)
Rash Erythematous	0	0	0	2 (7)	0	0	2 (7)
Seizure	0	0	0	0	1 (3)	1 (6)	2 (7)

[a] Prolonged neutropenia (neutropenia beyond Day 45 post-treatment)
Abbreviations: GT=gene therapy; PT=preferred term; Tx=treatment.

Deaths

To date, three deaths have been reported in subjects treated with Libmeldy during the clinical development programme (two subjects -Patient 19 and Patient20- in Study 201222; one subject -Patient 27- in Study 206258), all deemed to be unrelated to Libmeldy-f.

Two of these deaths were attributed to rapid progression of the underlying disease; in both cases the subjects were reported to be early symptomatic at the time of GT. One death was due to left hemisphere cerebral ischemic stroke, deemed unrelated to Libmeldy-f. All three events are further described below.

Two subjects (Patient 19,20) died during the registrational study as a result of events associated with rapid disease progression (dysphagia) approximately 15 and 8 months, respectively, after receiving treatment.

Immunological events

AAA were detected in four of 29 subjects treated with the fresh formulation of Libmeldy.

Antibody titres in all 4 subjects were generally low and at the time of the data cut, all had resolved to negative test results, either spontaneously (n=1) or after 1 cycle of rituximab (n=3). In two cases (Patient 25 and 28), gait disturbance developed after the detection of AAAs.

For Study 201222 (where AAA were tested from 3 months post-treatment onwards), no subjects have tested positive for AAA and none of the treated subjects under EAPs tested positive for antibodies at the baseline visit.

Study 201222:

All 20 patients included in the Safety population experienced at least 1 AE following AA-f treatment, of which at least 1 was of severity NCI CTC Grade 3. Five patients experienced a Grade 4, life-threatening event, and 2 patients experienced a Grade 5, fatal AE. Additionally, a total of 16 patients reported at least 1 SAE. None of the AEs reported as of the data cut-off date were considered by the investigator as related to AA-f.
The majority of AEs occurring in 2 or more subjects were reported during the 3-month post-treatment and short-term phases. No adverse reactions or suspected unexpected adverse reactions were reported for AA-f.
Within 3 months post-treatment, febrile neutropenia, neutropenia, stomatitis, device-related infection, serum ferritin increase, ataxia, renal tubular acidosis, and epistaxis were more evident in subjects treated with the MAC regimen compared with the SMAC regimen, though these kinds of events were common to both conditioning regimens. Mucosal inflammation was more commonly reported in the SMAC regimen (56%) than in the MAC regimen (9%).

A total of 352 AEs were reported in 20 patients during the Follow-up phase. The majority of events (275 AEs) were reported either during the 3-month post-GT phase (112 AEs) or the short-term phase (163 AEs). In total, 76% of the AEs (266 events) were reported as recovered/resolved up to the data cut-off date. The majority of AEs reported during both the 3-month post-GT phase and the short-term phase (85% and 70%, respectively) were reported as resolved. The ongoing AEs were generally deemed related to the underlying disease.

Table 36 Overview of Adverse Events (Safety Population)

Description	Total Subjects who Received OTL-200-f (N=20)	
	n (%)	Number of AEs
AEs occurring after OTL-200-f administration		
Any AE	20 (100)	352
Any deaths	2 (10)	2
Any SAE	16 (80)	34
Any AE leading to withdrawal from the study	2 (10)	2
Any treatment-related AE (including SAEs)	0	0
AEs by intensity (Follow-up phase)		
Grade 1	19 (95)	95
Grade 2	18 (90)	129
Grade 3	20 (100)	121
Grade 4	5 (25)	5
Grade 5	2 (10)	2
Any AE by Treatment phase		
Pre-treatment	20 (100)	59
Treatment	13 (65)	18
Acute phase	2 (10)	2
3 months post-OTL-200-f	20 (100)	112
Short-term	19 (95)	163
Long-term	13 (87)	75

n refers to the number of subjects who experienced the AE.
Note: Treatment phase was from Day -4 to Day 1, Acute phase was within 48 hours of GT, 3 Months post-GT phase was from 48 hours post-GT and 3 months, Short-term phase was from month 3 to 3 years after GT, and Long-term phase was >3 years after GT.
Source: Table 2.11, Table 2.34, Table 2.38, Table 2.39, Table 2.40, Table 2.41, Table 2.42, and Table 2.57.

Table 37 Summary of Adverse Events (Number of Subjects and Occurrences) by Busulfan Regimen (Safety Population)

Description	SMAC Regimen (N=9)	MAC Regimen (N=11)	Total (N=20)
Treatment phase			
Number of subjects with AEs	5 (56)	8 (73)	13 (65)
Number of AEs	5	13	18
Acute phase			
Number of subjects with AEs	1 (11)	1 (9)	2 (10)
Number of AEs	1	1	2
3 Months Post-GT phase			
Number of subjects with AEs	9 (100)	11 (100)	20 (100)
Number of AEs	45	67	112

n refers to the number of subjects who experienced the AE.
Note: Treatment phase was from Day -4 to Day 1, Acute phase was within 48 hours of GT, 3 Months post-GT phase was from 48 hours post-GT and 3 months
Source: Table 2.44, Table 2.45, and Table 2.46.

Table 38 Summary of Adverse Events (Number of Subjects and Occurrences) by Treatment Phase and Busulfan Regimen (Safety Population)

System Organ Class / Preferred Term	Number of Subjects with AEs (%) (Number of Events)					
	Treatment (N=20)		Acute (N=20)		3 Month Post-GT (N=20)	
	SMAC (N=9)	MAC (N=11)	SMAC	MAC	SMAC	MAC
Any event	**5 (56) 5**	**8 (73) 13**	**1 (11) 1**	**1 (9) 1**	**9 (100) 45**	**11 (100) 67**
Blood and lymphatic disorders						
Febrile neutropenia	0	0	0	0	5 (56) 5	10 (91) 10
Neutropenia	0	0	0	0	0	2 (18) 2
Eye disorders						
Ocular hyperaemia	0	0	0	0	0	1 (9) 1
Cardiac disorders						
Bradyarrhythmia	0	1 (9) 1	0	0	0	0
Gastrointestinal disorders						
Ascites	0	0	0	0	1 (11) 1	0
Diarrhoea	0	0	0	0	0	1 (9) 1
Stomatitis	0	0	0	0	0	8 (73) 8
Vomiting	0	0	0	0	0	1 (9) 4
General disorders and administration site conditions						
Gait disturbance	0	0	0	0	2 (22) 2	3 (27) 3
Mucosal inflammation	0	0	0	0	5 (56) 5	1 (9) 1
Pyrexia	0	0	0	0	1 (11) 2	0
Hepatobiliary disorders						
Drug-induced liver injury	0	0	0	1 (9)	0	0
Gallbladder enlargement	0	0	0	0	0	1 (9) 1
Hepatomegaly	1 (11) 1	1 (9) 1	1 (11) 1	0	2 (22) 2	1 (9) 1
Infections and infestations						
Clostridium difficile colitis	0	0	0	0	1 (11) 1	2 (18) 2
Conjunctivitis	0	0	0	0	0	1 (9) 1
Cytomegalovirus viraemia	0	0	0	0	1 (11) 1	0
Device related infection	0	0	0	0	0	2 (18) 2
Ear infection	0	0	0	0	1 (11) 1	0
Escherichia infection	0	0	0	0	1 (11) 1	0
Gastroenteritis aeromonas	0	0	0	0	0	1 (9) 1

Versie préCTG:

System Organ Class / Preferred Term	Number of Subjects with AEs (%) (Number of Events)					
	Treatment (N=20)		Acute (N=20)		3 Month Post-GT (N=20)	
	SMAC (N=9)	MAC (N=11)	SMAC	MAC	SMAC	MAC
Haemophilius infection	0	0	0	0	1 (11) 1	0
Oral candidiasis	0	0	0	0	0	1 (9) 1
Respiratory tract infection	1 (11) 1	0	0	0	0	0
Skin infection	0	1 (9) 1	0	0	0	0
Staphylococcal infection	0	0	0	0	1 (11) 1	0
Upper respiratory fungal infection	0	0	0	0	1 (11) 1	0
Upper respiratory tract infection	0	0	0	0	1 (11) 1	1 (9) 1
Urinary tract infection	0	0	0	0	1 (11) 1	0
Injury, poisoning, and procedural complications						
Head injury	1 (11) 1	0	0	0	0	1 (9) 1
Investigations						
Acinetobacter test positive					1 (11) 2	0
Alanine aminotransferase increased	0	1 (9) 1	0	0	0	1 (9) 1
Aspartate aminotransferase increased	0	1 (9) 1	0	0	0	1 (9) 1
Aspergillus test positive	0	0	0	0	1 (11) 1	0
Blood immunoglobulin E increased	0	0	0	0	2 (22) 2	1 (9) 1
Candida test positive	0	0	0	0	1 (11) 1	0
Moraxella test positive	0	0	0	0	1 (11) 1	0
Penicillium test positive	0	0	0	0	0	1 (9) 1
Serum ferratin increased	0	0	0	0	0	5 (45) 5
Staphylococcus test positive	0	1 (9) 1	0	0	0	0
Stenotrophonas test positive	0	0	0	0	1 (11) 1	0
Metabolism and nutrition disorders						
Metabolic acidosis	0	4 (36) 4	0	0	2 (22) 2	0
Musculoskeletal and connective tissue disorders						
Bone pain	0	0	0	0	1 (11) 1	0
Nervous system disorders						
Aphasia	0	0	0	0	1 (11) 1	0
Ataxia	0	0	0	0	0	2 (18) 2
Dysarthria	0	0	0	0	1 (11) 1	0
Headache	0	0	0	0	0	1 (9) 1
Motor dysfunction	0	0	0	0	1 (11) 1	
Muscle spasticity	0	0	0	0	0	1 (9) 1

System Organ Class / Preferred Term	Number of Subjects with AEs (%) (Number of Events)					
	Treatment (N=20)		Acute (N=20)		3 Month Post-GT (N=20)	
	SMAC (N=9)	MAC (N=11)	SMAC	MAC	SMAC	MAC
Renal and urinary disorders						
Oliguria					1 (11) 1	0
Renal tubular acidosis	2 (22) 2	1 (9) 1	0	0	0	2 (18) 2
Respiratory, thoracic, and mediastinal disorders						
Epistaxis					0	2 (18) 4
Oropharyngeal pain					1 (11) 1	0
Skin and subcutaneous tissue disorders						
Dermatitis					1 (11) 1	0
Dermatitis diaper					0	1 (9) 1
Eczema	0	1 (9) 1	0	0		
Rash erythematous	0	1 (9) 1	0	0	2 (22) 2	1 (9) 2
Rash pruritic					0	1 (9) 1
Skin exfoliation					0	1 (9) 1
Skin lesion					0	1 (9) 1
Vascular disorders						
Haematoma					0	1 (9) 1

n refers to the number of subjects who experienced the AE.
Phase of Treatment is based on the AE onset. Treatment phase is on Day -4 to Day 1, Acute Phase is within 48 hours of GT, 3 Months Post-GT phase is from 48 hours post-GT and 3 months.
Source: Table 2.44, Table 2.45, and Table 2.46.

Study 205756:

After busulfan conditioning, all subjects experienced severe neutropenia (ANC <500/µL) and 3 patients had prolonged neutropenia (ANC <500 µL at Day +45) requiring G-CSF administration (single administration in 2 cases and 2 doses for the third subject). None of the patients had ANC <500/µL at Day +60, and none of the subjects met the prespecified definition of engraftment failure, defined as an ANC <500/µL at Day +60 with no evidence of BM recovery, requiring cellular back-up administration.

During the treatment fase 1 patients experienced a Grade 3 hypertransaminasemia, and during the 3 month follow-up period, all 4 patients experienced Grade 3 AE's, being febrile neutropenia (5 events, 4 patients), neutropenia (3 events, 3 patients) and stomatitis (3 events, 3 patients).

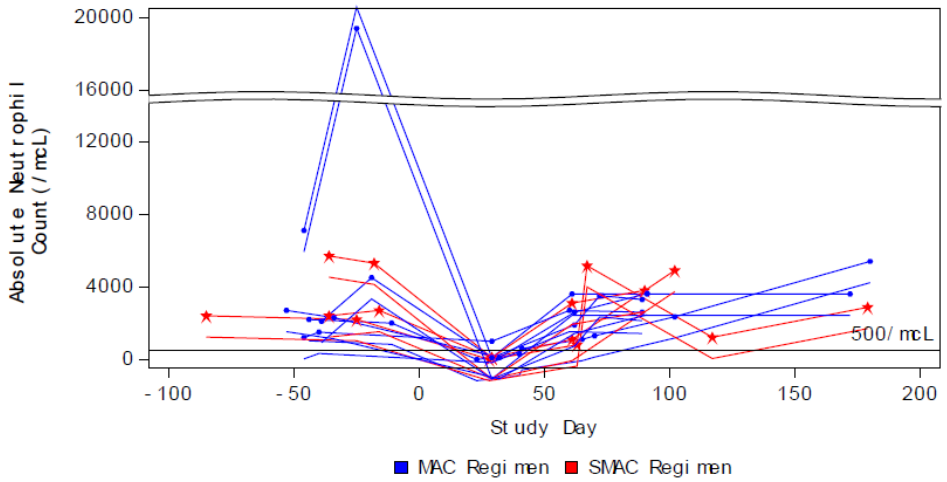
Description	OTL-200-c (N=4)	
	n (%)	Number of AEs
AEs Occurring after OTL-200-c Administration (Follow-up Phase), by NCI CTC Grade		
Grade 1	3 (75)	6
Grade 2	3 (75)	21
Grade 3	4 (100)	14
Grade 4	0	0
Grade 5	0	0

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

HE 205029 – CUP 206258

As expected following busulfan conditioning, all patients experienced severe neutropenia (ANC<500/µL) at one or more time points prior to day 60. The median number of days with ANC<500/µL was 30,0 days (range: 13 to 39 days) in all patients (N=8). Severe neutropenia (ANC<500/µL) was slightly longer in patients who received a SMAC regimen (n=3; median: 35,0 days, range: 22 to 37 days) than in those who received a MAC regimen (n=5; median: 28,0 days, range: 13 to 39 days).

Figure 19: Patient Profiles of Absolute Neutrophil Count by Conditioning Regimen



Source: Figure 14.3.4.5
MAC=myeloablative conditioning; SMAC=sub-myeloablative conditioning

No patients experienced an NCI CTC Grade ≥2 AE during the treatment (day -4 to day 1) or acute (within the first 48 hours after AA-f administration) phases of the programs. During the 3-Month Post-Treatment phase, 7 of 8 patients (88%) experienced an NCI CTC Grade ≥2 AE. The majority of NCI CTC Grade ≥2 AEs during this phase were events commonly associated with busulfan conditioning, including hematologic events, infections, hepatobiliary disorders, and gastrointestinal events.

All 8 patients experienced at least 1 AE after AA-f treatment and all patients had at least 1 AE that was NCI CTC Grade ≥3. One patient experienced 2 Grade 4 events and 1 patient experienced a fatal event.

Versie préCTG:
The most common AEs during the 3 Months Post-Treatment phase were febrile neutropenia in 7 patients (88%), mucosal inflammation in 4 patients (50%), and neutropenia, stomatitis, veno-occlusive liver disease, blood immunoglobulin E increased, and rash erythematous in 3 patients (38%) each.

A total of 4 patients (50%) had treatment-emergent AEs that were considered related to study treatment by the investigator, being a Grade 2 positive antibody test (anti-ARSA antibodies) within the 3-month post-treatment phase in 2 patients and within the short-term phase (month 3 to year 3) in 3 patients.

Table 29: Adverse Events Reported in at Least 2 Patients by Treatment Phase (Continued)

System Organ Class Preferred Term	Pre-Treatment (N=8)	Treatment (N=8)	Acute (N=8)	3 Month Post-GT (N=8)	Short-Term (N=8)	Follow-up (N=8)
Renal and urinary disorders	3 (38)	1 (13)	0	0	0	0
Renal tubular acidosis	3 (38)	1 (13)	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	4 (50)	1 (13)	4 (50)
Rash erythematous	0	0	0	3 (38)	0	3 (38)
Rash papular	0	0	0	2 (25)	0	2 (25)
Injury, poisoning and procedural complications	0	1 (13)	0	2 (25)	0	2 (25)[b]
Nervous system disorders	0	0	0	1 (13)	2 (25)	3 (38)[c]
Motor dysfunction	0	0	0	1 (13)	1 (13)	2 (25)

Source: Table 14.3.2.1
Pre-treatment phase was prior to Day -4. Treatment phase was Day -4 to Day 1. Acute was within 48 hours of gene therapy. Three months post-gene therapy was from 48 hours post-gene therapy to 3 months. Short-term was from month 3 to 3 years after gene therapy. Follow-up included all AEs after gene therapy.
[a] Prolonged neutropenia (neutropenia beyond Day 45 post-treatment) or neutropenia requiring G-CSF administration (Listing 16.2.7.1).
[b] Events included allergic transfusion reaction in 1 patient and head injury in 1 patient.
[c] In addition to motor dysfunction, events included cerebral microhemorrhage in 1 patient and ischemic cerebral infarction in 1 patient.
AE=adverse event; GT=gene therapy; IgE=immunoglobulin E.

CUP 207394:

A total of 10 AE's were recorded, but no SAE.

AEs occurring in the first 3 months after gene therapy included nausea (CTC grade 2), stomatitis, and febrile neutropenia (both CTC grade 3) and upper respiratory tract infection (CTC Grade 1) within the first few weeks following administration of the treatment. Between Month 3 and 3 years after gene therapy, the patient experienced an AE of gastroenteritis (CTC grade 1) and influenza (CTC grade 1), both of which resolved without concomitant treatment.

Serious adverse reactions

Study 201222:

Two patients died during the study because of events associated with disease progression (dysphagia), respectively approximately 15 and 8 months after receiving the treatment.

A total of 35 SAEs (with 1 SAE reported after the database lock and therefore not presented in the statistical outputs) were reported in 16 patients during the follow-up phase, and generally fell under SOCs of Infections and Infestations (10/35), Nervous System Disorders (11/35), and Gastrointestinal Disorders (7/35). No SAEs were reported during the Treatment or the acute phase. Two patients experienced an SAE in the 3-month post-treatment phase, 14 subjects in the short-term phase, and 3 patients in the long-term phase post-treatment.
No SAE was considered related to AA-f.

Infections typically included device-related infections, pneumonia, and respiratory tract infections. Gastrointestinal disorders included SAEs of dysphagia, enteritis, and vomiting. SAEs of metabolic acidosis have been reported in 2 patients, one of which was considered life threatening.

Table 39 Number (%) of Subjects with Serious Adverse Events by Treatment Phase (Safety Population)

Preferred Term	Treatment Phase					
	Treatment (N=20)	Acute (N=20)	3 Month Post-GT (N=20)	Short -Term (N=20)	Long-Term (N=15)	All Follow-Up (N=20)
Any serious adverse event, n (%)	**0**	**0**	**2 (10)**	**14 (70)**	**3 (20)**	**16 (80)**
Dysphagia[a]	0	0	0	3 (15)	1 (7)	4 (20)
Motor dysfunction[a]	0	0	1 (5)	3 (15)	0	4 (20)
Device related infection	0	0	0	2 (10)	0	2 (10)
Enteritis	0	0	0	2 (10)	0	2 (10)
Gallbladder polyp	0	0	0	2 (10)	0	2 (10)
Metabolic acidosis	0	0	1 (5)	1 (5)	0	2 (10)
Muscle spasticity[a]	0	0	1 (5)	1 (5)	0	2 (10)
Pneumonia	0	0	0	2 (10)	0	2 (10)
Respiratory tract infection	0	0	0	1 (5)	1 (7)	2 (10)
Bacterial sepsis	0	0	0	1 (5)	0	1 (5)
Escherichia infection	0	0	0	1 (5)	0	1 (5)
Foot deformity[a]	0	0	0	1 (5)	0	1 (5)
Gastroenteritis	0	0	0	1 (5)	0	1 (5)
Kawasaki's disease	0	0	0	1 (5)	0	1 (5)
Lung infection	0	0	0	1 (5)	0	1 (5)
Pneumonia aspiration	0	0	0	1 (5)	0	1 (5)
Seizure[a]	0	0	0	1 (5)	1 (7)	2 (10)
Status epilepticus[a]	0	0	0	1 (5)	0	1 (5)
Vomiting	0	0	0	0	1 (7)	1 (5)

n refers to the number of subjects who experienced the AE.
[a] Considered a neurological event.
Note: Treatment phase was from Day -4 to Day 1, Acute phase was within 48 hours of GT, 3 Months Post-GT was from 48 hours post-GT and 3 months, Short-term phase was from Month 3 to 3 years after GT, Long-term phase was >3 years after GT, and Follow-up was all events after GT.
Source: Table 2.47.

Study 205756:

There were no deaths, and a total of 4 SAE's occurred in 2 patients during the study (2 Grade 3 central venous catheter infection, 1 Grade 3 respiratory distress and 1 Grade 3 sepsis.

Table 28: Summary of Serious Adverse Events (Number of Subjects and Occurrences)

Preferred Term	OTL-200-c (N=4)						
	Number of Subjects with Adverse Events (%) [Number of Events]						
	Pre-Treatment (n=4)	Treatment (n=4)	Acute (n=4)	3 Months Post-Treatment (n=4)	Short-Term (n=2)	Long-Term (n=0)	Follow-Up (n=4)
Any Event	**2 (50) [3]**	**0**	**0**	**1 (25) [1]**	**0**	**0**	**1 (25) [1]**
Infections and Infestations							
Device Related Infection	2 (50) [2]	0	0	0	0	0	0
Sepsis	0	0	0	1 (25) [1]	0	0	1 (25) [1]
Respiratory, Thoracic and Mediastinal Disorders							
Respiratory Distress	1 (25) [1]	0	0	0	0	0	0

Source: Table 14.3.2.1

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

HE 205029 – CUP 206258

A total of 4 patients (50%) experienced at least 1 SAE after AA-f treatment.

CUP 207394:

No SAE recorded.

Withdrawal because of adverse reactions

Study 201222:

A total of 2 patients were did leave the study because of adverse effects, being grade 5 fatal dysphagia at month 15 and month 18 respectively.

Study 205756:

Not applicable.

Supportive studies (CUP 207394, CUP 206258 and HE 205029):

HE 205029 – CUP 206258

One patient died due to an ischemic cerebral infarction of day 415. This event was not considered related to AA-f.

CUP 207394:

Not applicable.

Main adverse effects of the reference therapy (ref. 25)

With respect to HSCT, the major adverse events as described in literature, are Transplant related Mortality (TRM), reported in some series to be as high as 17%, mostly due to infections (bacterial, fungal or viral) and GvHD, of which the cumulative incidence of Grade II-IV GvHD is reported in some series to be about 44 % (CI95 26 % - 62 %) and Grade III-IV GvHD 16 % (CI95 4 % - 29 %).

Comparative elements and justification

The company didn't perform any indirect comparison with regards to safety outcome of AA and HSCT in eligible patients.

- APPLICABILITY

Limitations in the use :

Contra-indications – interactions – special precautions

As was discussed in point 3.1.3, the publication of Page et al., 2019 proposes a treatment guideline stating that symptomatic patients with LI-MLD are unlikely to derive significant benefit from HSCT. Those transplanted before symptoms will experience some benefit, although most will later develop peripheral neuropathy.
Juvenile and adult MLD patients with early symptoms are appropriate candidates for HSCT. Cognitive function is generally preserved, but motor and expressive language functions are more variable. Peripheral nerve disease appears to be less responsive to HSCT. MRI typically demonstrates increased white matter changes in the first 6 to 12 months post HSCT, followed by stability or even slight improvement. HSCT benefit in patients with advanced disease is minimal and therefore is not recommended with significant neurologic deficits.

Table 7
Guidelines for Determining HSCT Candidacy for Patients with Juvenile and Adult MLD

	Benefit > Risk	Benefit ~ Risk*	Risk > Benefit
General	Pre- or mildly symptomatic	Mild to moderate symptoms	Moderate to severe symptoms and/or rapid progression of symptoms over previous 3 months
Motor function	M0, mildly increased tone or abnormal reflexes	M1-2, mild to moderately increased tone	M3-5, moderate to severely increased tone, abnormal reflexes
Oral motor function/feeding	Normal feeding	Can communicate in complete sentences; reduced quality for age; no signs or symptoms of aspiration	Cannot communicate in complete sentences; signs or symptoms of aspiration
Seizure	None	None	Present
Neuroimaging†	Minimal T2 hyperintensity	Moderate T2 hyperintensity with extension	Extensive T2 hyperintensity with further extension
Neurocognitive testing	IQ ≥ 85	IQ 70-84	IQ < 70
NCS‡	Normal or mildly abnormal	Moderately abnormal	Severely abnormal
EEG	Normal	Normal	Seizure activity or regions of epileptic potential
VEP§	Normal	Normal	Normal or abnormal
BAER¶	Normal or mildly abnormal	Abnormal	Abnormal

* For these patients, it is important to acknowledge that these guidelines are based on clinical experience and, to a lesser degree, published literature.
† Neuroimaging progression and severity well described [112,130]. Mild disease is characterized by T2 hyperintensity of the frontal, periventricular, corpus callosum, or central white matter. Moderate disease is additionally characterized by extension into subcortical white matter (U-fibers) or basal ganglia/thalamic regions. Severe disease is additionally characterized by involvement of projection fibers or cerebellar white matter, with tigroid appearance of white matter common.
‡ NCS were considered abnormal if prolonged distal latency, low amplitude, no evoked response, or prolonged F-wave latency was present [131]. Designation of severity is based on the neurologist interpretation.
§ VEPs are considered abnormal if the P100 wave is absent or delayed [128].
¶ BAERs are considered abnormal if wave I to V interpeak latency is prolonged or if any of the obligate wave forms (I, III, V) are absent [129].

Regarding the applicability of an AA treatment, the SmPc mentions following precautions:

Contra-indications:

- Hypersensitivity to the active substance or to any of the excipients listed
- Previous treatment with haematopoietic stem cells gene therapy.
- Contraindications to the mobilisation and the myeloablative medicinal products must be considered.

Interactions:

The nature of Libmeldy is such that no pharmacokinetic interactions are expected with other medicinal products. Patients should not take anti-retroviral medicinal products from at least one month prior to mobilisation and/or bone marrow harvest until at least 7 days after Libmeldy infusion.

Live vaccines

The safety of immunisation with live viral vaccines during or following Libmeldy treatment has not been studied. Vaccination with live virus vaccines is not recommended during the 6 weeks preceding the start of myeloablative conditioning, and until haematological recovery following treatment with Libmeldy.

Special precautions:

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.

Autologous use

Libmeldy is intended solely for autologous use and should under no circumstances be administered to other patients. Do not infuse Libmeldy if the information on the product labels and lot information sheet do not match the patient's identity.

Rapidly progressive phase of the disease

Treatment with Libmeldy should be performed before the disease enters its rapidly progressive phase. Eligibility to treatment with Libmeldy should initially be assessed by the treating physician via full neurological examination, motor function assessment and neurocognitive assessment, as appropriate for the patients' age. Prior to the commencement of cellular harvest, the treating physician should ensure that the patient has not clinically deteriorated. Thereafter, prior to the commencement of conditioning, the treating physician should ensure that autologous HSPC gene therapy administration remains clinically appropriate for the patient, and that treatment with Libmeldy is still indicated.

Mobilisation and myeloablative conditioning medicinal products

Warnings and precautions of the mobilisation and myeloablative conditioning medicinal products must be considered.

Central venous catheter (CVC) complications including infections and thromboses

Infections related to the use of CVCs have been reported in clinical studies and there is a risk of thrombosis associated with the CVC. Patients should be closely monitored for potential infections and catheter-related events.

Hypersensitivity and infusion-related reactions

Dimethylsulfoxide (DMSO), one of the excipients of Libmeldy, is known to possibly cause anaphylactic reactions following parenteral administration. Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored prior to the start of the infusion, approximately every ten minutes during the infusion and every hour, for 3 hours, after the infusion.
When more than one bag of Libmeldy is needed, it should be ensured prior to infusion that the volume of medicinal product to be infused is compatible with the recommended limit of DMSO, i.e. the total volume of DMSO administered should remain <1% of the patient's estimated plasma volume. The maximum volume of Libmeldy to be administered should therefore remain < 20% of the patient's estimated plasma volume. Also, when more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour.

Engraftment failure

In clinical studies, no patients failed to engraft bone marrow, as measured by neutrophil count in peripheral blood. Failure of neutrophil engraftment is a short-term but potentially important risk, defined as failure to reach an absolute neutrophil count (ANC) >500 cells/µL associated with no evidence of bone marrow recovery (i.e. hypocellular marrow) by day 60 after Libmeldy infusion. In case of engraftment failure, the non-transduced back-up stem cells should be infused according to local standards.

Prolonged cytopenia

Patients may exhibit severe cytopenias, including severe neutropenia [defined as Absolute Neutrophil Count (ANC) <500/µL] and prolonged thrombocytopenia, for several weeks following myeloablative conditioning and Libmeldy infusion. In clinical studies, haematological recovery after conditioning with busulfan was typically seen four to five weeks from the day of infusion of Libmeldy. In the clinical study with the cryopreserved (commercial) formulation, neutrophil engraftment occurred after a median (min, max) of 36.5 (31-40) days after gene-therapy. Patients should, therefore, be monitored for signs and symptoms of cytopenia for at least 6 weeks after infusion. Red blood cells should be monitored according to medical judgment until engraftment of these cells and recovery are achieved. Supportive transfusion of red cells and platelets should be given according to medical judgement and institutional practice. Blood cell count determination and other appropriate testing should be promptly considered whenever clinical symptoms suggestive of anaemia arise.
cytopenia persists beyond six to seven weeks, despite the use of granulocyte mobilising medicinal products, the non-transduced back up stem cells should be infused. If cytopenia persists despite infusion of non-transduced back-up stem cells, alternative treatments should be considered.

Delayed platelet engraftment

Platelet engraftment is defined as the first of 3 consecutive days with platelet values ≥ 20 x 109/L obtained on different days after Libmeldy infusion, with no platelet transfusion administered for 7 days immediately preceding and during the evaluation period (up to 60 days post gene therapy). During the clinical development, 4/35 patients (11.4%) reported delayed platelet engraftment (median: 73.5 days, range 65-109 days) which was not correlated with an increased incidence of bleeding. As part of the standard of care/prophylaxis, all patients in the integrated safety set (N=29) received transfusion support with platelets. Platelets counts should be monitored according to medical judgment until engraftment of these cells and recovery is achieved. Supportive transfusion of platelets should be given according to medical judgement and institutional practice.

Metabolic acidosis

Prior to a treatment with Libmeldy, the presence of renal tubular acidosis should be evaluated alongside risks of the conditioning medicinal product and risks of the gene therapy procedure, which may contribute to the development of metabolic acidosis. Acid-base status should be monitored throughout conditioning and until the patient is no longer under metabolic stress. The treating physician should consider sodium bicarbonate replacement alongside any other required treatment and should aim to correct any concurrent adverse reaction(s) that might contribute to metabolic acidosis.

Transmission of an infectious agent

Although Libmeldy is tested for sterility and mycoplasma at release, a small risk of transmission of infectious agents exists. Healthcare professionals administering Libmeldy should therefore monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Thyroid monitoring

Transient increases in thyroid stimulating hormone (TSH), free T4 (FT4; thyroxine) and free T3 (FT3; tri-iodothyronine) were observed in some patients during clinical studies. Considering that thyroid disorders could potentially be masked by critical illness or induced by concomitant medication, patients should be assessed for thyroid function and structure prior to treatment with Libmeldy. Thyroid function and structure should also be monitored in the short term after treatment, and as necessary thereafter.

Risk of insertional oncogenesis

There is a theoretical risk of leukaemia or lymphoma after treatment with Libmeldy. In the event that leukaemia or lymphoma is detected in any patient who received Libmeldy, blood samples should be collected for integration site analysis.

Anti-ARSA antibodies

During clinical development, anti-ARSA antibodies (AAA) were reported in 5 patients. Titers were generally low and resolved spontaneously or after treatment with rituximab (see section 4.8). No impacts on the clinical efficacy or safety

outcomes were observed. Monitoring of AAA is recommended prior to treatment, between 1 and 2 months after gene therapy, and then at 6 months, 1 year, 3 years, 5 years, 7 years, 9 years, 12 years, 15 years post treatment. In a case of disease onset or significant disease progression, additional AAA monitoring is recommended.

Serological testing

Libmeldy has not been studied in patients with HIV-1, HIV-2, HTLV-1, HTLV-2, HBV, HCV or mycoplasma infection. All patients should be tested for HIV-1/2, HTLV-1/2, HBV, HCV and mycoplasma prior to mobilisation or bone marrow harvest to ensure acceptance of the cellular source material for Libmeldy manufacturing.

Anti-retroviral use

Patients should not take anti-retroviral medicinal products from at least one month prior to mobilisation and/or bone marrow harvest until at least 7 days after Libmeldy infusion (see section 4.5). If a patient requires anti-retrovirals following exposure to HIV/HTLV, initiation of Libmeldy treatment should be delayed until an HIV/HTLV western blot and viral load assay have been performed at 6 months post-exposure.

Interference with HIV testing

Patients who have received Libmeldy are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to LVV provirus insertion, resulting in a false positive test for HIV. Therefore, patients who have received Libmeldy should not be screened for HIV infection using a PCR-based assay.

Blood, organ, tissue and cell donation

Patients treated with Libmeldy should not donate blood, organs, tissues and cells for transplantation at any time in the future. This information is provided in the Patient Alert Card which should be given to the patient after treatment.

After Libmeldy administration

After the infusion, standard procedures for patient management after HSPC transplantation should be followed. Immunoglobulin G should be maintained above 5g/l to prevent potential late infections (occurring later than 100 days post therapy) associated with severe hypogammaglobinaemia, resulting from apheresis/bone marrow harvest and conditioning. Any blood products required within the first 3 months after Libmeldy infusion should be irradiated.

Sodium content

This medicinal product contains 35 – 560 mg sodium per dose, which is equivalent to 2 to 28% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Comparative elements and justification

Not applicable.

3.3.1.2. PRACTICAL USE

Aspects of administration

Libmeldy must be administered in a qualified treatment centre with experience in Haematopoietic Stem Cell Transplantation (HSCT). Patients are expected to enrol and be followed in a long-term follow-up study in order to better understand the long-term safety and efficacy of Libmeldy.

Posology

The dose of Libmeldy to be administered is defined based on the patient's weight at the time of infusion. The minimum recommended dose of Libmeldy is 3 × 106 CD34+ cells/kg. In clinical studies, doses up to 30 × 106 CD34+ cells/kg have been administered. The maximum volume of Libmeldy to be administered should remain < 20% of the patient's estimated plasma volume. Libmeldy is intended for autologous use (see section 4.4) and should only be administered once.

Bone marrow harvest or peripheral blood mobilisation and apheresis

The autologous CD34+ cells are isolated from bone marrow (BM) harvest or mobilised peripheral blood (mPB). In the case CD34+ cells are isolated from mPB, apheresis procedure(s) will be performed after peripheral blood mobilisation. The decision to use BM or mPB as the source material for isolation of CD34+ cells is at the discretion of the treating physician, taking into consideration the patient's age and weight, clinical condition and suitability of venous access. In general, mPB is the preferred cellular source for the manufacture of Libmeldy as it is less invasive for the patient. BM would nonetheless be the cellular source of choice in infants and children with a body weight less than 7 kg, in case of contraindication to use growth factors/mobilizing agents, and when venous access is deemed unsuitable for apheresis catheter placement.
Depending on the cellular source material, the patient must be able to donate a minimum of 8-10 ×106 CD34+ cells/kg, required for manufacture of Libmeldy (see Table 1). If CD34+ cells are isolated from BM, when possible, the minimum CD34+ cell quantity should be collected in a single BM harvest procedure. Prior to this procedure, an initial bone marrow aspirate is generally used in order to perform a test cell count, which allows to estimate the total volume of BM that will be required to obtain sufficient cell numbers for medicinal product manufacturing. If CD34+ cells are isolated from mPB, the minimum CD34+ cell quantity may be achieved using one or more cycles of apheresis.

Table 1 Quantity of CD34+ cells required for the manufacture of Libmeldy depending on the cellular source (number of cells expressed as 106 CD34+ cells/kg) Cellular source	Minimum number	Optimal range
BM	10	20-40
mPB	8	20-30

A back-up collection of HSPC containing at least 2 x 106 CD34+ cells/kg is also required for use as rescue treatment should the quality of Libmeldy be compromised after initiation of myeloablative conditioning and before Libmeldy infusion, failure of primary engraftment, or prolonged bone marrow aplasia after treatment with Libmeldy. These cells must be collected from the patient at time of BM harvest or mPB apheresis and be cryopreserved according to institutional procedures prior to myeloablative conditioning.

Peripheral blood mobilization

When a decision is made to use mPB as the source material, patients are required to undergo HSPC mobilisation with Granulocyte colony-stimulating factor (G-CSF) with or without plerixafor followed by apheresis to obtain CD34+ stem cells for medicinal product manufacturing.

Recommended pre-treatment conditioning

The treating physician should confirm that autologous HSPC gene therapy administration is clinically appropriate for the patient before myeloablative conditioning is initiated. A myeloablative conditioning is required before infusion of Libmeldy to promote efficient engraftment of the genetically modified autologous CD34+. Busulfan is the recommended conditioning medicinal product. Myeloablative conditioning should not begin until the complete set of infusion bag(s) constituting the dose of Libmeldy has been received and stored at the qualified treatment centre, and the availability of the back-up collection is confirmed. Concurrently with the conditioning regimen, and prior to treatment with Libmeldy, it

is recommended that patients receive prophylaxis for veno-occlusive disease (VOD) and related endothelial injury complications i.e. transplant-associated thrombotic microangiopathy (TA-TMA) or atypical haemolytic uremic syndrome (aHUS), in line with local guidelines. Depending on the myeloablative conditioning regimen administered, prophylaxis for seizures should also be considered. Phenytoin is not recommended as it may increase busulfan clearance. Prophylactic and empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections especially during the neutropenic period following conditioning. Routine monitoring of most common viruses subject to re-activation is recommended as per local guidelines. Infection control measures and isolation procedures should be employed during the hospitalization according to local standards.

Pre-medication

It is recommended that pre-medication with intravenous chlorpheniramine (0.25 mg/kg, max. dose 10 mg), or an equivalent medicinal product be administered 15-30 minutes before the infusion of Libmeldy to reduce the possibility of an allergic reaction to the infusion.

Special populations

Elderly: Libmeldy has not been studied in patients >65 years of age.

Renal impairment: Libmeldy has not been studied in patients with renal impairment. Patients should be assessed for renal impairment to ensure autologous HSPC gene therapy administration is appropriate. No dose adjustment is required.

Hepatic impairment: Libmeldy has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure autologous HSPC gene therapy administration is appropriate. No dose adjustment is required.

Paediatric population: The safety and efficacy of Libmeldy have not yet been established in patients with the late juvenile form of the disease (i.e. with a typical onset after 7 years of age). No data are available.

Method of administration

Libmeldy is for intravenous infusion only. Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human cells. Healthcare professionals should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases when handling the product.
Prior to Libmeldy infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the infusion bag(s) labels and the accompanying lot information sheet. The timing of thaw and infusion of Libmeldy should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that Libmeldy is available for infusion when the patient is ready. To maintain product viability, as soon as thawing is complete, it is recommended that Libmeldy be administered immediately. Administration must be completed within 2 hours from the time of thawing.

Administer the product as an intravenous infusion via a central venous catheter. When more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour. Each bag should be infused at an infusion rate which does not exceed 5 mL/kg/h, within approximately 30 minutes. The recommended administration set consists of a blood transfusion set equipped with a 200µm filter.

Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Libmeldy should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

- Libmeldy must remain at <-130 °C at all times, until the content of the bag is thawed for infusion.

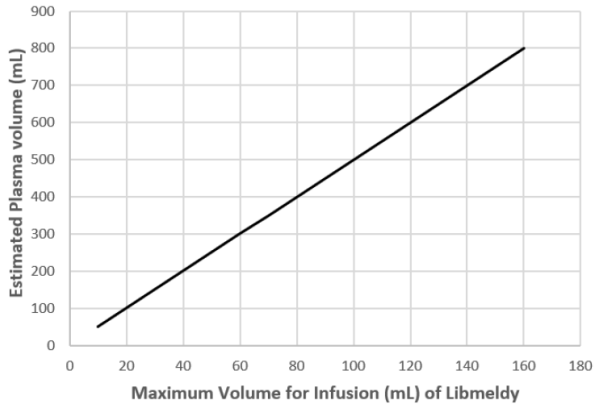
Definition of the dose to be administered

• Considering the posology information provided in section 4.2, the dose to be infused and number of infusion bags to be used should be defined based on the total number of CD34+ cells supplied indicated on the Lot Information Sheet (i.e. the 'supplied dose', calculated based on patient's weight at time of cell harvest). The dose of Libmeldy to be administered should also take into account the patient's weight at the time of treatment, and the fact that any bag used should be administered in its entirety.

• Careful consideration must be given to the volume of infusion in relation to age and weight of the patient. When the dose of Libmeldy to be infused represents more than one bag, it should be ensured prior to infusion that the volume of medicinal product to be infused is compatible with the recommended limit of DMSO, i.e. the total volume of DMSO administered should remain <1% of the patient's estimated plasma volume. Therefore, the maximum volume of Libmeldy to be administered should remain < 20% of the patient's estimated plasma volume.

• The following graph is provided as a reference in order to determine the maximum volume of Libmeldy which can be infused to a patient based on their estimated plasma volume.

Figure 2 **Guidance on DMSO safety limit: the maximum volume of Libmeldy to be administered should remain < 20% of the patient's estimated plasma volume.**



Preparation for the infusion

- A patient may have multiple infusion bags. Each infusion bag is provided inside an overwrap bag, which is contained in a metal cassette.
- The overwrapped infusion bag(s) must be kept inside the metal cassette(s) in the vapour phase of liquid nitrogen at < -130 °C until ready to thaw and infuse.
- Account for all infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be available to prime the tubing prior to infusion, and to flush the infusion bag and tubing after infusion.

Checking prior to thawing

- Do not remove the metal cassette from cryogenic storage or thaw Libmeldy until the patient is ready to be infused. The timing of thaw of the infusion bag(s) containing Libmeldy and of the infusion should be coordinated. Confirm the infusion time in advance and adjust the start time for thaw so that the treatment is available for infusion when the patient is ready.
- Open the metal cassette and inspect the overwrap bag and infusion bag for any breaches of integrity before thawing. If an infusion bag is compromised, follow the local guidelines for handling of waste of human-derived material and contact Orchard Therapeutics immediately.
- Prior to thawing Libmeldy, it must be verified that the patient identity matches the unique patient information reported on the packaging labels and on the accompanying Lot Information Sheet. Libmeldy is intended solely for autologous use. Do not thaw or infuse Libmeldy if the information on the patient-specific label on the infusion bag does not match the intended patient.

Thawing

- After careful removal from the metal cassette, thaw the infusion bag in its sealed overwrap bag at 37 °C in a controlled thawing device until there is no visible ice in the infusion bag.
- Once thawing is complete, the bag should be removed immediately from the thawing device.
- The overwrap bag should be carefully opened to remove the infusion bag which should be kept at room temperature (20 °C-25 °C) until infusion.
- Gently massage the infusion bag to resuspend the cells. The content of the infusion bag should be inspected for any remaining visible cellular aggregates. Small clumps of cellular material should disperse with gentle manual mixing. Do not shake the bag.
- The infusion bag should not be washed, spun down, sampled and/or resuspended in new media prior to infusion.
- Libmeldy should not be irradiated as irradiation could lead to inactivation of the product.
- If more than one infusion bag is provided for the patient treatment dose, the next bag should only be thawed after the content of the preceding bag has been fully infused.

Administration

• Libmeldy should be administered as an intravenous infusion via a central venous catheter, per the administration site's standard procedures for cell therapy products.
• The recommended administration set consists of a blood transfusion set equipped with a 200µm filter.
• Each bag should be infused by gravity within 2 hours of thaw, including any interruption during the infusion, to maintain maximum product viability.
• The maximum infusion rate is 5 mL/kg/h, and the content of each bag should be infused within approximately 30 minutes.
• When more than one bag of Libmeldy is needed, only one bag of product should be infused per hour.
• Patients not previously exposed to DMSO should be observed closely. Vital signs (blood pressure, heart rate, and oxygen saturation) and the occurrence of any symptom should be monitored for up to 3 hours following the infusion.
• At the end of the infusion, flush all Libmeldy remaining in the infusion bag and any associated tubing with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure that as many cells as possible are infused into the patient. Careful consideration must be given to the volume of infusion in relation to the age and weight of the patient.

Precautions to be taken for the disposal of the medicinal product

• Libmeldy contains genetically-modified human cells. Local guidelines on handling human-derived material should be followed for unused medicinal products or waste material.
- All material that has been in contact with Libmeldy (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.

Accidental exposure

• Accidental exposure to Libmeldy must be avoided. Local guidelines on handling of human derived materials should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Libmeldy must be decontaminated with appropriate disinfectant.

Comparative elements and justification

Please see point 3.1.3 regarding other current treatment options.

3.3.1.3. DEGREE OF EVIDENCE, RISK OF BIAS AND GRADE-SCALE

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.

Table Risk of Bias

	201222	**205756**	**CUP**
Were there clear criteria for inclusion in the case series?	Yes, but original fresh OTL-formulation used	Yes, but other formulation used (AA-cryopreserved)	Yes, but original fresh OTL-formulation used
Was the condition measured in a standard, reliable way for all participants included in the case series?	yes	Yes (but only limited individual data available)	Yes (but only limited individual data available)
Were valid methods used for identification of the condition for all participants included in the case series?	yes	yes	yes
Did the case series have consecutive inclusion of participants?	yes	yes	yes
Did the case series have complete inclusion of participants?	Yes, but missing datapoints in some patients	Yes, but missing datapoints in some patients	Yes, but missing datapoints in some patients
Was there clear reporting of the demographics of the participants in the study?	yes	Yes (but only limited individual data available)	Yes (but only limited individual data available)
Was there clear reporting of clinical information of the participants?	yes	Yes (but only limited individual data available)	Yes (but only limited individual data available)
Were the outcomes or follow up results of cases clearly reported?	Yes, but missing datapoints in some patients	Yes, but missing datapoints in some patients	Yes, but missing datapoints in some patients
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	yes	yes	yes
Was statistical analysis appropriate?	Yes as to descriptive statistics.	Yes as to descriptive statistics.	No statistics

Table GRADE evidence profile

GRADE Evidence profile of the in-patient comparison (*efficacy*) – LI-MLD

Note: Given the challenges with undertaking GRADE with this type of evidence we have not included a GRADE table for this report and we would welcome the opinion on what comparisons are most relevant to the committee, and if the committee can agree not including a GRADE evidence profile table in the final assessment report.

3.3.2. Real world evidence

No other RWE data available than discussed (cfr. CUP) .

3.3.2.1. EFFICACY IN PRACTICE

Not applicable.

3.3.2.2. ADVERSE EVENTS

Not applicable.

EPAR elements of the Risk Management Plan

Safety concerns

Important identified risks	Delayed platelet engraftment
Important potential risks	Malignancy due to insertional oncogenesis Anti-ARSA antibodies Engraftment failure Off label use in other MLD subgroups
Missing information	Long-term safety and efficacy data

Pharmacovigilance plan

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
LongTERM-MLD study: Long-term, Efficacy and Safety follow-up of MLD patients treated with *ex vivo* Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced with ARSA Lentiviral Vector (Libmeldy) Planned	To continue to monitor long-term safety and efficacy outcomes data from patients treated with Libmeldy for up to 15 years post treatment	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	Submission of the full protocol for the LongTERM-MLD study Information on the progress in the identification of a suitable registry FPFV: Interim reports: Final study report:	Within 3 months of the European Commission MA decision With every PSUR 2021 Sep-2023 Dec-2026 Mar-2029 Mar-2034 Mar-2039 31-Mar-2041
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Study 201222: A Phase I/II clinical trial	To evaluate the safety and efficacy of the fresh	• Delayed platelet engraftment	First patient first visit (FPFV):	09-Apr-2010

Versie préCTG:

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
of hematopoietic stem cell gene therapy for the treatment of Metachromatic Leukodystrophy Ongoing	formulation of OTL-200 in 20 early-onset MLD patients followed up for 8 years after treatment with OTL-200	• Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	Interim reports: No.1: No. 2: No. 2.1: No. 2.2: Final study report:	 06-Dec-2017 19-Feb-2019 28-Mar-2019 Sep-2019 31- Mar-2024
Study 205756: A Phase II, single arm, open label, clinical study of cryopreserved autologous CD34⁺ cells transduced with lentiviral vector containing human ARSA cDNA OTL-200, for the treatment of early onset Metachromatic Leukodystrophy (MLD) Ongoing	To evaluate the safety and efficacy of the cryopreserved formulation of OTL-200 (OTL-200-c) in up to 10 pre-symptomatic, early-onset MLD patients followed up for 8 years after treatment with OTL-200-c	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim reports: Final study report:	25-Jan-2018 14-Mar-2019 31 December 2029
Study OTL-200-07: An open label, non-randomised trial to evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) Metachromatic Leukodystrophy (MLD) Planned	To evaluate the safety and efficacy of a single infusion of OTL-200 in patients with Late Juvenile (LJ) Metachromatic Leukodystrophy (MLD)	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final study report:	Q3 2020 (anticipated) 2028 30 June 2032
CUP 206258: Compassionate use programme for hematopoietic stem cell gene therapy OTL-200 in pre-symptomatic early onset Metachromatic Leukodystrophy patients Ongoing	To provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final study report:	16-Jan-2017 05-Dec-2018 (data cut-off) 31 December 2026
Single-patient CUP 207394 (MLD-C02): Gene therapy protocol using autologous haematopoietic stem cells for MLD-C02, a patient with metachromatic leukodystrophy (MLD) Ongoing	To provide a mechanism to supply OTL-200 on a compassionate use basis to a patient (MLD-C02) with early symptomatic EJ MLD	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final report:	23-Apr-2013 05-Jan-2018 (data cut-off) 30 September 2022
HE 205029: Hematopoietic stem cell gene therapy for pre-symptomatic Late Infantile Metachromatic Leukodystrophy Ongoing	To provide an alternative treatment option to MLD patients with high unmet need, in advance of OTL-200 being commercially available	• Delayed platelet engraftment • Malignancy due to insertional oncogenesis • Anti-ARSA antibodies • Engraftment failure • Off label use in other MLD subgroups • Long-term safety and efficacy data	FPFV: Interim report: Final study report:	29-Dec-2015 05-Dec-2018 (data cut-off) 31 December 2026

3.3.2.3. APPLICABILITY

For patients with a presymptomatic diagnosis of LI or EJ MLD following a newborn screening (if applicable in the near future) or screening after diagnosis of MLD in an affected sibling.

For patients with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

Only to be used in patients without a previous treatment with haematopoietic stem cells gene therapy and without contraindications to the mobilisation and the myeloablative medicinal products must be considered (in casu busulfan).

3.3.2.4. PRACTICAL USE

Autologous CD34+ HSPCs are collected from patient bone marrow (BM) harvest or from mobilised peripheral blood (mPB) and transduced with a lentiviral vector (ARSA LVV), taking about 40 days from cell collection to product availability takes approximately.
A myeloablative conditioning is required before infusion of Libmeldy to promote efficient engraftment of the genetically modified autologous CD34+ cells .
AA will be given via a central venous catheter. When more than one bag of Libmeldy is needed, only one bag of medicinal product should be infused per hour.

4. ABBREVIATIONS

Abbreviation	Description
AA	Atidarsagene autotemcel
AEs	Adverse events
ARSA	Arylsulfatase A
BM	Bone marrow
BSC	Best supportive care
CSR	Clinical study report
CUP	Compassionate Use Program
DQp	Development quotient performance
EJ	Early juvenile
ES	Early symptomatic
GMFC-MLD	Gross motor function classification in metachromatic leukodystrophy
GvHD	Graft versus host disease
HSCT	Haematopoietic stem cell transplant
HSPC	Haematopoietic stem and progenitor cells
IQ	intelligence quotient
LI	Late infantile
ML	Milliliter
MLD	Metachromatic leucodystrophy
PS	Pre-symptomatic
QoL	Quality of life

5. QUESTIONS TO THE COMPANY

1. As typing of an LI or EJ type MLD was based on the age of first symptoms of the affected sibling, it is not certain the newly diagnosed child will have a similar development of the disease. A rationale on phenotype development after screening is leaking. A stratification based on genotype of the affected child and/or residual ARSA activity upon diagnosis might be a better predictor of a positive clinical effect of the intervention in presymptomatic patients and has to be added to the dossier. The company is asked to provide an additional analysis on clinical outcome parameters using genotype and baseline ARSA activity in presymptomatic LI and EJ patients, and plot the correlation of the outcome of this additional analysis on the outcome data of the currently used classification.

Answer of the company:

The company acknowledges that the Clinical Assessors have asked for more information regarding the genotypes of the metachromatic leukodystrophy (MLD) sibling pairs and the predicted pattern of disease for both LI and EJ patients, which are addressed in Section **Fout! Verwijzingsbron niet gevonden.**. However, to summarise here: age of onset of s ymptoms is a widely accepted and robust method to classify MLD phenotype. All the patients in the NHx and arsa-cel trials had a confirmed diagnosis of either LI or EJ disease based on age and genetic profiling. Whilst there are many mutations responsible for MLD, there is a notable grouping of mutations for LI, EJ, late juvenile and adult-onset populations, which can be observed from the arsa-cel clinical trials and the NHx study. Further, data from both the Fumagalli et al 2021 and Kehrer 2021 studies show that the median time for the LI patients to be in GMFC-MLD 5 from onset of symptoms was 1.12 years and 1.15 years, respectively. Therefore, even if there is a slight variation in the pattern of disease progression, the superior outcomes for arsa-cel treated LI patients are so in excess of this time frame that the treatment benefit cannot be disputed.

The company can confirm that for all the LI and EJ patients included in the arsa-cel clinical trials, baseline ARSA enzyme levels were below the quantifiable range or very low (i.e. at the lower level of quantification) (see Appendix 1, which lists baseline ARSA levels and the genetic profiles of all arsa-cel treated patients and natural history patients including siblings), which indicate patients had little or no functional ARSA protein. Following treatment with arsa-cel, patients' ARSA levels were normal or supraphysiological levels, which is indicative of a positive pharmacodynamic effect. As such, it is not possible to stratify patients into different categories using their residual ARSA activity as all patients had little or no functional ARSA protein at baseline.
All the pre-symptomatic LI patients in the arsa-cel clinical trials had the 0/0 or 0/R genotype, which have been shown to have rapid disease progression following onset of symptoms because there is very little or no functional protein, of which 14/16 LI patients in the arsa-cel clinical trials had the unambiguous 0/0 genotype. The one LI patient without this genotype was a certain 0/R genotype.
Patients effected by the early juvenile (EJ) MLD variant carry either 1 null allele and 1 residual allele (0/R genotype), or less frequently two residual alleles (R/R genotype) and have symptom onset between the ages of 30 months and <7 years of age. . Of the EJ patients in the arsa-cel clinical trials, 11 out of 13 had the 0/R genotype. The two EJ patients without this genotype were MLD09 (c.931G>A / p. Gly311 Ser homozygous, R/R), who was confirmed as having intermediate late infantile/early juvenile disease as the sibling in the NHx cohort had onset around the LI/EJ cut-off but disease progression more in line with EJ patients; the other patient (MLD-16) has a novel missense mutation in one allele (p.Pro67Leu) and the most common R mutation (c.1283C>T, p.Pro428Leu) in the other allele. It is uncertain if the novel p.Pro67Leu mutation can be described as 0 or R but in silico prediction tools (e.g., SIFT, PolyPhen-2) predict the amino acid substitution to have a deleterious effect on enzyme function.
Siblings have the same genotype, and out of the 20 pre-symptomatic patients in the arsa-cel clinical trials, 13 had a sibling in the natural history cohort. Given siblings have the exact same genotype and the same environmental factors, then we would expect the disease trajectories between the siblings to be similar. Examining the outcomes for the sibling pairs from the arsa-cel trials and the natural history study, the KM estimate for LI-MLD at 6 years old, 100% (n=7) of the arsa-cel treated pre-symptomatic LI patients with an untreated sibling were severe cognitive and motor impairment-free compared to 0% (n=6) matched siblings in the NHx LI cohort at the same age, p<0.001. In addition, for EJ-MLD at aged 11 years old, the KM estimate indicate that 100% of the PS EJ patients treated with arsa-cel were severe cognitive and motor impairment-free, compared to only 25% of the matched siblings in the NHx EJ cohort.

HTA assessment comment:

It should be noted that the approach based on an affected older sibling is only a valid method in case of absence of neonatal screening, and the cost of misfortune for affected older sibling showing clinical symptoms and a

correct diagnosis. In case a neonatal screening program for MLD would be implemented, given the possible AA treatment option, a genotypic screening is the only valid method avoiding first born affected children to progress to a clinical status. Therefore substantial data on correlation of AA treatment and genotype should be available in the future to detect affected children as soon as possible and tailor the optimal treamtment option. The company provided a listing of the genetic profiles of the patients included in the natural history study and AA-treated patients (cfr appendix 1 of the answer of the company), but didn't perform an updated analysis on clinical outcome of AA-treated patients in the respective clinical trials.

Genetic Profiles / Mutations, Natural History patients

Pt. ID	NHx Sibling ID	MLD Subtype	Study ID	Mutation 1* (HGVS)	Mutation 2* (HGVS)	Mutation Severity (0 or R)	Mutation Type	PD Allele	Screening/Baseline ARSA Activity	BL Urine Sulfa-tides
MLD01	LDM118	PS-LI	201222	c.827C>T; p.Thr276Met	c.827C>T; p.Thr276Met	0/0	Missense/ Missense	Absent	WBC MNC: 12 U PBMC: 3.27 nmol/mg/h	Not done
MLD02	LDM129	PS-LI	201222	c.736C>T;p.Arg246Cys	c. 737G>A; p.Arg246His	0/0	Missense/ Missense	Present, c.1055A>G, c.*96A>G	WBC MNC: 7.3 nmol/mg/h PBMC: 10.92 nmol/mg/h	Not done
MLD03	LDM134	PS-LI	201222	c.449C>G; p.Pro150Arg	c.449C>G; p.Pro150Arg	0/0	Missense/ Missense	Absent	WBC MNC: 4.7 nmol/mg/h PBMC: 3.17 nmol/mg/h	Not done
MLD04	N/A	Symp-EJ	201222	c.383T>G; p.Leu128Arg	c.1283C>T;p.Pro428Leu	0/R	Missense/ Missense	Absent	WBC MNC: 19 nmol/mg/h PBMC: 5.33 nmol/mg/h	Not done
MLD05	LDM121	PS-LI	201222	c.465+1G>A	c.980-1G>A	0/0	Splice donor / Splice Acceptor	Present, c.1055A>G	WBC MNC: 0.14 nmol/mg/h PBMC: 5.13 nmol/mg/h	Not done
MLD06	LDM122	PS-LI	201222	c.465+1G>A	c.855-1G>A	0/0	Splice donor / Splice Acceptor	Present, c.*96A>G	WBC MNC: 61.6 nmol/mg/h PBMC: 16.67 nmol/mg/h	+
MLD07	Not enrolled	PS-LI	201222	c.465+1G>A	c.465+1G>A	0/0	Splice donor / Splice donor	Absent	WBC MNC: 9.144 nmol/mg/h PBMC: No Scr/BL value	+
MLD08	N/A	ES-EJ	201222	c.1150G>A; p.Glu384Lys	c.1223_1231del; p.Ser408_Thr410del)	R/0	Missense / In-frame deletion of 3 amino acid residues	Present, c.*96A>G, c.1055A>G	WBC MNC: 63.5 nmol/mg/h PBMC: 18.39 nmol/mg/h	+
MLD09	LDM136	PS-EJ	201222	c.931G>A; p.Gly311Ser	c.931G>A; p.Gly311Ser	R/R	Missense/ Missense	Absent	WBC MNC: 18 nmol/mg/h PBMC: 17.86 nmol/mg/h	+
MLD11	LDM141	Symp-LI	201222	c.1108-2A>G	c.1108-2A>G	0/0	Splice acceptor / splice acceptor	Absent	BM MNC: 13.54 nmol/mg/h PBMC: 9.85 nmol/mg/h	+
MLD12	MLDC02	PS-EJ	201222	c.465+1G>A	c.1283C>T; p.Pro428Leu	0/R	Splice donor / Missense	Absent	BM MNC: 30.09 nmol/mg/h PBMC: 5.41 nmol/mg/h	+

Versie préCTG:

MLD13	N/A	ES-EJ	2012 22	c.465+1G>A	c.1283C>T; p.Pro428Leu	0/R	Splice donor / Missense	Absent	WBC MNC: Undetectable PBMC: 3.45 nmol/mg/h	+
MLD14	LDM1 43	ES-EJ	2012 22	c.465+1G>A	c.1283C>T; p.Pro428Leu	0/R	Splice donor / Missense	Absent	WBC MNC: 3.852 nmol/mg/h PBMC: 14.45 nmol/mg/h	+
MLD15	LDM1 29	PS-LI	2012 22	c.736C>T; p.Arg246Cys	c. 737G>A; p.Arg246His	0/0	Missense / Missense	Present, c.1055A>G, *96A>G	BM MNC: 4.51 nmol/mg/h PBMC: 4.23 nmol/mg/h	+
MLD16	LDM1 46	PS-EJ	2012 22	c.200C>T (p.Pro67Leu)	c.1283C>T; p.Pro428Leu	Unk/R	Missense / Missense	Present, c.1055A>G	WCP TNC: 2.4 nmol/mg/h PBMC: 4.07 nmol/mg/h	+
MLD17	N/A	ES-EJ	2012 22	c.1175G>A; p.Arg392Gln	c.1283C>T; p.Pro428Leu	0/R	Missense / Missense	Absent	PBMC: 27.98 nmol/mg/h BM MNC: 7.24 nmol/mg/h	+
MLD19	N/A	Symp-EJ	2012 22	c.465+1G>A	c.1283C>T; p.Pro428Leu	0/R	Splice donor / Missense	Absent	WBC MNC: 2 nmol/mg/h PBMC: 12.04 nmol/mg/h	+
MLD20	LDM1 47	PS-EJ	2012 22	c.465+1G>A	c.1283C>T; p.Pro428Leu	0/R	Splice donor / Missense	Absent	WBC MNC: 9.6 nmol/mg/h PBMC: 0.69 nmol/mg/h	+
MLD21	N/A	Symp-EJ	2012 22	c.1283C>T; p.Pro428Leu	c.929delG;p.Gly310fs	R/0	Missense / frameshift	Absent	WBC MNC: 8.9 nmol/mg/h PBMC: 8.56 nmol/mg/h	+
MLD22	Not enrolled	PS-LI	2012 22	c.937C>T; p.Arg313*	c.937C>T; p.Arg313*	0/0	Nonsense/ nonsense	Present, c.1055A>G, *c.96A>G	WBC: 2 nmol/mg/h PBMC: 2.98 nmol/mg/h	+
MLD-HE01	MLD-HE02, LDM153	PS-LI	2050 29	c.240dup; p.Gly81fs	c.465+1G>A	0/0	Duplication, frameshift / Splice donor	Absent	WBC MNC: 1.4 nmol/mg/h PBMC: 1.84 nmol/mg/h	Not done
MLD-HE02	MLD-HE01, LDM153	PS-LI	2050 29	c.240dup; p.Gly81fs	c.465+1G>A	0/0	Duplication, frameshift / Splice donor	Absent	WBC MNC: 1.4 nmol/mg/h PBMC: 8.76 nmol/mg/h	-
MLD-HE03	LDM1 59	PS-LI	2050 29	c.346C>T;p.Arg116*	c.677C>T; p.Ala226Val	0/R	Nonsense / Missense	Present, c.1055A>G (p.Asn352Ser), *c.96A>G	WBC MNC: 8 nmol/mg/h PBMC: 3.67 nmol/mg/h	+
MLD-CUP01	LDM1 48	PS-LI	2062 58	c.418dup; p.His140fs	c.1210+1G>A	0/0	Insertion, frameshift / splice donor	Absent	WBC MNC: 0.04 mU/mg PBMC: 0.25 nmol/mg/h	+
MLD-CUP02	LDM1 52	PS-LI	2062 58	c.293C>T; p.Ser98Phe	c.225-20_854+39delins411_685-18inv	0/0	Missense / complex rearrangement, exons 2, 3, and 4	Present, c.1055A>G (p.Asn352Ser), *c.96A>G	Lymphocytes, TNC: 5 nmol/mg/h PBMC: 1.59 nmol/mg/h	Not done
MLD-CUP03	LDM1 55	PS-LI	2062 58	c.371G>A; p.Gly124Asp	c.929G>T, p.Gly310Val	0/0	Missense / Missense	**Not done**	BM MNC: 79.6 nmol/mg/h PBMC: 25.79* nmol/mg/h	**+**
MLD-CUP04	Not enrolled	PS-EJ	2062 58	c.1283C>T; p.Pro428Leu	c.1010A>T; p.Asp337Val	R/0	Missense / Missense	**Not done**	WBC MNC: 0.1 nmol/mg/min PBMC: 53.13 nmol/mg/h	**+**

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MLD-CUP05	Not enrolled	PS-LI	206258	c.465+1G>A	c.1108-1G>A	0/0	Splice donor, Splice acceptor	**Not done**	WBC MNC: 16.1 nmol/17h(sic) PBMC: 28.34 nmol/mg/h	**+**
MLD-CO2	MLD12	ES-EJ	207394	C.465+1G>A	c.1283C>T; p.Pro428Leu	0/R	Splice donor / Missense	Absent	WBC MNC: 10.8 nmol/mg/h PBMC: 19.18 nmol/mg/h	+
MLDCRY02	LDM149	PS-LI	205756	c.370G>A; p.Gly124Ser	c.685-1G>A	0/0	Missense / Splice acceptor	Present	BM MNC: 87.3 nmol/mg/h	+
MLDCRY03	Not enrolled	PS-LI	205756	c.465+1G>A	c.1108-3C>G	0/0	Splice donor / Splice acceptor	Absent	WBC MNC: 5 nmol/mg/h PBMC: 25.79 nmol/mg/h*	Not done
MLDCRY04	MLD-CRY01, LDM154	PS-EJ	205756	c.931G>A; p.Gly311Ser	c.931G>A; p.Gly311Ser	R/R	Missense / Missense	Absent	BM MNC: 26.79 nmol/mg/h PBMC: 25.79 nmol/mg/h*	+
MLDCRY06	Not enrolled	PS-EJ	205756	c.869G>A (p.Arg290His)	c.465+1G>A	R/0	Missense, Splice donor	Absent	BM MNC: 66.33 nmol/mg/h PBMC: 25.79 nmol/mg/h*	Not done
MLDCRY08	LDM161	PS-EJ	205756	c.1136 C>T; p.Pro379Leu	c.1136 C>T; p.Pro379Leu	Unk/Unk	Missense / Missense	Absent	BM MNC: 25.79 nmol/mg/h* PBMC: 25.79 nmol/mg/h*	+
MLDCRY09	Not enrolled	PS-LI	205756	c.338 T>C; p.Leu113Pro	c.338 T>C; p.Leu113Pro	0/0	Missense / Missense	Absent	WBC MNC: 6 nmol/mg/h PBMC: 25.79 nmol/mg/h*	+
MLDCRY10	LDM162	PS-LI	205756	c.465+1G>A	c.763 G>A; p.Glu255Lys	0/0	Splice Donor / Missense	Not listed	WCP TNC: 0 nmol/mg/h PBMC: 25.79 nmol/mg/h*	+
MLDCRY11	Not enrolled	PS-EJ	205756	c.925 G>A; p.Glu309Lys	c.1162G>T; p.Val388Phe	0/Unk	Missense / Missense	Not done	WBC MNC: 21 nmol/mg/h PBMC: 25.79 nmol/mg/h*	+
MLDCRY12	Not enrolled	PS-EJ	205756	c.293C>T; p.Ser98Phe	c.1283C>T; p.Pro428Leu	0/R	Missense / Missense	Not applicable	WBC MNC: Undetectable PBMC: 25.79 nmol/mg/h*	+
MLDCRY13	Not enrolled	PS-EJ	205756	c.1107+1G>A	c.607 T>C; pTyr203His	0/R	Splice donor / Missense	Unknown	WCP TNC: 16.8 nmol/mg/h PBMC: 25.79 nmol/mg/h*	+

Pt. ID	**OTL-200 Sibling ID**	**MLD Subtype**	**Mutation 1***	**Mutation 2***	**Mutation Severity (0 or R)**	**Mutation Type**	**PD Allele**	**Baseline ARSA Activity**	**Urine Sulfatides**
LDM103		**EJ**	**c.251C>T (p.Pro84Leu)**	**c.256C>T (p.Arg86Trp)**	**0/R**	**Missense / Missense**	**Absent**	**WBC MNC: 16 nmol/mg/h**	+
LDM104		**EJ**	**c.256C>T (p.Arg86Trp)**	**c.465+1G>A (splice donor)**	**R/0**	**Missense / Splice donor**	**Absent**	**WBC MNC: 15.8 nmol/mg/h**	Not Done
LDM105		**LI**	**c.465+1G>A (splice donor)**	**c.465+1G>A (splice donor)**	**0/0**	**Splice donor / Splice donor**	**Present, c.1055A>G**	**WBC MNC: 4 nmol/mg/h**	+

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LDM107		**LI**	**c.161T>C (p.Leu54Pro)**	**c.449C>T (p.Pro150Leu)**	**0/0**	**Missense / Missense**	**Absent**	**WBC MNC: 34.6 nmol/mg/h**	Not done
LDM108		**LI**	**c.1228_1229del (p.Thr410Hisfs*16)**	**c.1228_1229del (p.Thr410Hisfs*16)**	**0/0**	**Deletion, frameshift / Deletion, frameshift**	**Absent**	**WBC MNC: 22.1 nmol/mg/h**	+
LDM109		**EJ**	**c.465+1G>A (splice donor)**	**c.256C>T (p.Arg86Trp)**	**0/R**	**Splice donor / Missense**	**Absent**	**WBC MNC:0.04 ukat/kg**	+
LDM111		**LI**	**c.465+1G>A (splice donor)**	**c.465+1G>A (splice donor)**	**0/0**	**Splice donor / Splice donor**	**Absent**	**WBC MNC: 3.24 nmol/mg/h**	Not done
LDM114		**EJ**	**c.465+1G>A (splice donor)**	**c.608A>G (p.Tyr203Cys)**	**0/R**	**Splice donor / Missense**	**Absent**	**WBC MNC: 6.8 nmol/mg/h**	Not done
LDM115		**LI**	**c.465+1G>A (splice donor)**	**c.763G>A (p.Glu255Lys)**	**0/0**	**Splice donor / Missense**	**Absent**	**WBC MNC: 12 nmol/mg/h**	+
LDM118	**MLD01**	**LI**	**c.827C>T (p.Thr276Met)**	**c.827C>T (p.Thr276Met)**	**0/0**	**Missense / Missense**	**Absent**	**WBC MNC: 4.61 nmol/mg/h**	Not done
LDM121	**MLD05**	**LI**	**c.465+1G>A (splice donor)**	**c.980-1G>A (splice acceptor)**	**0/0**	**Splice donor / Splice acceptor**	**Present, c.1055A>G**	**WBC MNC: 0.71 nmol/mg/h**	+
LDM122	**MLD06**	**LI**	**c.465+1G>A (splice donor)**	**c.855-1G>A(splice acceptor)**	**0/0**	**Splice donor / Splice acceptor**	**Present, c.*96A>G**	**WBC MNC: 17.2 nmol/mg/h**	+
LDM123		**LI**	**c.1114C>T (p.Arg372Trp)**	**c.1114C>T (p.Arg372Trp)**	**0/0**	**Missense / Missense**	**Absent**	**WBC MNC: 36.5 nmol/mg/h**	+
LDM124		**LI**	**c.917C>T (p.Thr306Met)**	**c.1223_1231del (p.Ser408_Thr410del)**	**0/0**	**Missense, In-frame deletion of 3 amino acid residues**	**Present, c.1055A>G**	**WBC MNC: 14.6 nmol/mg/h**	+
LDM127		**LI**	**c.640G>C(p.Ala214Pro)**	**c.465+1G>A (splice donor)**	**0/0**	**Missense, Splice donor**	**Absent**	**WBC MNC: 8.5 nmol/mg/h**	Not done
LDM128		**EJ**	**c.608A>G (p.Tyr203Cys)**	**c.465+1G>A (splice donor)**	**R/0**	**Missense / Splice donor**	**Absent**	**WBC MNC: 18 nmol/mg/h**	Not done
LDM129	**MLD02, MLD15**	**LI**	**c.736C>T (p.Arg246Cys)**	**c.737G>A (p.Arg246His)**	**0/0**	**Missense / Missense**	**Present, c.1055A>G, c.*96A>G**	**WBC MNC: 9.7 nmol/mg/h**	+
LDM130		**LI**	**c.465+1G>A (splice donor)**	**c.465+1G>A (splice donor)**	**0/0**	**Splice donor / Splice donor**	**Absent**	**WBC MNC: 5 nmol/mg/h**	Not done
LDM131		**LI**	**c.465+1G>A (splice donor)**	**c.855-1G>A**	**0/0**	**Splice donor / Splice acceptor**	**Absent**	**WBC MNC: 58 nmol/mg/h**	+
LDM133		**LI**	**c.883G>A (p.Gly295Ser)**	**c.938G>A (p.Arg313Gln)**	**0/0**	**Missense / Missense**	**Absent**	**WBC MNC: 11%**	+
LDM134	**MLD03**	**LI**	**c.449C>G (p.Pro150Arg)**	**c.449C>G (p.Pro150Arg)**	**0/0**	**Missense / Missense**	**Absent**	**WBC MNC: 9 nmol/mg/h**	Not done
LDM135		**EJ**	**c.465+1G>A(splice donor)**	**c.256C>T (p.Arg86Trp)**	**0/R**	**Splice donor / Missense**	**Absent**	**WBC MNC: 2 ukat/kg**	+
LDM136	**MLD09**	**EJ**	**c.931G>A (p.Gly311Ser)**	**c.931G>A (p.Gly311Ser)**	**R/R**	**Missense / Missense**	**Absent**	**WBC MNC: 6.5 nmol/mg/h**	Not done

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LDM138		**LI**	**c.350G>T (p.Gly117Val)**	**c.350G>T (p.Gly117Val)**	**0/0**	**Missense / Missense**	**Present, c.1055A>G**	**WBC MNC: 12 nmol/mg/h**	Not done
LDM139		**EJ**	**c.418C>G (p.His140Asp)**	**c.925G>A (p.Glu309Lys)**	**R/0**	**Missense / Missense**	**Absent**	**WBC MNC: 27 nmol/mg/h**	+
LDM140		**EJ**	**c.465+1G>A (splice donor)**	**c.1283C>T (p.Pro428Leu)**	**0/R**	**Splice donor / Missense**	**Not done**	**WBC MNC: 5 nmol/mg/h**	**+**
LDM141	**MLD11**	**LI**	**c.1108-2A>G (splice acceptor)**	**c.1108-2A>G (splice acceptor)**	**0/0**	**Splice acceptor / Splice acceptor**	**Absent**	**WBC MNC: 0.11**	Not done
LDM143	**MLD14**	**EJ**	**c.465+1G>A**	**c.1283C>T (p.Pro428Leu)**	**0/R**	**Splice donor / Missense**	**Absent**	**WBC MNC: 1%**	+
LDM146	**MLD16**	**EJ**	**c.200C>T (p.Pro67Leu)**	**c.1283C>T (p.Pro428Leu)**	**Unk/R**	**Missense / Missense**	**Present, c.1055A>G**	**WCP TNC: 5.4 nmol/mg/h**	Not done
LDM147	**MLD20**	**EJ**	**c.465+1G>A (splice donor)**	**c.1283C>T (p.Pro428Leu)**	**0/R**	**Splice donor / Missense**	**Not done**	**WBC MNC: 12.8 nmol/mg/h**	**+**
LDM148	**MLD-CUP01**	**LI**	**c.418dup (p.His140fs)**	**C.1210+1G>A(splice donor)**	**0/0**	**Duplication, frameshift / Splice donor**	**Absent**	**Lymphocytes, TNC: 5%**	Not done
LDM149	**MLDCRY02**	**LI**	**c.370G>A (p.Gly124Ser)**	**c.685-1G>A (splice acceptor)**	**0/0**	**Missense / Splice acceptor**	**Present**	**WBC MNC: 15 nmol/mg/h**	+
LDM152	**MLD-CUP02**	**LI**	**c.293C>T (p.Ser98Phe)**	**c.293C>T (p.Ser98Phe)** ***Per FF, patient most likely has the same complex rearrangement of allele 2 as sibling**	**0/0**	**Missense / Missense**	**Present**	**PBMC: 8 nmol/mg/h**	Not done
LDM153	**MLDHE-01, MLDHE-02**	**LI**	**c.240dup (p.Gly81fs)**	**c.465+1G>A (splice donor)**	**0/0**	**Duplication, frameshift / Splice donor**	**Absent**	**WBC MNC: 1.8 nmol/mg/h**	Not done
LDM154	**MLDCRY04**	**EJ**	**c.931G>A (p.Gly311Ser)**	**c.931G>A (p.Gly311Ser)**	**R/R**	**Missense / Missense**	**Not done**	**MNC: 4.29 nmol/mg/h**	**Not done**
LDM155	**MLD-CUP03**	**LI**	**c.371G>A (p.Gly124Asp)**	**c.929G>T (p.Gly310Val)**	**Unk/R**	**Missense/Missense**	**Not done**	**MNC: Undetectable**	Not done
LDM156		**LI**	**c.465+1G>A(splice donor)**	**c.465+1G>A(splice donor)**	**0/0**	**Splice donor/splice donor**	**Not done**	**MNC: 0 nmol/mg/h**	Not done
LDM157		**LI**	**c.465+1G>A (splice donor)**	**c.1195C>T (p.His399Tyr)**	**0/R**	**Splice donor/ Missense**	**Not done**	**WBC MNC: 12 nmol/mg/h**	+
LDM159	**MLD-HE03**	**LI**	**c.346C>T (p.Arg116*)**	**c.677C>T (p.Ala226Val)**	**0/R**	**Nonsense/ Missense**	**Present, c.*96A>G, c.1055A>G**	**WBC MNC: 6 nmol/mg/h**	Not done
LDM160		**LI**	**c.465+1G>A (splice donor)**	**c.548T>C (p.Leu183Pro)**	**0/Unk**	**Splice donor / Missense**	**Not done**	**WBC MNC: 2 ukat/kg**	+
LDM161	**MLDCRY08**		**c.1136C>T (p.Pro379Leu)**	**c.1136C>T (p.Pro379Leu)**	**Unk/Unk**	**Missense / Missense**	**Not done**		+
LDM162	**MLDCRY10**	**LI**	**c.465+1G>A (splice donor)**	**c.763G>A (p.Glu255Lys)**	**0/0**	**Splice donor / Missense**	**Not done**		Not done

LDM163		**LI**	**c.418dup (p.His140fs)**	**c.608A>G (p.Tyr203Cys)**	**0/0**	**Duplication, frameshift / Splice donor**			

The clinical experts consulted by ZIN in the Dutch reimbursement procedure provided following answer to this question:

> This is absolutely not in line with the international consensus on the predictive value of genotype and residual ARSA activity. Predicting phenotype based on genotype and/or residual enzymatic activity is only possible to a very limited extent. Moreover, predicting the exact age of onset is impossible. A few studies have found correlations between certain genotypes and phenotypes, the highest level of accuracy is a range spanning from 2 to 32 years for the age of onset. Only in case of known biallelic null mutations, we are able to predict early onset MLD. More accurate predictions cannot be made. Biochemical tests to measure residual ARSA activity are currently not accurate enough. Literature and expert opinion supports the use of age at onset of the affected sibling (index patient) as a good method for early onset forms (LI and EJ MLD). (11) We therefore do not consider it useful to plot correlations with genotype and ARSA activity.
>
> HTA assessment comment:
>
> It should be noted that the approach based on an affected older sibling is only a valid method in case of absence of neonatal screening, and the cost of misfortune for affected older sibling showing clinical symptoms and a correct diagnosis. In case a neonatal screening program for MLD would be implemented, given the possible AA treatment option, a genotypic screening is the only valid method avoiding first born affected children to progress to a clinical status. Therefore substantial data on correlation of AA treatment and genotype should be available in the future to detect affected children as soon as possible and tailor the optimal treatment option.

2. For presymptomatic EJ patients, the follow-up period and the number of treated patients in the clinical trials was rather limited. The company is asked to provide an additional analysis in this patient group to demonstrate the clinical course observed in the clinical trials was significantly different compared to the expected natural history (also based on genotype and ARSA activity) because of the intervention.

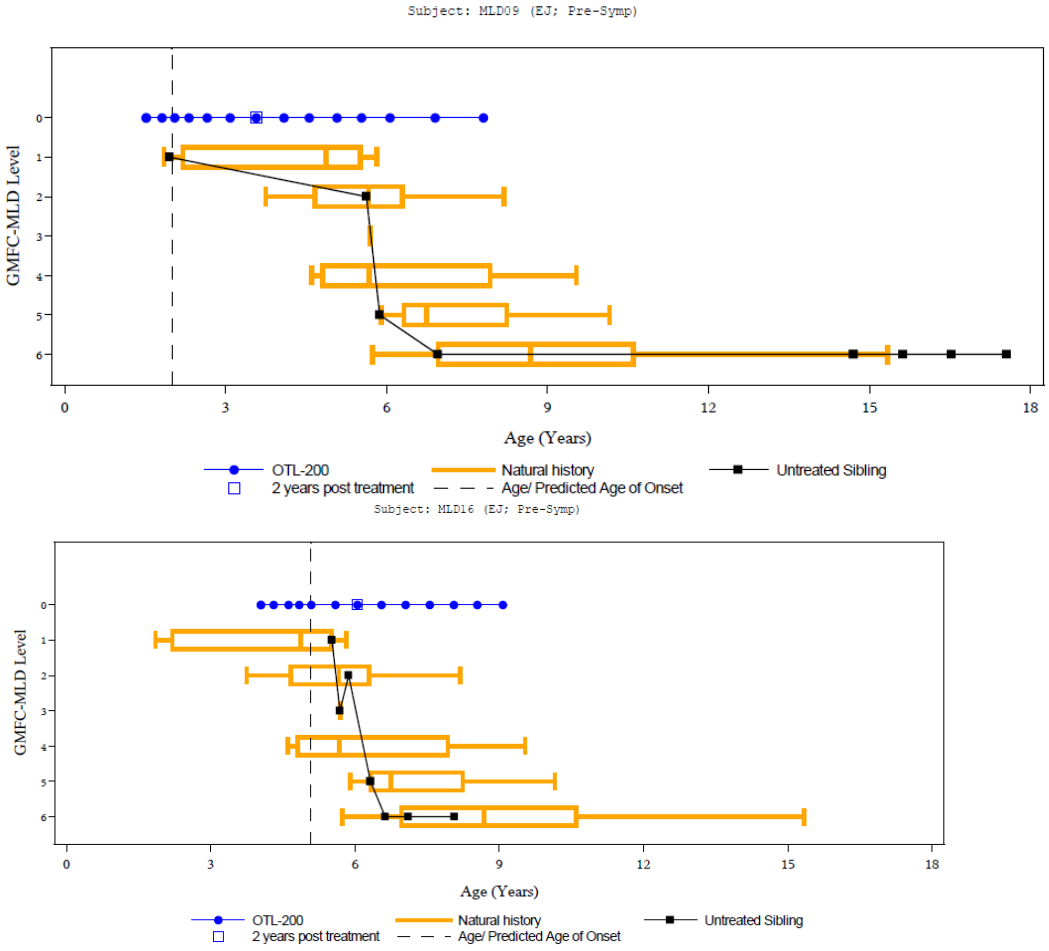
Answer of the company:

All of the PS-EJ patients were identified asymptomatically through an affected older sibling, three of whom are in the NHx study and one sibling who was treated as an ES EJ patient (see Appendix 1). All the clinical trial subjects had low levels of ARSA at baseline and the sibling pairs have the same genotype. Therefore, given the same genotype and the same environmental factors, we would expect the disease trajectories to be similar.
Seventy-five percent of PS-EJ patients have been classified as a full responder (i.e. remained at GMFC-0) in the final submission, for which the company is claiming a treatment benefit. MLD-12's sibling with the same mutation is a treated ES-EJ patient, so a comparison of disease trajectory based on genotype is not relevant here. However, MLD-09 and MLD-16 each have a sibling in the NHx study diagnosed with the same ARSA genotype, abnormally low ARSA activity, and the same environmental factors.

Figure 1 below shows the results for the treated patients (blue line) vs. the siblings (black line) with the same genotype. MLD-09's sibling was at GMFC-MLD 1 aged 3 and had declined to GMFC 6 by age 7. Yet, MLD-09 remains at GMFC 0 aged 8 years old. Similarly, for MLD-16's sibling, this patient was in GMFC 6 aged 7 but MLD-16 is still at GMFC 0 aged 9. In addition, MLD-20 was at GMFC 2 after 4 years of treatment compared to the untreated sibling who was at GMFC 6 at the same age. Therefore, even accounting for some degree of variation between siblings in terms of age of onset of symptoms, the length of time from treatment to last follow-up far exceeds even the most extreme variation in onset

of symptoms for EJ-MLD published, and this coupled with the change from low levels of ARSA at baseline to supraphysiological levels following treatment, is indicative of treatment effect.

Figure 1: GMFC-MLD scores for arsa-cel treated PS-EJ patients vs. siblings with the same genotype and baseline ARSA activity



The clinical experts consulted by ZIN in the Dutch reimbursement procedure provided following answer to this question:

> Early juvenile patients do not differ much from late-infantile patients. Both are considered early-onset MLD with a devastating disease course, characterized by rapid decline in motor and cognitive abilities. In the literature, similar steep regression curves can be seen. Thus significant differences between LI and EJ are not to be expected. In addition, as stated above, we do not consider it useful to correlate outcomes with genotype and/or ARSA activity. There is no reason to expect different effects of gene therapy in the presymptomatic EJ patient group compared with LI patients.

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NCPE Assessment Report on the Cost Effectiveness of:

Drug:	Atidarsagene autotemcel(Libmeldy®)
Therapeutic indication:	Metachromatic leukodystrophy (MLD)
Applicant Company:	Orchard Therapeutics Ltd.
Date of report:	4th July 2022

Report content

This report outlines the background to the decision problem, documents the evidence submitted to the Beneluxa Initiative by the Applicant Orchard Therapeutics Ltd. 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.

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Abbreviations

AA	Atidarsagene autotemcel
AEs	Adverse events
ARSA	arysulfatase A
BIM	Budget impact model
BSC	Best supportive care
CEM	Cost effectiveness Model
cDNA	complementary deoxyribonucleic acid
DSA	Deterministic sensitivity analyses

DQp	Development quotient performance
EJ	Early juvenile
ES	Early symptomatic
GMFC-MLD	Gross motor function classification in metachromatic leukodystrophy
GvHD	Graft versus Host Disease
HRQoL	Health related quality of life
HSCT	Haematopoietic stem cell transplant
HSPCs	haematopoietic stem and progenitor cells
ICER	Incremental cost effectiveness ratio
IQ	intelligence quotient
LI	Late infantile
LY	Life Years
MLD	Metachromatic leukodystrophy
NHx	Natural history
OOPCs	Out of pocket costs
PS	Pre-symptomatic
PSA	Probabilistic Sensitivity Analysis
PTW	Price to wholesaler
QALY	Quality adjusted life year
QoL	Quality of Life
TTO	Time trade off
VAS	Visual analogue scale
VAT	Value-added tax
X-ALD	X-linked adrenal leukodystrophy

Key points

- Metachromatic leukodystrophy (MLD) is a rare inherited lysosomal storage disease caused by deficiency of arylsulfatase A (ARSA).

- The intervention assessed in this dossier is atidarsagene autotemcel (AA) (Libmeldy®) licensed by the EMA in December 2020. It a one-time gene therapy consisting of genetically modified autologous CD34+ haematopoietic stem and progenitor cells which contain the functional human arylsulfatase A *(ARSA)* gene.

- A pharmacoeconomic cost utility model examines the cost effectiveness in three patient subgroups: pre-symptomatic late infantile (PS LI); pre-symptomatic early juvenile (PS EJ); and early symptomatic early juvenile (ES EJ). The groups are modelled separately and combined for the full population using a weighted average of each subgroup per country.

- The model structure adequately maps the disease and treatment pathway however choices around how patients progress through the model are overly optimistic for the intervention being assessed.

- BSC is considered as comparator for all three countries.

- The data used to inform treatment effectiveness in the model for the BSC arm comes from the natural history study (OSR-TIGET NHx). Treatment effect for the intervention is informed by a subset of patients from the registrational single-arm clinical study (Study 201222 (N=16 March 2018 data cut) and data from expanded access programmes.

- Assumptions in relation to treatment effects have a significant impact on the model; in particular, the classification of response and the assumption of cure. Patients treated with AA are classified as ‘full responders’, ‘stable partial reponders’ or ‘unstable partial responders’. The classification of response includes GMFC-MLD stage, along with additional criteria. However, it is not clear how the various criteria were weighted relative to one another, and how the various thresholds were established.

- As quality-of-life data was not gathered in the clinical trials, a study was commissioned to inform the cost utility model. This study and the subsequent analysis are not considered to be robust by the review group.

- The costs of treatments for individual countries are included however, given that the designated treatment centres are not in all the countries included these may change pending the country of administration. As there are currently few treatment options for these patients the cost offsets from other treatments are not considered to be a significant driver.

- The Review Group has presented a proposal for an alternative cost effectiveness base case where a treatment waning effect is considered after 10 years in a proportion of patients. This has a significant impact of the ICERs increasing them across all patients' groups.

- The budget impact is appropriately estimated to include incident patients only. The cumulative impact in Belgium over three years ranges from €6.1 to €23.6 million depending on assumptions around babies born and prenatal screening; for the Netherlands for three years is €14.4m, and for Ireland for five years is €9.8m.

- The estimates of cost effectiveness lie above all explicit country specific thresholds and therefore is not considered to be cost effective.

Executive Summary

Metachromatic leukodystrophy (MLD) is a rare inherited lysosomal storage disease caused by deficiency of arylsulfatase A (ARSA), due to mutations in the *ARSA* gene. Accumulation of sulfatides in the central and peripheral nervous system lead to progressive demyelination, neuroinflammation and neurodegeneration. This leads to loss of motor and neurocognitive functions and eventually death. The forms of the disease commonly described include late infantile (<30mths), early juvenile (30mths to 6 years), late juvenile (7-16 years) and adult MLD (≥17 years). Treatment for early onset forms mainly focuses on palliative care and stem cell transplant and there is an unmet need for these patients.

Atidarsagene autotemcel (AA) (previously OTL-200) (Libmeldy®) is a one-time gene therapy consisting of autologous CD34+ haematopoietic stem and progenitor cells which have been genetically modified *ex vivo* to contain the functional human arylsulfatase A *(ARSA)* gene. It was licensed by the European Medicines Agency (EMA) on 17th December 2020. It has orphan disease designation. The licence includes patients with MLD characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,
- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

The comparator for all countries is Best Supportive Care (BSC). MLD is a condition affecting many facets of bodily functions and therefore BSC follows a broad spectrum of symptomatic treatments aimed at improving patients' quality of life (QoL). AA is considered to be added to BSC.

The population included in the pharmacoeconomic model is a a combination of the following three patient subgroups: pre-symptomatic late infantile (PS LI); pre-symptomatic early juvenile (PS EJ); and early symptomatic early juvenile (ES EJ). The groups are modelled separately and combined for the full group using a weighted average of each subgroup per country.

The model is a cost-utility one with eight health states: seven motor function health states defined by GMFC-MLD score and a death state. Only forward transitions to worse health states are allowed in the model. The Applicant assumed that changes in motor function would be sequential. Cognitive substates within each motor function health state were also modelled for EJ populations to allow for cognitive decline to occur at a different rate to motor function decline. The Applicant assumes that mortality related to MLD will only occur from the worst motor function health state. A lifetime horizon is used.

The data used to inform treatment effectiveness in the model for the BSC arm comes from the natural history study (OSR-TIGET NHx) (N=31; LI n=19, EJ n=12). Treatment effect for the intervention is informed by a subset of patients from the registrational single-arm clinical study (Study 201222 (N=16 March 2018 data cut) and data from expanded access programmes, including two compassionate use (CUP207394 (N=1) and CUP206258 (N=5)) and from one hospital exemption (HE205029 (N=3)). The Applicant did not use available data from Study 205756 of the AA commercial cryopreserved formulation to inform cost-effectiveness.

Transitions between motor function health states are derived from the data described. For patients in the treatment group it is assumed that patients who receive treatment will have improved outcomes; the possibility of non-response is not considered. Responders are considered to be full or partial. Partial responders are further classified into stable and unstable responders. The assumptions in relation to classification of patient response are overly optimistic e.g. patients who experience declines in clinical outcomes are classified as ‘full’ or ‘stable partial’ responders. In the model the Applicant assumes that full responders will not deteriorate, from MLD for life. The Review Group consider that the data does not reflect these assumptions. The data demonstrates that three patients who were modelled as full or stable partial responders who received AA showed declines in a number of clinical outcomes.

The Review Group had significant concerns in relation to how the applicant approached a number of aspects in relation to the modelled treatment effectiveness. The post hoc nature of responder classification is highly subjective and given the small number of patients included will have a significant impact on the outputs of the model. The Applicant makes an assumption of cure for patients classified as full responders or stable partial responders which is not supported by robust

evidence. Other biases include the approach to calculate the transition probabilities for mean time to next GMFC state which impacts on the relative treatment effects. The limited data available for EJ patients is problematic given the variable disease course.

Health state utilities are primarily informed by a UK study commissioned by the applicant using vignettes and the time trade off approach to utility calculation. The study predicted a large number of worse than death states which according to clinical opinion was not plausible. There is inconsistency in the valuation of these states where better health states were valued lower than worse states. There are also large differences in the values for LI and EJ groups which the Review Group consider implausible. The Applicant rescaled the utility data obtained in the elicitation study, so that the minimum and maximum utility values were bounded by the EQ-5D-5L tariff for the respective country, in order to reduce the number of worse than death health states. It is assumed that cognitive and motor decline occur at the same rate for LI patients and juvenile patients after the age of four which is implying that the course of disease is different depending on the age of onset

The Review Group have concerns regarding the plausibility of the utility values applied in the model. These concerns extend to the predicted outcomes of the model, where negative QALY gains are accrued for patients treated with BSC. Thus, the model suggests that receiving BSC (rather than no treatment) may reduce their QoL over time and will reach negative values which suggests harm; the Review Group consider that this lacks face validity. No alternative plausible values were identified through literature review, and while the Review Group conducted various scenario analyses, alternative approaches did not have significant impact on the cost-effectiveness estimates, which are driven primarily by the modelling of treatment effects.

The Price to Wholesaler of AA is €2,875,000. Costs for administration of AA and BSC are also included, as well as the cost components of long-term provision of BSC. Clinical input was sought to validate the costs. The estimation of the anticipated cost of administering AA and follow-up of these patients is complicated by the fact that for both Ireland and Belgium, patients will receive treatment in other jurisdictions. While the cost inputs applied in the model are associated with uncertainties, they have

limited impact on the cost-effectiveness estimates, which are driven primarily by the modelling of treatment effects.

The Applicant estimated ICERs for AA versus BSC for four groups.

1. The combined weighted average ICER of AA versus BSC was: Belgium €118,234/QALY; Netherlands €107,777/QALY and for Ireland €146,642/QALY.
2. For the presymptomatic LI group the ICER was: Belgium €112,676/QALY; Netherlands €99,035/QALY and Ireland €144,078/QALY.
3. For the Presymptomatic EJ group for: Belgium €92,374/QALY; Netherlands €70,299/QALY and for Ireland €120,207/QALY.
4. For the early symptomatic EJ group: Belgium €172,761/QALY; for Netherlands €166,671/QALY and for Ireland €216,567/QALY.

The Review Group considered the main uncertainties in the model and have made some adjustments to those which we consider will have an impact on the outputs. Treatment waning is a reasonable scenario that should be incorporated given the dearth of data on long-term response at this point. The Review Group have recalculated the ICERs incorporating a treatment waning effect, where after ten years all full and stable partial responders start to experience decline in motor function in line with transitions modelled for unstable partial responders.

1. The combined weighted average ICER of AA versus BSC was: Belgium €369,048/QALY; Netherlands €327,423/QALY and for Ireland €382,069/QALY.
2. For the pre-symptomatic LI group the ICER was: Belgium €484,711/QALY; Netherlands €462,632/QALY and Ireland €438,495/QALY.
3. For the pre-symptomatic EJ group for Belgium: €269,672/QALY; Netherlands €225,400/QALY and for Ireland €260,467/QALY.
4. For the early symptomatic EJ group: Belgium €408,461/QALY; for Netherlands €396,882/QALY and for Ireland €392,864/QALY.

The Applicant undertook both one way and probabilistic sensitivity analysis. The review group do not consider the approach to the variance around parameters to be transparent with inadequate explanation for choices made. A proportional shortfall calculation was conducted for the Netherlands at a threshold of €80,000/QALY. The Review Group have presented the relationship between price and cost effectiveness. In order to reach cost-effectiveness thresholds, the price would need to be significantly less than that requested by the Applicant.

The gross budget impact for Belgium for three years Is €6,095,000 (based on one patient in year 1 and 3). For the Netherlands for three years it is €14,375,000 (based on two patients in year 1, one patient in year 2 and two patients in year 3) and for Ireland for five years it is €9,940,314 (three patients over five years). The net budget impact is similar as there are no significant cost offsets from comparator therapies. A scenario analysis was included for the Belgium where 100% of patients of early onset patients born receive treatment. In this case the three year cumulative net budget impact increases to €23,529,274.

The decision problem and model structure

1.1. Population

The modelled population included in the cost-utility analysis consists of a combination of the following three patient subgroups:

- pre-symptomatic late infantile (PS LI): children with a confirmed diagnosis of late infantile (LI) metachromatic leukodystrophy (MLD) without clinical manifestations of the disease.
- pre-symptomatic early juvenile (PS EJ): children with a confirmed diagnosis early juvenile (EJ) MLD without clinical manifestations of the disease.
- early symptomatic early juvenile (ES EJ): children with EJ MLD who have early clinical manifestations of the disease with the ability to walk independently and before the onset of cognitive decline (defined as gross motor function classification in MLD (GMFC-MLD) ≤1 and intelligence quotient (IQ) ≥85).

The Applicant presents cost-effectiveness modelling and results separately for each subgroup and combined for the full population (as a weighted average across the subgroups). The proportion of patients belonging to each subgroup is assumed to vary between countries (Table 1). For Belgium and Ireland, the Applicant used figures sourced from Wang et al that reported 40 to 60% LI and 20 to 35% juvenile onset MLD (1). The Applicant also sourced clinical opinion from Belgium regarding the proportion of each subgroup (60% LI, 25% EJ, 10% late juvenile) which aligned with the upper estimates from Wang et al. The Applicant used the midpoint of estimates from Wang et al for Ireland and assumed that 50% of juvenile patients would be EJ. For the Netherlands the Applicant used figures sourced from a study by Beerepoot et al, of 67 patients with a confirmed MLD diagnosis treated at Amsterdam University Medical Centre, that reported 16% LI and 21% EJ onset MLD (2). The Applicant then applied estimates of eligibility for treatment (proportions PS or ES) sourced from clinical opinion for Belgium (LI: < 5% PS, EJ: 10 to 15% PS and 10 to 15% ES) and the Netherlands (LI: 10 to 20% PS, EJ: 20% PS and 20 to 30% ES). For Ireland the Applicant used the same estimates of eligibility for treatment as applied in the Applicant submission to NICE in the UK (LI: 16% PS, EJ: 17% PS and 13% ES). The Applicant stated that values used for Ireland were validated by clinical opinion

from Ireland; however, the Review Group were unable to verify this as it was not recorded in the meeting minutes provided.

Table 1 Proportions of each MLD subgroup in the modelled population by country

	PS LI	PS EJ	ES EJ
Belgium	32.4%	33.8%	33.8%
Ireland	65.9%	19.2%	14.9%
The Netherlands	20.3%	35.4%	44.3%

EJ early juvenile, **E**S early symptomatic, **LI** late infantile, **PS** presymptomatic

1.2. Intervention

Atidarsagene autotemcel (AA) (previously OTL-200) (Libmeldy®) is a one-time gene therapy consisting of autologous CD34+ haematopoietic stem and progenitor cells which have been genetically modified *ex vivo* to contain the functional human arylsulfatase A *(ARSA)* gene.

The EMA licensed AA on 17th December 2020. AA is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity:

- in children with late infantile or early juvenile forms, without clinical manifestations of the disease,
- in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

Autologous $CD34^+$ haematopoietic stem and progenitor cells (HSPCs) are collected from patient bone marrow harvest or from mobilised peripheral blood. They are transduced with a lentiviral vector (ARSA LVV), which inserts one or more copies of the human ARSA complementary deoxyribonucleic acid (cDNA) into the cell's genome so that genetically modified cells become capable of expressing the functional ARSA enzyme. When administered to the patient following the administration of a myeloablative conditioning regimen, the genetically modified cells engraft and are able to repopulate the haematopoietic compartment.

Administration of AA is via intravenous infusion and should only be administered once. The finished cryopreserved product is a dispersion for infusion composed of 10 – 20 mL of cryoformulation medium (5% DMSO, 7% Human Serum Albumin, and 0.9% saline solution) containing 2-10 x 10^6 CD34+ enriched cells transduced *ex vivo* using a lentiviral vector encoding the ARSA gene per mL.

AA must be administered in a qualified treatment centre with experience in HSCT. Once a patient has been identified as suitable for treatment the harvesting of the autologous stem cells takes place and the manufacture of the product takes approximately 40 days from harvest. A pre-conditioning regimen consisting of 14 doses of busulfan is administered 4 days before the AA infusion. The patient will remain in hospital for between 4 and 12 weeks.

The dose of AA to be administered is defined based on the patient's weight at the time of infusion. The minimum recommended dose of AA is 3×10^6 $CD34^+$ cells/kg. In clinical studies, doses up to 30×10^6 $CD34^+$ cells/kg have been administered. The maximum volume of AA to be administered should remain < 20% of the patient's estimated plasma volume (see SmPC).

Currently AA has been administered to three patients; two patients in the Netherlands (one via a clinical trial and one via the early access programme) and one in Ireland via the early access programme. All three were treated in Milan. Whilst results from the two EAP patients are presented within this dossier, results from the Dutch patient that received OTL-200 as part of a clinical study are not included in this dossier; as the patient has only recently received treatment these data are not currently available.

AA needs to be administered in a qualified treatment centre of which there are five in Europe; in the Netherlands, UK, Germany, France and Italy. Belgian patients are anticipated to be treated at the Princess Maxima Hospital, the QTC in Utrecht (the Netherlands), or the Robert Debre Hospital, the QTC in Paris (France), for Flemish and French- speaking Belgians, respectively. Dutch patients will also receive treatment with AA at the Princess Maxima Hospital in Utrecht (the Netherlands). A Dutch clinical expert has confirmed that MLD patients are already being jointly assessed at Amsterdam UMC and the transplant centre in Utrecht. Irish patients are expected to be treated at the treatment centre in Manchester (UK). An Irish expert has confirmed that the pathway of referral between the

Irish MLD specialist centre (Temple Street) and the expert treatment centre in Manchester has already been established, and is currently being used for bone marrow transplantation for lysosomal storage diseases other than MLD.

AA is anticipated to be administered in addition to BSC. The Applicant has proposed that an indication committee would be set up to organise the identification and management of MLD patients deemed to be eligible for treatment.

1.3. Comparators

In all jurisdictions, the main comparator is Best Supportive Care (BSC). MLD is a condition affecting many facets of bodily functions and therefore BSC follows a broad spectrum of symptomatic treatments aimed at improving patients' quality of Life (QoL). It includes physical therapy to maintain mobility, muscle relaxation medications for spasticity (inc. baclofen pump although not as readily available in Ireland), analgesic medications, respiratory physiotherapy, anti-convulsant medicines, anti-psychotic medicines for psychiatric symptoms, dietary support including enteral feeding in the case of dysphagia and family and patient counselling. Skeletal deformity such as scoliosis can occur and measures to treat this include braces, frames, spinal orthoses and rarely spinal surgery.

Clinical opinion indicates that allogeneic HSCT could be considered an additional comparator for The Netherlands. This is indicated in a subset of the population i.e. EJ MLD (approx. 20-30% of the MLD population). HSCT was initially considered for inclusion as a scenario in the model. However, due to the lack of data, the Review Group do not consider it possible to give a reliable conclusion as to the relative effectiveness and therefore cost effectiveness of AA versus HSCT.

1.4. Model type and structure

The Applicant submitted a cost-utility model in Microsoft Excel with eight health states: seven motor function health states defined mainly by GMFC-MLD score and a death state (Figure 2). Only forward transitions to worse health states are allowed in the model. The Applicant assumed that changes in motor function would be sequential.

The Applicant assumes that mortality related to MLD will only occur from the worst motor function health state. Mortality from other motor function health states was informed by general population mortality with a multiplier applied to account for increased mortality due to neurological disability. No additional mortality risk from myeloablative conditioning (busulfan) as part of treatment with AA was modelled by the Applicant.

Cognitive substates within each motor function health state were also modelled for EJ populations to allow for cognitive decline to occur at a different rate to motor function decline. These cognitive substates were defined based on development quotient performance (DQp): DQp ≥70 'normal cognitive function', DQp 70 to 55 'moderate cognitive impairment', and DQp ≤55 'severe cognitive impairment'. Cognitive substates were not modelled for the LI population as the Applicant assumes that motor and cognitive function decline occur at the same rate for patients with LI MLD.

A lifetime horizon is used with a monthly cycle length and a half cycle correction applied. At model entry 100% of patients with PS LI and PS EJ MLD are assumed to start in the GMFC-MLD 0 health state. At model entry 40% of patients with ES EJ MLD are assumed to start in GMFC-MLD 0 health state and 60% are assumed to start in GMFC-MLD 1 health state based on the distribution of ES EJ patients in AA clinical data (see Section 2.1.1). The age at model entry for EJ populations is informed by age at baseline in the AA clinical data (PS EJ 45 months, ES EJ 80 months). For the PS LI population age at model entry is assumed to be 18 months. The Applicant states that GMFC-MLD stages are only validated for use in patients older than 18 months of age, as GMFC-MLD 0 is based on an un-impacted patient's ability to achieve walking without support within the range of normal development.

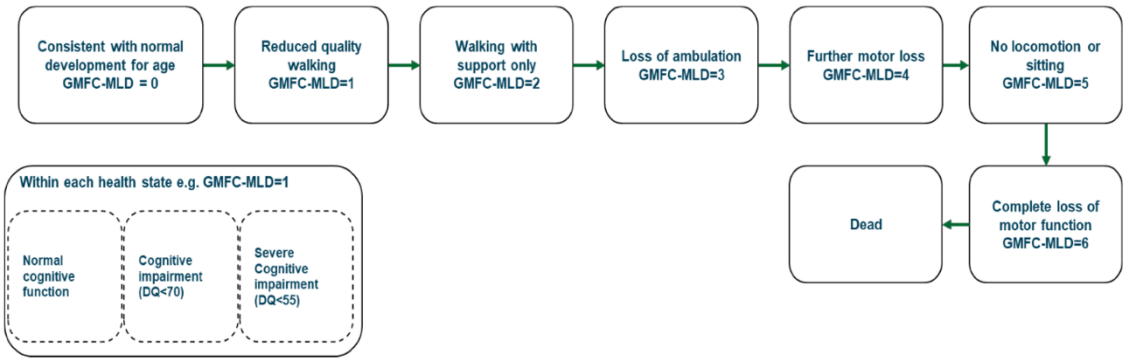

Figure 2 Model Schematic

Footnotes: Cognitive substates (normal cognitive function, cognitive impairment and severe cognitive impairment) were applied to the EJ MLD population only. In PS LI MLD, cognitive decline occurs at a similar rate to motor function decline. In contrast, for PS EJ and ES EJ MLD, cognitive decline can occur before or after motor function loss.(60) Though patients can only progress to MLD-related death from GMFC-MLD stage 6, general population mortality is applied to every health state.

1.5. Perspective

The perspective is that of the payer for all countries. For the Netherlands the societal viewpoint is the base case. Scenario analyses from societal perspective and including carer utilities were also presented for Belgium and Ireland.

2. Economic model inputs

2.1. Treatment effectiveness

- **Data sources**

Best Supportive Care

A natural history study from Ospedale San Raffaele – Telethon Institute for Gene Therapy (OSR-TIGET NHx) (N=31; LI n=19, EJ n=12) was used to inform BSC. The data contained a mixture of cross-sectional and longitudinal data with some subjects contributing data at multiple time points and others providing data from a single visit. In addition to prospective data collection, retrospective data available prior to study enrolment was also collected with the objective of reconstructing disease progression. However, there is still a large amount of missing data.

AA

The clinical evidence for patients treated with AA comprises two single-arm clinical studies (Study 201222 (N=20 with median follow up 5.7 years as at December 2019) and Study 205756 (n=6 with median follow up 0.71 years as at November 2019)) and data from expanded access programmes, including two compassionate use (CUP207394 (N=1) and CUP206258 (N=5)) and one hospital exemption (HE205029 (N=3)). Only Study 205756 used the cryopreserved formulation of AA that the Applicant is applying for reimbursement of, while the rest used a fresh formulation of AA.

Study 205756 of the cryopreserved formulation of AA is not used to inform the cost-effectiveness analyses. The Applicant states that this was due to the available length of follow-up, which is likely too short to draw any conclusions (one patient has follow-up to 1.5 years, remaining patients have follow-up ranging from 9 months to 1 year).The base case is thus informed solely by data for the fresh formulation of AA. Given limited data available for the cryopreserved formulation it is unclear whether treatment outcomes will be the same as for the fresh formulation. A scenario was provided whereby data from two evaluable LI patients from Study 205756 were used to inform the cost-effectiveness model. The Review Group does not consider this scenario to address the underlying issue of limited data availability.

The Applicant uses pooled data from a subset of patients who met the definition of the modelled population (see Section 1.1) from earlier data cuts for Study 201222 (March 2018) and the expanded access programmes to inform the cost-effectiveness analyses (pooled AA clinical data, N=25). An updated analysis using data from December 2019 data cut off providing an additional ~2 years of data for 17 patients (8 PS LI; 4 PS EJ; and 5 ES EJ) presented as part of clinical evidence was also available. The extent to which various aspects of the cost-effectiveness model were informed by the most recent data cut were unclear, and relevant data presented in the model were not updated to align with their corresponding treatment effectiveness parameters. Furthermore, between submission of the concept dossier and the final submission only certain parameters were updated to include the most recent data cut, without any justification provided. Relevant updates were only undertaken by the Applicant after the Review Group's concerns were noted following review of the Day 60 report .

Treatment effects for AA were informed by a naïve ITC using pooled AA clinical data and natural history data (OSR-TIGET NHx). Treatment effects for AA were modelled for each of the three subgroups separately based on analysis of the relevant patients from the pooled AA clinical data (PS LI n=15, PS EJ n=5, ES EJ n=5). Nine of the OSR-TIGET NHx study patients were siblings of patients in Study 201222 of AA, who may be expected to show similar disease course. However, the overall comparability of patients in OSR-TIGET and the pooled AA clinical data is unclear. Differences between study populations may bias treatment effect estimates. Differences in outcome

ascertainment (GMFC-MLD score over time) between the AA clinical studies where data was collected prospectively and OSR-TIGET NHx where data collection was also retrospective may also lead to bias in the estimated treatment effects.

- **Transitions between health states**

Motor Function (GMFC-MLD)

BSC

For BSC the Applicant calculated transition probabilities between health states from the mean time to next GMFC-MLD state using OSR-TIGET NHx data, assuming rate of transition is constant over time. LI and EJ populations were modelled and analysed separately. Time to next GMFC-MLD state was calculated by subtracting the age at entry to the lower GMFC-MLD score from the age at entry to the next higher GMFC-MLD score. Given the partially retrospective nature of data collection in OSR-TIGET NHx it is not clear how age at entry was determined or how well patient records at given GMFC-MLD scores reflect age at entry. The Applicant assumed that transitions from GMFC-MLD 2 to 5 would be evenly distributed and calculated these using data from patients with age at entry to GMFC-MLD 2 and 5. Mean time from GMFC-MLD 0 to 1 was calculated based on the difference between modelled age at entry for the cost-effectiveness model and mean age at entry into GMFC-MLD 1 in OSR-TIGET NHx.

Patients who did not have an observation at a given GMFC-MLD score available were excluded from the calculations of the mean time to next GMFC-MLD state. For example, patients who were not recorded/observed at GMFC-MLD 2 were excluded from calculations of mean time from GMFC-MLD 1 to 2. Where patients did not have age at entry to GMFC-MLD 2 and/or 5 available, data for intermediate transitions (for example from GMFC-MLD 3 to 4) that could have been used to inform the model were not used by the Applicant. The Applicant's analysis approach also does not incorporate data from patients who were observed to remain in a given GMFC-MLD state for a period of time, without a subsequent change in GMFC-MLD being recorded. The Review Group consider this exclusion of relevant available data to be inappropriate.

AA

The Applicant classified patients in the pooled AA clinical data as either full or partial responders. The Applicant assumes that all patients treated with AA will have improved outcomes – the possibility of non-response is not considered. Partial responders were additionally separated into stable and unstable partial responders. There were inconsistencies in how the response classification criteria were specified in the submission and how classifications were applied in the analysis. For example, in the submission document (pg. 233) the Applicant states "full responders are equivalent to GMFC 0". However, in the model, patients who progress to GMFC >0 continue to be classified as full responders (e.g. MLD-03). During model development, response classification was based on GFMC-MLD score alone. However, the classification methodology was subsequently revised to incorporate additional criteria (GMFM, DQp, MRI, PBMC, ARSA, NCV). No information was provided on how the relevant thresholds for the various criteria were established, or how the criteria were weighted relative to one another. The Review Group considers the classification methodology used in the analysis to be highly subjective, and lacks both rigour and transparency.

The proportion of patients in each response classification for PS LI and PS EJ subgroups was applied to the cost-effectiveness model. For the PS EJ population, one patient who died was excluded from the calculation of response status. For ES EJ population, the Applicant did not use clinical study data directly to inform response proportions; the Applicant assumed that ES EJ population are partial responders with an equal chance of stabilising at GMFC-MLD 1 through 4 or experiencing decline in motor function. This is more optimistic than the outcomes observed in the clinical data. Transition between GMFC-MLD health states depend on this response classification (Table 2). In the cost-effectiveness model the Applicant assumes that full responders will not experience any deterioration or symptoms of MLD; they remain in GMFC-MLD 0 health state for life. The Applicant also assumes stable partial responders will stabilise at a GMFC-MLD level (>0) after which they will not experience any further decline or disease progression. The Review Group do not consider these assumptions to fully reflect the available clinical data, which shows a deterioration in multiple parameters for patients treated with AA who are modelled as either full or stable partial responders.

Table 2 Responder classification used for AA in cost-effectiveness model by population subgroup

Response Classification	PS LI	PS EJ*	ES EJ**
Full Responder	40%	75%	0%
Stable partial responder stabilising at GMFC 1	20%	0%	20%
Stable partial responder stabilising at GMFC 2	33.3%	0%	20%
Stable partial responder stabilising at GMFC 3	0%	0%	20%
Stable partial responder stabilising at GMFC 4	0%	0%	20%
Unstable partial responder	6.7%	25%	20%

EJ: early juvenile; **ES:** early symptomatic; **LI:** late infantile; **PS:** pre-symptomatic
***One PS EJ patient died and was excluded from calculations informing these proportions.
** Applicant assumption

Transition probabilities for partial responders are calculated from a mean time to transition, assuming rate of transition is constant over time. The Applicant calculated this mean time to transition by applying 'progression modifiers' to mean time to next GMFC-MLD state for BSC. This assumes that patients treated with AA will experience slower decline in motor function. The Applicant assumes transition probabilities from GMFC-MLD 0 to 1 and 5 to 6 for AA will be the same as for BSC (progression modifier of 1). For transitions from GMFC-MLD states 1 to 2 and from 2 to 5 progression modifiers were obtained by deriving a ratio comparing the mean time between lower and higher GMFC-MLD score (1 to 2 and 2 to 5 respectively) in OSR-TIGET NHx and partial responders in pooled AA clinical data. This assumes that the same progression modifier (treatment effect) applies for transitions from GMFC-MLD 2 to 3, 3 to 4 and 4 to 5. The Applicant's approach to calculating mean times for this naive comparison is similar to that described previously (for BSC) and is subject to the same limitations. Differences in outcome ascertainment (age at entry to GMFC-MLD state) between the AA clinical studies where data was collected prospectively and OSR-TIGET NHx where data collection was also retrospective may also lead to bias in the estimated treatment effects. The Applicant originally calculated the progression modifiers based on data for AA from the 2018 data cut, but subsequently updated based on data from the 2019 data cut. A comparison of the time-to-transition data at the 2018 and 2019 data cuts, and corresponding progression modifiers, are presented in Table 3. The impact of the updated data on the cost-

effectiveness results is minimal (for all jurisdictions, changing from 2018 to 2019 data increased the ICER by <1%).

Table 3 Mean time to transition (2018 and 2019 data cuts) and progression modifiers

	Pooled (LI+EJ) NHx Data			Pooled (LI+EJ) AA Data (partial responders) – 2018 data cut			Pooled (LI+EJ) AA Data (partial responders) – 2019 data cut		
Time to transition between GMFC-MLD states (months)	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**
from 0 to 1	N/A	N/A	0	41.5		4	41.4	21.3	4
from 1 to 2	12.3	9.5	17	17.5	14.9	5	20.1	16.8	7
from 2 to 3	3.7			12.6			15.3		
from 3 to 4	3.7			12.6			15.3		
from 4 to 5	3.7			12.6			15.3		
from 5 to 6	17.5	17.2	16	N/A	N/A	0	N/A	N/A	0
from 6 to death	57.1	36.9	15	N/A	N/A	0	N/A	N/A	0
Time from GMFC-MLD 2 to 5	11.2	7.8	12	37.7	19.0	7	46.0	24.4	8
				Mean	**SD**	**SE**	**Mean**	**SD**	**SE**
Progression modifier (GMFC-MLD 1-2)				1.4	1.6	0.34	1.6	1.8	0.36
Progression modifier (GMFC-MLD 2-5)				3.4	2.4	0.56	4.1	3.1	0.70

Abbreviations: BSC: best supportive care; EJ: early juvenile; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; LI: late infantile; NHx: natural history study; SD: standard deviation; SE: standard error.

The mechanism of action of AA centres on engraftment of genetically modified cells (see Section 1.2). The Applicant assumes that this engraftment will occur before symptom onset for PS LI and PS EJ patients. Clinical opinion to the Applicant indicated that as ES EJ patients were already symptomatic at the time of treatment, MLD disease progression will continue for ES EJ patients until engraftment of the gene corrected stem cells occurs in the brain. In the ES EJ population, the time required before AA treatment takes effect is captured by applying a 'time to engraftment' parameter. The 'time to engraftment' parameter dictates the duration of time post-treatment before patients receive the benefits of AA treatment. For the base case, this was assumed to be six months post-treatment.

Cognitive sub-states in EJ populations

The Applicant models cognitive sub-states within each GMFC-MLD health state for EJ populations. The distribution of patients between these cognitive sub-states is assumed to depend on GMFC-MLD state and treatment received. The cognitive sub-states were used to apply sub-state specific HRQoL utility scores associated with each GMFC-MLD stage (see Section 2.3).

For patients in GMFC-MLD 0 health states, it is assumed all enter the model with normal cognitive function, and cognitive decline may only occur after a specified time interval. This assumption was based on clinical opinion obtained by the Applicant, which indicated that, in some patients, cognitive decline could occur in the absence of any gross motor signs. The 'time to cognitive decline' parameter varied by treatment arm.

BSC

The proportion in each cognitive sub-state within each GMFC-MLD state was based on clinical opinion from a modified Delphi panel carried out by the Applicant with six UK clinicians (**Table 4**). Clinicians were asked to estimate the proportion of untreated patients who would:

- experience cognitive decline before GMFC decline (i.e. while still in GMFC-MLD 0),
- have normal cognitive function (as opposed to moderately or severely impaired) in GMFC-MLD 1 and 2,
- have severely impacted cognitive function (as opposed to normal or moderately impaired) in GMFC-MLD 1 and 2,
- have moderate cognitive function (as opposed to severely impaired) in GMFC-MLD 6,
- have severely impacted cognitive function (as opposed to moderately impaired) in GMFC-MLD 6.

For GMFC-MLD 3 to 5 the Applicant assumed that proportion in each cognitive state would change linearly in equal increments between values estimated for GMFC 2 to GMFC 6. The Applicant assumes that cognitive decline will occur after 12 months from model entry for those in GMFC-MLD 0 treated with BSC. Clinical opinion obtained by the Review Group indicated that patients with GMFC-MLD 0 would tend to have normal cognitive function, wherease those with GMFC-MLD 1 would have normal or mildly impaired cognitive function.

Table 4 Proportion* in each cognitive sub-state by GMFC-MLD state for BSC in EJ

GMFC-MLD state	Normal cognitive function	Moderate cognitive impairment	Severe cognitive impairment
GMFC-MLD 0 after cognitive decline**	73%	27% (5 to 40%)	0%

GMFC-MLD 1	54% (30 to 90%)	38%	9% (0 to 20%)
GMFC-MLD 2	33% (10 to 85%)	43%	25% (3 to 70%)
GMFC-MLD 3	25%	35%	40%
GMFC-MLD 4	16%	28%	55%
GMFC-MLD 5	8%	21%	71%
GMFC-MLD 6	0%	14% (0 to 50%)	86%

*For mean values elicited from UK clinicians the range of responses are also provided in brackets.
**Cognitive decline is assumed to occur after 12 months from model entry for those in GMFC-MLD 0.

AA

The Applicant states that the cognitive substates for AA used in the cost-effectiveness analysis were based on both clinical opinion and the clinical trial. It is unclear how clinical opinion and clinical data were weighted in determining the cognitive substate distributions.

Cognitive decline for AA treated patients is linked to GMFC-MLD health state and modelled using the response classification applied the Applicant. Therefore, full responders are assumed not to experience any cognitive decline (100% normal cognitive function). In the Applicant's base case, both stable and unstable partial responders are also assumed to maintain cognitive function across their lifetime (dependent on GMFC-MLD state at which they stabilise; see **Table 5**). This assumption is subject to significant uncertainty.

The Applicant included a scenario where separate cognitive distributions could be applied to stable and unstable partial responders. Under this scenario, stable partial responders maintained the cognitive distributions presented in **Table 5**, and unstable partial responders were assigned cognitive distributions outlined in Table 6. Implementation of this scenario resulted in an increase in the pooled cohort ICER of ~€2,000 to €3,000, depending on the country.

The Review Group ran a scenario where all partial responders were assigned the cognitive distributions outlined in Table 6. Implementation of this scenario resulted in an increased in the ICER for the pooled cohort of ~€5,000 to €9,000, depending on the country. The Review Group consider this scenario to be of relevance, given the lack of data in patients classed as stable partial

responders in GMFC-MLD ≥5. Limited clinical data is available for patients classed as stable partial responders in GMFC-MLD stages 3 and 4 (n=2). It is acknowledged, based on the observed data, that netither patient experienced a cognitive decline; however, both subjects are noted to be missing data on cognitive outcomes for five most recent consecutive assessmets.

Clinical opinion to the Applicant suggested that cognitive impairment data from allogenic transplantation in MLD patients could be used as a proxy to estimate cognitive impairment over longer follow-up periods for AA; these data do not appear to have been incorporated into the Applicant's analysis.

As there were no data on patients who received AA and experienced cognitive decline whilst in GMFC-MLD 0, the minimum amount of time spent in GMFC-MLD 0 before transitioning to GMFC-MLD 1 was used (24 months).

Table 5 Proportion in each cognitive substate by GMFC-MLD state for AA in EJ partial responders

GMFC-MLD state	Normal cognitive function	Moderate cognitive impairment	Severe cognitive impairment
GMFC-MLD 0 after cognitive decline**	95%	5%	0%
GMFC-MLD 1	95%	5%	0%
GMFC-MLD 2	90%	5%	0%
GMFC-MLD 3	80%	5%	5%
GMFC-MLD 4	80%	10%	10%
GMFC-MLD 5	80%	10%	10%
GMFC-MLD 6	80%	10%	10%

**Cognitive decline is assumed to occur after 24 months from model entry for those in GMFC-MLD 0.

Table 6 Proportion in each cognitive substate by GMFC-MLD state for AA in EJ unstable partial responders (scenario)

GMFC-MLD state	Normal cognitive function	Moderate cognitive impairment	Severe cognitive impairment
GMFC-MLD 0 after cognitive decline**	100%	0%	0%
GMFC-MLD 1	100%	0%	0%

GMFC-MLD 2	100%	0%	0%
GMFC-MLD 3	67%	33%	0%
GMFC-MLD 4	67%	0%	33%
GMFC-MLD 5	50%	0%	50%
GMFC-MLD 6	0%	0%	100%

**Cognitive decline is assumed to occur after 24 months from model entry for those in GMFC-MLD 0.

Mortality

As mortality was modelled dependent on GMFC-MLD health state, treatment effects on motor function imply a treatment effect on overall survival. The Applicant assumed MLD-related death only occurs from GMFC-MLD 6. Mortality for patients in GMFC-MLD 6 health state were informed by parametric survival extrapolation of overall survival data from OSR-TIGET NHx data pooled across LI and EJ subgroups. To account for death from other causes, general population mortality was applied to other health states. The Applicant assumes that patients in GMFC-MLD 0 health state will have same life expectancy as the general population. To model the impact of neurological disability a multiplier was applied to the general population mortality for other GMFC-MLD health states (multiplier: 1.4 in GMFC-MLD 1 or 2, 2.0 in GMFC-MLD 3 or 4, and 9.92 in GMFC-MLD 5), informed by data characterising the long-term mortality effects of traumatic brain injury (3). The applicability of data on traumatic brain injury to MLD patients is unclear. Clinical opinion to the Applicant (from UK clinicians) indicated that life expectancy of a treated MLD patient would be shorter than in the general population, even if the patient remains in a low GMFC-MLD state.

The model predicts similar life years gained for PS and ES EJ patients treated with BSC. However, the Applicant assumes that PS patients enter the model earlier than ES patients and therefore mean age at death for ES EJ is higher than for PS EJ. This highlights limitations in the Applicant's approach to modelling BSC and possible differences in age at onset between OSR-TIGET NHx and AA clinical study EJ populations.

- **Exploration of uncertainty in treatment effects**

The Applicant provided scenario analyses using published literature to inform BSC transition probabilities from GMFC-MLD 1 to 2, 2 to 3, 3 to 4 and 4 to 5 (4, 5). A scenario analysis using data from MLDi registry to inform BSC transition probabilities was also provided. The cost-effectiveness results were not sensitive to the choice of data used.

The Applicant presented scenario analyses examining partial loss of treatment effect where full and partial stable responders experience disease progression in line with that modelled for unstable partial responders after either 20, 30 or 50 years. Clinical opinion to the Review Group indicates that outcomes for MLD patients treated with HSCT may be a suitable proxy regarding likely long term treatment outcomes and suggested patients may experience decline after ten years.

Originally, a number of treatment effect parameters are varied assuming a standard error of 20% of the deterministic input parameter value for sensitivity analyses which likely underestimated the uncertainty associated with these parameters. An updated model was provided where certain treatment effect parameters were varied according to the variance of the observed data. However, data were not available for all parameters, meaning it is likely that uncertainty remains underestimated.

- **Review Group concerns with treatment effects**

The comparability of OSR-TIGET NHx and AA clinical studies is unclear. Differences between study populations may lead to bias in estimates of relative treatment effectiveness. Differences in data collection between studies and missing data may also bias estimates of relative treatment effectiveness.

The Applicant's post-hoc approach of classifying patients as full or partial responders is highly subjective and does not consider the limited and variable follow up available or the censored nature of the clinical data. Given the very small number of patients included in the clinical data cost-effectiveness results will be sensitive to the classification of individual patients. Combined with the strong assumptions regarding cure, the Applicant's approach likely biases the cost-effectiveness model outputs in favour of the intervention.

Given lifelong time horizon of the model and relatively short follow up available from clinical studies the Applicant's assumptions of cure (that full responders and stable partial responders will not experience further decline) are not well evidenced and subject to significant uncertainty.

The Applicant's approach to calculating transition probabilities and relative treatment effects (specifically the approach used to estimate mean time to next GMFC-MLD state) does not accommodate the panel nature of the data and will likely bias the transition probabilities and relative treatment effects used in the cost-effectiveness model.

The Review Group acknowledge the inherent limitations when studying rare diseases; however, clinical evidence is only available for a very small number of patients which increases uncertainty around treatment effectiveness. This is of particular concern for EJ patients where less data is available and disease course may be more variable. Many inputs to the cost-effectiveness model are informed by fewer than five patients.

The methodology and source data used to generate assumed cognitive substate distributions for AA remain unclear. The Applicant's values presume a substantial lifelong benefit for AA. The plausibility

of a high proportion of patients who have declined to GMFC-MLD 6 retaining normal cognitive function is unclear.

4.2. Identification of health outcomes

The primary health outcome of the model is the quality adjusted life year (QALY). Health related quality of life (HRQoL) parameters in the model include health state utilities associated with each model health state. A disutility value for adverse events (AEs) associated with busulfan conditioning is applied for three months only, post-administration of AA. Caregiver disutility is incorporated as a scenario analysis for all countries.

There was no HRQoL data collected during trials or expanded access programmes of AA, or from the natural history cohort. The Applicant conducted a systematic literature review, which included a search for HRQoL studies. This search identified three publications of relevance, a survey of caregivers on quality of life and disease burden with MLD (6), an assessment of disease burden (7), and a conference abstract reporting on a study to elicit utility values for MLD health states in the UK (8). This abstract is based on a study commissioned by the Applicant, and it provides the basis for the utility values applied in the cost-effectiveness model (CEM). An overview of the study is provided in Section 2.3.

- **Measurement and valuation of health outcomes**

Description of utility elicitation study commissioned by Applicant

The Applicant commissioned a study to provide estimates of utility for early-onset MLD in the UK. The outcomes of this study have been published as a conference abstract (8), but not as a full peer-reviewed publication. The study was divided into two parts:

a) development of health state descriptions or vignettes using a literature review and qualitative clinician interviews.

b) the valuation of the health states using the time trade-off (TTO) method exercise.

Health state vignettes were developed through a literature review and qualitative interviews with clinicians. The defined health states were largely informed by the CEM, so that health states were developed separately for LI (under 30 months) and juvenile patients (from 30 months to 16 years of age) and defined in terms of the GMFC-MLD characterisation of the disease progression. Five paediatric consultants in metabolic disorders, with experience of treating patients with either LI, juvenile or adult forms of MLD, were interviewed. Additionally, one clinical neuropsychologist with experience of assessing the cognitive performance of patients with MLD was interviewed. Three clinicians reviewed draft descriptions of the health states, and revised draft descriptions of the EJ health states were further reviewed by the three other participants. The health state vignettes used in the study have been provided to the Review Group as part of the submission dossier.

For LI patients, health states were defined by GMFC-MLD health state only. For juvenile patients, health states were defined by GMFC-MLD health state, and by DQ scores for three cognitive functioning levels: normal functioning/mild impairment (DQ>70), moderate impairment (DQ >55 to ≤70), and severe impairment (DQ≤55). The utility elicitation study included health state vignettes for LI patients with GMFC MLD stage 1 to 6. For juvenile patients, health states for GMFC-MLD stage 0 were only described for those with moderate and severe cognitive impairment. Health states were not presented for juvenile patients with GMFC-MLD stage 5 and 6 and normal cognition; a total of 18 health state vignettes for juvenile patients were presented to participants (**Table 7**).

Table 7 Health states described for the utility valuation study

Infantile MLD	Juvenile MLD		
	Normal cognition	Moderate cognitive impairment	Severe cognitive impairment
-	-	GMFC0	GMFC0
GMFC1	GMFC1	GMFC1	GMFC1
GMFC2	GMFC2	GMFC2	GMFC2
GMFC3	GMFC3	GMFC3	GMFC3
GMFC4	GMFC4	GMFC4	GMFC4
GMFC5	-	GMFC5	GMFC5
GMFC6	-	GMFC6	GMFC6

The valuations of the health states were estimated using the time tradeoff (TTO) method. Two rounds of TTO interviews were conducted to obtain values for health states by members of the general public in the UK, one cohort for the LI health states (n=100) and a separate cohort for the juvenile health states (n=115). For the juvenile health states, half of the participants each rated 9 of the 18 juvenile health states, presented to them in random order. Fourteen participants were excluded from the juvenile health states cohort as they valued more than seven states inconsistently or incorrectly, resulting in 101 participants. Additionally, participants in both cohorts also completed the VAS exercise for each health state they valued.

For the LI health states, the mean TTO scores ranged from 0.71 (GMFC-MLD stage 1) to -0.47 (GMFC-MLD stage 6) (**Table 8**). All the states from GMFC-MLD stage 3 onwards were rated as worse than dead i.e., utility value less than zero. The largest incremental decline in utility was seen between GMFC-MLD stages 2 and 3. No additional data manipulation of the mean values elicited in the study was reported.

For the juvenile health states, a linear regression model was used to predict utility values based on GMFC stage and cognition scores. . The Applicant reports that the outputs from this linear regression model were generated primarily to address inconsistencies in the mean TTO values. The linear regression model also allowed for estimation of utility values for GMFC-MLD 5 and 6 states with normal/mild impairment cognitive functioning, as these were not included in the utility elicitation study.

Values for juvenile health states ranged from 0.91 (GMFC-MLD 1 and normal cognition) to -0.8 (GMFC-MLD 6 with severe cognitive impairment) (**Table 8**). All states from GMFC-MLD stage 4 onwards on the normal and moderate cognitive impact states were rated as worse than dead, as were the states from GMFC-MLD stage 3 onwards in the severe cognitive impact set. The largest incremental decline in utility was seen between GMFC-MLD stage 3 and 4 in those with normal cognition. There were sometimes large differences in the utility values generated via the linear regression model, and the mean values elicited directly from participants in the study.

The Review Group highlight some inconsistencies in the valuations applied by the participants in the study, where milder health states are valued as worse than more severe illness, e.g., GMFC MLD stage 1 and 2 with severe cognitive impairment. The Review Group also highlight the much lower values applied to some of the early GMFC-MLD health states in the LI population compared to the EJ population with normal cognition, and conversely how much worse some of the later GMFC-MLD health states are valued for EJ patients with normal cognition compared with the same states in the LI population.

Table 8 Utility values elicited directly from participants, and predicted utility values generated by the linear regression model

		Mean values derived from utility elicitation exercise		Predicted utility values generated from LRM	
	Health states	**Utility**	**95% CI**	**Utility**	**95% CI**
Infantile MLD Health state descriptions	GMFC 0	Not considered	NA		
	GMFC 1	0.71	0.64, 0.77	NA	NA
	GMFC 2	0.44	0.35, 0.52	NA	NA
	GMFC 3	−0.07	−0.2, 0.05	NA	NA
	GMFC 4	−0.22	−0.34, −0.1	NA	NA
	GMFC 5	−0.35	−0.47, −0.23	NA	NA
	GMFC 6	−0.47	−0.58, −0.36	NA	NA
	GMFC health state plus normal cognition				
Early juvenile MLD Health state descriptions	GMFC-MLD 0	Not considered	NA	Not considered	NA
	GMFC-MLD 1	0.90	NP	0.91	NP
	GMFC-MLD 2	0.81	NP	0.84	NP
	GMFC-MLD 3	0.47	NP	0.38	NP
	GMFC-MLD 4	-0.07	NP	0.00	NP
	GMFC-MLD 5	Not considered	NA	Not provided	NA
	GMFC-MLD 6	Not considered	NA	Not provided	NA

	GMFC health state plus moderate cognitive impairment				
	GMFC-MLD 0	0.85	NP	0.75	NP
	GMFC-MLD 1	0.76	NP	0.63	NP
	GMFC-MLD 2	0.55	NP	0.56	NP
	GMFC-MLD 3	0.08	NP	0.10	NP
	GMFC-MLD 4	-0.41	NP	-0.28	NP
	GMFC-MLD 5	-0.42	NP	-0.43	NP
	GMFC-MLD 6	-0.62	NP	-0.51	NP
	GMFC health state plus severe cognitive impairment				
	GMFC-MLD 0	0.37	NP	0.46	NP
	GMFC-MLD 1	0.18	NP	0.34	NP
	GMFC-MLD 2	0.30	NP	0.27	NP
	GMFC-MLD 3	-0.27	NP	-0.20	NP
	GMFC-MLD 4	-0.39	NP	-0.57	NP
	GMFC-MLD 5	-0.70	NP	-0.72	NP
	GMFC-MLD 6	-0.68	NP	-0.80	NP

GMFC-MLD: Gross Motor Function Classification; **95% CI:** 95% confidence intervals; **MLD**: metachromatic leukodystrophy; **NA:** not applicable; **NP:** not provided; **LRM:** linear regression model

The estimated utility values were presented to clinical experts at an advisory board meeting, to assess reasonableness. The Applicant additionally sought to validate the health state descriptions and the estimated utility values with patient advocacy groups, after the study was complete.

- **Utility values applied in the economic model**

The utility values derived from the Applicant elicitation study underwent further manipulation prior to application in the CEM.

For the juvenile health states the Applicant rescaled the utility values so that the lowest value that could be assigned to a health state corresponded to the lowest possible value from the Netherlands EQ-5D-5L tariff (for NE and BE), or from the UK EQ-5D-3L tariff (for IE), rather than a lowest value of -1 in the elicitation study. The Applicant states that this was performed by multiplying the original TTO utility values which were negative by the lowest possibly utility according to each countries' respective EQ 5D value set (UK: -0.594; Netherlands: -0.329) (9, 10). The justification and implications for rescaling only the negative TTO utility values were not proposed. Utilising the rescaled values reduces the number of health states rated as worse than dead. The impact of using the values generated from the linear regression model rather than the mean utility values elicited directly from participants is unclear, as the effects varied between health states. However, the Review Group

highlight some important differences in the values predicted via both methods, for example the mean value for GMFC-MLD stage 6 with severe cognitive impairment was –0.68, whereas the value derived from the linear regression model and implemented in the CEM was –0.8.

For LI patients, the Applicant uses the mean values for the infantile health states elicited in the study and rescaled them to match the national tariffs as described above. These rescaled values were applied up to 48 months of age. Thereafter it was assumed that the utility values from the juvenile cohorts would be more appropriate, and the average value across the three cognitive sub-states from the rescaled juvenile health states was applied.

For both EJ and LI patients in GMFC-MLD stage 0 with no cognitive impairment, utility was assumed to match the country-specific age-adjusted general population utility. This leads to implausible declines in utility from GMFC-MLD stage 0 to stage 1 for the LI cohort (from 0.951 in the BE model to 0.67); the decline is less marked for the juvenile cohort. . The health state utility values applied in the model are outlined in **Table 9**.

Table 9 Health state utility values applied in the economic model for each country, and those derived from the utility study commissioned by the Applicant

		Values applied in the model (BE, NE)		Values applied in the model (IE)	
	Health states	**Utility**	**95% CI**	**Utility**	**95% CI**
Late infantile (up to 48 months)	GMFC-MLD 0*	0.936 (NE) 0.951 (BE)	NP	0.949	
	GMFC-MLD 1	0.67	0.616, 0.723	0.66	0.586, 0.719
	GMFC-MLD 2	0.58	0.525, 0.636	0.57	0.501, 0.639
	GMFC-MLD 3	0.25	0.188, 0.301	0.19	0.116, 0.255
	GMFC-MLD 4	-0.01	-0.07, 0.045	-0.12	-0.191, -0.049
	GMFC-MLD 5	-0.04	-0.1, 0.02	-0.19	-0.264, -0.115
	GMFC-MLD 6	-0.08	-0.139, -0.019	-0.24	-0.320, -0.168
	GMFC MLD health state and normal cognition				
Early juvenile¥	GMFC-MLD 0*	0.936	NP		
	GMFC-MLD 1	0.884	0.827, 0.941	0.893	0.823, 0.963
	GMFC-MLD 2	0.795	0.733, 0.858	0.812	0.735, 0.889
	GMFC-MLD 3	0.459	0.398, 0.519	0.426	0.351, 0.500
	GMFC-MLD 4	0.203	0.139, 0.266	0.122	0.044, 0.200
	GMFC-MLD 5	0.175	0.097, 0.252	0.053	-0.043, 0.148
	GMFC-MLD 6	0.136	0.059, 0.213	-0.003	-0.098, 0.093
	GMFC MLD health state and MCI				
	GMFC-MLD 0	0.733	0.669, 0.797	0.740	0.661, 0.819

	GMFC-MLD 1	0.669	0.616, 0.723	0.651	0.585, 0.717
	GMFC-MLD 2	0.580	0.525, 0.636	0.570	0.501, 0.639
	GMFC-MLD 3	0.244	0.187, 0.300	0.184	0.114, 0.253
	GMFC-MLD 4	-0.012	-0.07, 0.045	-0.12	-0.191, -0.049
	GMFC-MLD 5	-0.040	-0.1, 0.02	-0.189	-0.264, -0.115
	GMFC-MLD 6	-0.079	-0.141, -0.017	-0.245	-0.321, -0.169
	GMFC-MLD health state and SCI				
	GMFC-MLD 0	0.529	0.465, 0.593	0.505	0.426, 0.583
	GMFC-MLD 1	0.465	0.410, 0.519	0.416	0.348, 0.483
	GMFC-MLD 2	0.376	0.321, 0.431	0.335	0.267 0.402
	GMFC-MLD 3	0.039	-0.017, 0.096	-0.052	-0.121, 0.018
	GMFC-MLD 4	-0.217	-0.274, -0.160	-0.355	-0.426, -0.285
	GMFC-MLD 5	-0.244	-0.306, -0.183	-0.425	-0.501, -0.348
	GMFC-MLD 6	-0.283	-0.344, -0.223	-0.480	-0.555, -0.406

CI: Confidence interval; GMFC-MLD: Gross Motor Functional Classification in metachromatic leukodystrophy; SD: Standard deviation; NP: not provided; NA: not applicable; MCI: moderate cognitive impairment; SCI: severe cognitive impairment
*Corresponds to age adjusted general population utility.
¥ From the elicitation study, these values were derived by linear regression models accounting for both GMFC-MLD stage and cognition and are not the values elicited directly from patients.

As an additional validation step, the Applicant provided a comparison of the elicited and applied utility values with values sourced from the literature for a comparable illness, X-linked adrenal leukodystrophy (X-ALD)(**Table 10**).

Table 10 Comparison of applied utility values with literature values for X-ALD.

GMFC MLD stage	Utility value (average across three juvenile cognitive substates)-NE/BE	Utility value (average across three juvenile cognitive substates)-IE	ALD	Utility value
1	0.67	0.65	ALD-DRS I	0.68
2	0.58	0.57	ALD-DRS II	0.59
3	0.25	0.19	ALD-DRS III	0.11
4	-0.01	-0.12	ALD-DRS IV	0.03
5	-0.04	-0.19	-	-
6	-0.08	-0.24	-	-

GMFC: Gross motor function classification; **MLD:** metachromatic leukodystrophy; **X-ALD:** linked adrenal leukodystrophy

Caregiver disutility is applied in a scenario analysis for all three countries (**Table 11**). This disutility is assumed to occur from GMFC-MLD stage 2 and above. The calculations are based on the mean index utility value (0.773) for all respondents (n=21) completing the EQ-5D in an MLD Caregiver Survey (6), subtracted from General Population Utility at 40 years of age for the relevant country. It is assumed

that one full-time caregiver is required for GMFC-MLD stages 3 and 4, and that two are required full-time for GMFC-MLD stages 6 and 7. This disutility is assumed to last until the patient is 30 years old.

Table 11 Calculation of caregiver disutility

GMFC-MLD stage	Number of caregivers required (NE)	Total Caregiver disutility (NE)	Number of caregivers required BE/IE	Total Caregiver disutility (BE)	Total Caregiver disutility (IE)
GMFC-MLD 0	0	0	0	0	0
GMFC-MLD 1	0	0	0	0	0
GMFC-MLD 2	0	0	0.5	-0.06	-0.06
GMFC-MLD 3	0	0	1	-0.11	-0.13
GMFC-MLD 4	0	0	1	-0.11	-0.13
GMFC-MLD 5	2	-0.22	2	-0.22	-0.25
GMFC-MLD 6	2	-0.22	2	-0.22	-0.25

GMFC: Gross motor function classification; **MLD:** metachromatic leukodystrophy;

A disutility for complications due to busulfan conditioning has been applied in the model (-0.57), informed by the utility decrement applied in a previous HTA assessment of a gene therapy requiring busulfan conditioning, in the UK setting (11). The disutility is applied for just three months post-transplant in the model, as side-effects are assumed to be short lived. No disutility for adverse events due to AA is applied in the model.

A decrement representing the general decline in utility with age is applied in the model, using the methods described by Ara and Brazier (12), from age 18 years onwards.

- **Exploration of uncertainty in utility values**

Uncertainty in health outcomes is considered through scenario analysis, and in the DSA and PSA. Values were varied according to a normal distribution in the PSA.

The Applicant presents a scenario where utility values were based the rescaled mean TTO values elicited during the vignette study. Under this scenario, the values for GMFC-MLD 5 and 6 normal cognition states were retained from the regression analysis as these were not elicited using vignettes. Implementing this scenario results in a minor increase the ICER. The Applicant provides a

scenario analysis for all countries where an alternative set of utility values is applied, where only the values for GMFC levels with normal cognitive function (with a utility value greater than zero) are used, with an additional modifier of a top-up of 0.1 applied to 80% patients of AA treated patients in GMFC 3 to 6. For both BE and NE, this has the impact of reducing the combined ICER versus BSC by approximately 6,500 euro; for IE the ICER is increased slightly. The Review Group do not consider this a particularly useful scenario analysis as there is no clear basis for these altered assumptions. The Applicant also presented a scenario including disutility for caregivers, which reduced the combined ICER vs BSC for BE and NE by ~1,500 to 2,500 euro per QALY. For IE, including caregiver disutility had a greater impact on the ICER, reducing it by 8,628 per QALY. An additional scenario for IE is presented where utility values are rescaled using the EQ-5D 5L UK value set (13), as opposed to the 3L value set, resulting in an increase in the ICER of €9,128/QALY.

In deterministic analyses, health state utility values were varied by +/- 20%. The impact on the Applicant base case ICERs was as follows:

- For BE and NE, using the combined ICER versus BSC, the utility value applied for GMFC MLD stage 0 with moderate or severe cognitive impairment varied the ICER +/-1%. This was driven by the impact in the PS LI cohort, where varying the utility value applied for the EJ GMFC-MLD stage 0 moderate or severe cognitive impairment patients varied the ICER by +/-3% and +/-2% respectively. Utility did not have a relevant impact on the ICER for the PS EJ or ES EJ cohorts.
- For IE, using the combined ICER versus BSC, the utility value applied for GMFC MLD stage 0 with moderate or severe cognitive impairment varied the ICER +/-2% and 1% respectively This was driven by the impact in the PS LI cohort, where varying the utility value applied for the EJ GMFC-MLD stage 0 moderate or severe cognitive impairment patients varied the ICER by +/-3% and +/-2% respectively. Utility did not have an important impact on model outcomes in the ES EJ and PS EJ cohorts.

Clinical opinion obtained by the Review Group indicated that the health states GMFC-MLD 0 with both moderate and severe cognitive impairment were implausible, due to the relationship between deteriorating motor and cognitive function. The Review Group are concerned by the impact of the values applied to these clinically implausible values on the ICER.

Limitations of utility values applied in the model

The Review Group acknowledge that measuring robust utility values in babies and young children is challenging, particularly in the rare disease setting.

Concerns regarding the Applicant utility elicitation study

There are several concerns regarding the utility study conducted by the Applicant:

- The study predicts a large number of worse than death health states (11 out of the 24 included in the study). Clinical opinion provided to the Review Group indicates that this is not plausible, due to adaptation of people living with the condition.
- Some of the valuations do not appear to correlate well with the severity of the GMFC-MLD health state, for example -0.07 (worse than dead) for GMFC-MLD stage 3 in LI patients, where sitting without support and locomotion are possible, but the patient is not able to walk.
- Health states which were not considered clinically plausible by clinical opinion provided to the Applicant (GMFC-MLD 0 with moderate or severe cognitive impairment) were included in the valuation exercise and in calculations to estimate the values applied in the model.
- In the mean TTO values collected directly from participants, there is inconsistency in some of the valuations, where worse health states are valued higher than better health states, suggesting that the participants failed to complete or comprehend the task adequately. There is inconsistency between the reported TTO and VAS scores, with many health states valued at worse than death in the TTO exercise, but greater than zero in the VAS score.
- The Review Group highlight that in the value set generated by the Applicant study, many health states lie outside the range of established EQ-5D preference weights based on both the UK and Dutch tariffs.
- The health state vignettes fail to provide important context, such as reminding participants that they are imagining the life of a young child. They provide an objective description of the symptoms of the illness, rather than an attempt to describe the illness as it may be perceived by the person experiencing the illness, with the accompanying cognitive impairment. There are also inconsistencies between the descriptions of equivalent GMFC-MLD stages between the LI and EJ variants.

- There are large differences in the utility values applied for the LI and EJ groups for the same GMFC-MLD health states. The Review Group consider this implausible.
- The sample of participants is a convenience sample rather than a sample representative of the UK population, and its applicability to the Beneluxa setting is unclear. Also, experiences of the health state are not derived from those with lived experiences of the disease, and valued with a societal tariff as is the preferred method; instead a value is derived for these health states based on their direct evaluation by members of the public who have no experience of living with this illness.

Concerns regarding the data manipulation to derive values for the model.

For the late infantile states, the Applicant applied the rescaled mean values directly in the model. For the juvenile health states, the rescaled values generated from the linear regression model are used. Thus, different approaches are used to derive the utility values applied to both cohorts, without any explanation provided as to why this was necessary or appropriate. The Review Group are concerned by the approach, particularly given the large differences in utility applied to the same health state, depending on age of onset of the illness, and the implausibly low values applied to the early stages of the disease for the LI cohort. The Review Group also highlight the implausible drop in utility when moving from GMFC-MLD stage 0 (standard population utility) to GMFC-MLD stage 1 for the LI patients. To consider the impact of this on the model outcomes for LI patients, the Review Group performed a scenario analysis where the values for EJ patients with normal cognition were applied to the LI patients (see section x.x); the model was insensitive to this change.

The application of the average utility value across each cognitive sub-state of the GMFC-MLD juvenile health states, to patients in the LI cohort after 48 months, assumes that cognitive and motor decline occur at the same rate for LI patients as juvenile patients after age four, rather than modelling the disease course as for EJ patients with separate health states. Thus, an implicit assumption is made that the course of the illness is different depending on age of onset of the illness. This is contrary to clinical opinion provided to the Review Group. Clinical opinion highlighted that cognitive and motor decline do not occur in tandem, and also suggests that there is no difference in disease course, other than time of onset, between LI and juvenile patients.

The effect of rescaling the utility values to reflect the limits in the national tariff reduces the number of negative health states for NE/BE from 11 to nine.

Concerns regarding other utility values obtained in the model

The Review Group note that the caregiver disutility applied in the model is higher than those applied in previous assessments of similar conditions such as spinal muscular atrophy.

The Review Group note that the value applied for disutility due to busulfan conditioning (-0.57) is referenced to a NICE assessment of a gene therapy called Strimvelis®. Further review of the original publication shows that this value, representing 'disutility of undergoing bone marrow transplant' was obtained from clinicians (n=12) based on unpublished health state vignettes, using a visual analogue scoring system which was then converted into a standard gamble utility value (14). Thus, it is not possible for the Review Group to determine its plausibility, appropriateness, and relevance to this population.

Overall, the relevance of utility values obtained in the setting of haematological malignancy to patients undergoing gene therapy is unknown. However, until gene therapy specific data becomes available, it will be necessary to use alternative reference sources, and the literature are of haematological malignancy may be most appropriate.

The Review Group note that based on clinical opinion, a cost for the installation of a baclofen pump has been included for patients as a component of BSC in the NE model. The purpose of this treatment is to alleviate spasticity and pain and would be expected to have an impact on QOL. However, while the costs have been incurred in the BSC arm, no corresponding improvement in utility has been applied. The Review Group highlight that this biases the model in favour of AA.

Concerns regarding compliance with national reference case

For IE, national HTA guidelines require that "information on the changes in the health state should be reported directly by the patient (or their carer, where relevant). A valuation of these changes in the health state should then be obtained using preferences elicited from a representative sample of the general population". Therefore, contrary to claims by the Applicant, the utility values reported do not meet the requirements of the Irish reference case. There is no suggestion that the population

sample used to derive the utility estimates via the TTO method was a representative sample from the UK population.

Overall, the Review Group consider that there is significant uncertainty associated with the health state utility values applied in the model, partially due to the scarcity of data in the population of interest, and to the methodological challenges of utility valuation in young children. The Applicant did conduct a utility elicitation study, which does not meet the requirements of the national reference case for IE. Several methodological concerns with the study were highlighted by the Review Group, and the plausibility of the utility values derived from this study are highly uncertain. These values then underwent further manipulation prior to implementation in the CEM, rendering all outcome estimates highly uncertain. It is highlighted that the varying of utilities in the PSA does not address the issues of methodological uncertainty identified above, nor adequately capture the uncertainty related to quality-of-life outcomes in the model.

Concerns regarding the plausibility of model outcomes

The Review Group highlight that using the combined ICERs, the model predicts zero QALYs for patients receiving BSC and living in Belgium, -0.1 QALYs for those living in the Netherlands, and –1 QALY for those living in Ireland. This implies that providing BSC to patients with MLD may reduce their quality of life over their lifetime, an outcome which lacks face validity. This is particularly the case for patients in the ES EJ cohort, where the QALYs accrued with BSC are –0.4 for BE and NE, and –1.4 for IE. The net effect of these negative QALY gains with BSC is to further increase the incremental QALY gain with AA.

4.3. Identification of costs

The model included drug acquisition cost and administration costs for AA. AA is a single, one-off treatment. The price to wholesaler/chemist (PtW/c) in all three countries is €2,875,000. No specific drug acquisition costs were applied for BSC; BSC was assumed to consist of background resource use in each health state, and therefore these costs are captured in the model health state costs. Health care costs associated with BSC are applied to all treatment arms, and include:

- Drug costs
- Medical tests and visits
- Hospitalisations
- General practice and emergency visits
- Healthcare equipment
- Social services

A societal perspective is taken for the model base case for NE, and lost family income, out of pocket costs and productivity gains due to treatment are included in the model. For BE and IE, the base case perspective is that of the health system, as per national guidance. For BE and NE, administration costs are informed by national datasets and publications; for NE cost year was 2021, for BE it is unspecified. For IE, administration and follow-up costs from the UK are applied as patients will travel to UK for treatment. UK costs were inflated using the UK 2020 Consumer Price Index for Health, then applied to Ireland using the Purchasing Power Parity Index (2019).

- **Measurement and valuation of intervention and comparator costs**

The Applicant conducted a model advisory board to obtain clinical input to inform the health economic model. Qualitative clinical opinion was sought to validate utility data and model assumptions, via discussions. Quantitative clinical opinion was sought using a single-round on-line survey, and an exercise in Microsoft Excel, to inform healthcare and resource use (HCRU) inputs. Additionally, a quantitative structured expert elicitation (SEE) process using a modified Delphi panel was conducted to inform other health economic variables (see section 2.2). Participants (n=6) were recruited from three UK reference centres for the treatment of lyposomal storage disorders; an additional consultant haematologist provided input outside of the formal board. Clinicians had no direct experience of using AA, but some were involved in managing patients who have received AA in clinical trials. No conflicts of interest were declared. Participants included paediatric haematologists, consultants in inherited metabolic diseases and clinical neurophyschologists. Only five contributed to the structured expert elicitation exercise to estimate HCRU. No practitioners other than those specified were involved, to give a broader view of HCRU outside of hospital. The HCRU study presented by the Applicant noted that the UK clinicians did not feel the Italian data used to anchor HCRU estimates was fully generalizable to the UK setting; there is no discussion of whether

the UK or Italian data would be most relevant to this submission. Of note, the Italian data comes from a single physician, and so may be less generalizable.

- **Intervention and Comparator Costs**

The price to wholesaler/chemist (PtW/c) in all three countries is €2,875,000. The final pricing including VAT, mark-ups, and rebates etc. for each country is shown in **Table 12**.

Table 12 Acquisition cost for AA

	PTW/c	Total reimbursement price per pack (incl. VAT)[a, b]	Total reimbursement price per pack (ex. VAT)[a, b]
Belgium	€2,875,000	€3,047,500	€2,875,000
Netherlands	€2,875,000	€3,133,750	€2,875,000
Ireland	€2,875,000	€3,313,437.50	€2,213,750

PTW/c: price to wholesaler/chemist

[a]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 for Belgium. Price exclusive of VAT is used in CEM and BIM in Netherlands. Price exclusive of VAT is used in the CEM, and price inclusive of VAT in the BIM, in Ireland. VAT=6% in Belgium, 9% in Netherlands, 23% in Ireland.

[b]Total reimbursement price in Ireland includes a 7.75% rebate on the price to wholesaler, applied in all economic evaluations in Ireland.

HSCT: haematopoietic stem cell transplant; **MLDi: GvHD**: graft versus host disease; **AE**: adverse events; **IVIG:** intravenous immunoglobulin

- **Administration costs**

Administration costs for AA were applied in the model (Table 13), and were assumed to consist of the following, based on clinical opinion provided by UK clinicians:

- Leukapheresis
- Conditioning including the cost of busulfan (includes hospitalisation for 4-7 days)
- Following administration, it is assumed that a four to 12-week hospital stay will be required
- Follow-up transplant costs for at least two years after administration.

Table 13 Administration costs applied in the model

	Belgium	Netherlands	Ireland
Leukapheresis	€1,307	€40,587	€2,187

Conditioning	€36,831	€7,328	€5,183
Administration and hospitalisation		€38,032	€24,425
Total conditioning, administration, and hospitalisation	**€38,138**	**€85,947**	**€31,796**
Travel	**€547**		**€186**
Follow-up transplant costs	**€1,907**	**€17,983**	**€74,566**
Rituximab costs*	€160	€295	€186
Proportion of patients requiring rituximab	14%	14%	14%
Rituximab total costs	€22	€41	€26
Total cost per patient	**€40,614**	**€103,882**	**€106,574**
*Costs are included for rituximab for the treatment of autoantibodies following administration of AA, which occurred in 4/29 patients (14%) of patients treated.			
Belgium: Costs for leukapheresis were obtained from the Nomen-oft: 470536. Assumed patients spend an average of 7.5 weeks in the hospital following administration. The hospitalisation costs is calculated by multiplying the per diem cost of hospitalisation in an acute hospital by the anticipated length of stay (€578.05*52.5 days). Note, the costs associated with conditioning are combined with administration and hospitalisation in Belgium. Travel costs are based on the average round-trip cost of a flight for two persons from Brussels to Amsterdam. Follow-up costs are assumed to be similar to follow-up costs for liver transplantation, sourced from the literature.			
Netherlands: Costs for leukapharesis (NZa 14E728). Costs for conditioning: To calculate the mean cost for 5.5 days, the weighted average was calculated (91% 1-5 days, 9% 6-28 days). For 6-28 days: NZa declarationcode: 14E123. Inpatient admission for 6-28 days with special activities for paediatric metabolic diseases. Max NZa tarif is set at €15,581.12. Costs for inpatient admission for 1-5 days are €5,598.15 (NZa declaration code 14E118). Busulfan used for paediatric conditioning is considered an add-on drug and the price is not included in hospitalization. Busulfan costs were taken from medicijnkosten.nl. Average price of Busilvex (EU number: EU/1/03/254/002) and Busulfan Teva (RVG number: 120583) was used. Average price for Busulfan 6mg/ml 10ml = € 277.19. Average dose 176.102mg. Three packages of 60ml assumed per patient. Busulfan costs per patient € 831.57. For administration and hospitalisation costs, a cost for Stem cell transplant administration + continuous hospitalization during transplant phase. Paediatric autologous stem cell transplantation. Source: NZa database (2021). Zorgproductcode: 979003056. Treatment / follow-up after autologous stem cell transplantation. Declaration code specifically for paediatric follow-up costs: 14E770 (2021).(15) The NZa maximum tariff of €17,893.12 was used.			
Ireland: as it is expected that Irish patients will receive treatment in Manchester, the Applicant applied UK national reference costs for the estimation of costs (2018/2019), inflated to 2020 costs and converted to euro using the purchasing power parity index (2019). Leukapheresis cost is based on a weighted average of HRGs for stem cell (SA34Z) and bone marrow harvest (SA18Z). Conditioning cost was based on the weighted average of HRG paediatric metabolic disorders admissions-elective (PK72A, PK72B, PK72C). Additional drug cost for busulfan was applied, assuming average dose from clinical development programme (176.102mg), leading to a cost per patient of £93.14. A weighted average of UK HRG costs for paediatric metabolic disorders (elective inpatient ((PK72A, PK72B, PK72C)) was applied for administration costs, which covered a length of stay of 11 days, supplemented with an additional daily cost sourced from the average cost of elective inpatient excess bed day HRGs (£412.23) to cover the remaining six weeks (7.5 weeks average hospitalisation post-transplant). Travel costs are based on the average round-trip cost of a flight for two persons from Dublin to Manchester. Costs for follow-up were sourced from a UK report, and assumes that follow-up will be the same as for allogeneic SCT, and that patients will be discharged to metabolic care after 2 years.			

APR-DRG: All Patient Refined Diagnosis Related Group; **EU:** European Union; **NZa:** Nederlandse Zorgautoriteit; **SmPC:** Summary of Product Characteristics; U**K:** United Kingdom; **ABF:** Activity Based Funding; **CPI:** Consumer Price Index; **DRG:** Diagnosis Related Groups; **HRG:** Healthcare resource group; **NCPE,** National Centre for Pharmacoeconomics; **PPP,** purchasing power parity; **SmPC,** Summary of Product Characteristics; **UK,** United Kingdom.

Costs were included for rituximab for the treatment of autoantibodies to AA for 14% patients; the Applicant gave no details of how the applied costs were estimated. The Review Group note the challenge in estimating administration costs for Ireland and Belgium, where if reimbursed, AA will be administered within a different health system (patients from Belgium may receive treatment in the Netherlands or France, and patients from Ireland will receive treatment in the UK). This means that the costs incurred for administration may not reflect the costs that would be incurred in the national setting. The Review Group explored the impact of this in scenario analyses, where for Belgium they applied the same costs for administration as used in the Netherlands, and for Ireland they used the cost of HSCT, as billed from UK hospitals. See section 3.1.3 for more detail. Travel costs were included for both BE and IE.

Deterministic sensitivity analyses highlighted that these administration costs had very minor impacts on the composite ICER. The costs for NL are largely based on the maximum values of the national tariff set by the Dutch Health Authority. The Review Group highlight inconsistencies in the approach taken to the estimation of IE costs, using a mixture of UK and Irish costs, and also not utilizing the extensive costing information presented in Hettle et al regarding the administration of regenerative medicines such as AA.

- **Health state, adverse events and other costs**

HCRU of patients with MLD was estimated using the structured expert elicitation study described above. Clinical opinion provided information on the frequency and proportion of HCRU in each GMFC-MLD stage. Weighted means of proportions of patients using specific resources, as well as frequency and duration of each type of resource use were calculated. Additionally, the cost of installing and maintaining a baclofen pump is included for patients in NE, for all patients at GMFC-MLD stage 5 and 6, based on expert opinion. Unit costs were applied for each country. Costs were applied according to two age categories, ages 0-18 years, and ages 19+. This was to model greater costs for adult patients, where a larger proportion are expected to receive residential care rather than care provided at home. For all countries, for costs in the GMFC-MLD 6 health state, it was assumed that 90% patients would live at home, with 10% in hospital care. Monthly costs increase with increasing severity of disease.

For the DSA, cost parameters were varied by +/-20% rather than within any calculated estimates of uncertainty around the point estimate. In the PSA, summed cost parameters were varied according to a gamma distribution. Importantly, resource use estimates and individual component costs were not varied in the PSA, despite the important uncertainty associated with these parameters.

Belgium

The costs applied per health state, per month are tabulated in Table 14 and Table 15.

Table 14 Summary of monthly MLD-related costs (Belgium, ages 0-18)

Cost category	Health State									Sources
	0	**1**	**2**	**0**	**1**	**5**	**0**	**1**	**6 (In Hospital)**	**0**
Drugs	€ 0	€ 67	Drugs	€ 0	€ 67	Drugs	€ 0	€ 67	Drugs	€ 0
Medical tests	€ 0	€ 32	Medical tests	€ 0	€ 32	Medical tests	€ 0	€ 32	Medical tests	€ 0
Medical visits	€ 0	€ 39	Medical visits	€ 0	€ 39	Medical visits	€ 0	€ 39	Medical visits	€ 0
Hospitalisations	€ 48	€ 77	Hospitalisations	€ 48	€ 77	Hospitalisations	€ 48	€ 77	Hospitalisations	€ 48
GP & Emergency	€ 0	€ 32	GP & Emergency	€ 0	€ 32	GP & Emergency	€ 0	€ 32	GP & Emergency	€ 0
Healthcare equipment	€ 0	€ 16	Healthcare equipment	€ 0	€ 16	Healthcare equipment	€ 0	€ 16	Healthcare equipment	€ 0
Respite Care	€ 0	€ 0	Respite Care	€ 0	€ 0	Respite Care	€ 0	€ 0	Respite Care	€ 0
Social services	€ 0	€ 0	Social services	€ 0	€ 0	Social services	€ 0	€ 0	Social services	€ 0
Total	**€ 48**	**€ 262**	**Total**	**€ 48**	**€ 262**	**Total**	**€ 48**	**€ 262**	**Total**	**€ 48**

Footnotes: *GMFC-MLD 6 patients living at home = 90%; GMFC-MLD 6 patients in hospital = 10%, based on clinical expert advice. †As of January 2019, the competencies related to the reimbursement of assistance devices for people with reduced mobility are entirely the responsibility of the federated entities (Communities, Regions). Therefore, the cost of mobility equipment (wheelchairs, walkers and frames [standing and walking]) is not a relevant cost from the national payer body (RIZIV/INAMI) perspective.
Neuromuscular annual lump sum costs (€8,990) are included for patients in GMFC-MLD and 6 health states. Includes drugs, material, nursing for patients in home care and in a vegetative state; drugs, medical tests and medical visits assumed to be 0 when lump sum costs applied.
Abbreviations: GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy; GP: General Practitioner.

Table 15 Summary of monthly MLD-related medical costs (Belgium, ages 19+)

	Health State	

Cost category	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 2	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 5	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 6 (In Hospital)	Sources GMFC-MLD 0
Drugs	-	€ 67	Drugs	-	€ 67	Drugs	-	€ 67	Drugs	-
Medical tests	-	€ 32	Medical tests	-	€ 32	Medical tests	-	€ 32	Medical tests	-
Medical visits	-	€ 39	Medical visits	-	€ 39	Medical visits	-	€ 39	Medical visits	-
Hospitalisations	-	€ 0	Hospitalisations	-	€ 0	Hospitalisations	-	€ 0	Hospitalisations	-
GP & Emergency	-	€ 32	GP & Emergency	-	€ 32	GP & Emergency	-	€ 32	GP & Emergency	-
Healthcare equipment	-	€ 16	Healthcare equipment	-	€ 16	Healthcare equipment	-	€ 16	Healthcare equipment	-
Respite Care	-	€ 0	Respite Care	-	€ 0	Respite Care	-	€ 0	Respite Care	-
Social services	-	€ 2	Social services	-	€ 2	Social services	-	€ 2	Social services	-
Total	**-**	**€ 187**	**Total**	**-**	**€ 187**	**Total**	**-**	**€ 187**	**Total**	**-**

Footnotes: *GMFC-MLD 6 patients living at home = 90%; GMFC-MLD 6 patients in hospital = 10%, based on clinical expert advice. †As of January 2019, the competencies related to the reimbursement of assistance devices for people with reduced mobility are entirely the responsibility of the federated entities (Communities, Regions). Therefore, the cost of mobility equipment (wheelchairs, walkers and frames [standing and walking]) is not a relevant cost from the national payer body (RIZIV/INAMI) perspective.

Neuromuscular annual lump sum costs (€8,990) are included for patients in GMFC-MLD and 6 health states. Includes drugs, material, nursing for patients in home care and in a vegetative state; drugs, medical tests and medical visits assumed to be 0 when lump sum costs applied. **Abbreviations:** GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy; GP: General Practitioner.

The Applicant did not provide any justification for the generalisability of the UK estimates of resource use to BE, and no clinical validation was provided from BE clinicians. Unit costs for Belgium were sourced from national reference sources and validated by the Review Group. The Applicant excluded many components of the cost of care for MLD, based on the assumption that these are financed through federal mechanisms rather than through the national payer, an assumption which was validated by the Review Group internally.

The outcomes of the DSA (combined ICER) suggested that cost components have limited impact on the model outcomes; the cost parameter with the greatest influence on outcomes was the total cost of administering AA but varying this by +/-20% only shifted the ICER +/-1%. In the individual cohorts, the cost parameter with greatest influence was total administration costs for AA, but again the ICER only varied +/- 1%.

Netherlands

The costs applied per health state, per month are tabulated (Table 16 and Table 17).

Table 16 Summary of monthly MLD-related medical costs (the Netherlands, ages 0–18)

Cost category	Health State									Sources
	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 2	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 5	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 6 (In Hospital)	GMFC-MLD 0
Drugs	€ 0	€ 384	Drugs	€ 0	€ 384	Drugs	€ 0	€ 384	Drugs	€ 0
Medical tests	€ 0	€ 106	Medical tests	€ 0	€ 106	Medical tests	€ 0	€ 106	Medical tests	€ 0
Medical visits	€ 0	€ 163	Medical visits	€ 0	€ 163	Medical visits	€ 0	€ 163	Medical visits	€ 0
Hospitalisations	€ 44	€ 70	Hospitalisations	€ 44	€ 70	Hospitalisations	€ 44	€ 70	Hospitalisations	€ 44
GP & Emergency	€ 0	€ 16	GP & Emergency	€ 0	€ 16	GP & Emergency	€ 0	€ 16	GP & Emergency	€ 0
Healthcare equipment	€ 0	€ 103	Healthcare equipment	€ 0	€ 103	Healthcare equipment	€ 0	€ 103	Healthcare equipment	€ 0
Respite Care	€ 0	€ 0	Respite Care	€ 0	€ 0	Respite Care	€ 0	€ 0	Respite Care	€ 0
Social services	€ 0	€ 0	Social services	€ 0	€ 0	Social services	€ 0	€ 0	Social services	€ 0
Total	**€ 44**	**€ 841**	**Total**	**€ 44**	**€ 841**	**Total**	**€ 44**	**€ 841**	**Total**	**€ 44**

Footnotes: *GMFC-MLD 6 patients living at home = 90%; GMFC-MLD 6 patients in hospital = 10%, based on clinical expert advice.
Abbreviations: GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy; GP: General Practitioner.

Table 17 Summary of monthly MLD-related medical costs (the Netherlands, ages 19+)

Cost category	Health State									Sources
	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 2	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 5	GMFC-MLD 0	GMC-MLD 1	GMFC-MLD 6 (In Hospital)	GMFC-MLD 0
Drugs	-	€ 384	Drugs	-	€ 384	Drugs	-	€ 384	Drugs	-
Medical tests	-	€ 106	Medical tests	-	€ 106	Medical tests	-	€ 106	Medical tests	-
Medical visits	-	€ 163	Medical visits	-	€ 163	Medical visits	-	€ 163	Medical visits	-
Hospitalisations	-	€ 0	Hospitalisations	-	€ 0	Hospitalisations	-	€ 0	Hospitalisations	-
GP & Emergency	-	€ 16	GP & Emergency	-	€ 16	GP & Emergency	-	€ 16	GP & Emergency	-
Healthcare equipment	-	€ 103	Healthcare equipment	-	€ 103	Healthcare equipment	-	€ 103	Healthcare equipment	-
Respite Care	-	€ 0	Respite Care	-	€ 0	Respite Care	-	€ 0	Respite Care	-
Social services	-	€ 0	Social services	-	€ 0	Social services	-	€ 0	Social services	-
Total	**-**	**€ 771**	**Total**	**-**	**€ 771**	**Total**	**-**	**€ 771**	**Total**	**-**

Footnotes: *GMFC-MLD 6 patients living at home = 90%; GMFC-MLD 6 patients in hospital = 10%, based on clinical expert advice.
Abbreviations: GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy; GP: General Practitioner.

The Applicant did not provide any justification of the generalisability of the UK resource use estimates to NL. Unit costs for NL were sourced from a range of national reference sources and validated by the Review Group. The Review Group note that no costs for respite care or palliative care were included in the model. Based on clinical opinion provided by a clinician practicing in the Netherlands, a cost was also applied for the installation and maintenance of a baclofen pump, for patients in GMFC-MLD stage 5 and 6. The costs applied were €22,696.35 for the initial installation costs, and €4,539.54 on an ongoing basis.

In the model base case for NE, societal costs related to MLD are included. The additional costs considered as part of this broader perspective are loss of family income, out of pocket costs, and patient productivity costs, detailed below. These costs were not included for BE or IE.

In the Applicant's base case, loss of family income was calculated by estimating the number of hours caregiving per day multipled by the standard Dutch tariff for informal caregiving (€15.45 per hour, 2021 cost). The average number of hours spent caregiving per day was based on data from an MLD caregiver survey. Based on reported symptoms, patients with MLD included in the survey were

assigned a mild (GMFC-MLD stage 1-2), moderate (GMFC-MLD 3-4) or severe (GMFC-MLD 5-6) state. The annual costs related to informal care were calculated by multiplying the daily cost by 255 (number of working days in 2021) in the base case. A scenario where the daily costs were multiplied by 365 was also presented. An additional scenario was presented, whereby the Applicant calculated informal care costs based on the MLD caregiver survey, and Dutch salaries (Table 18**Fout! Verwijzingsbron niet gevonden.**). To obtain an average annual salary for NE, the Applicant used 2019 earnings, averaged across males and females ((43,410+27,120)/2), and inflated these to 2021 earnings (35,265*1.026), which gave a figure of 36,165. It was assumed there were 261 working days in the year. Methods were as follows:

- For respondents who were in full-time employment, the number of days of work missed in the preceding 12 months were summed and valued at a rate of 139 per day. Loss of earnings for any workdays missed that were unpaid were included.
- For respondents in part-time employment who had forgone a significant amount of income due to caring for a patient with MLD, it was assumed that they lost half of the average annual income due to being part-time rather than full-time, in addition to any missed unpaid days of work.
- For respondents who did not lose significant income due to MLD, then only workdays missed that were unpaid were included.

3. For respondents that were unemployed and answered that they had forgone a significant amount of income, it was assumed that loss of earnings was equivalent to the average annual income.

Table 18 Loss of family income calculations (Netherlands only)

Health state	Average number of hours spent caregiving/day	Costs related to informal care per day	Annual costs related to informal care* (base case)	Annual costs related to informal care** (scenario analysis)	Annual costs using scenario based on MLD survey and Dutch salary
GMFC-MLD 1 & 2	15.57	€240.50	€ 61,328	€ 87,783	€638
GMFC-MLD 3 & 4	21.48	€331.79	€ 84,606	€ 121,103	€16,299
GMFC-MLD 5 & 6	21.71	€335.34	€ 85,512	€ 122,399	€31,698

Footnotes: * This has been calculated by multiplying the daily cost by 255, the number of working days in 2021 to make it comparable to the original calculation.
** This has been calculated by multiplying the daily cost by 365 as carers perform their task every day.

Abbreviations: GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy.

Out of pocket costs (OOPCs) were estimated using data from the MLD Caregiver survey, where respondents were asked to record their OOPCs they had incurred because of having a child with MLD. These included adaptations to the house, family vehicle, travel costs specialised equipment not covered by the healthcare system etc. Costs were summed and averaged, to obtain a single cost of €3,475.80. The Applicant then apportioned these costs across health states, where most of the OOPCs were assumed to occur in more severe health states. The costs applied in the CEM per health state are detailed in **Table 19**

Table 19 Predicted out of pocket costs used in the model

Health state	Annual out-of-pocket costs	Monthly out-of-pocket costs
GMFC-MLD 0	-	-
GMFC-MLD 1	€1,738	€145
GMFC-MLD 2	€1,738	€145
GMFC-MLD 3	€3,476	€290
GMFC-MLD 4	€3,476	€290
GMFC-MLD 5	€5,214	€434
GMFC-MLD 6	€5,214	€434

Abbreviations: GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy.

In the model base case, the Applicant uses the Friction Cost method to derive estimates for patient productivity. The Applicant states that, as AA is administered in childhood and not to employable adults, the future productivity is conservatively assumed to be €0 for the Friction Cost method. The Human Capital Approach is included as a scenario. Here, productivity costs were applied to patients of working age, 18-64 years of age. Potential educational achievement for the Dutch population was used in combination with the Dutch median annual earnings, to estimate the median annual earnings per patient. The Applicant has used employment data from two other diseases as a proxy for the health states in the model. For MLD patients with normal cognitive function but no or some loss of motor function, employment data for people with cerebral palsy has been applied as a surrogate. The proportion that would be employed in GMFC-MLD stage 2 was reduced from 71% to 60% to reflect Dutch clinical opinion. To estimate the percentage of MLD patients with mild/moderate cognitive impairment in employment, data from people with Down's syndrome was used. For patients with severe cognitive impairment, and for all patients in GMFC-MLD stage 5 and

6, 100% were assumed to be unemployed. The estimated productivity gains applied in this scenario are shown in **Table 20**.

Table 20 Total annual productivity gains by GMFC-MLD stage and cognitive sub-state used in the scenario using the Human Capital Approach*

Age band	GMFC-MLD 0	GMFC-MLD 1	GMFC-MLD 2	GMFC-MLD 3	GMFC-MLD 4	GMFC-MLD 5	GMFC-MLD 6
	Normal Cognitive Function						
18–64 years	€33,978	€ 27,862	€ 24,125	€ 12,572	€ 6,116	-	-
	Cognitive Impairment (DQ <70)						
18–64 years	€ 19,368	€15,970	€ 13,931	€ 7,135	€ 3,398	-	-
	Severe Cognitive Impairment (DQ <55)						
18–64 years	-	-	-	-	-	-	-

Abbreviations: DQ: developmental quotient; GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy.
*A Friction Cost method is used in the Applicant's base case, where future productivity assumed to be €0 for all health states

In a scenario analysis, the Applicant included costs related to future health care unrelated to MLD, that are likely to be incurred because of extended patient survival. These costs are applied using the PAID v3.0 tool. They are applied from 9.86 years for LI patients and 17.4 years for juvenile patients (average age of death for untreated patients). These costs are applied using NE general population mortality rates for the time horizon of the model, and applied using weighted male/female costs, discounted at a rate of 4%. Including future unrelated medical costs increases the combined ICER for NE by 4,172 (societal perspective) in the Applicant base case.

In the DSA for the combined ICER for the Applicant base case, varying the productivity gains for patients in GMFC 0 with normal cognitive function increased the ICER by up to 6%. Varying productivity gains for those in GMFC 2 with normal cognitive function increased the ICER by up to 2%. Total administration costs for AA, and loss of family income in GMFC-MLD 6 changed the ICER +/-1%.

- For the PS LI cohort, productivity gains for patients in GMFC-MLD 0 with normal cognitive function was the most important cost parameter, increasing the ICER by 7%, followed by gains for those in GMFC-MLD 1 or 2 with normal cognitive function (+3%). Loss of income for parents of patients in GMFC-MLD stage 6 varied the ICER +/-1%.

- For the PS EJ cohort, again productivity gains in GMFC 0 with normal cognitive function was the most important cost parameter, but the impact on the ICER was significant, increasing it by up to 14% or reducing it by 3%. Loss of income for parents of patients in GMFC-MLD 6, and total administration costs were the next most important cost parameters, impacting the ICER +/-1%.
- For the ES EJ cohort, productivity gains for those in GMFC 2 with normal cognitive function was the most influential cost parameter, increasing the ICER by 2%. Loss of income for parents of patients in GMFC MLD stage 6 and administration costs were the next most important cost parameters, impacting the ICER +/-1%.

Ireland

The costs applied per health state, per month are tabulated (**Table 21** and **Table 22**).

Table 21 Summary of monthly MLD-related medical costs (Ireland, ages 0–18)

Cost category	Health State									Sources
	0	1	2	3	4	5	6 (Calculated from proportion: Living at Home and In Hospital)*	6 (Living at Home)	6 (In Hospital)	
Drugs	€ 0	€ 194	€ 195	€ 195	€ 197	€ 221	€ 232	€ 232	€ 232	HSE - Primary Care Reimbursement Service (PCRS),(16) Irish Pharmaceutical Healthcare Association (IPHA) 2018(17)
Medical tests	€ 0	€ 176	€ 81	€ 81	€ 81	€ 83	€ 80	€ 80	€ 80	Ireland costs assumed equal to UK costs, inflated and transferred to Ireland(18)
Medical visits	€ 0	€ 157	€ 151	€ 389	€ 494	€ 321	€ 326	€ 326	€ 326	HSE Consolidated Pay Scales,(19) Healthcare Pricing Office(20)
Hospitalisations	€ 136	€ 218	€ 654	€ 980	€ 1,544	€ 1,798	€ 6,542	€ 2,833	€ 39,928	Healthcare Pricing Office(20)
GP & Emergency	€ 0	€ 12	€ 17	€ 20	€ 26	€ 29	€ 34	€ 34	€ 34	Accident and Emergency Visits NHS reference costs 2018–19 average value, inflated and converted to Euros.(18)
Healthcare equipment	€ 0	€ 59	€ 70	€ 117	€ 117	€ 135	€ 135	€ 135	€ 135	Various sources, please refer to model for details(21)
Respite Care	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	NHS reference costs 2015–16.(22) Ireland costs assumed to be equal to UK costs, inflated and transferred to

										Ireland
Social services	€ 0	€ 0	€ 0	€ 0	€ 0	€ 0	€ 2,310	€ 1,837	€ 6,570	PSSRU,(23) HSE consolidated pay scales(19)
Total	**€ 136**	**€ 815**	**€ 1,167**	**€ 1,782**	**€ 2,460**	**€ 2,588**	**€ 9,659**	**€ 5,477**	**€ 47,305**	

Footnotes: *GMFC-MLD 6 patients living at home = 90%; GMFC-MLD 6 patients in hospital = 10%, based on clinical expert advice. **Abbreviations:** GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy; GP: General Practitioner.

Table 22 Summary of monthly MLD-related medical costs (Ireland, ages 19+)

Cost category	**Health State**									**Sources**
	0	**1**	**2**	**3**	**4**	**5**	**6 (Calculated from proportion: Living at Home and In Hospital)***	**6 (Home)**	**6 (Hospital)**	
Drugs	-	194	195	195	197	221	232	232	232	HSE - PCRS (16) (IPHA) 2018 (17)
Medical tests	-	176	81	81	81	83	80	80	80	UK costs (18)
Medical visits	-	157	151	389	494	321	326	326	326	HSE Pay Scales,(19) HPO (20)
Hospitalisations	-	0	436	735	1,272	1,498	6,210	2,478	39,792	HPO (20)
GP & Emergency	-	12	17	20	26	29	34	34	34	NHS reference costs 2018–19 (18)
Healthcare equipment	-	59	70	117	117	135	135	135	135	Various sources (21)
Respite Care	-	0	0	0	0	0	0	0	0	NHS reference costs 2015–16.(22)
Social services	-	11	24	30	38	46	2,356	1,883	6,616	PSSRU,(23) HSE pay scales(19)
Total (€)	**-**	**608**	**973**	**1,567**	**2,225**	**2,334**	**9,373**	**5,168**	**47,214**	

Footnotes: *GMFC-MLD 6 patients living at home = 90%; GMFC-MLD 6 patients in hospital = 10%, based on clinical expert advice **Abbreviations:** GMFC-MLD: Gross Motor Function Classification in metachromatic leukodystrophy; GP: General Practitioner.

Clinician input from IE stated that the UK estimates would be applicable to IE. No respite care or palliative care costs were included. The Review Group attempted to validate the Applicant approach (using UK costs and converted directly to Irish Euro costs), with the HSE Treatment Abroad Scheme Office.

The HCRU study presented by the Applicant noted that the UK clinicians did not feel the Italian data used to anchor HCRU estimates was fully generalizable to the UK setting; there is no discussion of whether the UK or Italian data would be most relevant to this submission. Of note, the Italian data comes from a single physician, and so may be less generalizable.

In the DSA for the combined ICER for IE, cost parameters did not have an important impact on the model outcomes, with only AA hospital administration costs varying the ICER by +/-1%. This was the same for both the PS LI and PS EJ cohorts. For the ES EJ cohort, medical costs for those aged 19+ in GMFC-MLD stage 4 and AA hospital administration costs varied the ICER +/-1%. Other cost parameters did not have important impact on the model outcomes.

- **Critique of the estimation and application of costs in the model**

- Drug acquisition costs for AA make up a substantial proportion of the total costs accrued in the treatment arm of the model; however, as this is a one-time treatment it is a largely fixed cost with limited uncertainty.
- Calculation of administration costs for BE and IE likely an underestimate as the model does not consider the implications of the reimbursement of expenses incurred by the patient and family.
- While there is uncertainty in the health care resource use and costs estimated in the model, the cost of health care resource use is not a driver in the model..

4.4. Discount rate

Discount rates applied in the base-case for each country are detailed in **Table 23**. The ranges used in the sensitivity analyses are also indicated. Discount rates have an important impact on model outcomes. Differing discount rates NE, BE and Ireland leads to large variation in predicted LYG and QALYs, with a much smaller gain in predicted survival and quality adjusted survival benefit for the Irish population.

Table 23 Discount rates for costs and benefits

Country	Discount rate for costs	Discount rate for benefits	Range used in scenario analysis
Belgium	3%	1.5%	0–6%
The Netherlands	4%	1.5%	0–6%
Ireland	4%	4%	0–10%

5. Results of incremental cost effectiveness analysis

Incremental analysis of costs and benefits

- **Applicant base-case analysis**

The Applicant presented for AA versus BSC for all countries. The results are presented for the combined cohort (as a weighted average using the proportions described in **Table 1**) (**Table 24**), and the individual subgroups PS LI (**Table 25**), PS EJ (**Table 26**) and ES EJ (**Table 27**). Note that, following feedback from the Review Group, a number of changes were made to the Applicant's base case cost-effectiveness model. Therefore, the results presented here differ slightly from those presented in the Applicant's original submission.

Table 24 Base case results for the combined cohort (discounted)

Intervention	Total Costs (€)	Total Lys	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Belgium						
AA	3,187,424	39.90	25.40	3,011,290	25.47	118,234
BSC	176,135	11.30	0.00	-	-	
The Netherlands						

AA	3,648,703	39.51	24.48	2,649,787	24.59	107,777
BSC	998,916	11.58	-0.11	-	-	-
Ireland						
AA	2,991,128	22.74	14.49	2,269,761	15.48	146,642
BSC	721,367	8.92	-0.99	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years, QALY: Quality Adjusted Life Year
For Belgium and Ireland, the health service perspective is taken. For The Netherlands, the societal perspective is taken (FC method used, assuming no productivity gains).

Table 25 Base case results for the PS LI sub group (discounted)

Intervention	Total Costs (€ per patient)	Total LYs (Per patient)	Total QALYs (per patient)	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Belgium						
AA	3,165,215	43.82	26.77	2,997,291	26.60	112,676
BSC	167,924	9.40	0.17	-	-	
The Netherlands						
AA	3,607,596	44.14	26.82	2,639,667	26.65	99,035
BSC	967,929	9.40	0.17	-	-	-
Ireland						
AA	2,957,293	23.39	14.53	2,224,505	15.44	144,078
BSC	732,788	8.20	-0.91	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years, QALY: Quality Adjusted Life Year

Table 26 Base case results for the PS EJ sub group (discounted)

Intervention	Total Costs (€ per patient)	Total LYs (Per patient)	Total QALYs (per patient)	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Belgium						
AA	3,138,381	38.51	32.12	2,958,946	32.03	92,374
BSC	179,435	12.36	0.09	-	-	
The Netherlands						
AA	3,256,280	38.77	31.80	2,229,654	31.72	70,299
BSC	1,026,625	12.36	0.08	-	-	-
Ireland						
AA	2,934,128	21.48	17.69	2,238,988	18.63	120,207
BSC	695,140	10.43	-0.94	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years, QALY: Quality Adjusted Life Year
Year

Table 27 Base case results for the ES EJ sub group (discounted)

Intervention	Total Costs (€ per patient)	Total LYs (Per patient)	Total QALYs (per patient)	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
Belgium						
AA	3,257,757	37.61	17.44	3,077,053	17.82	172,671
BSC	180,704	11.95	-0.38	-	-	
The Netherlands						
AA	3,981,147	37.99	17.56	2,990,215	17.94	166,671
BSC	990,931	11.95	-0.39	-	-	-
Ireland						

AA	3,214,112	21.47	10.16	2,509,341	11.59	216,567
BSC	704,772	10.11	-1.43	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years, QALY: Quality Adjusted Life Year

- **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 better explore the potential cost effectiveness of AA in the modelled population. The results of the alternative base case for AA are presented below (**Table 29**, **Table 30**, **Table 31**). The Review Group highlights the assumption of cure to be subject to considerable uncertainty given the limited data availability. Implementation of this alternative base case evaluates the maximum impact of this key uncertainty on the cost effectiveness results. Other concerns regarding the Applicant's approach for response classifications remain for this alternative base case. The combined cohort ICER has limited usefulness given the considerable differences in treatment benefit (and therefore cost effectiveness) and the associated uncertainty between disease subgroups.

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

- Treatment waning after ten years where full and stable partial responders are assumed to experience decline in GMFC-MLD state as per transition probabilities for unstable partial responders.

The Review Group highlights the assumption of cure to be subject to considerable uncertainty given the limited data availability. Implementation of this alternative base case evaluates the maximum impact of this key uncertainty on the cost effectiveness results. Other concerns regarding the Applicant's approach for response classifications remain for this alternative base case. The combined cohort ICER has limited usefulness given the considerable differences in treatment benefit (and therefore cost effectiveness) and the associated uncertainty between disease subgroups.

Table 28 Alternative base case results for the combined cohort (discounted)

	Total costs (€)	Total Lys	Total QALYS	inc cost (€)	inc QALY	ICER (€ per QALY)
Belgium						
AA	3,246,072	19.62	8.39	3,069,938	8.43	364,048
BSC	176,135	11.26	-0.04	-	-	-
The Netherlands (Societal)						
AA	3,815,220	19.73	8.49	2,816,304	8.60	327,423
BSC	998,916	11.58	-0.11	-	-	-
Ireland						
AA	3,307,102	14.88	5.78	2,585,735	6.77	382,069
BSC	721,367	8.92	-0.99	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years. QALY: Quality Adjusted Life Year; inc: incremental

Table 29 Alternative base case results for the PS LI sub group (discounted)

	Total costs (€)	Total Lys	Total QALYS	inc cost (€)	inc QALY	ICER (€ per QALY)
Belgium						
AA	3,238,154	18.54	6.51	3,070,230	6.33	484,711
BSC	167,924	9.40	0.17	-	-	-
The Netherlands (Societal)						
AA	3,884,761	18.54	6.47	2,916,832	6.30	462,632
BSC	967,929	9.40	0.17	-	-	-
Ireland						
AA	3,309,802	14.57	4.97	2,577,014	5.88	438,495
BSC	732,788	8.20	-0.91	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years. QALY: Quality Adjusted Life Year; inc: incremental

Table 30 Alternative base case results for the PS EJ sub group (discounted)

	Total costs (€)	Total Lys	Total QALYS	inc cost (€)	inc QALY	ICER (€ per QALY)
Belgium						
AA	3,232,047	21.25	11.41	3,052,612	11.32	269,672
BSC	179,435	12.36	0.09	-	-	-
The Netherlands (Societal)						
AA	3,555,048	21.26	11.30	2,528,422	11.22	225,400
BSC	1,026,625	12.36	0.08	-	-	-
Ireland						
AA	3,247,812	16.01	8.86	2,552,672	9.80	260,467
BSC	695,140	10.43	-0.94	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years. QALY: Quality Adjusted Life Year; inc: incremental

Table 31 Alternative base case results for the ES EJ sub group (discounted)

	Total costs (€)	Total Lys	Total QALYS	inc cost (€)	inc QALY	ICER (€ per QALY)
Belgium						
AA	3,267,688	19.03	7.18	3,086,984	7.56	408,461
BSC	180,704	11.95	-0.38	-	-	-
The Netherlands (Societal)						
AA	3,991,388	19.04	7.17	3,000,457	7.56	396,882
BSC	990,931	11.95	-0.39	-	-	-
Ireland						
AA	3,371,687	14.80	5.36	2,666,915	6.79	392,864
BSC	704,772	10.11	-1.43	-	-	-

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life adjusted life years. QALY: Quality Adjusted Life Year; inc: incremental

- **Analysis of Uncertainty**

Sensitivity analysis and scenario analysis are presented to explore the considerable uncertainty highlighted in the treatment effectiveness section and for both costs and utilities. Both deterministic and probabilistic analysis were provided by the Applicant.

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

The Applicant undertook a deterministic sensitivity analysis for each country (Figure 3, Figure 4 and Figure 5). Across all countries, variation in parameters relating to the responder classification for various subgroups had the greatest impacts on the model results. The Review Group do not consider the Applicant's approach to parameter variation used in this analysis, which varied parameters by +/- 20%, is sufficient to adequately explore the significant uncertainty in the model. Given the limited data informing the cost effectiveness model, sensitivity analysis based on arbitrary +/-20% variation is limited in its ability to meaningfully capture uncertainty in the model inputs and their impact on cost effectiveness. Areas of particular uncertainty that should be further explored are detailed in the individual sections under treatment effectiveness, costs and utilities.

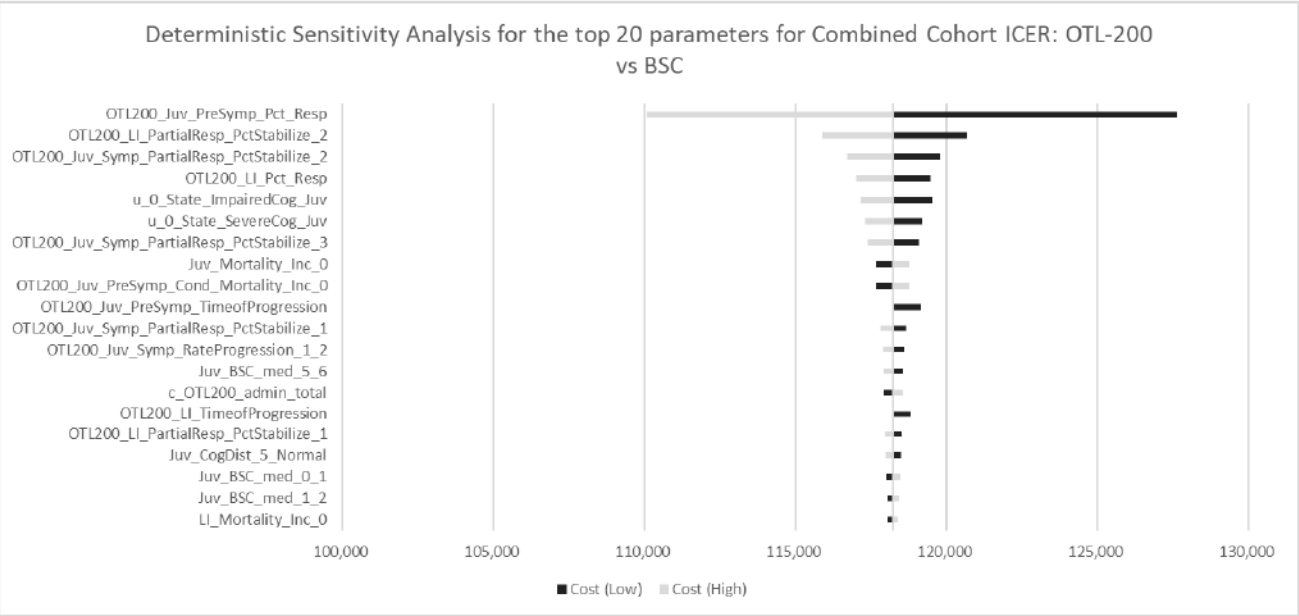

Figure 3 Tornado plot for DSA results for combined cohort, Belgium

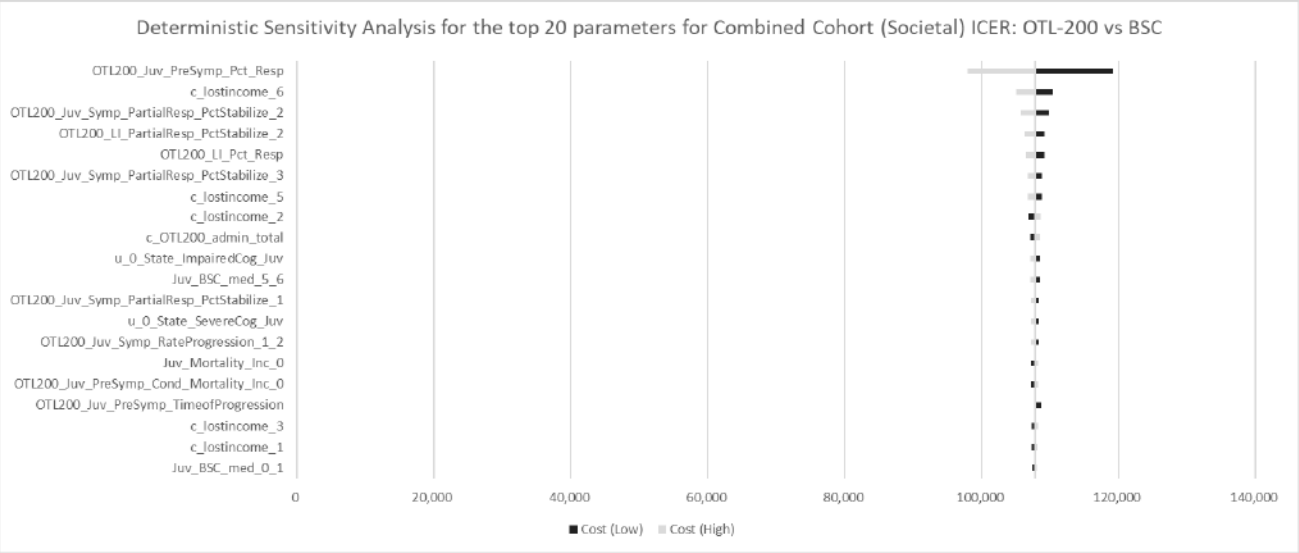

Figure 4 Tornado plot for DSA results for combined cohort, Netherlands

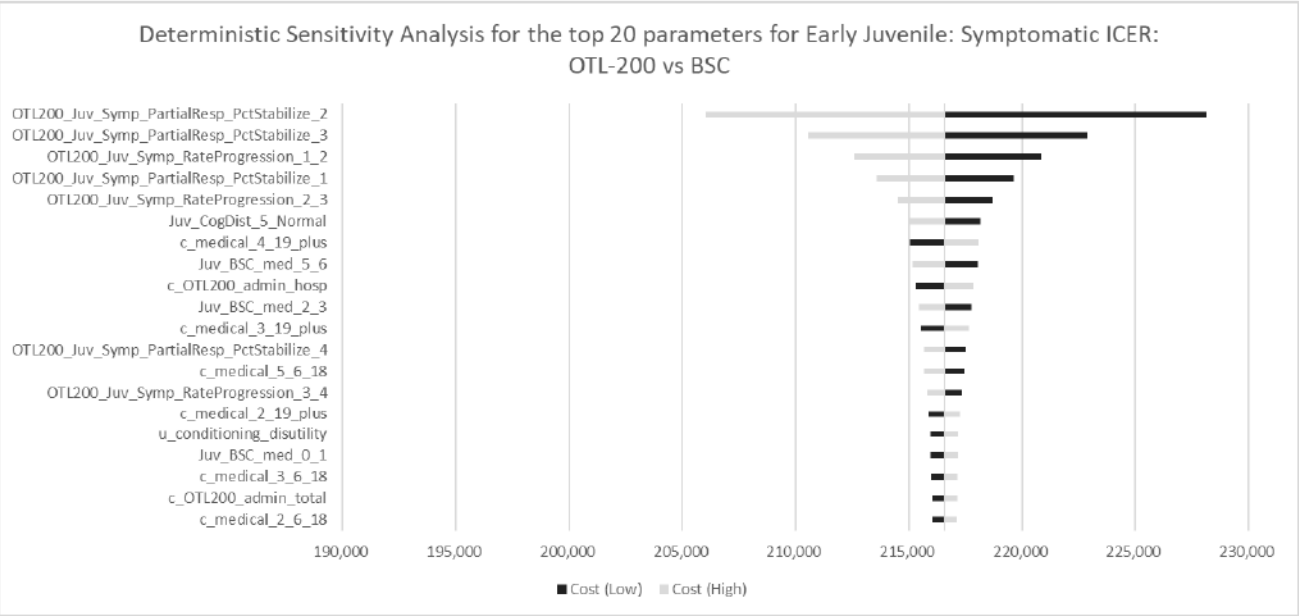

Figure 5 Tornado plot for DSA results for combined cohort, Ireland

Applicant's probabilistic sensitivity analysis

The Applicant presented a PSA, using 10,000 simulations, where all parameters were varied except for discounting. The Review Group do not consider the approach to the variance around parameters to adequately capture the uncertainty associated with the inputs. A probability of cost effectiveness at appropriate willingness to pay (WTP) thresholds was not presented in the dossier or the Day 60 response document, and the Review Group were not able to locate this in the Excel models. The Review Group consider the Applicant's approach to the PSA to be associated with an underestimation of the overall uncertainty associated with the cost effectiveness.

The Applicant estimated the proportional QALY shortfall in the NE model (Table 32) and evaluated the probability of cost-effectiveness against a threshold of €80,000 per QALY. As the probability of cost effectiveness is not clearly presented the Review Group cannot provide this information.

Table 32 Proportional Shortfall Calculation for Netherlands

MLD disease variant	Proportion of patients	Absolute QALY shortfall	Proportional QALY shortfall	Fair innings (proportional QALY shortfall from birth)

PS LI	29.53%	*71.47-0.101=* 71.36	*71.36/71.47=* *0.999*	*71.47-(1.50+0.1)=* *69.86*
PS EJ	39.93%	*69.22-1=* 69.12	*69.22/69.22=* 0.999	*69.22-(3.75+0.1)=* *65.37*
ES EJ	30.54%	*66.30-0.00=* 66.30	*71.47/71.47=* *1.00*	*66.30-(6.66+0)=* *59.63*
Weighted average		**68.32**	**0.999**	**63.74**

Footnotes: Average weighted by the proportion of patients for each MLD disease variant. Age at treatment and average lifespan for MLD patients receiving BSC is based on data from the OTL-200 clinical trial programme. *Any negative QALYs for BSC were set to 0 to prevent proportional QALY shortfall values greater than 1. **Dutch average life expectancy 2018. ***Dutch data from EQ-5D index population norms (average utility of individuals aged 1-82).
Abbreviations: BSC: best supportive care; ES EJ: early symptomatic early juvenile; MLD: metachromatic leukodystrophy; PS EJ: pre-symptomatic early juvenile; PS LI: pre-symptomatic late infantile; QALY: quality-adjusted life year

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

A value of information analysis was conducted by the Applicant. Very limited information regarding conduct of the value of information analyses was provided. Given the limitations with the PSA it is likely that this underestimates uncertainty and therefore potentially the value of information.

Other sensitivity and scenario analyses

The outcomes of various scenario analyses presented by the Applicant or conducted by the Review Group are presented below (**Table 33**). The Applicant also presented a scenario analysis where patients who experienced disease progression between leukapharesis and planned AA administration, thus rendering the patients ineligible for treatment. Under this scenario, patients incurred the cost of leukapharesis without any incremental change in outcomes. The cost of AA was not incurred; the Applicant stated that AA costs would be absorbed by the company, if such a scenario occured.

The Review Group highlights that there are limited opportunities to investigate the impact of changes to responder classification on the model. This is a major source of uncertainty, and has implications for subpopulations where limited data are available. For example, in the case of PS EJ subpopulation, only four patients were used in to inform responder classification, three of whom were classed as full responders. The combined cohort ICER has limited usefulness given the considerable uncertainty in treatment effectiveness between disease subgroups.

6. Table 33 Scenario analyses of model outcomes

Parameter input	Base case combined ICER (€/QALY)	Alternative scenario	Alternative combined ICER (€/QALY)	Impact on combined ICER*
Belgium				
Treatment effectiveness parameters				
Proportion of PS-LI cohort in each responder classification calculated based on data from patients treated with fresh formulation only	112,676**	Data from two (PS-LI) patients treated with cryopreserved formulation (Study 205756)† also used to calculated proportion of responders in LI cohort	109,676**	-3,000
Responder classification status for PS EJ: full responder 75%, unstable partial responder 25%	Full: 118,234 PS EJ: 92,374	PS EJ: full responder 60%, unstable partial responder 40%	Full: 127,885 PS EJ: 111,816	+9,651 +19,442
Majority of EJ stable and unstable partial responders treated with AA maintain DQp ≥70 for all GMFC-MLD stages	118,234	Separate cognitive substate distribution applied for EJ unstable responders; 100% DQp <50 for GMFC-MLD ≥5	120,667	+2,433
		All EJ partial responders have cognitive substate distribution were 100% DQp <50 for GMFC-MLD ≥5	125,631	+7,397
Treatment outcomes for BSC based on data from the TIGET NHx study	118,234	NHx based on MLDi database	118,906	+672
		NHX based on Elgun et al	119,258	+1,024
		NHx based on Kehrer et al	120,615	+2,381
Progression modifiers based on data from 2019 data cut	118,234	Progression modifiers based on data from 2018 data cut	119,066	+832
Utility parameters				
Utility values for EJ cohort are based on the rescaled regression outputs	118,234	Utility values for the EJ cohort are based on the rescaled mean TTO values	119,400	+1,166
Utility values for EJ cohort are based on the rescaled regression outputs	118,234	Utility values for the EJ cohort are based on non-rescaled mean TTO values	108,252	-9,982
Utility values for LI cohort are based on the rescaled TTO values	112,676**	Utility values for LI cohort are based on non-rescaled mean TTO values	110,882**	-1,794
Utility values for LI cohort are based on rescaled TTO values, and for the EJ cohort are based on rescaled regression outputs	118,234	Utility values for both LI and EJ are based on non-rescaled mean TTO values	107,712	-10,522
Caregiver disutility excluded	118,234	Caregiver utility included	115,635	+2,599
Cost parameters				
Administration costs calculated using Belgian national costs (€40,614)	118,234	Administration costs calculated using costs from the Netherlands (€103,882)	120,719	+2,485
Model structure parameters				
No Newborn screening programme in place	118,234	Implementation of Newborn Screening‡	A. 101,585	-16,649
			B. 79,962	-38,272

Discount rate: 3% costs & 1.5% benefits per annum	118,234	0% for both costs and benefits	75,073	-43,161
		6% for both costs and benefits	290,200	+149,201
Time horizon: 100 years	118,234	20 years	267,619	+149,385
		30 years	197,978	+79,744
		50 years	144,068	+25,834
Netherlands				
Treatment effectiveness parameters				
Proportion of PS-LI cohort in each responder classification calculated based on data from patients treated with fresh formulation only	99,035**	Data from two (PS-LI) patients treated with cryopreserved formulation (Study 205756)† also used to calculated proportion of responders in LI cohort	94,084**	-4,951
Responder classification status for PS EJ: full responder 75%, unstable partial responder 25%	Full: 107,777 PS EJ: 70,299	PS EJ: full responder 60%, unstable partial responder 40%	Full: 119,467 PS EJ: 90,487	+11,690 +20,188
Majority of EJ stable and unstable partial responders treated with AA maintain DQp ≥70 for all GMFC-MLD stages	107,777	Separate cognitive substate distribution applied for EJ unstable responders; 100% DQp <50 for GMFC-MLD ≥5	110,469	+2,692
		All EJ partial responders have cognitive substate distribution were 100% DQp <50 for GMFC-MLD ≥5	116,848	+9,071
Treatment outcomes for BSC based on data from the TIGET NHx study	107,777	NHx based on MLDi database	112,823	+5,045
		NHX based on Elgun et al	111,475	+3,697
		NHx based on Kehrer et al	111,527	+3,750
Progression modifiers based on data from 2019 data cut	107,777	Progression modifiers based on data from 2018 data cut	108,809	+1,032
Utility parameters				
Utility values for EJ cohort are based on the rescaled regression outputs	107,777	Utility values for the EJ cohort are based on the rescaled mean TTO values	109,191	+1,414
Utility values for EJ cohort are based on the rescaled regression outputs	107,777	Utility values for the EJ cohort are based on non-rescaled mean TTO values	98,341	-9,436
Utility values for LI cohort are based on the rescaled TTO values	99,035**	Utility values for LI cohort are based on non-rescaled mean TTO values	97,462**	-1,573
Utility values for LI cohort are based on rescaled TTO values, and for the EJ cohort are based on rescaled regression outputs	107,777	Utility values for both LI and EJ are based on non-rescaled mean TTO values	98,024	-9,753
Caregiver disutility excluded	107,777	Caregiver utility included	106,416	-1,361
Cost parameters				
Societal perspective	107,777	Healthcare payer perspective	116,283	+8,506
Exclude future unrelated health care costs	107,777	Include future unrelated health care costs (NL PAID data)	111,907	+4,130

Family lost income calculation based on standard Dutch tariff	107,777	Family lost income calculated using MLD Caregiver survey	110,215	+2,437
Direct non-medical costs not included	107,777	Direct non-medical costs included	107,502	-275
Productivity gains calculated using Friction Cost Method	107,777	Productivity gains calculated using Human Capital Approach	98,001	-9,776
Model structure parameters				
No Newborn screening programme in place	107,777	Implementation of Newborn Screening‡	A. 79,631	-28,146
			B. 52,883	-54,894
Discount rate: 4% costs & 1.5% benefits per annum	107,777	0% for both costs and benefits	71,551	36,226
		6% for both costs and benefits	263,082	153,305
Time horizon: 100 years	107,777	20 years	237,196	+129,419
		30 years	177,403	+69,626
		50 years	123,320	+15,543
Ireland				
Treatment effectiveness parameters				
Proportion of PS-LI cohort in each responder classification calculated based on data from patients treated with fresh formulation only	144,078**	Data from two (PS-LI) patients treated with cryopreserved formulation (Study 205756)† also used to calculated proportion of responders in LI cohort	139,384**	-4,694
Responder classification status for PS EJ: full responder 75%, unstable partial responder 25%	Full: 146,642 PS EJ: 120,207	PS EJ: full responder 60%, unstable partial responder 40%	Full: 153,784 PS EJ: 147,018	+7,142 +26,811
Majority of EJ stable and unstable partial responders treated with AA maintain DQp ≥70 for all GMFC-MLD stages	146,642	Separate cognitive substate distribution applied for EJ unstable responders; 100% DQp <50 for GMFC-MLD ≥5	148,774	+2,132
		All EJ partial responders have cognitive substate distribution were 100% DQp <50 for GMFC-MLD ≥5	151,283	+4,641
Treatment outcomes for BSC based on data from the TIGET NHx study	146,642	NHx based on MLDi database	145,521	-1,121
		NHX based on Elgun et al	147,281	+639
		NHx based on Kehrer et al	150,390	+3,748
Progression modifiers based on data from 2019 data cut	146,642	Progression modifiers based on data from 2018 data cut	147,585	+943
Utility parameters				
Utility values for EJ cohort are based on the rescaled regression outputs	146,642	Utility values for the EJ cohort are based on the rescaled mean TTO values	147,308	+846
Utility values for EJ cohort are based on the rescaled regression outputs	146,642	Utility values for the EJ cohort are based on non-rescaled mean TTO values	135,416	-11,226
Utility values for LI cohort are based on the rescaled TTO values	144,078**	Utility values for LI cohort are based on non-rescaled mean TTO values	141,852**	-2,226

Utility values for LI cohort are based on rescaled TTO values, and for the EJ cohort are based on rescaled regression outputs	146,642	Utility values for both LI and EJ are based on non-rescaled mean TTO values	134,139	-12,503
Caregiver disutility excluded	146,642	Caregiver utility included	138,014	-8,628
Model structure parameters				
No Newborn screening programme in place	146,642	Implementation of Newborn Screening‡	A. 137,860§	-8,782
			B. 104,649§	-41,993
Discount rate: 4% for both costs and benefits per annum	146,642	0% for both costs and benefits	55,086	-91,556
		10% for both costs and benefits	326,198	+179,556
Time horizon: 100 years	146,642	20 years	225,780	+79,138
		30 years	184,353	+37,711
		50 years	156,206	-9,564

*+Indicates ICER under given scenario higher than base case ICER; - indicates the ICER under a given scenario is lower than the base case ICER
**Impact on LI model outcomes only presented here, since scenario applies to LI patients.
†Maximum duration of follow-up 1.5 years
‡Newborn screening is implemented under two scenarios: A and B. Under A, there are no ES-EJ patients, and the remaining PS-LI and PS-EJ patient subpopulations are distributed in the same ratio between PS-LI and PS-EJ in the base case. Under B, in addition to parameters set in A, 100% of AA treated patients are full responders.
§The Review Group were unable to replicate the results reported by the Applicant for this scenario. The results presented are derived from the model, using the parameters described by the Applicant. The Applicant's reported results were A. 131,026 and B. 98,751

Review Group's alternative base case, Price-ICER relationship

The Review Group examined the price-ICER relationship for varying levels of price reduction of AA. The results for each country, by cohort, are presented in Table 34, Table 35 and Table 36.

The Review Group again highlights that the alternative base case does not address the key uncertainties relating to the classification of responder status on the model. This is particularly relevant for subpopulations where limited data are available. For example, in the case of PS EJ subpopulation, only four patients were used in to inform responder classification, three of whom were classed as full responders. The combined cohort ICER has limited usefulness given the considerable uncertainty in treatment effectiveness between disease subgroups.

Table 34 Price-ICER relationship for Review Group's alternative base case (Belgium)

Drug cost value	Combined cohort ICER (€/QALY)	PS LI ICER (€/QALY)	PS EJ ICER (€/QALY)	ES EJ ICER (€/QALY)

100%	364,048	484,711	269,672	408,461
90%	327,909	436,598	242,780	368,137
80%	291,770	388,486	215,828	327,814
70%	255,631	340,374	188,906	287,490
60%	219,493	292,262	161,984	247,166
50%	183,354	244,150	135,062	206,843
40%	147,215	196,037	108,140	166,519
30%	111,077	147,925	81,218	126,195
20%	74,938	99,813	54,296	85,872
10%	38,799	51,701	27,634	45,548

For simplicity, the price reduction is implemented as a % reduction off the drug cost plus VAT (e.g. €3,047,500 * 90%)

Table 35 Price-ICER relationship for Review Group's alternative base case (Netherlands)

Drug cost value	Combined cohort ICER (€/QALY)	PS LI ICER (€/QALY)	PS EJ ICER (€/QALY)	ES EJ ICER (€/QALY)
100%	327,423	462,632	225,400	396,882
90%	293,999	417,032	199,771	358,853
80%	260,574	371,433	174,141	320,824
70%	227,149	325,833	148,511	282,796
60%	193,724	280,233	122,882	244,767
50%	160,300	234,633	97,252	206,738
40%	126,875	189,034	71,622	168,710
30%	93,450	143,434	45,993	130,681
20%	60,026	97,834	20,363	92,652
10%	26,601	52,235	Dominant*	54,623

*AA is associated with a reduction in incremental costs versus BSC, and an increase in incremental QALYs
Price reduction is implemented as a % reduction off the PTW/c (e.g. €2,875,000 * 90%)

Table 36 Price-ICER relationship for Review Group's alternative base case (Ireland)

Drug cost value	Combined cohort ICER (€/QALY)	PS LI ICER (€/QALY)	PS EJ ICER (€/QALY)	ES EJ ICER (€/QALY)
100%	382,069	438,495	260,467	392,864
90%	342,880	393,366	233,405	353,795
80%	303,692	348,238	206,343	314,725
70%	264,503	303,109	179,281	275,656
60%	225,314	257,980	152,219	236,586
50%	186,125	212,852	125,156	197,517
40%	146,936	167,723	98,094	158,447
30%	107,747	122,594	71,032	119,378
20%	68,559	77,466	43,970	80,309
10%	29,370	32,337	16,908	41,239

Price reduction is implemented as a % reduction off the drug cost including 7.75% rebate (e.g. €2,652,187.50 * 90%)

Budget Impact Analysis

The Applicant submitted three separate budget impact models, one for each country. The general assumptions are discussed here, and individual results provided for each country.

a. Eligible population and market share

- **Definition of eligible patients under the Reimbursement Claim**

It was assumed that only patients eligible for treatment under the indication specified by the EMA would receive treatment, which is patients with early-onset MLD characterised by biallelic mutations in the *ARSA* gene leading to a reduction of ARSA enzymatic activity, in children with LI or EJ forms, without clinical manifestations of the disease (pre-symptomatic), and in children with the EJ form, with early clinical manifestations of the disease (early symptomatic), who still have the ability to walk independently and before the onset of cognitive decline.

- **Size of the Eligible Population**

The global prevalence of MLD is estimated at 0.1-0.9 per 100,000. It is assumed that all prevalent patients would not be eligible for treatment, on the basis that they would have already progressed beyond the treatment window. This was supported by clinical opinion provided to the Review Group.

The population in the budget impact model (BIM) assumes only incident patients may become eligible for treatment. An incidence rate of between 1.4 and 1.8/100,000 is assumed, using a midpoint of 1.6 per 100,000 for all countries. The Applicant highlights that because of difficulties in diagnosing MLD, not all incident patients will receive a diagnosis prior to deteriorating and becoming ineligible for treatment. Patient numbers have been rounded up to the nearest whole patient. The base case assumes no new-born screening (NBS) programme is in place, which reflects current clinical practice in NE, BE and IE. Given the specificity of the treatment, the Applicant considers off-label or unlicensed use is not likely.

Belgium

The number of live births in Belgium (113,739 in 2020), an incidence rate of 1.6 per 100,000 live births (n=1.82), and clinical opinion (n=2 to 3 patients incident patients annually), lead to the Applicant estimate of 3 patients with MLD born in Belgium annually. The distribution of phenotype is based on clinical opinion as for the CEM (**Table 1** in CEM section); 1.8 patients are assumed to be LI and 0.75 are assumed to be EJ, and thus may fall within the licensed for AA. However, the Applicant assumes that less than 5% of the 1.8 LI patients born annually will be diagnosed pre-symptomatically, and that between 10-15% (midpoint 12.5%) of EJ patients with be PS or ES at diagnosis. These assumptions result in a cumulative total of 0.26 incident patients being eligible for treatment annually, or 1 patient every four years. Clinical opinion provided to the Applicant for BE suggested there may only be one eligible patient every 5-10 years. The low proportion of incident LI patients diagnosed annually assumes that these patients are likely to be siblings of previously diagnosed children, and parents would undergo in utero genetic testing for MLD, and likely opt for a termination of the pregnancy. In the Applicant base case, it is assumed that if an effective treatment is available, then less parents would choose this option, and more children with LI MLD would be born and become eligible for treatment annually. Thus, the Applicant assumes that two patients are eligible for treatment over the three-year time horizon of the model. The Applicant presents a scenario where all incident patients with early onset MLD are eligible for treatment, through the application of a NBS programme, and in this scenario assumes eight patients are eligible for treatment over three years.

The Netherlands

The Applicant presented two scenarios for the budget impact for NE, one based on an epidemiology calculation with some clinical input, and one using Dutch clinical opinion only.

- For the epidemiology scenario, the number of live births in the Netherlands in 2020 (n=174,058), along with an incidence rate of 1.6 per 100,000 live births leads to an estimate of 2.78 incident patients annually. Clinical opinion suggests 4-5 incident patients annually, while from the literature, the estimate was 3.7 annually (2). Thus, the Applicant applied an estimate of 3 to 5 incident patients annually. The Applicant

applied the same proportions of each phenotype as were used in the CEM, and 37% incident patients are assumed to be LI or EJ annually, leading to an estimate of 1-2 incident patients per year with early onset MLD. The Applicant then applied the midpoint of estimates from clinical opinion on the proportion of patients who would be diagnosed pre-symptomatically (or ES EJ) and therefore eligible for treatment, which was assumed to be 32% of all early onset MLD patients. From this the Applicant estimated 0.48 patients would be eligible annually, or one patient every other year (two patients over a three-year time horizon).

- For the scenario based on clinical opinion, it was estimated that of the eight early-onset patients diagnosed over the past five years, 1.6 would have been eligible for treatment annually, resulting in 4.8 patients being eligible for AA over three years.

Ireland

The number of live births (n=60,258 in 2021), the incidence rate of 1.6/100,000, and the proportions of each phenotype applied in the CEM, the estimated number of incidence patients per year is 0.4, equating to 1 incident patient every other year. These estimates were validated by clinical opinion from a clinician in Ireland. A total of three patients over five years are assumed to receive treatment in the budget impact model.

6.2 Results of budget impact analysis.

The Applicant assumes 100% market share for BSC at present, and assumes that where AA becomes available, the market share will be 100%. . The drug acquisition costs applied in the BIM for each country are shown in Table 37. Since treatment is a one-off occurrence, discontinuation rates or mortality are not considered in the BIM. The time horizon of the BIM model for IE is five years, and for NE and BE is three years, in line with national requirements. The gross and net budget impacts presented consider the drug acquisition costs only; see 'Additional costs and cost offsets' for scenarios including additional costs and offsets including administration costs.

Table 37 Drug acquisition costs applied in the budget impact model

	PTW/c	Total reimbursement price per pack (incl. VAT)[a, b]	Total reimbursement price per pack (ex. VAT)[a, b]
Belgium	€2,875,000	€3,047,500	€2,875,000
Netherlands	€2,875,000	€3,133,750	€2,875,000
Ireland	€2,875,000	€3,313,438	€2,213,750
PTW/c: price to wholesaler/chemist			
PTW/c: price to wholesaler/chemist			
[a]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 for Belgium. Price exclusive of VAT is used in CEM and BIM in Netherlands. Price exclusive of VAT is used in the CEM, and price inclusive of VAT in the BIM, in Ireland. VAT=6% in Belgium, 9% in Netherlands, 23% in Ireland. [b]Total reimbursement price in Ireland includes a 7.75% rebate on the price to wholesaler, applied in all economic evaluations in Ireland.			

- **Gross drug budget impact**

The estimated gross drugs budget impact and number of treated patients assumed for each country are shown in Table 38, Table 39 and Table 40.

Table 38 Gross Drugs budget impact Belgium (Level 1)

	Year 1	Year 2	Year 3
Number of patients receiving intervention	1	0	1
Cost of intervention each year	€3,047,500	€0	€3,047,500
Gross drug budget impact	**€3,047,500**	**€0**	**€3,047,500**
Cumulative gross budget impact BE			**€ 6,095,000**

Table 39 Gross drugs budget impact The Netherlands*

	Year 1	Year 2	Year 3
Number of patients receiving intervention	2	1	2
Cost of intervention each year	€ 5,750,000	€ 2,875,000	€ 5,750,000
Cumulative gross budget impact NL			**€ 14,375,000**

*This scenario uses clinical opinion to estimate the number of eligible patients. Using the epidemiological model, two patients were estimated to be eligible for treatment over five years, at a gross drugs budget impact of 5,750,000.

Table 40 Gross drugs budget impact Ireland

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients receiving intervention	1	0	1	0	1
Cost of intervention each year	€3,313,438	€3,3313,438	€3,3313,438	€3,3313,438	€3,3313,438
Total cost of intervention (including VAT)	€3,3313,438	€0.00	€3,3313,438	€0.00	€3,3313,438
Gross drug budget impact incl VAT	**€3,3313,438**	**€0.00**	**€3,3313,438**	**€0.00**	**€3,3313,438**
Cumulative gross budget impact IE					**€9,940,314**

- **Net drug budget impact**

The estimated net drug budget impact from the introduction of AA is the same as the gross budget impact, as no comparator drugs are directly displaced. The Applicant did not take into account the additional costs to the drugs budget of busulfan conditioning and rituximab for autoantibodies, or cost offsets of reduction in the use of medicines to control symptoms of the disease. These costs are negligible relative to the acquisition cost of AA, and their omission will not have a meaningful impact on the estimated net drug budget impact. The net drug budget impact in each country is tabulated in Table 41.

Table 41 Net drug budget impact inclusive of VAT, in each country*

Country	Net budget impact incl VAT (€)
Belgium	6,095,000
Netherlands	14,375,000
Ireland	9,940,314

*For Belgium and Netherlands, the net budget impact is cumulative over three years. For Ireland, the net budget impact is cumulative over five years.

- **Additional costs and cost-offsets**

The Applicant considers additional non-drugs budget costs and cost-offsets. In this scenario, it is assumed that patients treated with AA are either full-responders, stable partial responders and unstable partial responders, as per the CEM. Thus, the CEM is used to estimate the cost offsets because of delayed entry into more costly, later GMFC health states,

by converting monthly costs from the CEM into annual costs (Table 42) . Table 43 shows the total administration costs associated with AA. The impact of the inclusion of these costs on the net budget impact is shown in Table 44 and Table 45.

Table 42 Cost offsets estimated in the cost-effectiveness model

Country	Annual costs per patient offset (€)	
Belgium	Year 1 post-AA	4,244
	Year 2 post-AA	7,637
	Year 3 post-AA	9,173
Netherlands	Not estimated	
Ireland	Year 1 post-AA	16,319
	Year 2 post-AA	55,120
	Year 3 post-AA	82,006
	Year 4 post-AA	87,267
	Year 5 post-AA	86,548

Belgium and Ireland: The percentage of AA and BSC patients in each GMFC health state is taken from the OTL-200 LI Engine and BSC LI engine in the health economic model at each year post-gene therapy. The annual medical costs are calculated by multiplying the monthly medical costs for each GMFC state from the economic model by 12. Multiplying the annual costs by the proportion in each state provides the total average annual medical cost per patient for each group.

The cost offsets are calculated as annual costs offset per person, which will accrue for each year of BI time horizon and differ depending how many years post-gene therapy the person is. For example, one patient in year 1 will have cost offsets in year 1, offsets in year 2, and in year 3. Also accounted for in year 3 are the year 1 cost offsets for the new patient in year 3.

Table 43 Administration costs estimated in the cost-effectiveness model

Country	Total administration cost estimated in CEM (€)
Belgium	40,614
Netherlands	Not applied
Ireland	106,574

Table 44 Net budget impact in Belgium with costs and cost offsets included (Level 3)

	Year 1	Year 2	Year 3	Cumulative
Eligible patients treated with intervention	1	0	1	**2**
Level 1: impact of reimbursement of AA on the pharmaceutical drugs budget	€ 3,047,500	€ 0	€ 3,047,500	**€ 6,095,000**
Cost-offsets	-€ 4,244	-€ 7,637	-€ 13,417	**-€ 25,297**
Additional costs	€ 40,614	€ 0	€ 40,614	**€ 81,229**
Level 3: incremental impact of reimbursement of AA on the healthcare budget	**€ 3,083,871**	**-€ 7,637**	**€ 3,074,698**	**€ 6,150,932**

Table 45 Net budget impact in Ireland with costs and cost offsets included

	Year 1	Year 2	Year 3	Year 4	Year 5

Eligible patients treated with intervention	1	0	1	0	1
Gross/net drug budget impact	€3,313,438	€0	€3,313,438	€0	€3,313,438
Cost-offsets	-€ 16,319	-€55,120	-€ 98,325	-€142,386	-€ 184,873
Additional costs	€ 106,574	€0	€ 106,574	€0	€ 106,574
Net budget impact	**€3,403,692**	**-€55,120**	**€3,321,687**	**-€142,386**	**€3,235,139**
Cumulative net budget impact					**€9,763,011**

- **Scenario Analysis**

The Applicant presented a scenario analysis for BE, where it is assumed that there is a higher number of incident patients, and that 100% of these patients are identified through a NBS programme. The result is a large increase in projected budget impact, as shown in Table 46.

Table 46 Belgian net budget impact scenario analysis, 100% early onset MLD patients are born and receive treatment.

	Year 1	Year 2	Year 3	Cumulative
Eligible patients treated with intervention	2.55	2.55	2.55	8
Level 1: impact of reimbursement of AA on the pharmaceutical drugs budget	€ 7,771,125	€ 7,771,125	€ 7,771,125	**€ 23,313,375**
Cost-offsets	-€ 10,821	-€ 30,294	-€ 53,685	**-€ 94,801**
Additional costs	€ 103,567	€ 103,567	€ 103,567	**€ 310,700**
Level 3: incremental impact of reimbursement of AA on the healthcare budget	**€ 7,863,871**	**€ 7,844,397**	**€ 7,821,006**	**€ 23,529,274**

Concluding Remarks:

This cost effectiveness of this treatment is specifically examined in three main subgroups; patients with early juvenile pre-symptomatic disease; with early juvenile early symptomatic disease and those with pre-symptomatic late infantile disease. The Applicant also presented a weighted average ICER across all three subgroups. The ICERs in all scenarios lie above the explicit cost effectiveness thresholds. The usefulness of the weighted average ICER is limited given the considerable uncertainty in treatment effectiveness between disease subgroups.

The Review Group consider the quantity of overly optimistic assumptions and the lack of transparency around how data is used to inform key parameters to be problematic. The Review Group highlights that the assumption of cure is subject to considerable uncertainty given the limited data availability. Implementation of the Review Group's alternative base case, which attempts to evaluate the impact of this key uncertainty on the cost effectiveness results, results in ICERs which are substantially higher than the Applicant's base case. Other concerns regarding the Applicant's approach for response classification remain. There are limited opportunities to investigate the impact of changes to responder classification on the model. This is a major source of uncertainty, and has implications for subpopulations where limited data are available, in particular the PS EJ and ES EJ cohorts.

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Appendix 1

Questions for Applicant

The RG consider the quantity of overly optimistic assumptions and the exclusion of recent data cuts to be significantly problematic and therefore cannot draw conclusions on cost effectiveness at this time. We suggest further questions to be posed to the applicant before any conclusions can be drawn.

General observations

- Please vary the discount rate between 0-10% in the IE scenario analysis on discount rate, as per NCPE guidelines.
- Please update the rebate applied to PTW for IE, from 5.5% to 7.75% in line with the recently published Framework Agreement. Please update BI model accordingly also.
- Commercial in confidence (CIC) information-drug costs, eligible patients and budget impact are not considered CIC in Ireland and will not be marked as such in the report. In general all aspects of the report will be available in the public domain under the Dutch procedure therefore please take this into account.

The Review Group acknowledges that the observations listed here were addressed by the Applicant.

Treatment effect inputs

1. The data for AA used to inform the cost-effectiveness model is from March 2018 data cut, as was presented in concept dossier model. Clinical outcomes from later 2019 data cut are presented in the pharmacotherapeutic evidence submitted but were not used in the cost-effectiveness analyses. Study 205756 of the cryopreserved formulation of AA was also not used to inform the cost-effectiveness analyses. The Review Group consider the cost-effectiveness analyses should have been informed by the latest available data. **Please update the cost-effectiveness model to use the latest available AA clinical data.**

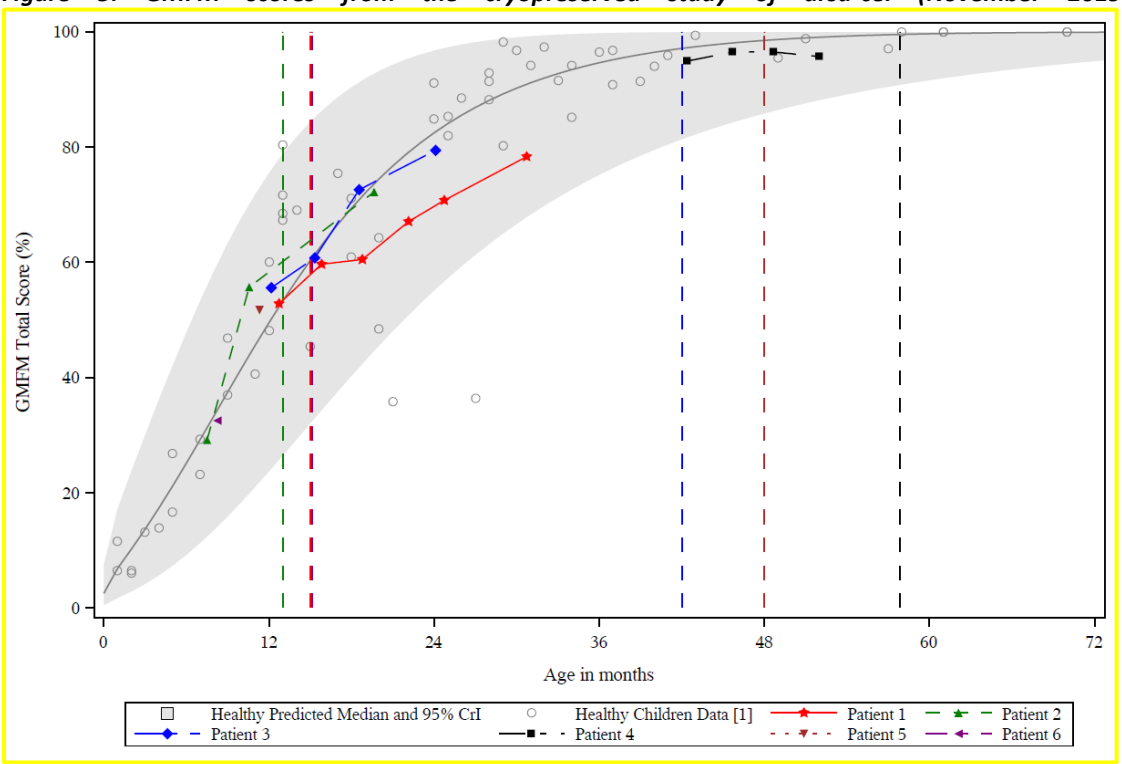
Applicant's response:

Orchard completely agrees with the Review Group that the cost-effectiveness analyses should be informed by the latest available data, which is why the data for arsa-cel used to inform the cost-effectiveness model is from the December 2019 data cut and not based on the March

2018 data cut. Orchard acknowledges that not updating the Clinical Trial Data Worksheet with the most recent data cut could have given the incorrect impression that the most recent data were not used and apologises for that. However, the assessors can trace that there are no dependents from these data – this was an information only worksheet and does not feed into any of the parameter inputs used in the cost-effectiveness modelling. The company would also like to point out that it intentionally retained the progression modifiers that were derived from the March 2018 data cut in the final submission because they were more conservative at 3.4 for GMFC-MLD 2 to GMFC-MLD 5 than the 4.1 from the updated data analysis. The OTL_200 LI, OTL_200_Juv_PreSymp and the OTL_200_Juv_Symp worksheets which all feed into the modelling definitively use the most recent 2019 data cut.

With regards to the exclusion of preliminary outcome data from the cryopreserved study, Orchard believes it would have been criticised had the data been included in the cost-effectiveness analyses, because the period of follow-up post gene therapy might have been deemed to be too short to draw any conclusions (under 2 years). Of the four evaluable patients from the cryopreserved study, one LI patient has follow-up data 1.5 years post-gene therapy (GT), two more have data 1-year post GT (one LI and one EJ patient); and the final EJ patient has data up to 9 months post treatment. Figure below shows that all the evaluable patients have GMFM scores in line with healthy peers of the same age (i.e., no signs and symptoms of disease; GMFC-MLD 0). The two EJ patients (Patient 3 and Patient 4) have yet to pass the age of predicted onset of symptoms and so it is not possible to claim any treatment effect in these patients yet. However, the two LI patients (Patient 1 and Patient 2) with 1.5 and 1 years' worth of follow-up data, respectively, have passed the age of predicted onset of symptoms and are still continuing to report GMFM scores well within the normal range of healthy children at the same age. Consequently, a scenario analysis has been provided in Section 5.2.3.1 that includes these two evaluable LI patients.

Figure 5. GMFM scores from the cryopreserved study of arsa-cel (November 2019 DCO)



***Footnotes**: Vertical dotted lines represent expected age of disease onset. Results based on the November 2019 DCO. **Abbreviations**: CrI: Credible interval; DCO: Data cut-off; GMFM: Gross Motor Function Measure.*

As can be seen from the table, inclusion of the cryopreserved patients improves the incremental cost-effectiveness ratio (ICER) of arsa-cel vs. best supportive care (BSC) for the LI cohort and the combined ICER in all three countries.

Review Group's response:

The Review Group considers the failure to update the Clinical Trial Data worksheet as a considerable oversight on the Applicant's part. Regarding the retention of the progression modifiers derived from the March 2018 data cut-off, this decision was not explicitly discussed in the submission, nor were the progression modifiers based on the 2019 data cut-off reported in the submission. Therefore, while the Review Group acknowledges that data from the later 2019 data cut-off were used in the cost-effectiveness analysis, there was incomplete information as to when and how the data were used to inform the analysis.

The report has been updated in to reflect the inclusion of data from the 2019 data cut to inform responder classification. The report has also been updated to highlight that important elements of the model were not aligned with the relevant parameter udpates. Finally, the report has been updated to highlight that only certain elements of the report were updated to include the 2019 data cut, and that no justification was provided in the final submission dossier as to why these decisions were made.

Regarding the scenario with the preliminary data from patients who received the cryopreserved formulation, the Review Group acknowledges that Applicant's position that the duration of follow-up is likely too short to draw any conclusions. The Review Group have highlighted this concern as a key uncertainty with regard to the generalisability of the efficacy data based on the fresh formulation to the cryopreserved formulation, and do not consider that this scenario addresses the key underlying issue of lack of available data.

2. Please clarify the criteria used for outcomes measures other than GMFC-MLD to classify response. Please present data for these outcomes to support classifications used.

Applicant's response:

Orchard would like to point out that the criteria for outcome measures other than GMFC-MLD to classify response were described on pages 231–232 of the final submission. The classification into the so-called "full responder", "stable partial responder" and "unstable partial responder" groups for the purposes of economic modelling was based on a holistic approach to the data, such that an assessment of response is not reliant on just a single outcome, for example GMFC-MLD, which does not capture all the clinical signs and symptoms of the disease, but instead encompasses all the relevant clinical outcomes and disease markers

including GMFC-MLD, GMFM, DQp and MRI, PBMC ARSA, nerve conduction velocity (NCV). This holisitic approach to classification was done in response to the HTA assessment by NICE in the UK and validated by the clinical experts at the 2nd NICE committee meeting (verbal communication).

The individual patient data are presented numerically over time in this response as per RIZIV's request following review of the clinical section. From these data, the Review Group can see that examining the totality of data for each patient fully supports Orchard's classification of treatment response. In addition, Section earlier in this response above provides further explanation for the classification of treatment response in each patient, which the company hopes will alleviate some of the Review Group's concerns in relation to the modelled treatment effectiveness.

For clarity the clinically validated model decision rules are as follows:

- ***Patients are classified as full responders** if their motor and cognitive function remained stable throughout the follow-up period i.e., no disease progression was observed throughout the follow-up period.*
- ***Patients are classified as stable partial responders** if their motor and cognitive function appear to have stabilised after an initial period of worsening. To determine GMFC-MLD level the patient stabilised at, the following were considered:*
    - *DQ and MRI should have stabilised or continue to improve for 12 months*
    - *GMFM total score or relevant subdomain is stabilising*
- ***Patient were classified as unstable partial responders if they had a** consistent trend of worsening in motor (GMFM and GMFC-MLD) and/or cognitive function, albeit at a slower rate than natural history subjects.*

Definition of disease progression: Disease progression is defined as a worsening in motor impairment and/or cognitive function.

- ***Progression of motor impairment: worsening of GMFC-MLD and GMFM total score***
    - *If the patient had a drop in only GMFC-MLD score but the GMFM total score remained stable and the additional disease markers (MRI and NCV) also remained stable, then the patient was assumed to be stable. This was based on the clinical opinion from trial investigators and other MLD experts who indicated that this would not be disease progression, as the GMFC-MLD changes may be as a result of previous mild functional impairment becoming more perceptible as the patient becomes older (e.g. GMFC-MLD 0 to 1) or reflect life style changes (e.g. patients using mobility aids to better socialisation, GMFC-MLD 1 to 2).*
- ***Progression of cognitive impairment**:*

- *due to fluctuations in DQ performance scores, progression was defined as an unreversed categorical change in DQ performance i.e., patient goes from normal (>85) to mild (70 – 85) or from mild to moderate (55 to 70) etc.*

In addition, the clinical rationale for each patient's disease trajectory is underpinned by the mechanism of action of arsa-cel. Once arsa-cel is administered to the patient, the treatment effect becomes apparent only after corrected cells have engrafted in the haematopoietic compartment, migrated to the central nervous system (CNS), and delivered enough enzyme to the surrounding cells to prevent further sulphatide accumulation. Given that these sequence of events takes some time coupled with the progressive nature of MLD, the clinical effect across patients will vary depending on their clinical status at the time of treatment. The earlier patients are treated in relation to the onset of symptoms, the greater the potential clinical effect. Based on this rationale, the three response categories used in the health economic model to capture the degree to which patients can benefit from arsa-cel, taking into consideration the clinical patient status at point of treatment, are outlined below:

***Full responders**: These are patients treated pre-symptomatically and well before the onset of symptoms and who have stabilised (i.e. no clinically relevant decline in motor or cognitive function). Clinical investigators have indicated that these patients have the potential to live normal lives that would be experienced by the general population, as they were treated early enough for the corrected cells to engraft and start having an effect before the onset of clinical symptoms.*

***Partial responder – stable**: These are patients who have stabilised at a GMFC-MLD score of 1 or more. These include the following types of patients:*

- *PS patients who stabilised at a GMFC-MLD score of 1 or more after an initial period of disease progression. It is worth highlighting that for patients treated before 18 months (earliest time point GMFC-MLD score can be administered), any disease progression between treatment and the first GMFC-MLD data point would not be apparent. However, the company has inferred that disease progression occurred in any pre-symptomatically treated patient whose GMFC-MLD score was 1 or greater after treatment. The initial disease progression is due to the time required for the drug's effect to become apparent as described above. In addition, although there were some pre-symptomatically treated patients who seemed to have improvements in their GMFC-MLD score (MLD-HE02 and MLD-HE01), the company has conservatively included them in the partial responder-stabilised group as these patients seemed to have stabilised at a GMFC-MLD score of 1 as well as in other endpoints such as DQp, MRI and GMFM. Clinical investigators have indicated that the improvements in GMFC-MLD score may be due to a developmental delay in the patients walking, and not associated with MLD as the measurements were taken under 18 months of age.*

ES-EJ patients who stabilised after an initial period of disease progression. Due to the lag time required for treatment to have an effect, and the fact the ES-EJ patients were treated after onset of clinical symptoms, it has been assumed that none of them would be full-responders (i.e., stabilise at GMFC-MLD score of 0). However, although not observed in the clinical trial results, in clinical practice it is possible for ES EJ patients to stabilise at 0, if treated early enough.

Partial responder – unstable*: These are patients who after treatment with Libmeldy continued to progress (i.e., see worsening of GMFC-MLD score as well as DQp, MRI, and GMFM) albeit at a slower rate compared to natural history patients. Clinical experts believe this could possibly be because the mechanisms of neurodegeneration could have already settled at time of treatment and cannot be stopped or reversed but can be modified (Dr F Fumagalli).*

Whilst the numerical IPD data are presented in the following figures below for patients MLD-02, MLD-01 and MLD-07 provide visual exemplars of the three categories of response for all the clinical outcomes mentioned above.

Review Group's response:

The Review Group noted the information presented on pages 231-232 of the submission. However, much information remains lacking as to how the criteria for determining classification were derived, what thresholds were considered clinically relevant, and how the various criteria were weighted relative to one another in terms of determining responder classification.

Regarding the definition of 'full responders' presented in the submission, on page 232 it is stated that 'Full responders are equivalent to GMFC 0'. This is not consistent with the response classification used in the cost-effectiveness model, where patients are observed to deteriorate to GMFC-MLD >0 and continue to be classified as full responders. Furthermore, the term 'stable' lacks definition. Again, it is unclear what thresholds are considered relevant, how they were derived, and how the various criteria used to determine responder classification are weighted against one another to determine responder status.

The report has been updated to reflect the Review Group's response here, which specifically notes the lack of transparency and rigour surrounding the classification methodology used. Given the major impact responder classification has on the model results, this has been identified as a key issue in the submission.

3.

a. It is unclear how the Applicant derived proportions in each cognitive substate for AA. The Applicant states distribution was informed by clinical study data. However, the analysis methodology was not described by the Applicant and data summarising cognitive substate over time and by GMFC-MLD state was not provided for the pooled AA clinical data. The Review group note that no patient in the AA clinical study was recorded in GMFC-MLD 5 or 6 so source for these health states is unclear. Within the submission reference is also made to expert elicitation, but no results in relation to treated patients are provided in reference 25 OTL-200 HE Advisory Board_Expert Judgement Report_Final_16Nov2020. Please provide detailed explanation of how cognitive substate distributions for AA were derived. Please present

supporting data on DQp and cognitive substate by GMFC over time from the AA clinical studies.

Applicant's response:

Orchard can confirm that the cognitive substates for arsa-cel used in the economic model were based on clinical expert opinion and the clinical trial data available during model development. However, in response to this request from the Review Group, Orchard has further analysed the DQp data by GMFC-MLD over time from the updated 2019 data cut for the arsa-cel clinical studies. As can be seen from Table , Table 48, Figure and Figure below, for the patients classified as full responders and stable partial responders, the DQp data remains stable and with the range for normal cognitive function[1], for all patients at each visit over time. Importantly for the stable partial responders, DQ remains in the normal range irrespective of the GMFC-MLD score (GMFC-MLD 1 to 4) that the patients stabilised at. These data support the cognitive substate distributions used in the model for the full responders and stable partial responders.

Table 47: DQp scores over time for all patients classified as full responders by colour coded GMFC-MLD score at each visit (data CiC)

Time since GT (years)	Mean	SEM	MLD-2 (LI)	MLD-3 (LI)	MLD-5 (LI)	MLD-9 (PS-EJ)	MLD-12 (PS-EJ)	MLD-15 (LI)	MLD-16 (PS-EJ)	MLD-HE03 (LI)	MLD-CUP03 (LI)
0	106	6	116.8	95.5	103.0	91.7	.	.	124.0	.	.
0.5	101	11	.	88.7	80.2	85.0	113.0	.	140.0	89	.
0.75	107	.		.	.	.		106.7	.	.	.
1	105	8	97.8	97.5	91.0	79.0	122.0	104.6	140.0	93.9	100
1.5	106	11	104.7	91.8		80.7	108.0		146.0	.	
2	99	8	88.7	92.1	79.8	93.0	113.0		130.0	101.2	
2.5	106	8	90.0	85.4	91.0	115.0	119.0		135.0		
3	115	5	.	103.0	102.0	124.0	119.0	.	126.0		
3.5	113	6	104.0	109.0	104.0	109.0	.		137.0		
4	122	7	131.0	109.0	107.0	118.0	.		145.0		
4.5	110	6	.	107.0	104.0	102.0	.		128.0		
5	115	10		107.0	104.0	.	.		135.0		
5.5	110	3		111.0	104.0	115.0	.		.		
6	112	6		104.0	102.0	128.0	115.0		.		
6.5	104	2		106.0	102.0				.		
7	102	2	.	100.0	104.0				.		
7.5	108	.		108.0		.		.	.		
8	104	4		108.0	100.0	.		.	.		

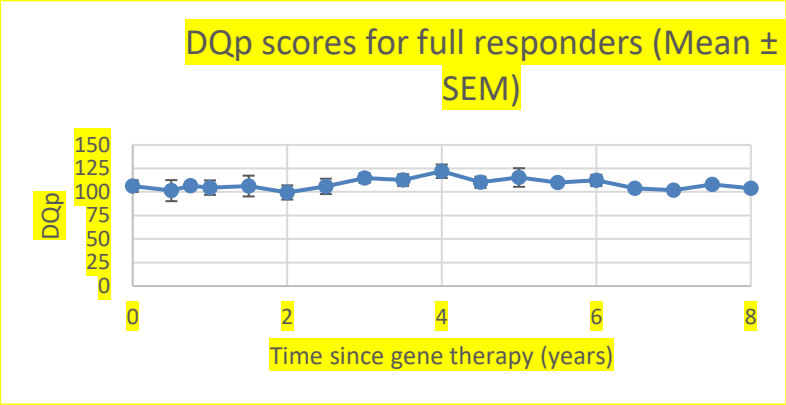
***Footnotes**: GMFC-MLD scores per visit are colour coded as per below and GMFC-MLD scores are recorded more frequently at follow-up visits than DQp scores which are indicated by the coloured cells in the table.*

GMFC-MLD 0	GMFC-MLD 1	GMFC-MLD 2	GMFC-MLD 3	GMFC-MLD 4

[1] Please note that for the purpose of the development of cognitive substate distributions, normal cognitive function was considered to be above a DQp score of 70. This is in line with the threshold used within the EPAR, and therefore considered appropriate by the EMA.

Abbreviations: *GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; GT: gene therapy; LI: late infantile; MLD: metachromatic leukodystrophy; PS-EJ: pre-symptomatic early juvenile; SEM: standard error of the mean.*

Figure 6: Mean ± SEM DQp scores over time for patients classified as full responders



Abbreviations: *DQp: development quotient performance; SEM: standard error of the mean.*

Table 48: DQp scores over time for patients classified as stable partial responders, colour coded by GMFC-MLD score at each visit (data CiC)

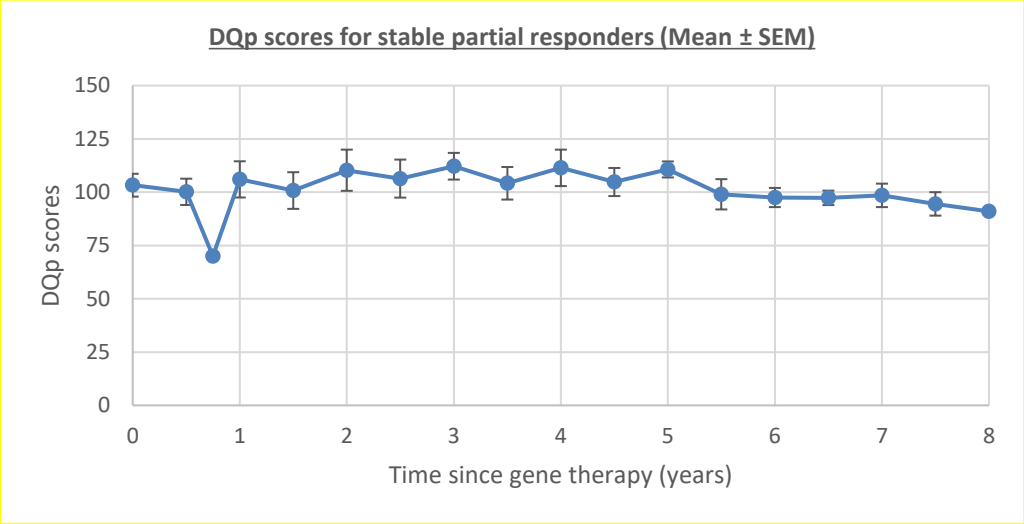
Time since GT (years)	*Mean*	*SEM*	*MLD-1 (LI)*	*MLD-6 (LI)*	*MLD-13 (ES-EJ)*	*MLD-14 (ES-EJ)*	*MLD-22 (LI)*	*MLD-CO2 (ES-EJ)*	*MLD-CUP01 (LI)*	*MLD-CUP02 (LI)*	*MLD-CUP05 (LI)*
0	*101*	*5*	*96*	*97*	*119.0*	*119.0*	*102*	*87.0*			*85.6*
0.5	*98*	*4*	*89.1*	*97.0*	*98.0*	*124.0*	*93*	*.*	*93.9*	*86.1*	*103.1*
0.75	*70*	*.*		*.*	*.*	*.*	*.*	*70.0*			
1	*108*	*6*	*89.2*	*111.9*	*102.0*	*139.0*	*113.8*	*80.0*	*125.2*	*109.8*	*102.5*
1.5	*101*	*9*	*82.8*	*106.5*	*104.0*	*137.0*	*96.3*	*78.0*			
2	*110*	*10*	*78.9*	*105.5*	*115.0*	*143.0*	*128.4*	*91.0*			
2.5	*106*	*9*	*71.0*	*109.0*	*111.0*	*139.0*	*108.1*	*100.0*			
3	*112*	*6*	*87.0*	*113.0*	*111.0*	*135.0*	*116.0*	*111.0*			
3.5	*104*	*8*	*78.0*	*115.0*	*89.0*	*130.0*	*102.0*	*111.0*			
4	*111*	*9*	*96.0*	*129.0*	*95.0*	*135.0*	*102.0*				
4.5	*105*	*7*	*91.0*	*115.0*	*117.0*	*.*	*96.0*	*.*			
5	*111*	*4*	*111.0*	*104.0*	*117.0*	*.*	*.*				
5.5	*99*	*7*	*85.0*	*104.0*	*108.0*	*.*	*.*				
6	*98*	*5*	*93.0*	*102.0*	*.*	*.*					
6.5	*97*	*3*	*93.0*	*104.0*	*.*	*.*		*95.0*			
7	*99*	*6*	*93.0*	*104.0*	*.*						
7.5	*95*	*6*	*89.0*	*100.0*	*.*						
8	*91*	*0*	*91.0*	*91.0*	*.*						

GMFC-MLD scores per visit are colour coded as per below and GMFC-MLD scores are recorded more frequently at follow-up visits than DQp scores which are indicated by the coloured cells in the Table.

GMFC-MLD 0	*GMFC-MLD 1*	*GMFC-MLD 2*	*GMFC-MLD 3*	*GMFC-MLD 4*

Abbreviations: *ES-EJ: early symptomatic early juvenile; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; GT: gene therapy; LI: late infantile; MLD: metachromatic leukodystrophy; SEM: standard error of the mean.*

Figure 7: Mean ± SEM DQp scores over time for patients classified as stable partial responders



Abbreviations: *DQp: development quotient performance; SEM: standard error of the mean.*

For patients classified as unstable partial responders, the data are limited as only four patients from the 25 patients who fulfil the eligibility criteria for arsa-cel continued to have disease progression following gene therapy. Furthermore, only 2 of the 25 patients from the entire indicated population had any decline in cognitive function at all.

Table 49 provides the data for DQp over time for the four unstable partial responders; only unstable partial responders with follow-up data longer than 5 years had deteriorating cognitive function (despite previously having normal cognitive function). Consequently, a scenario has been included in Q3c) below where these patients have continued cognitive decline.

Table 49: DQp over time for patients classified as unstable partial responders, colour coded by GMFC-MLD score at each visit (data CiC)

Time since GT	*Mean*	*SEM*	*MLD-07 (LI)*	*MLD-08 (ES-EJ)*	*MLD-17 (ES-EJ)*	*MLD-20 (PS-EJ)*
0	*98*	*6*	*97.0*	*90.9*	*89.0*	*115.0*
0.5	*98*	*5*	*87.2*	*93.6*	*104.0*	*109.0*
1	*98*	*7*	*94.5*	*91.0*	*87.0*	*119.0*
1.5	*99*	*2*	*98.3*	*98.0*	*106.0*	*95.0*
2	*97*	*4*	*85.3*	*104.0*	*98.0*	*100.0*
2.5	*96*	*6*	*84.0*	*104.0*	*100.0*	
3	*85*	*3*	*80.0*	*85.0*	*89.0*	
3.5	*87*	*.*	*87.0*	*.*		
4	*74*	*11*	*73.0*	*56.0*	*93.0*	
4.5	*78*	*.*	*78.0*			
5	*36*	*11*	*47.0*	*24.8*		
5.5			*.*			
6	*26*	*5*	*31.2*	*21.2*	*.*	
7			*.*			
7.5	*13*	*.*	*12.9*	*.*	*.*	

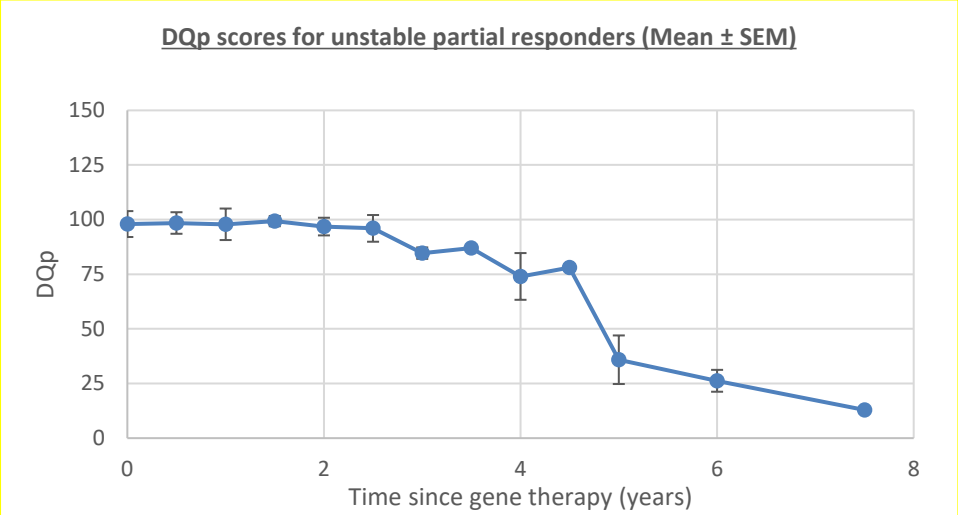
8			.	.	.	

GMFC-MLD scores per visit are colour coded as per below and GMFC-MLD scores are recorded more frequently at follow-up visits than DQp scores which are indicated by the coloured cells in the Table.

GMFC-MLD 0	*GMFC-MLD 1*	*GMFC-MLD 2*	*GMFC-MLD 3*	*GMFC-MLD 4*	*GMFC-MLD 5*

Abbreviations: *ES-EJ: early symptomatic early juvenile; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; GT: gene therapy; LI: late infantile; MLD: metachromatic leukodystrophy; PS-EJ: pre-symptomatic early juvenile; SEM: standard error of the mean.*

Figure 8: Mean ± SEM DQ scores over time for patients classified as unstable partial responders



Abbreviations: *DQp: development quotient performance; SEM: standard error of the mean.*

Review Group's response:

The Applicant's response has highlighted a number of issues:

i. The most up to date clinical trial data does not appear to have been used to inform this aspect of the model. No justification was provided as to why this was excluded. The Review Group have updated the model to highlight this.

ii. There is inconsistency in terms of how patients were classified in terms of response between the information provided in the final submission (November 2021), despite the claim that response classification at both time points is informed by the same data (2019 data cut). Here, it is stated that these patients are MLD-07, MLD-08, MLD17 and MLD-20. On page 252 of the submission dossier, it is stated that the four unstable patients are MLD-07, MLD-08, MLD-14 and MLD-17. This is further evidence of the lack of transparency surrounding response classification.

b. Please justify the assumption that patiREvents who progress to GMFC-MLD 5 and 6 would maintain cognitive function.

Applicant's response:

Of the entire indicated population (n=25), only one LI patient treated with arsa-cel falls within the criteria for this question – at the last follow-up MLD-07 had progressed to GMFC-MLD 5 (MLD-07) and had a DQp score of 12.9. Furthermore, only two patients out of the indicated population treated with arsa-cel had any decline in cognitive function. Therefore, there is a lack of evidence on which to base this assumption . Clinical expert opinion indicated that arsa-cel confers a cognitive benefit even in patients who experience a decline in their motor function, which is not seen with HSCT (MLDi registry, and data from Groeschel et al2) or BSC. In the absence of any other data, it seemed a reasonable assumption to maintain cognitive function for the majority of patients (80%) despite disease progression. However, in response to the Review Group's question Q3c, the company has provided a scenario analysis with an alternative assumption to the base case i.e., patients treated with arsa-cel who progress to GMFC-MLD 5 and 6 are modelled to have severe cognitive impairment. The cognitive substate distribution for patients that progress is presented in Table 7 below.

Review Group's response:

The Review Group acknowledge the limited number of patients. However, the evidence available (albeit n=1) does not support the assumption based on clinical opinion that patients treated with AA who progressed to advanced GMFC-MLD stages would maintain cognitive function. The Review Group acknowledges the scenario, which is discussed in the next section.

c. Please present scenario analyses for treatment waning where patients experience cognitive decline in addition to decline in GMFC state.

Applicant's response:

Based on the DQp data for patients that have continued progression presented in Table 49 above, Orchard has devised an alternative cognitive substate distribution such that for patients who have continued disease progression despite treatment (i.e. unstable partial responders), patients will experience both cognitive and motor decline as opposed to just motor decline, which has been assumed in the base case. Table 50 details the revised distribution, which is based on the clinical data presented in response to Q3a.

Table 50: Cognitive substate distributions for arsa-cel treated patients classified as unstable partial responders

Cognitive substate distribution	***Normal cognitive function (DQp ≥70)***	***Moderate cognitive impairment (DQp ≥55 and <70)***	***Severe cognitive impairment (DQp <55)***
Before cognitive decline: GMFC-MLD 0	*100%*	*0%*	*0%*
After cognitive decline: GMFC-MLD 0	*100%*	*0%*	*0%*
GMFC-MLD 1	*100%*	*0%*	*0%*
GMFC-MLD 2	*67%*	*33%*	*0%*
GMFC-MLD 3	*67%*	*0%†*	*33%†*
GMFC-MLD 4	*50%**	*0%*	*50%**
GMFC-MLD 5	*0%*	*0%*	*100%*
GMFC-MLD 6	*0%*	*0%*	*100%*

***Note**: The percentages of patients in each GMFC-MLD health state with normal cognitive function, moderate or severe cognitive impairment are calculated based on the percentage of patients within each cognitive substate in each of the GMFC-MLD health states for patients classified as unstable partial responders from the arsa-cel clinical trial data presented in e continued* cognitive decline.

***Table** .*

** One patient reported both normal and severe DQp scores in GMFC-MLD 4 so the time has been split into both categories.*

† As shown in e continued cognitive decline.

***Table** , no patient reported moderate cognitive impairment in GMFC-MLD 3, but one patient reported severe cognitive impairment in GMFC-MLD 3. Therefore, no patients can be categorised as having both moderate cognitive impairment and GMFC-MLD 3.*

***Abbreviations**: DQp: Development quotient performance; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy.*

In the economic model, the "include unstable partial responder" box in the OTL_200_Juv_PreSymp and OTL_200_Juv_Symp needs to be checked to apply this distribution. As can be seen from the results of the scenario analysis in ***Fout! Verwijzingsbron niet gevonden.*** *in Section 5.2.3.1, modelling cognitive d ecline as well as motor decline in patients treated with arsa-cel who have continued progression marginally worsens the ICER versus BSC in all three countries.*

Review Group's response:

The Review Group acknowledges the Applicant's response and have included details of the updated analysis in the report.

4. Please provide justification for the time to cognitive decline used for GMFC-MLD 0 for AA, BSC and HSCT. The values used for AA are substantially longer than the available clinical trial follow up.

Applicant response:

The "time until cognitive decline parameter" was included based on feedback from the MLD clinical experts during the economic model development that initial cognitive decline may occur prior to motor decline.29 In Kehrer et al, of the 36 juvenile patients in the study, 6 (17%) presented exclusively with non-gross motor signs as first symptoms – presenting with behavioural and concentration problems rather than any gait disturbance.30 For the model,

the cognitive distributions were included for patients "Before Cognitive Decline: GMFC-MLD 0" and "After Cognitive Decline: GMFC-MLD 0" to reflect this assumption. The time until cognitive decline was based on the 192 months of follow up time, which was the maximum duration of follow-up in the natural history trial for EJ patients. For example, in ES EJ patients, the time until cognitive decline was assumed to be 112 months, such that for the first 112 months post-treatment, patients in GMFC-MLD-0 would use the "Before Cognitive Decline: GMFC-MLD 0" cognitive distributions. After 112 months, patients in GMFC-MLD-0 would use the "After Cognitive Decline: GMFC-MLD 0" cognitive distributions i.e., remain in GMFC-MLD 0, but a proportion of patients would start to experience cognitive impairment. If patients transitioned to GMFC-MLD 1, then it was assumed that they would experience cognitive decline aligned with the GMFC-MLD 1 stage. i.e., time until cognitive decline was only applied to patients in GMFC-MLD 0.

Because arsa-cel treated patients classified as full-responders retain 100% normal cognitive function until GMFC-MLD-4, there is no impact from this parameter as the "Before" and "After" distributions are identical. However, for arsa-cel treated patients classified as partial responders, HSCT treated patients and BSC, the functionality only has a minimal impact as the probability of transitioning from GMFC-MLD 0 to GMFC-MLD 1 due to motor decline far exceeds the probability of remaining in GMFC-MLD 0 for the length of time assumed (112- or 142-months post gene therapy) and only 5% of arsa-cel treated patients classified as partial responders are modelled to remain in GMFC-MLD 0 with moderate cognitive impairment.

Nevertheless, Orchard can appreciate that the values used exceed the maximum duration of clinical trial follow up for arsa-cel and acknowledges the Review Group's concerns. Consequently, the inputs for this parameter have been amended and all subsequent analyses presented in this document utilize the updated parameter inputs. No arsa-cel treated patient experienced cognitive decline whilst in GMFC-MLD 0, it was therefore not possible to use the clinical data to inform this parameter. Therefore, in the absence of actual data, the company has assumed the minimum amount of time spent in GMFC-MLD 0 before a patient transitioned to GMFC-MLD 1 as a proxy for the updated "time to cognitive decline" parameter. Patients MLD-06 and MLD-20 (both classified as unstable partial responders) were in GMFC-MLD 0 for 2 years prior to transitioning to GMFC-MLD 1. Consequently, for partial responders the time until cognitive decline parameter has been updated to 24 months for both PS-EJ and ES-EJ arsa-cel treated patients rather than the 112 and 147 used previously .

Orchard reiterates that modifying these values for arsa-cel has a very small impact on the results as only 5% of partial responders are still in GMFC-MLD 0 after this time who would experience cognitive impairment.

Review Group's response:

The Review Group have updated the 'Cognitive sub-sates in EJ populations' section in the report to reflect the clarifications and changes made as part of the response to this question.

5. Please provide methodology, data, results (including appropriate measures of uncertainty (eg standard errors, 95% CI) and source references for the analyses of the MLDi registry, both for HSCT and BSC.

Applicant's response:

Orchard received the MLDi registry data directly from the MLDi as an anonymised Excel file with the following variables: baseline characteristics (such as ID), MLD type, date of diagnosis, date of onset of symptoms, age at onset of symptoms, date and age at treatment (HSCT only), whether a second HSCT was required, and total IQ at time of diagnosis. The data also included the following outcome measures: year of total IQ assessment, total IQ at follow-up, total IQ last measured and year of last IQ measure, as well as the GMFC-MLD states recorded with the date of GMFC-MLD score at first date and a date for GMFC-MLD score at last date; other details included the date of death and the time between date of treatment and date of death (HSCT only). Note, with permission from the MLDi registry – the Review Group would also be able to access the same file to confirm the analyses.

Patients' progression through GMFC-MLD stages were tracked from entry into a GMFC-MLD stage until entry into the next reported GMFC-MLD stage. Patients "missing" or "skipping" GMFC-MLD stages were assumed to have transitioned through the missing GMFC-MLD stage in the time elapsed between visits and therefore progression occurred but was not observed. To estimate the time spent in each GMFC-MLD health state, the difference in months between the GMFC-MLD first date to the first date of the next GMFC-MLD level was calculated – the same approach was taken to calculate the mean time in state for arsa-cel treated patients and the natural history cohort from OSR TIGET.

Similarly to the data reported for the natural history cohort, some patients from the MLDi registry (HSCT and BSC) progress through several GMFC-MLD levels without an intervening visit due to the rapid phase of the disease from GMFC-MLD 2 to 5. However, for the modelling, data for the time spent in each GMFC-MLD health state before progression to the next level is needed; therefore it has been assumed that the time taken from the last reported GMFC-MLD state to the next reported GMFC-MLD state has been split evenly across the intervening GMFC-MLD states. For example, ES EJ patient ID 6 went from GMFC-MLD 1 to GMFC-MLD 5 in four months, with no intervening visits, therefore the time taken to transition between GMFC-MLD 1 to 2, GMFC-MLD 2 to 3, GMFC-MLD 3 to 4, and GMFC-MLD 4 to 5 was split evenly across all four states e.g., one month spent in each state. This was deemed acceptable by the clinical expert from the Netherlands in the absence of knowing exactly when the patient transitioned to each state during the very short period of time. The data for HSCT treated patients from the MLDi registry were presented in Table 53 in the final submission and are reproduced below in Table 8, but which now also include appropriate measures of uncertainty. Table 9 presents the data for the BSC patients from the MLDi registry as requested by the Review Group.

Table 51. HSCT individual patient transition times (months) from one GMFC-MLD state to the next, from the MLDi registry data for EJ patients

MLD	GMFC-MLD 0 to 1*	GMFC-MLD 1 to 2	GMFC-MLD 2 to 3	GMFC-MLD 3 to 4	GMFC-MLD 4 to 5	GMFC-MLD 5 to 6	GMFC-MLD 6 to death	DQp at last follow-up
PS EJ[a]	*9*	*33*	*27.6*	*27.6*	*27.6*	*-*	*-*	*DQp <50*
PS EJ	*9*	*67*	*46*	*-*	*-*	*-*	*-*	*DQp =80*
ES EJ[b]	*9*	*1*	*1*	*1*	*1*	*1*	*8*	*DQp <50*
ES EJ	*9*	*142*	*-*	*-*	*-*	*-*	*-*	*DQp <50*
Mean time in state		***60.75***	***24.87***	***14.3***	***14.3***	***1***	***8***	
SD		*52.39*	*18.47*	*13.3*	*13.3*	*-*	*-*	
SE		*26.20*	*10.67*	*9.40*	*9.40*	*-*	*-*	
% SE		*43.12%*	*42.89%*	*65.77%*	*65.77%*	*-*	*-*	

Footnotes: **Cannot quantify based on available data, so set the same as arsa-cel and OSR-TIGET natural history; [a] Time from GMFC-MLD 2 to 5 was 83 months spread evenly across health states; [b] Time from GMFC-MLD 2 to 5 was 4 months spread evenly across health states, patient died 9 months after last GMFC-MLD 5 date.*

Abbreviations: *DQp: developmental quotient performance; ES: early symptomatic; EJ: early-juvenile; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; HSCT: haematopoietic stem cell transplantation; MLDi: metachromatic leukodystrophy initiative; PS: pre-symptomatic; SD: standard deviation; SE: standard error.*

Table 52. BSC individual patient transition times (months) from one GMFC-MLD state to the next, from the MLDi registry data for both LI and EJ patients

MLD	GMFC-MLD 0 to 1*	GMFC-MLD 1 to 2	GMFC-MLD 2 to 3	GMFC-MLD 3 to 4	GMFC-MLD 4 to 5	GMFC-MLD 5 to 6	GMFC-MLD 6 to death
BSC – LI MLD							
LI-1	*3*	*2*	*0.75*	*0.75*	*0.75*	*0.75*	*39*
LS-2	*3*						
LI-3	*3*	*-*	*2.5*	*2.5*	*3*	*3*	*66*
LI- 4	*3*						
LI-5	*3*	*-*	*-*	*-*	*-*	*-*	*41*
LI-6	*3*	*-*	*-*	*0.5*	*0.5*	*0.5*	*44*
LI-7	*3*	*-*	*2.5*	*2.5*	*0.75*	*0.75*	*49*
LI-8	*3*						*-*
LI-9	*3*						*-*
LI-10	*3*	*-*	*3*				
LI-11	*3*	*-*	*0.66*	*0.66*	*0.66*		*-*
Mean time in state	***3***	***2***	***1.882***	***1.382***	***1.25***	***1.25***	***47.8***
SD		*0*	*0.98*	*0.92*	*0.99*	*1.02*	*9.70*
SE		*0*	*0.44*	*0.41*	*0.44*	*0.51*	*4.34*
% SE		*0.00%*	*23.25%*	*29.65%*	*35.35%*	*40.62%*	*9.08%*

BSC – EJ MLD							
EJ-1	*9*	*21.5*	*7.75*	*7.75*	*7.75*	*7.75*	*13*
EJ-2	*9*	*3.5*	*3.5*	*28.7*	*28.7*	*28.7*	*12*
EJ-3	*9*	*11.75*	*11.75*	*11.75*	*11.75*	*21*	*5*
EJ-4	*9*	*11.75*	*11.75*	*11.75*	*11.75*	*11*	*9*
EJ-5	*9*	*10*	*2.5*	*5.5*	*1*	*32*	*32*
EJ-6	*9*	*60*	*60*	*3.5*	*-*	*-*	*-*
EJ-7	*9*	*6.5*	*2.5*	*2.5*	*2.5*	*2.5*	*50*
EJ-8	*9*	*6*	*8*	*17.25*	*17.25*	*11.5*	*11.5*
EJ-9	*9*	*7*	*9*	*7.3*	*7.3*	*7.3*	*44*
EJ-10	*9*	*2.3*	*0.9*	*0.9*	*0.9*	*0.9*	*0.9*
EJ-11	*9*	*4.8*	*2.35*	*2.35*	*6*	*-*	*-*
EJ-12	*9*	*4.75*	*4.75*	*4.75*	*4.75*	*-*	*-*
EJ-13	*9*	*2.25*	*2.25*	*2.25*	*2.25*	*7*	*-*
Mean time in state	***9***	***11.70***	***9.77***	***8.17***	***8.49***	***12.97***	***19.71***
SD	*-*	*14.82*	*14.93*	*7.47*	*7.73*	*10.15*	*16.71*
SE	*-*	*4.28*	*4.31*	*2.16*	*2.33*	*3.38*	*5.57*
% SE	*-*	*36.56%*	*44.13%*	*26.38%*	*27.45%*	*26.10%*	*28.27%*

Footnotes: **Cannot quantify based on available data, so set the same as arsa-cel and OSR-TIGET natural history*

Abbreviations: *BSC: best supportive care; EJ: early-juvenile; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; LI: late infantile; MLD: metachromatic leukodystrophy; OSR-TIGET: Ospedale San Raffaele – Telethon Institute for Gene Therapy; SD: standard deviation; SE: standard error.*

Review Group's response:

The Review Group acknowledges the Applicant's response.

6. Please provide appropriate measures of uncertainty (standard errors, 95% CI) for all 'mean time to transition' and progression modifier estimates from OSR-TIGET and AA clinical study data.

Applicant's response:

In the final submission, Orchard intentionally retained the progression modifiers from the March 2018 data cut as they were more conservative than the calculations based on the updated data cut, these data including appropriate measure of uncertainty are presented in Table below and can be found on the "Clinical Trial Data" worksheet in the model. The progression modifiers calculated from the updated December 2019 data cut are presented below in Table below and have been used in the alternative base case to fulfil the request from the Review Group to use the latest available data for arsa-cel in the economic model. These data can also be found in the model on the "Alternative PM Calculations" worksheet with updated cells highlighted in yellow.

Table 53. Mean time to transition and progression modifiers calculated from the March 2018 data cut

Pooled (LI+EJ) NHx Data

Time to transition between GMFC-MLD states	Mean	SD	n
from 0 to 1	N/A	N/A	0
from 1 to 2	12.3	9.48	17
from 2 to 3	3.72		
from 3 to 4	3.72		
from 4 to 5	3.72		
from 5 to 6	17.53	17.22	16
from 6 to death	57.13	36.86	15
Time from GMFC-MLD 2 to 5	11.2	7.82	12
Pooled (LI+EJ) OTL-200 Data (Partial Responders)			
Time to transition between GMFC-MLD states	**Mean**	**SD**	**n**
from 0 to 1	41.46		4
from 1 to 2	17.46	14.88	5
from 2 to 3	12.57		
from 3 to 4	12.57		
from 4 to 5	12.57		
from 5 to 6	N/A	N/A	0
from 6 to death	N/A	N/A	0
from 2 to 5	37.72086	18.98	7
Resulting arsa-cel progression modifier model inputs			
Mean time to transition	**Avg. Time (months)**		
BSC from GMFC-MLD 2 to GMFC-MLD 5 (Pooled)	11.2		
OTL-200 from GMFC-MLD 2 to GMFC-MLD 5 (Pooled)	37.7		
	Mean	**SD**	**SE**	**% SE**
Progression Modifier (GMFC-MLD 2–5)	3.4	2.4	0.557	16.47
Mean time to transition	**Avg. Time (months)**		
BSC from GMFC-MLD 1 to GMFC-MLD 2 (Pooled)	12.3		
OTL-200 from GMFC-MLD 1 to GMFC-MLD 2 (Pooled)	17.5		
	Mean	**SD**	**SE**	**% SE**
Progression Modifier (GMFC-MLD 1–2)	1.4	1.6	0.335	23.60

Table 54. Mean time to transition and progression modifiers calculated from the December 2019 updated data cut

Pooled (LI+EJ) NHx Data			
Time to transition between GMFC-MLD states	**Mean**	**SD**	**N**
from 0 to 1	N/A	N/A	0
from 1 to 2	12.3	9.48	17

from 2 to 3	*3.72*		
from 3 to 4	*3.72*		
from 4 to 5	*3.72*		
from 5 to 6	*17.53*	*17.22*	*16*
from 6 to death	*57.13*	*36.86*	*15*
Time from GMFC-MLD 2 to 5	*11.2*	*7.82*	*12*
Pooled (LI+EJ) OTL-200 Data (Partial Responders)			
Time to transition between GMFC-MLD states	***Mean***	***SD***	***n***
from 0 to 1	*41.4*	*21.34*	*4*
from 1 to 2	*20.1*	*16.78*	*7*
from 2 to 3	*15.34*		
from 3 to 4	*15.34*		
from 4 to 5	*15.34*		
from 5 to 6	*N/A*	*N/A*	*0*
from 6 to death	*N/A*	*N/A*	*0*
from 2 to 5	*46.0*	*24.37*	*8*

Resulting arsa-cel progression modifier model inputs					
Mean time to transition		***Avg. Time (months)***			
BSC from GMFC-MLD 2 to GMFC-MLD 5 (Pooled)		*11.2*			
OTL-200 from GMFC-MLD 2 to GMFC-MLD 5 (Pooled)		*46.0*			
		Mean	***SD***	***SE***	***% SE***
Progression Modifier (GMFC-MLD2–5)		*4.1*	*3.1*	*0.697*	*16.09*
Mean time to transition		***Avg. Time (months)***			
BSC from GMFC-MLD 1 to GMFC-MLD 2 (Pooled)		*12.3*			
OTL-200 from GMFC-MLD 1 to GMFC-MLD 2 (Pooled)		*20.1*			
		Mean	***SD***	***SE***	***% SE***
Progression Modifier (GMFC-MLD 1–2)		*1.6*	*1.77*	*0.361*	*22.13*

Abbreviations: *BSC: best supportive care; EJ: early juvenile; GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; LI: late infantile; NHx: natural history study; SD: standard deviation; SE: standard error.*

Review Group's response:

The Review Group acknowledges the Applicant's response. The report has been updated to include the updated progression modifier data (Section 2.1). A scenario has also been presented in the Results section, which evaluates the impact of switching from the progression modifiers derived in 2019 to those derived in 2018.

7. The population subgroup proportions (PS LI, PS EJ, ES EJ) are based on published data and are therefore not considered AIC.

Applicant's response:

Orchard would like to express apologies for any confusion, the population subgroup proportions for Ireland are based on the published information in the Evidence Review Group report as part of the UK NICE HST appraisal of arsa-cel. For Belgium and the Netherlands, Orchard agrees with the Review Group that the proportion of LI and EJ MLD patients are published in Beerepoot et al 2020;(2) however the proportion of LI patients that would be pre-symptomatic, and therefore eligible for treatment with arsa-cel, and the proportion of EJ patients that would be pre-symptomatic or very early symptomatic and again eligible for treatment, were based on unpublished clinical opinion from Dr Servais in Belgium and Dr Wolfe in the Netherlands. However, Orchard agrees for this information to not be academic in confidence (AIC).

Review Group's response:

The Review Group acknowledges the Applicant's response. No changes to the report are required.

8. Please ensure the probabilistic sensitivity analyses are informed by standard errors calculated for response proportions, mean time to transition, and progression modifiers estimates using the same source data that informed these model inputs.

Applicant's response:

The updated probabilistic sensitivity analyses (PSAs) for the combined cohort and the MLD sub-groups are presented in the Results section. The standard errors for the following variables have all been calculated from the same data source that informed these model inputs i.e., the clinical data, and therefore better capture the uncertainty in these inputs compared to the arbitrary ±20% estimated standard error:

a) Percentage of full responders

b) Percentage of partial stabilisers – please note in cases where the number of partial responders stabilizing was 0%, a default SE value of 20% was used as it would have no impact

c) Updated progression modifiers – please note in cases where the progression modifier was 1 (e.g., the transition from GMFC-MLD 5 to GMFC-MLD 6), the SE value was set to 20% because this progression modifier was derived from clinical expert advice obtained in the structured expert elicitation (SEE) rather than data, because no arsa-cel treated patients have progressed beyond GMFC-MLD 5

d) Mean time to transition between each state

e) Percentage of patients in the cognitive sub-states

Review Group's response:

The Review Group acknowledges the response. To avoid duplication, see response to Q32.

9. The applicant assumes that mortality related to MLD will only occur from the worst motor function health state, but because of the fact there are cycles of 1 month, this means that for patients being in the best health state ,the earliest chance to die is after a half year (40% PS LI, 75% PS-EJ and ES-EJ 0 %). The company is asked to demonstrate if this is clinically valid/plausible?

Applicant response:

Orchard is unsure whether the Review Group is implying that 6 months is too early to progress from the best health state to death, or whether the one-month cycles limit the chance a patient could die earlier . However, the company can provide some detailed information around the likelihood of death six months after being in the best health state (GMFC-MLD 0) predicted from the model and compare this to the age of death reported in the literature. This should demonstrate that the modelling assumptions for death are clinically valid and plausible, and the probability of death that the model predicts aligns with the clinical data. During model development, care was taken to ensure internal validity of the model predictions versus the observed data measured in the clinical trials.

Firstly, the assumption that mortality related to MLD will only occur from the worst health state was informed by multiple clinical experts experienced in the management of MLD (see clinical expert details during model development in Appendix 12.1.1 of the final submission). Also, it is worth noting that there is an additional mortality risk included in the modelling as a consequence of MLD-related neurodisability i.e., because a patient is bedridden they are more susceptible to life threatening infections like pneumonia. This functionality was added to capture the fact that gene therapy patients have much longer resident time in GMFC-MLD states than NHx patients.

In a long-term follow-up study of 45 MLD patients, Fumagalli et al found that the median time from onset of symptoms in years for OS in LI MLD patients was between 8.42 (non-ambulant) and 9.17 (ambulant).15 The age of onset for LI patients in the Fumagalli study ranged from < 15 months (n=13) to n=6 around 18 months, and n=5 around 24 months. Therefore, the age of LI patients where 50% survived ranges approximately between 9 years and 11 years old. In the economic model, 50% survival for LI patients is estimated at 126 months of age i.e., 10.5 years old, which aligns with the data from Fumagalli et al.15

Finally, if we look at the probability of being dead 6 months after being in the best health state for LI patients in the economic model, the probability of being dead is only 0.0293%. Therefore, whilst the earliest chance to die after being in the best health state could occur within 6 months based on the monthly cycles, the probability is extremely low, and comparison of the

predicted data vs. published literature supports the modelling of MLD-related death. Similar results have been observed for the EJ cohort and were presented in Table 63 of the final submission.

Review Group's response:

The Review Group had questioned the clinical plausibility of limiting survival to a minimum of six months, and if, in reality, patients may die before this. Data from the observational study cited here relates to median survival from time of symptom onset, but does not describe the distribution of these data. Therefore, the Review Group remain unable to conclude as to the clinical plausibility of this assumption.

10. The model assumes most patients are stable partial responders to the intervention, without further progression to the worst health state or dying because of MLD. The company is asked to demonstrate this is clinically valid/plausible, and patients won't be dying earlier in the MLD-evolution?

Applicant response:

Orchard considers that the data to date in combination with the underlying biological mechanism of action of arsa-cel, means that the assumption of stabilisation in partial responders is clinically valid, logical and plausible. First, none of the patients in the clinical trials who fulfil the eligibility criteria for arsa-cel have died from MLD disease progression or progressed to the worst health state (with up to 8 years of follow-up currently available). One death in a PS-EJ patient was due to cerebral ischaemia unrelated to the disease or arsa-cel (patient was in GMFC-MLD 0 prior to death).

In addition, as discussed in Section 2.2 above looking at the long-term stabilisation, long-term data from mucopolysaccharidosis type I (MPS 1; Hurlers' syndrome) patients treated with HSCT show that disease stabilises after an initial period of decline and that the decline will occur early on if it's going to happen . Similarly, for MLD patients treated with arsa-cel, there is a degree of variability amongst patients as to when the gene therapy will have its full effect i.e., it is dependent on the amount of sulphatide accumulation at time of treatment and how long it takes the newly restored ARSA enzyme to break down this accumulation. Consequently, for partial responders there will be some level of treatment effect during the period of repopulation of tissues and cross correction (see Table 12), enough to halt or slow down disease depending on the level of damage already present, which is why in some patients there is an initial decline in clinical outcomes post gene therapy up to 2 years , but then once the sulphatide accumulation has been broken down, these patients remain stable at that state across multiple outcome measures (see Figure 6).

For example, patient MLD-01 experienced an increase in MRI from 0 to 4.0 in the first 2 years post gene therapy showing an initial progression during the repopulation phase, such that at first recordable GMFC-MLD visit at 6 months the patient was in GMFC-MLD 2, but this patient has remained at this GMFC-MLD level with the same MRI score, and stable DQ and GMFM scores, 8 years post gene therapy.

Table 55: Three stage mechanism of action of arsa-cel

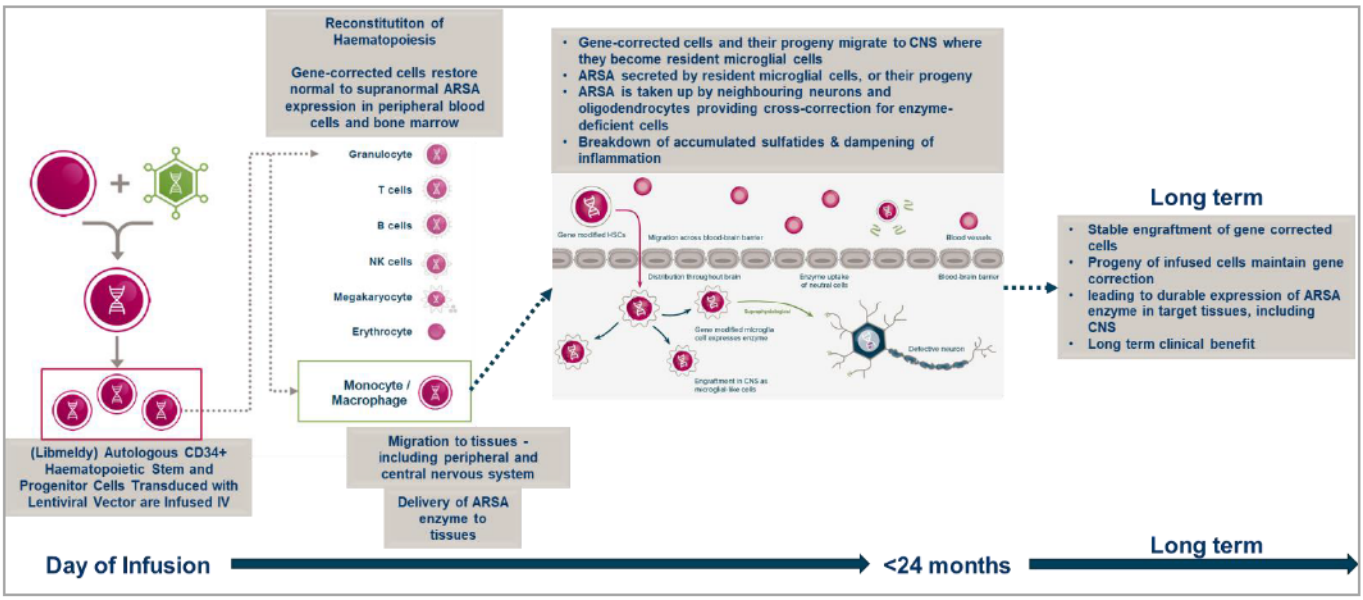
	Stage 1: Peripheral engraftment and reconstitution of BM	***Stage 2: Repopulation of the tissues and cross-correction***	***Stage 3: Long term***
Process	***Engraftment:*** *Following myeloablation, the gene-corrected stem cells migrate to and engraft in the BM.* ***Reconstitution****: Following engraftment reconstitution of the patient's haematopoietic and immune system occurs as evidenced by ANC ≥500/µL.*	***Repopulation:*** *Progenies of the gene corrected stem cells migrate to multiple tissues, including the brain, where they become resident and deliver ARSA enzyme.* ***Cross-correction:*** *ARSA secreted by gene-corrected cells is taken up by neighbouring neurons and oligodendrocytes providing cross-correction for enzyme-deficient cells. Depending on the level of cell damage present, it may take up to 24 months for the ARSA enzyme to breakdown already accumulated sulfatides and halt the inflammatory processes that causes cell damage.*	*The gene corrected stem cell progenies that have become resident in the brain compartment and other tissues are stably engrafted. Gene correction is maintained. These cells continue to durably produce and secrete ARSA enzyme, preventing further sulfatide accumulation and cell damage.*
Duration	*0 – 3 months*	*0 – 24 months*	*24 months onwards*
Biological markers	*PBMC ARSA and VCN*	*PBMC ARSA and VCN*	*Clinical outcomes*
Therapeutic effect	***No overt impact on disease course is expected at this stage.*** ***However, lack of successful engraftment would result in treatment failure.***	***Treatment effect starts to become apparent.*** ***It may take up to 24 months for the full effect of the drug to become apparent.***	***Depending on the stage in the disease course that treatment took place, treatment would slow or stop disease progression.***

Abbreviations: ARSA: arylsulfatase A; BM: bone marrow; PBMC: peripheral blood mononuclear cells VCN: vector copy number.

As Table 12 above highlights, autologous stem cells and progenitors are able to cross the blood brain barrier and produce progeny with the corrected gene for ARSA production. There is no evidence to support loss of engraftment or stabilisation based on the MoA of arsa-cel and available follow up data. Therefore, it is clinically valid and plausible that most stable partial responders have disease stabilisation without progression to GMFC-MLD 6 or dying.

Figure 9: Schematic of the MoA of arsa-cel

Abbreviations: ARSA: arylsulfatase A; CNS: central nervous system; NK cells: natural killer cells.



Review Group's response:

Here, the Review Group requested clarification on the clinical plausibility of the assumptions used to inform the model structure (i.e. as patients can only transition to death from the GMFC-MLD 6 state, it is implicitly assumed that patients cannot die earlier in the MLD evolution). The plausibility of the assumptions regarding the long-term durability of treatment effect are addressed separately (reference where/question).

It is acknowledged that general population mortality has been applied to health states other than GMFC-MLD 6, and that a GMFC-MLD state-dependent multiplier has been applied to the general population mortality rate to model the impact of neurologic disability on survival. However, the applicability of the data used to inform this multiplier to MLD is uncertain.

The Review Group is unsure as to the applicability of data from patients with mucopolysaccharidosis type I (Hurler's syndrome), who are treated with HSCT, to the question posed here.

11. The company is asked to provide an updated analysis in which all EJ patients are compared with HSCT (instead of only 10% in the actual model).

Applicant's response:

Firstly, for clarification, in the model for the PS-EJ cohort, arsa-cel is compared to 100% of patients treated with HSCT. It is the ES-EJ population where it is a blend of 90% BSC and 10% HSCT, the rationale for this assumption is discussed below.

The company sought clinical advice to estimate the proportion of eligible patients that would be treated with HSCT from the Dutch clinical expert. The expert indicated that in a world without gene therapy, they would treat 100% of PS-EJ patients with HSCT. However, for their ES-EJ patients, Dr Wolf indicated that even in a world without gene therapy, she would only treat 10% of them because in the clinical team's experience for the majority of these patients who are treated with HSCT, the prognosis is poor as "they are just too late at diagnosis " for HSCT to have an effect. The fact that in the 20 years of data collection in the MLDi registry, only two ES EJ patients have been treated with HSCT confirms this. It is highly likely that the reduced proportion (i.e. the estimated 10% who would be treated with HSCT) is due to (i) the difficulties in identifying a suitable donor within the very limited period ES EJ patients have to be treated; and (ii) even when finding a suitable donor, the slower onset of action of HSCT (discussed in Section ***Fout! Verwijzingsbron niet gevonden.****) may make the clinical expert u nlikely to treat the ES EJ patients unless the patients symptoms are at a very early stage; whereas because arsa-cel is able to generate supra-physiological levels of ARSA and the speed of repopulation of the brain compartment is quicker, this may allow a slightly wider window of treatment for patients.*

Nevertheless, as requested by the Review Group, Orchard has presented a scenario analysis with differing proportions of ES EJ patients treated with HSCT. Rather than provide an implausible scenario where all EJ patients are treated with HSCT, which does not align with the clinical opinion the company received, please see ***Fout! Verwijzingsbron niet gevonden.*** *i n Section 5.3.2.1 for the scenario analysis in which the proportion of ES EJ patients treated with HSCT is varied from 10% in the base case to 30% and 50% to assess the impact of this uncertainty on the ICER (keeping the 100% comparison for the PS EJ cohort) for the Netherlands only.*

Review Group's response:

The Review Group acknowledges the clarification. The use of HSCT has been removed from the base case for The Netherlands, and is presented now as a scenario analysis.

12. The company is asked to provide clinical data for the 67% GVHD used in the model?

Applicant's response:

Orchard would like to clarify that the 67% refers to an episode of acute GvHD, which has to occur within 100 days of treatment and is grouped in the costs for HSCT adverse events. Chronic GvHD is included under chronic complication costs and was modelled to occur in 23% of patients, based on cGVHD data from the MLDi registry and supported by published literature. The MLDi registry did not report any data for the occurrence of acute GvHD, therefore the 67% was taken from the supplementary file attached to the Groeschel et al 2016 study.In this paper, 6 of the 24 MLD patients treated with HSCT fulfilled the same eligibility criteria that would apply to arsa-cel– i.e., either having PS-EJ disease or early symptomatic EJ disease (GMFC-MLD $\leq$1) at time of treatment. Of these 6 patients, 4 experienced acute GvHD - 3 had I^o disease, and 1 patient had II^o disease (4/6 = 67%).

Review Group's response:

The Review Group acknowledges the clarification.

13. A model using a Human Capital approach can only be a scenario analysis, but the base case analysis should be using a Friction cost method.

Applicant's response:

Orchard understands that the Friction Cost method is the preferred approach for NL, however given the age at which patients with MLD are treated (between 0 months and ≤ 6 years old), there is going to be zero productivity gains as a result of treating patients with arsa-cel. Whilst Orchard recognises this is the preferred methodology, the company considers that paediatric treatments are unfairly penalised as a consequence of this. The fact that arsa-cel has the ability to enable patients to reach the age of employment and contribute to society, when previously these patients would either be dead or in a vegetative state, should be taken into account when considering the cost-effectiveness of arsa-cel.

However, as requested by the Review Group, the base case for NL has been updated to include the Friction Cost method and the Human Capital Approach is included as a scenario analysis instead (see Section 5.2.3.2). Orchard would also like to request that when reporting the outcome of the base case, that it is explicitly mentioned that the friction cost method was applied and thus no productivity gains at all are considered when evaluating the value of arsa-cel.

Review Group's response:

The Review Group have updated the report to reflect the response.

14. For the Netherlands, income loss of the family it is preferred to use the standard method of ZIN, estimating the informal care costs. These costs are estimated by assumed number of hours of caregiving per day or per week multiplied by the standard Dutch tariff for informal caregiving (€14 per hour in 2014, Dutch Kostenhandleiding).

Applicant's response:

Orchard acknowledges that ZIN's preferred method to calculate loss of family income is to estimate the number of hours of caregiving per day or per week multiplied by the standard

Dutch tariff for informal caregiving, it has therefore amended the base case accordingly (see Table below).

It is worth noting that due to the age of the patients being cared for – LI patients and EJ, there will be a degree of necessary caregiving associated with the child's age irrespective of whether they have MLD or not. For example, one would expect to spend at least 14–16 hours per day caring for a <6-month-old baby irrespective of whether they had an illness. One of the benefits of the caregiver survey in relation to loss of income was that it specifically asked about work and losing income as a result of caring for someone with MLD. This meant it was possible to calculate loss of income for carers in full time employment, as well as part time workers and the unemployed, so that only respondents who that felt they had lost a significant amount of income because of being a carer were included. Consequently, whilst the base case analyses use the informal care costs to calculate loss of family income, a scenario analysis is presented in Section 5.2.3.2 using the Caregiver Survey as the source for lost family income.

To calculate the informal care costs necessary for this approach, the average number of total hours per day spent caregiving were collected from respondents from the MLD caregiver survey and are presented in Table . Note, the reason the number of caregiving hours per day are so high is partly due to the age of the patients being cared for and also because from GMFC-MLD 4 onwards, patients need night-time supervision to prevent choking – so care almost becomes almost 24 hours per day in the later stages of disease. The standard Dutch tariff for informal caregiving, which was €14 per hour in 2014, updated to June 2021, is €15,45 per hour. The costs have been inflated to June 2021, as this was the Consumer Price Index (CPI) used in the final dossier. The annual costs related to informal care are also presented in Table by GMFC-MLD health state groupings of mild (GMFC-MLD 1 and 2), moderate (GMFC-MLD 3 and 4) and severe disease (GMFC-MLD 5 and 6) as was done for the base case calculations. No informal caregiving costs were assumed for patients in GMFC-MLD 0.

As can be seen from the table, loss of family income using the informal care cost method generates far higher annual costs then the method employed in the final submission. As previously mentioned, this is most likely due to the age of the patients being cared for, the need to have 24 hr supervision from GMFC-MLD 4 onwards, and the fact that all caregiving hours are included and not just those for carers who have forgone work to care for a patient with MLD.

Table 56: Informal care costs derived from the caregiver survey using the Dutch tariff for informal caregiving

Health state	***Average number of hours spent caregiving/day***	***Costs related to informal care per day***	***Annual costs related to informal care* (base case)***	***Annual costs related to informal care** (scenario analysis)***
GMFC-MLD 1 & 2	*15.57*	*€240.50*	*€ 61,328*	*€ 87,783*
GMFC-MLD 3 & 4	*21.48*	*€331.79*	*€ 84,606*	*€ 121,103*
GMFC-MLD 5 & 6	*21.71*	*€335.34*	*€ 85,512*	*€ 122,399*

Footnotes: ** This has been calculated by multiplying the daily cost by 255, the number of working days in 2021 to make it comparable to the original calculation.*
*** This has been calculated by multiplying the daily cost by 365 as carers perform their task every day.*
Abbreviations: *GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy.*

In Section ***Fout! Verwijzingsbron niet gevonden.*** *detailing the alternative base case results, t he impact of the changes requested by the Review Group to the original base case ICERs are*

presented in a stepwise manner to the alternative base case results to ensure the Review Group has visibility of the changes made to the model. A comparison of the loss of family income parameter inputs used in the original base case values and the alternative base case values are presented in Table below.

Table 57: Original base case values versus updated base case values for loss of family income by GMFC-MLD health state for the Netherlands only

Parameter	***Original Base case parameter values***	***Updated base case parameter values***	
		255 working days	***365 days***
Loss of family income	*GMFC-MLD 1 & 2 = €638*	*GMFC-MLD 1 &2 = €61,328*	*GMFC-MLD 1 & 2 = €87,783*
	GMFC-MLD 3 & 4 = €16,299	*GMFC-MLD 3 & 4 = €84,606*	*GMFC-MLD 3 & 4 = €121,103*
	GMFC-MLD 5 & 6 = €31,698	*GMFC-MLD 5 & 6 = €85,512*	*GMFC-MLD 5 & 6 = €122,399*

Abbreviations: *GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy*

Review Group's response:

The Review Group acknowlege the amended base case, and have updated the Section 4.3 'Health state, adverse events and other costs'.

Cost inputs

15. Please apply the below suggested cost parameters in the BE model, in lieu of those chosen for the model base case.

Parameter	***Value (€)***	***Ref***	***Comment***
Hospitalisation cost/day – Acute hospital	*578.05*		*Nomenclature code 350313 used incorrectly, instead of mean hospitalisation cost*
Neuromuscular lump sum	*8,989.98*		*Annual cost including drugs, material, nursing for patients in home care and in a vegetative state*
Consultation/uptake emergency room care	*578.05*		*Nomenclature code 350313 used incorrectly, instead of mean hospitalisation cost*
Removal of submandibular salivary gland	*214*	*255533*	
Cost of Botox	*1.7164*		*Cost per unit Botox, 1 bottle contains 100 units*

Healthcare equipment	*8,989.98*		*Annual cost including drugs, material, nursing for patients in home care and in a vegetative state*
Palliative care	*610.99*		*Daily cost*
Leukapharesis	*1,307.11*	*470536*	*470956 is incorrect code, refers to plasmapheresis*
Conditioning regimen	*30,347.62*		*(52.5 days * 578.05)*
HSCTx	*2,487.42*	*470632*	
Busulfan	*3,996*		
Total for conditioning	*36,831.04*		*Sum of conditioning regimen+HSCTx+busulfan*
Rituximab	*159.74*		*per 100mg vial*
Follow-up for HSCT			*the applied cost of €20,131 annually based on liver transplant seems high, a specialist consultation costs ~€38.35 per consultation, plus extra costs of bloods, medical exam etc.*
Paediatrician visit	*38.35*		*Cost for a specialist consultation*

Review Group's response:

The Review Group acknowledge the updated cost parameters. The report has been updaed to reflect the response.

16. Please apply the below specified costs for NE model, in lieu of the costs applied in the submitted model.

Parameter name	***Suggested reference***	***Cost***
MLD-related acute event	*Hakkaart-van Roijen, Leona, et al. "Kostenhandleiding." Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie (2015)*	*259 (to be inflated to 2021 costs)*
Adaptable bed with anti-decubitus mattress		*710*
Enteral feeding pump		*264*
Graft vs Host Disease Episode (acute) (applied within one model cycle post-HSCT)	*please detail how the applied cost of €9,699 was derived*	*NA*
IVIG cost	*please provide product code used to price this product*	*NA*
Chronic GvHD and Immunological complications	*please detail how the applied cost of €6,579 was derived*	*NA*

Review Group's response:

The Review Group acknowledge the updated cost parameters, and the additional clarifications provided. The report has been updated to reflect the response.

17. Administration and hospitalisation costs are important costs in the model, and a component of the overall treatment cost. There is no consideration in the model of a scenario where a patient may undergo leukapheresis and manufacture of AA, but then not receive treatment due to clinical deterioration. **Please provide a scenario in the model considering this possibility.**

Applicant's response:

Orchard can understand the Review Group's concern should this scenario occur in clinical practice. However, the company would like to reassure the assessors that should such a scenario occur, Orchard would absorb the cost for the manufacture of arsa-cel. Indeed, the supply agreement with the qualified treatment centre (QTC) in Utrecht is very specific in this regard. However, the cost of leukapheresis would still be incurred by the health system. Therefore, a scenario has been provided in Section 5.2.3.1 where for the arsa-cel treatment arm the cost of leukapheresis only has been included and then patients are assumed to accrue all the costs and outcomes for BSC. As expected, given that the health outcomes accrued between the two arms would be the same (i.e. both arms follow natural history as no treatment is given), but there are greater costs in the arsa-cel arm due to the cost of leukapheresis, this scenario is not cost-effective.

Orchard would also like to highlight that the probability of this scenario occurring is extremely low and so the ICERs are highly implausible. Patients are rigorously assessed for treatment eligibility at multiple points during the patient journey (i.e., at baseline, before cellular harvest and then prior to conditioning by clinical experts at one of the five QTCs), and the decision whether to treat patients or not is only made by the expert at the QTC together with input from colleagues, all of whom are provided with regular training including the specifics of the eligibility criteria. Therefore, should a patient show any signs of deterioration in motor or cognitive function between baseline assessment and just prior to cellular harvest, treatment would not go ahead, even if that involved having the difficult conversation with the family and incurring an irrecoverable cost to Orchard.

Review Group's response:

The Applicant provided a scenario where the AA treatment arm were assumed to accrue the costs associated with leukopharesis, and subsequently accrue all costs and outcomes for BSC. The Review Group have described the analysis in the Results section of the report.

18. Please justify the use of US and UK data sources when estimating productivity costs for the Dutch population.

Applicant's response:

Orchard can confirm that US and UK data sources were not used to estimate productivity costs for the Dutch population. It is true that in the concept dossier these data sources were used, but for the final submission Orchard sourced Dutch data as requested by the BeNeLuxa Review Group. If the Review Group go to Page 314 of the final submission it explicitly states that, "In the Human Capital approach, potential educational achievement for the Dutch population was used in combination with the Dutch median annual earnings, based on educational attainment, to determine the median annual earnings per patient." Further, Table 86 shows the median annual earnings for specific levels of Dutch education system sourced from StatLine.

Review Group's response:

The Review Group acknowledges the clarification. No changes to the report are required.

19. Please identify the precise reference used to calculate the average NL salary? Please also explain the derivation of the figures applied in the CEM for NL, Sheet 'FamilyCosts', H35:H41, showing calculations.

Applicant's response:

The reference used to calculate the average NL salary is from Statline, the Netherlands data portal: Beroeps- en niet-beroepsbevolking; gemiddeld inkomen en arbeidspositie. Available at: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83687NED/table?ts=1627053725791".
*The calculations for the average salary are derived from the 2019 updated costs for the female and male annual wage from Statline (€43,410 + €27,120)/2 = €35,265. Inflating the 2019 median annual earnings to 2021 prices using the CPI multiplier from https://opendata.cbs.nl/statline/#/CBS/en/dataset/83131ENG/table?fromstatweb) gives the following calculation €35,265*1.026= €36,165.*

With regards to the derivation of the figures applied in the model for the Netherlands on sheet 'FamilyCosts', H35:H41, a thorough explanation of these figures and how they were calculated can be found on page 311–312 of the final submission. In order to calculate loss of family income as a result of caring for patients with MLD, an analysis of the MLD caregiver survey was performed.33 Based on a ranking system, where 1 = no problem and 5 = significant difficulty (for the following symptoms: walking/crawling; breathing; general loss of motor skills; seizures; swallowing; hearing; vision; pain and discomfort; trouble with speech; and gait spasticity), patients with MLD were assigned a mild (GMFC-MLD 1 and 2; n=2), moderate (GMFC-MLD 3 and 4, n=17) or severe GMFC-MLD state (GMFC-MLD 5 and 6; n=3). The caregiver survey collected data specifically related to work and consequently it was possible to calculate loss of family income due to caring for a patient with MLD using the average annual salary for the Netherlands described above. The following criteria were applied to calculate loss of income for full time, part-time and unemployed caregivers:

For caregivers who were in full time employment, data for the number of days of work missed in the preceding 12 months were summed, and loss of earnings for any workdays missed that were unpaid were included (€142/day – which is calculated from the 2021 median annual salary divided by the number of working days in 2021 - €36,165/255 working days). For example, one carer of a patient in GMFC-MLD 3/4 missed 25 days of work in the preceding 12 months, of which 50% of those days were unpaid. Therefore, to calculate the individual loss of income for this carer the calculation would be (€36,165/255)(25*50%) = €1,773.*

For all caregivers who were part-time and answered 'yes' that they had forgone a significant amount of income due to caring for a patient with MLD, it has been assumed that they lost half of the average annual income due to being part-time rather than full-time in addition to any missed unpaid days of work. For any respondent who answered 'no', i.e. they did not lose a significant income due to MLD, then only workdays missed that were unpaid were included. For example, a carer of a GMFC-MLD 3/4 patient who answered yes to foregoing a significant amount of income as a result of caring for a patient with MLD also missed 6 days of work in the preceding 12 months that were all unpaid. Therefore, to calculate the individual loss of income for this carer the calculation would be (€36,165/2) + (€36,165/255)(6*100%) = €18,933.*

Finally, for all caregivers that were unemployed and answered 'yes' that they had forgone a significant amount of income due to MLD, it has been assumed that loss of earnings were equivalent to the median annual income in the Netherlands. For any respondent who answered 'no', i.e. that they did not lose a significant income due to MLD, loss of earnings was set to zero. Any respondent who did not answer the significant income forgone question was excluded from the analysis.

Once all the individual carer loss of earnings were calculated, the mean annual loss of earnings for carers of MLD patients in the mild (GMFC-MLD 1 and 2), moderate (GMFC-MLD 3 and 4) and severe GMFC-MLD (GMFC-MLD 5 and 6) health states were calculated, which are the inputs in H35:H41 in the "FamilyCosts" sheet in the economic model.

Orchard acknowledges that ZIN's preferred method to calculate loss of family income is to estimate the number of hours of caregiving per day or per week multiplied by the standard Dutch tariff for informal caregiving (see Q14), due to the age of the patients being cared for (LI patients and EJ), there will be a degree of necessary caregiving associated with the child's age irrespective of whether they have MLD or not. This is why the caregiver survey specifically asked about work and losing income as a result of caring for someone with MLD; so that only respondents that felt they had lost a significant amount of income because of being a carer were included. The caregiver survey as a source for lost family income has been included as a scenario analysis in Section 5.2.3.

Review Group's response:

Additional clarification was provided and is acknowledged by the Review Group.

20. Please ensure that future unrelated medical costs are only included as a scenario analysis for the model for the Netherlands, not included in the base case.

Applicant's response:

Orchard can confirm that future unrelated medical costs were only included as a scenario analysis in the final submission to Beneluxa and were not in the base case. The company would like to draw attention to page 375 of the final submission which specifically states, "The base case societal perspective for the Netherlands does not include the Practical Application to Include Future Disease Costs (PAID) data, and the template for the Beneluxa submission requested a scenario analysis where these data are included." Furthermore, in Table 122 showing the results from the Scenario analyses for the Netherlands, the Review Group can see that inclusion of the future unrelated medical costs increases the ICER for arsa-cel versus BSC by approximately €4,000/quality-adjusted life year (QALY) gained.

Review Group's response:

The Review Group acknowledges the clarification. No changes to the report are required. The scenario is reported in the Results section.

21. Administration costs should also include cost for any expenses incurred to obtain treatment in a center in another country (given the limited number of treatment centers). All costs covered by the health insurance should be taken into account.

Applicant's response:

The costs associated with the administration of arsa-cel for the Belgian and Irish analyses have been updated to include the expenses incurred to obtain treatment in another country. No additional costs have been assumed for the Netherlands CE analyses. For Belgium, whilst it is likely that patients from Belgium would probably drive to Amsterdam (distance from Brussels to Utrecht is 175km), the mean cost for a flight to either Amsterdam or Paris for the patient and one carer have been added to the treatment. For the Irish analyses, the average cost of a flight from Dublin to Manchester for the patient and one carer has been added to the administration costs.

*There are four daily direct flights with Koninklijke Luchtvaart Maatschappi (KLM) from Brussels to Amsterdam ranging from €171 to €408 per person for a return trip. There are two direct flights from Brussels to Paris with Brussels Airlines at a cost of €241 for a round trip.34 Therefore, an additional average cost to travel from Belgium to the Netherlands of €546.67 has been added to the treatment costs for the Belgian cost-effectiveness analysis (average of €171, €408, €241 * 2 persons).*

*Both Ryanair and Aer Lingus fly directly from Dublin to Manchester and a round trip ranges from €29 to €157.34 Therefore, an average cost of €186 has been added to the treatment cost for the Irish cost-effectiveness analysis (average of €29, €157 * 2 persons).*

With regards to the cost of accommodation for the parent/carer accompanying the patient receiving treatment, neither Belgium or Ireland reimburse this cost according to local guidelines . For Ireland, the NCPE request that the cost perspective taken is that of the Health Service Executive (HSE). For patients to receive a treatment abroad, that is not available in Ireland but is approved by Irish authorities (as would be the case for arsa-cel), the HSE have the Treatment Abroad Scheme (TAS).35 The associated travel policy for E112 applicants (dated Nov 2021; applicable to patients travelling to the UK, post 2020) states that:36

- *The HSE and specifically the TAS may provide assistance towards reasonable economic air or sea travel fares for patients, and a travelling companion where appropriate.*

- *Where the patient is under the age of 18, the air or sea fares of two accompanying adults will also be provided, subject to available funding.*

- *The air or sea fares covered are restricted to the cost of the airline or ferry ticket charge and the government and airport/sea port charges only.*

- *Other travel costs (for example luggage charges, travel agent fees, etc.) are excluded.*

Therefore, just the cost of the flights have been added to the treatment costs in the Irish cost-effectiveness analysis.

Review Group's response:

The Review Group acknowledges the response and updated treatment costs. The report has been updated to reflect the response.

22. BSC is included in all treatment arms, including the treated patients. This is not consistent with the assumption that responder patients will have a comparable health state as the general non-affected population. Please clarify.

Applicant's response:

BSC costs are linked to the GMFC-MLD health states and are therefore included in all treatment arms, but the amount of healthcare resources consumed differs depending on GMFC-MLD score. For full responders who are in GMFC-MLD 0 and have comparable health to the general non-affected population, the only cost incurred is the cost for one hospital visit annually. Whilst Orchard acknowledges these patients are normal, given the commitment the company has made to monitor these patients for at least 15 years post-gene therapy, it has been assumed that these patients will have one hospital visit per year between the ages of 0 and 18 years.

Other than this cost, full responders to arsa-cel do not incur any other costs associated with BSC and so do have comparable health to the general population.

Review Group's response:

The Review Group acknowledges the clarification. No changes to the report are required.

Utility

23. Please describe the source of the utility values applied to the juvenile GMFC MLD 5 and 6 health states (normal cognition) as these health states were not included in the utility valuation study.

Applicant's response:

The Review Group is correct, these health state descriptions were not included in the vignette study. The values were estimated from the regression analysis. Given the ordinal nature of the states and the linear relationship between cognitive and motor dysfunction severity, it was possible to estimate these values based on the trajectory of the line of best fit for the other GMFC-MLD health states with normal cognition. However, as discussed in Q3) a scenario analysis has been provided where all arsa-cel patients that are modelled to progress to GMFC-MLD 5 and 6 are assumed to have severe cognitive impairment and the utility values associated with these health states.

Review Group's response:

The Review Group acknowledges the response. Section 4.2 has been updated to reflect the response. The scenario discussed in Section 3 is addressed elsewhere in the report.

24. The TTO exercise included vignettes for health states GMFC-MLD 0 with both moderate and severe cognitive impairment. Clinical opinion suggested these were not plausible health states due to the relationship between deteriorating motor and cognitive function. Therefore, these values, for health states which clinical opinion advises do not exist, should be removed from the calculations to estimate utility values for the model. If this is not possible, then the values estimated for the GMFC-MLD 0 (normal cognition) health state should be applied for GMFC MLD stage 0 (moderate cognitive impairment) and GMFC-MLD stage 0 (severe cognitive impairment).

Applicant's response:

Orchard is surprised that clinical opinion suggested that these were not plausible health states. During model conceptualisation and development, Orchard sought the opinions of several clinical experts in the management of MLD, including a neuropsychologist.29 The experts indicated that in EJ MLD, patients could present with cognitive impairment before any signs of motor dysfunction. In Kehrer et al, of the 36 juvenile patients in the study, 6 (17%) presented exclusively with non-gross motor signs as first symptoms –presenting with behavioural and concentration problems rather than any gait disturbance.30 Orchard acknowledges, that patients may not have a GMFC-MLD score of zero and have severe cognitive impairment, which is why in the economic model 0% of patients are assumed to have a GMFC-MLD 0 score and severe cognitive impairment. However, some EJ patients will present with cognitive impairment as first symptoms as demonstrated from the NHx clinical trial data,

clinical expert opinion, and the published literature30– consequently the model assumes that 27% of patients with a GMFC-MLD 0 score will have moderate cognitive impairment and 0% will have severe cognitive impairment to accurately capture disease progression in these patients .

Review Group's response:

Clinical opinion obtained by the Dutch team from clinicians in the Netherlands indicated the following: "Based on our experience, we believe that all patients with GMFC-MLD 0 have normal cognitive functions, patients with GMFC-MLD 1 have normal or mildly impaired cognitive functions." As the Applicant declined to undertake the requested analysis, the Review Group highlight that it was not possible to explore the impact of the uncertainty associated with this assumption. Section 4.2 has been updated to reflect the response.

25. For IE, the UK EQ-5D-5L dataset has been applied to derive the rescaled health state utility values. Guidelines from the NCPE stipulate that the EQ-5D-3L dataset should be used. Please update the utility values applied in the model for IE accordingly.

Applicant's response:

Orchard expresses its apologies in that the draft manuscript developed by the PRO specialist vendor who performed the vignette study and conducted the rescaling, stated they had used the EQ-5D-5L to calculate the rescaled health state utility values. However, the vendor confirmed that this was a typo and the EQ-5D-3L set had been used. This can be verified because the worst possible health state utility value from the EQ-5D-3L UK tariff is -0.594, whereas the worst possible health state in the EQ-5D-5L UK tariff is -0.285. The utility values applied for the Irish CE model for the worst health state exceeds this value (-0.48) and therefore confirms that the rescaled utility set applied in Ireland are constrained by the correct EQ-5D dataset (see Q26 below for calculation).

Orchard has also included a scenario analysis for Ireland in Section ***Fout! Verwijzingsbron niet g evonden.*** *of this document where the utility values have been rescaled using the EQ-5D-5L UK value set from Devlin et al. (2017) to explore the impact this tariff has on the cost-effectiveness estimates of arsa-cel versus BSC, as this value set has a much lower proportion of negative health states versus the 3L and the worst possible health state possible with the 5L is less negative than the 3L. The values used in the scenario are presented in Table below.*

Table 58. Predicted TTO utility values and 95% CIs from adjusted linear regression model by GMFC score and cognition

	Normal cognition	***Moderate cognitive impairment***	***Severe cognitive impairment***
GMFC score			
0	*0.943 (0.866, 1.020)*	*0.732 (0.671, 0.794)*	*0.533 (0.471, 0.594)*
1	*0.883 (0.828, 0.938)*	*0.672 (0.621, 0.724)*	*0.473 (0.420, 0.526)*
2	*0.793 (0.733, 0.853)*	*0.582 (0.528, 0.636)*	*0.383 (0.330, 0.436)*
3	*0.464 (0.406, 0.522)*	*0.254 (0.199, 0.308)*	*0.055 (0.000, 0.109)*
4	*0.216 (0.155, 0.277)*	*0.005 (-0.050, 0.061)*	*-0.194 (-0.249, -0.139)*
5	*0.195 (0.120, 0.270)*	*-0.015 (-0.074, 0.043)*	*-0.215 (-0.274, -0.155)*

6	*0.159 (0.084, 0.234)*	*-0.052 (-0.111, 0.008)*	*-0.251 (-0.309, -0.192)*

Review Group's response:

The Review Group acknowledges the clarification. Section 4.2 has been updated to reflect the response.

26. Please provide the reference to the tariff used to rescale the utility values for NE and IE, and provide the calculations. Please clarify if the values which are rescaled are those obtained directly from the participants in the utility study, or are the values derived through the linear regression exercise (i.e. The values provided in Appendix D of the Nafees 2020 paper, or those in Table 6 of the same paper).

Applicant's response:

The answers to this question have been split into three parts:

(i) To answer the first part of the Review Group's questions, the references to the tariffs used to rescale the utility values for the Netherlands and Ireland are as follows:

- *Netherlands - Lamers LM, McDonnell J, Stalmeier PFM, et al. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ 2006;15:1121–32.*

- *UK - Dolan P. Modelling valuations for EuroQol health states. Med Care 1997; 35(11): 1095–108.*

(ii) The rescaled value sets were calculated as follows: the original TTO utility values below 0 only were rescaled by multiplying each value by the lowest possible utility according to each country-specific EQ-5D-3L value set, meaning that the resultant values do not fall below the lowest possible utility in the respective EQ-5D-3L value sets (see calculation below). The lowest possible EQ-5D-3L utility values for the UK and Netherlands according to each country-specific value set were -0.594 and -0.329, respectively (Dolan et al., 1997 & Lamers et al., 2006).

*Rescaled TTO utility value = (Original Utility Value*Country-specific EQ-5D-3L lower anchor)*

*For example, for patients in GMFC-MLD 6 with severe cognitive impairment, the original utility value was -0.8 and the rescaled value using the UK EQ-5D-3L worst possible health state of -0.594 leads to a utility value for patients in GMFC-MLD 6 with severe cognitive impairment of -0.48 (i.e., 0.8*0.594 = 0.4752).*

(iii) Orchard can confirm that the values used in the base case analyses in the economic model are the rescaled values derived through the linear regression exercise and not the rescaled values obtained directly from the participants in the utility study. The rationale for this approach is explained below in response to (Q29) and a scenario analysis has also been provided, where the mean utility values elicited from participants have been rescaled, instead of the values generated by the linear regression model.

Review Group's response:

The Review Group acknowledges the clarification. Section 4.2 has been updated to reflect the response.

27. Please review the application of caregiver disutility in the NE model, in particular the number of caregivers required for GMFC stage 3 and 4, as the assumptions are different to those applied for BE and IE.

Applicant's response:

The application of caregiver disutility in the NE model has been reviewed and the number of caregivers required for GMFC-MLD 3 and 4 has been amended in line with what has been assumed for BE and IE. Consequently, caregiver disutility has been applied in the following manner for all three countries: 0.5 of a caregiver for patients in GMFC-MLD 2, 1 caregiver for patients in GMFC-MLD 3 and 4; and 2 caregivers for patients in GMFC-MLD 5 and 6.

Review Group's response:

The Review group acknowledges the updated input. Section 4.2 has been updated to reflect the response.

28. Please review the estimation of caregiver disutility in the model. For example, for the Netherlands the average utility at age 40 is 0.885, so subtracting the average MLD caregiver utility of 0.773 gives a decrement of –0.112, not the –0.108 applied in the model.

Applicant's response:

Thank you for noting this. Orchard has reviewed all the inputs for caregiver disutility in the model and has now ensured the correct values are being applied. For Ireland a caregiver disutility of -0.108 has been applied and is calculated from the difference in the mean utility value from the caregiver survey and the average utility at age 40 from the UK population. For the Netherlands and Belgium, a disutility of -0.112 has been applied and is based on the difference in the mean utility value reported in the caregiver survey and the average age of utility at age 40 from the Netherlands.

Review Group's response:

The Review Group acknowledges the updated input. No changes to the report are required.

29. Please explain the rationale for using a linear regression model to predict the utility values generated in the elicitation study, when mean health state values had been elicited directly from participants? Please provide a scenario where the mean utility values elicited from participants (Appendix D) are rescaled according to the

appropriate tariff and applied in the model (rather than using the values generated by the linear regression model).

Applicant's response:

The predominant reason for using a linear regression model to predict the utility values generated in the elicitation study was to remove any inconsistencies in the elicited values. Inconsistencies are defined as when respondents assign values to different health states that may violate the logical order expected. Inconsistencies between some of the health states is not surprising and would be expected given they are adjacent to each other, and some of the health state descriptions were very similar. Indeed, a study in 2006 showed that when a representative sample of 309 Dutch adults were asked to value 17 EQ-5D health states by VAS and TTO, 65% had inconsistencies for visual analogue scale (VAS) and 89% for TTO. But the authors concluded the presence of these inconsistencies did not affect the estimated tariffs (Lammers et al 2006).38 Furthermore, linear regression analysis is a widely accepted approach in the calculation of utility values and is used very effectively to estimate intervening health states to the ones valued in the TTO exercise in both the EQ-5D-3L and 5L value sets for most countries, as it is not possible to generate participant elicited values for every permutation of the 3L (243 unique health states) or 5L (3,125 unique health states).

Nevertheless, Orchard is willing to provide a scenario analysis where the mean utility values elicited directly from participants are rescaled using the same EQ-5D tariffs that were applied in the linear regression models. The rescaled values from the mean utility values elicited directly from the participants are presented in Table 17 and Table 18. Results of the scenario analysis using these utility value sets are presented in Table 49 in Section 5.2.3. Note, the values for GMFC 5 and 6 and normal cognition have been retained from the regression analysis as these were not directly asked to respondents.

Table 59: Mean TTO scores for all juvenile MLD health states using the rescaled approach in the Netherlands

Health States	***TTO score***	***SD***	***95% Confidence Intervals***
GMFC-MLD1 + normal cognition	*0.90*	*0.11*	*0.03*
GMFC-MLD2 + normal cognition	*0.81*	*0.17*	*0.05*
GMFC-MLD3 + normal cognition	*0.50*	*0.35*	*0.10*
GMFC-MLD4 + normal cognition	*0.12*	*0.35*	*0.11*
GMFC-MLD0 +moderate cognitive	*0.85*	*0.15*	*0.04*
GMFC-MLD1 +moderate cognitive	*0.77*	*0.24*	*0.06*
GMFC-MLD2 +moderate cognitive	*0.57*	*0.32*	*0.09*
GMFC-MLD3 +moderate cognitive	*0.23*	*0.39*	*0.11*
GMFC-MLD4 +moderate cognitive	*-0.09*	*0.26*	*0.07*
GMFC-MLD5 +moderate cognitive	*-0.08*	*0.30*	*0.08*
GMFC-MLD6 +moderate cognitive	*-0.18*	*0.25*	*0.07*
GMFC-MLD0 + severe cognitive impact	*0.43*	*0.37*	*0.10*
GMFC-MLD1 + severe cognitive impact	*0.33*	*0.45*	*0.12*
GMFC-MLD2 + severe cognitive impact	*0.39*	*0.39*	*0.10*
GMFC-MLD3 + severe cognitive impact	*-0.00*	*0.34*	*0.10*

GMFC-MLD4 + severe cognitive impact	*-0.08*	*0.30*	*0.09*
GMFC-MLD5 + severe cognitive impact	*-0.20*	*0.23*	*0.06*
GMFC-MLD6 + severe cognitive impact	*-0.21*	*0.23*	*0.06*

Abbreviations: *GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; MLD: metachromatic leukodystrophy; SD: standard deviation; TTO: time trade-off.*

Table 60: Mean TTO scores for all juvenile MLD health states using the rescaled approach in the UK

Health States	***TTO score***	***SD***	***95% Confidence Intervals***
GMFC-MLD1 + normal cognition	*0.90*	*0.11*	*0.03*
GMFC-MLD2 + normal cognition	*0.81*	*0.17*	*0.05*
GMFC-MLD3 + normal cognition	*0.48*	*0.39*	*0.11*
GMFC-MLD4 + normal cognition	*0.04*	*0.45*	*0.14*
GMFC-MLD0 +moderate cognitive	*0.85*	*0.15*	*0.04*
GMFC-MLD1 +moderate cognitive	*0.77*	*0.25*	*0.06*
GMFC-MLD2 +moderate cognitive	*0.56*	*0.34*	*0.09*
GMFC-MLD3 +moderate cognitive	*0.17*	*0.48*	*0.14*
GMFC-MLD4 +moderate cognitive	*-0.22*	*0.39*	*0.11*
GMFC-MLD5 +moderate cognitive	*-0.23*	*0.42*	*0.11*
GMFC-MLD6 +moderate cognitive	*-0.36*	*0.36*	*0.10*
GMFC-MLD0 + severe cognitive impact	*0.41*	*0.41*	*0.11*
GMFC-MLD1 + severe cognitive impact	*0.28*	*0.54*	*0.15*
GMFC-MLD2 + severe cognitive impact	*0.35*	*0.46*	*0.12*
GMFC-MLD3 + severe cognitive impact	*-0.11*	*0.46*	*0.13*
GMFC-MLD4 + severe cognitive impact	*-0.21*	*0.42*	*0.12*
GMFC-MLD5 + severe cognitive impact	*-0.40*	*0.34*	*0.09*
GMFC-MLD6 + severe cognitive	*-0.40*	*0.33*	*0.08*

Abbreviations: *GMFC-MLD: Gross Motor Function Classification in Metachromatic Leukodystrophy; MLD: metachromatic leukodystrophy; SD: standard deviation; TTO: time trade-off.*

Review Group's response:

The Review Group acknowledges the response, and the additional scenario which utilises the rescaled mean utility values directly elicited from participants, as opposed to those estimated using the linear regression models. Section 4.2 has been updated to reflect the response. The results of the scenario analysis have also been presented in the Results section of the report.

30. The sample size of participants recruited to the utility elicitation study has been published in the Evidence Review Group report for NICE, and so this information is no longer considered AIC.

The Applicant acknowledged that the information is no longer considered AIC. These data are not designated AIC in the report. No changes to the report are required.

31. Please identify where in the EBMT handbook the information regarding duration of GvHD is sourced.

The Review Group acknowledges the clarification. No changes to the report are required.

Uncertainty

32. Please provide justification for the distributions and standard errors used to vary inputs in the PSA. Please specify the source for all error estimates used.

Applicant's response:

Table 103 in the final submission provided a top-line summary of the distributions and the justification for the distributions, as well as specific information as to where the SEs for each parameter input can be found in the economic model. As indicated in the answer to (Q8), the standard errors for the following variables have all been calculated from the same data source that informed these model inputs i.e., the clinical data, and therefore better capture the uncertainty in these inputs compared to the arbitrary ±20% estimated standard error that had been used previously:

a) Percentage of full responders

b) Percentage of partial stabilisers – please note in cases where the number of partial responders stabilizing was 0%, a default SE value of 20% was used as it would have no impact

c) Progression modifiers – please note in cases where the progression modifier was 1 (e.g., the transition from GMFC-MLD 5 to GMFC-MLD 6), the SE value was set to 20% because this progression modifier was derived from clinical expert advice obtained in the SEE rather than data, because no arsa-cel treated patients have progressed beyond GMFC-MLD 5

d) Mean time to transition between each state

e) Percentage of patients in the cognitive sub-states – please note that for the arsa-cel values, whilst the model predicts for example that 5% of patients in GMFC-MLD 1 will have moderate cognitive impairment, this was not observed in the clinical trial as 100% patients in GMFC-MLD 1 had normal cognitive function so the arbitrary 20% SE has been used in the instances where there are no trial data.

There are over 500 parameter inputs, so rather than replicate such a large data set from the model into this document, Orchard would like to draw the Review Group's attention to the Parameters worksheet in the model where all the standard error and percentage standard errors are available for each input.

Review Group's response:

The Review Group have performed a comparison of the % SE values used in the original model, compared the updated model, and summarised in the table below. It is unclear why some values changed when the data informing them did not (e.g. (d)), whereas others had updated data but the % SE remained the same (e.g. progression modifiers (c)). As the full sources have not been specified, the Review Group is not in a position to further appraise this aspect of the submission. The Review Group continues to critique the transparency and application of parameter uncertainty estimates in the submission.

	Parameter	Original % SE	Updated % SE	Comments
(a)	OTL200_LI_Pct_Resp	20%	32%	
	OTL200_Juv_PreSymp_Pct_Resp	20%	29%	
	OTL200_Juv_Symp_Pct_Resp	20%	20%	
(b)	OTL200_LI_PartialResp_PctStabilize_1	20%	43%	
	OTL200_LI_PartialResp_PctStabilize_2	20%	26%	
	OTL200_LI_PartialResp_PctStabilize_3	20%	20%	
	OTL200_LI_PartialResp_PctStabilize_4	20%	20%	
	OTL200_LI_PartialResp_PctStabilize_5	20%	20%	
	OTL200_Juv_PreSymp_PartialResp_PctStabilize_1	20%	20%	
	OTL200_Juv_PreSymp_PartialResp_PctStabilize_2	20%	20%	
	OTL200_Juv_PreSymp_PartialResp_PctStabilize_3	20%	20%	
	OTL200_Juv_PreSymp_PartialResp_PctStabilize_4	20%	20%	
	OTL200_Juv_PreSymp_PartialResp_PctStabilize_5	20%	20%	
	OTL200_Juv_Symp_PartialResp_PctStabilize_1	20%	45%	
	OTL200_Juv_Symp_PartialResp_PctStabilize_2	20%	45%	
	OTL200_Juv_Symp_PartialResp_PctStabilize_3	20%	45%	
	OTL200_Juv_Symp_PartialResp_PctStabilize_4	20%	45%	
	OTL200_Juv_Symp_PartialResp_PctStabilize_5	20%	20%	
(c)	OTL200_LI_RateProgression_0_1	20%	20%	
	OTL200_LI_RateProgression_1_2	24%	24%	
	OTL200_LI_RateProgression_2_3	16%	16%	
	OTL200_LI_RateProgression_3_4	16%	16%	
	OTL200_LI_RateProgression_4_5	16%	16%	
	OTL200_LI_RateProgression_5_6	16%	20%	
	OTL200_LI_RateProgression_6_death	20%	20%	
	OTL200_Juv_PreSymp_RateProgression_0_1	20%	20%	
	OTL200_Juv_PreSymp_RateProgression_1_2	24%	24%	
	OTL200_Juv_PreSymp_RateProgression_2_3	16%	16%	
	OTL200_Juv_PreSymp_RateProgression_3_4	16%	16%	
	OTL200_Juv_PreSymp_RateProgression_4_5	16%	16%	
	OTL200_Juv_PreSymp_RateProgression_5_6	16%	20%	
	OTL200_Juv_PreSymp_RateProgression_6_death	20%	20%	
	OTL200_Juv_Symp_RateProgression_0_1	20%	20%	
	OTL200_Juv_Symp_RateProgression_1_2	24%	24%	
	OTL200_Juv_Symp_RateProgression_2_3	38%	16%	
	OTL200_Juv_Symp_RateProgression_3_4	17%	16%	
	OTL200_Juv_Symp_RateProgression_4_5	17%	16%	
	OTL200_Juv_Symp_RateProgression_5_6	20%	20%	
	OTL200_Juv_Symp_RateProgression_6_death	20%	20%	
(d)	LI_BSC_med_0_1	20%	38%	

	LI_BSC_med_1_2	25%	21%	
	LI_BSC_med_2_3	21%	18%	
	LI_BSC_med_3_4	21%	18%	
	LI_BSC_med_4_5	21%	18%	
	LI_BSC_med_5_6	34%	31%	
	LI_BSC_med_6_death	19%	18%	
	Juv_BSC_med_0_1	20%	69%	
	Juv_BSC_med_1_2	26%	24%	
	Juv_BSC_med_2_3	39%	33%	
	Juv_BSC_med_3_4	39%	33%	
	Juv_BSC_med_4_5	39%	33%	
	Juv_BSC_med_5_6	40%	35%	
	Juv_BSC_med_6_death	32%	28%	
(e)	Juv_CogDist_Pre0_Normal	20%	20%	
	Juv_CogDist_Pre0_Impaired	20%	20%	
	Juv_CogDist_Pre0_Severe	20%	20%	
	Juv_CogDist_0_Normal	49%	20%	
	Juv_CogDist_0_Impaired	49%	20%	
	Juv_CogDist_0_Severe	49%	20%	
	Juv_CogDist_1_Normal	22%	20%	
	Juv_CogDist_1_Impaired	20%	26%	
	Juv_CogDist_1_Severe	34%	32%	
	Juv_CogDist_2_Normal	36%	34%	
	Juv_CogDist_2_Impaired	20%	37%	
	Juv_CogDist_2_Severe	41%	39%	
	Juv_CogDist_3_Normal	20%	46%	
	Juv_CogDist_3_Impaired	20%	35%	
	Juv_CogDist_3_Severe	20%	24%	
	Juv_CogDist_4_Normal	20%	46%	
	Juv_CogDist_4_Impaired	20%	35%	
	Juv_CogDist_4_Severe	20%	24%	
	Juv_CogDist_5_Normal	20%	46%	
	Juv_CogDist_5_Impaired	20%	35%	
	Juv_CogDist_5_Severe	20%	24%	
	Juv_CogDist_6_Normal	60%	58%	
	Juv_CogDist_6_Impaired	20%	33%	
	Juv_CogDist_6_Severe	9%	9%	
	*			

*PS-EJ and ES-EJ cognitive distributions for AA (for each of full responder, stable partial and unstable partial responders) not shown here. For all, % SE = 20%

Green indicates % SE higher than original value; Red indicates % SE lower than original value. Black indicates unchanged

33. Given the limited data informing the cost effectiveness model, sensitivity analysis based on arbitrary +/-20% variation is limited in its ability to meaningfully capture uncertainty in the model inputs and their impact on cost effectiveness.

    a. Please rerun DSA, PSA and EVPI using more appropriate measures of uncertainty. Where available error estimates from the same source data used to inform the deterministic input parameter should be used.

b. Please present probability of cost-effectiveness at thresholds of €45,000 and €80,000 per QALY in line with Ireland and The Netherlands willingness to pay thresholds.

c. Please present mean probabilistic results for Table 105.

d. Please present PSA results separately by population subgroup (PS LI, PS EJ, ES EJ).

Applicant's response:

a. *In the final dossier, all the utility inputs and the progression modifiers used error estimates from the same data source as the deterministic input parameter – e.g., the SEs from the vignette study and SEs from the clinical trial data. However, some inputs did still use the arbitrary +/- 20% standard error estimate for the PSA. Section 5.2 presents the updated PSA, deterministic sensitivity analyses (DSA) and expected value of perfect information (EVPI) results, where the standard errors for the following variables have all been calculated from the clinical data and therefore capture the uncertainty in these inputs: a) percentage of full responders; b) percentage of partial stabilisers – please note in cases where the number of partial responders stabilizing was 0%, a default SE value of 20% was used as it would have no impact; c) progression modifiers checked – please note in cases where the progression modifier was 1 (e.g. GMFC-MLD 5 and GMFC-MLD 6), the SE value was set to 20% because this progression modifier was derived from clinical expert advice sought during model development and the UK SEE rather than data d) Mean time to transition between each state; e) percentage of patients in the cognitive sub-states.*

   For the DSA, all input parameters are purposefully varied by +/- 20%. The purpose of the DSA in this case was to determine using a fixed percentage change across all parameters, which inputs have the most impact on the cost-effectiveness as a result of this arbitrary change. The parameters that lead to > 5% change to the ICER can then be examined more thoroughly.

b. *The cost effectiveness acceptability curves (CEACs) depicting the probability of being cost-effective at the specific countries' willingness to pay (WTP) thresholds have also been included in Section* ***Fout! Verwijzingsbron niet gevonden.****.2.2*

   Orchard acknowledges that the PSA output for all three countries indicates that the cost per QALY gained where there is a 50% probability of arsa-cel being cost-effective vs BSC is higher than the country specific WTP thresholds (using the base case assumptions of country specific discount rates, exclusion of caregiver disutility, exclusion of productivity gains [applicable to Netherlands only] and no new-born screening [NBS]). Orchard understands that the formal Dutch WTP threshold is €80,000 per QALY gained, and the threshold for Ireland is €45,000 per QALY gained; there is no formal WTP threshold in Belgium. However, it should be noted that these

WTP thresholds are standard thresholds applied for all types of medicinal product, across a broad range of diseases. These 'traditional' thresholds therefore do not take into account that arsa-cel is an advanced therapy medicinal product offering considerable health benefits in the treatment of early-onset MLD, an ultra-rare condition associated with a severe disease burden.

There is increased recognition that conventional HTA processes and decision-making frameworks pose considerable challenges to rare disease treatments, particularly those in ultra-rare indications.(24) Aballea et al 2020, published a paper looking at the methodological issues with the health economic evaluation of gene replacement therapies and convened an expert panel to provide recommendations. The recommendations included the recognition of the importance of expert opinion due to limited data; in addition broader elements of value, beyond health gains directly related to treatment should be considered through the application of a factor to inflate the quality-adjusted life years (QALYs) or a higher cost-effectiveness threshold. Additionally, the use of cost-benefit analysis and saved young life equivalents (SAVE) were proposed as alternatives to QALYs for the valuations of outcomes of GRT as they can incorporate broader elements of value and avoid problems of eliciting utilities for paediatric diseases.

Greater flexibility is therefore required in the processes used to appraise ultra-orphan medicinal products, including in the decision rules applied. Indeed, supplementary processes are already being employed by a large number of regions internationally, as shown by recent research from Impact HTA (which explored HTA processes in most EU and EEA Member States, Canada and New Zealand). For example, the National Institute for Health and Care Excellence (NICE) has a dedicated, separate programme for appraisal of highly-specialised technology appraisals. Under this programme, NICE uses a higher WTP threshold of £100,000 per QALY gained; furthermore, where an ICER falls above £100,000 per QALY gained, a QALY weighting may be applied to take into account the magnitude of therapeutic benefit provided, as revealed through incremental QALY gain. The NICE process therefore acknowledges the additional value of highly specialised technologies that provide significant health benefits to patients with rare or ultra-rare conditions.

It is worth noting that arsa-cel is recommended for reimbursement in several European countries for its licensed indication, including the UK (by NICE), Germany (G-BA) and Italy (AIFA).(25-27) Additional considerations must be given for the reimbursement processes for ATMPs, including gene therapies. This has been the focus of a publication in Ireland conducted by Irish Pharmaceutical Healthcare Association (IPHA) and Price Waterhouse Coopers (PWC), where they published a pathfinder study for the adoption of cell and gene therapies in Ireland (MLD is one of the conditions mentioned).(28)

c. *The mean results have been added to the max and min results for the PSA output and are included in Section* ***Fout! Verwijzingsbron niet gevonden.****.2.2 of this document.*

d. *The PSA results were presented separately by population subgroup (PS LI, PS EJ, ES EJ) in Appendix 12.9 of the final dossier. Given there have been a few changes to the PSA distributions and some for the parameter inputs, the revised PSA results for each sub-group are presented in Section.*

Review Group's response:

As highlighted in response to Q32, the Review Group were not provided with full details as to the decisions regarding the parameter variation, and therefore cannot further appraise. As highlighted in the D60 report, which the Applicant has available to them, the arbritary +/-20% variance implemented in the DSA is unlikely to adequately capture the uncertainty in this analysis.

The Review Group have not been able to identify the CEACs incorporating the relevant WTP thresholds in Section 5.2.2. Furthermore, it is unclear where the probability of cost-effectiveness estimates at the various thresholds have been presented. These issues were highlighted in the D60 report, and do not appear to have been rectified at this stage. The additional reporting of the maximum and minimum of the PSA outputs are acknowledged, as are the individual PSA results.

Budget impact model

BE: Please update cost offsets to reflect parameter inputs changed in the CEM. Cost offsets incurred outside the time horizon of the BI model should be excluded from the model (i.e. cost offsets for only one patient should be included). Please update the scenario for NBS to include 8 patients (2.55*3=7.65 patients which rounds up to 8).

The Review Group acknowledge the updated model inputs and results. Corresponding changes have been made to Section 4.

IE: Please update cost offsets to reflect parameter inputs changed in the CEM. Cost offsets accrued outside the time horizon of the budget impact model should be excluded from the model (i.e. cost offsets for only one patient should be included).

The Review Group acknowledge the updated model inputs and results. Corresponding changes have been made to Section 4.

Additional comments from the Applicant regarding the budget impact analysis:

Orchard notes that in the D60 report for the budget impact analysis in the Netherlands, whilst two scenarios were included in the company final submission – one based on clinical opinion and the other on epidemiology, the report has only focused on the analysis incurring the highest budget impact. Since the estimations are uncertain, Orchard considers that the range

of likely budget impact should be presented in the summary and conclusion on budget impact. Alternatively, as the Review Group have done for the Belgian NBS scenario analysis, the budget impact based on the epidemiology could be presented here as an alternative scenario.

In addition, Orchard considers that Table 37 in the D60 report detailing the net budget impact is potentially confusing because it is not clear that the net budget impact is cumulative and that for Belgium this is over 3 years, but for the Netherlands and Ireland, this is over 5 years. If its possible, please can this information be made clear.

Review Group response:

The gross budget impact for The Netherlands includes the results of the scenario where the budget impact is estimated based on the epidemiological model (see footnotes, Table 35). A footnote has been added to Table 37 to clarify that the budget impacts for Belgium and the Netherlands are cumulative over three years, while the results for Ireland are cumulative over five years.