Defining Meaningful Outcomes for Patients with Spinal Muscular Atrophy in the Era of Gene Therapy

This industry sponsored symposium took place as part of the 15th Congress of the European Paediatric Neurology Society (EPNS), held 21st June 2023 in Prague, Czechia

Chairpeople:	Jana Haberlová[1,2]
Speakers:	Jana Haberlová,[1,2] Francesco Muntoni,[3,4] Eugenio Mercuri[5] 1. Charles University, Prague, Czechia 2. Motol University Hospital, Prague, Czechia 3. University College London, UK 4. Great Ormond Street Hospital, London, UK 5. Gemelli University Hospital, Rome, Italy
Disclosure:	All symposium presenters received an honorarium from Novartis Gene Therapies, and disclosed involvement in Novartis Gene Therapies educational events. Haberlová reports being a consultant for Novartis, Roche, and Biogen; and Principal Investigator for spinal muscular atrophy study BP42940 (Roche). Muntoni reports being a Principal Investigator for clinical trials sponsored by Novartis, Biogen, and Roche; receiving compensation for participation in advisory boards and symposia from Biogen, Novartis, and Roche; and institutional funding for an spinal muscular atrophy registry from Biogen and Roche. Mercuri reports being a Principal Investigator for, and receiving advisory board fees from, AveXis /Novartis Gene Therapies, Biogen, PTC Therapeutics, Roche, and Scholar Rock; and receiving an institutional research grant for a disease registry from Biogen.
Acknowledgements:	Medical writing assistance was provided by Eleanor Roberts, Beeline Science Communications, Ltd, London, UK.
Disclaimer:	The symposium content and views expressed herein are those of the speakers.
Support:	The publication of this article was supported by Novartis Gene Therapies.
Keywords:	Benefit/risk profile, functional goals, gene therapy, motor function, respiratory function, survival motor neuron protein.
Citation:	EMJ Neurol. 2023;11[1]:72-81. DOI/10.33590/emjneurol/10304219. https://doi.org/10.33590/emjneurol/10304219.

Meeting Summary

Spinal muscular atrophy (SMA) occurs due to a mutation in the *SMN1* gene. It most typically has an onset in early childhood and presents as impairment in motor, bulbar, and respiratory function. In a symposium at the European Paediatric Neurology Society's (EPNS) 2023 congress, three leading experts in SMA discussed the findings of real-world evidence (RWE) studies of the first gene therapy approved in NMD, in 2019 in the USA, and 2020 in Europe. Onasemnogene abeparvovec combines an adeno-associated virus (AAV9) vector with a functional copy of *SMN* complementary DNA, and is delivered in a single infusion. While clinical trials of onasemnogene abeparvovec show its efficacy and safety in populations with SMA who are symptomatic and pre-symptomatic, RWE studies have expanded the understanding of this therapy to wider SMA patient groups in the real-world clinical practice setting. Combined, such studies show how administration of onasemnogene abeparvovec in patients with symptomatic SMA can lead to motor and respiratory function improvement or stabilisation and achievement of motor milestones in naïve or pre-treated patients, while in patients who are pre-symptomatic, administration may lead to a normal development. The experts also discussed how understanding the benefit/risk profile of this gene therapy can help with decision-making over its use in patients with SMA. They highlighted how onasemnogene abeparvovec efficacy and safety can be affected by clinical status, disease severity, weight, age, and previous treatment at the time of infusion. Recently published RWE points to improvements being best predicted by baseline Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score and age at treatment initiation, and in regard to safety and tolerability profile, liver enzyme elevation is the most predominant treatment-emergent adverse event (TEAE) with onasemnogene abeparvovec; hence, a prednisolone (or equivalent) dosing regimen is administered prior to, during, and for at least 3 months following infusion. The experts discussed how careful monitoring and adequate multidisciplinary team discussion, including colleagues from other specialities, such as hepatologists and paediatric immunologists, is advised in all cases of SMA receiving an onasemnogene abeparvovec infusion.

Introduction

At the 15th Congress of the EPNS, Jana Haberlová, Charles University, Prague, Czechia, and Motol University Hospital, Prague, Czechia; Francesco Muntoni, University College London, UK, and Great Ormond Street Hospital, London, UK; and Eugenio Mercuri, Gemelli University Hospital, Rome, Italy, all of whom have been involved in a number of studies investigating SMA treatment, reviewed efficacy and safety data from RWE settings of onasemnogene abeparvovec. This is a non-replicating recombinant AAV vector that delivers a fully functional, stable, human SMN transgene to the nuclei of motor neurons via use of an AAV9 capsid that can cross the blood–brain barrier. The *SMN1* gene in transduced cells is expected to be stably expressed by post-mitotic cells for an extended time. The AAV9 virus is not known to cause disease in humans.[1,2] The experts also discussed benefit/cost considerations for this therapy, and managing patient and caregiver expectations in those eligible to receive it.

SMA occurs at a global incidence of approximately 1 out of 10,000 live births, though this can differ by region.[3] The muscular weakness and atrophy indicative of SMA is due to motor neuron loss, as a result of reduced expression of SMN protein. This occurs because of a mutation in the *SMN1* gene at chromosome 5q11.1–13.3.[4] More recently, progression of, and survival with SMA has been improved by disease-modifying therapies that work by allowing SMN expression, to the extent that if SMA is detected early, some

treatments may enable some patients who are pre-symptomatic to achieve age-appropriate motor milestones.[5-7] These therapies include onasemnogene abeparvovec;[1,2] nusinersen, a splice-switching antisense oligonucleotide;[8] and risdiplam, which binds to *SMN2* pre-messenger RNA.[9] Onasemnogene abeparvovec is a gene therapy approved for SMA treatment,[10] with the European indication being for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene, and either a clinical diagnosis of SMA Type 1, or up to three copies of the *SMN2* gene.[1]

Across clinical trials, managed access programmes and commercial settings, currently over 3,000 children with SMA have been treated with onasemnogene abeparvovec.[11] Completed trials include START,[12,13] STR1VE-US,[14] STR1VE-EU,[15] and STR1VE-AP[16,17] in patients who are symptomatic, and SPR1NT[6,7] in patients who are pre-symptomatic. There are ongoing or recruiting trials including long-term follow-up studies LT-001 and LT-002[18] in patients who are symptomatic;[13] and OFELIA,[19] and SMART[20] in symptomatic and previously treated patients. LT-002 also follows up patients who are pre-symptomatic, treated in the core SPRINT trial.[18] RESTORE is a sponsored SMA registry of patients treated in RWE in co-operation with the main Academic SMA Registries.[21]

Real-World Evidence of Onasemnogene Abeparvovec Efficacy in Spinal Muscular Atrophy Gene Therapy

Jana Haberlová

The first objective of the symposium was to discuss how RWE data have expanded the use and understanding of onasemnogene abeparvovec treatment beyond the cohorts investigated in the clinical trials. Haberlová discussed how, up to May 2023, there have been 27 peer-reviewed, independent, RWE publications of onasemnogene abeparvovec, including treatment-naïve, and those switched from nusinersen or risdiplam. These involved 574 patients with, where data are available, an age range of 2 weeks–6 years, and a weight range of 2.5–17.0 kg (Table 1).[2,22-47]

Table 1: Numbers and types of patient in real-world evidence studies of onasemnogene abeparvovec.[2,22-47]

SMA type	n (%)*	*SMN2* copy number	n (%)*	Other treatment	n (%)†
Pre-symptomatic	59 (10.3)	1 copy	3 (0.5)	Bridge	4 (0.7)
Type 0	1 (0.2)	2 copies	320 (55.7)	Switch	324 (56.4)
Type 1	380 (66.2)	3 copies	146 (25.4)	Add-on/ combination	10 (1.7)
Type 2	73 (12.7)	≥4 copies	17 (3.0)	Naïve	236 (41.4)
Type 3	1 (0.2)	Not reported	88 (15.3)	Not reported	0 (0.0)
Not reported	60 (10.5)	N/A			

*Not all studies report SMA Type or *SMN2* copy number.

†One patient in the combination group received only three of the four loading doses of nusinersen and was excluded from the analysis.

N/A: not applicable.

Overall, these RWE data found that administration of onasemnogene abeparvovec in patients with SMA led to stabilisation or improvement of motor function and achievement of motor milestones, and stabilisation or improvement of respiratory function.[2,22-24,27,29,31,33-36,39-41,43-47] Also shown was that the efficacy and safety of onasemnogene abeparvovec can be affected by several factors, including clinical status, weight, age, previous treatment, and disease severity at the time of infusion.[24,34,41,44,45]

Many of the published data of SMA use the CHOP-INTEND measure to ascertain baseline function and track changes over time. CHOP-INTEND was developed to capture specific targeted motor skills that are clinically significant for the SMA-I population. Each of the 16 motor skills, including neck flexion, rolling, hand grip, and spontaneous movement, is scored from 0–4, from none to full ability, for a total possible score of 64.[48] In regard to the efficacy of onasemnogene abeparvovec, RWE data of patients who are pre-symptomatic appear to attain the highest mean increase in CHOP-INTEND scores compared with patients with SMA Type 1 or 2,[24,41] with motor function outcomes not influenced by *SMN2* copy number or sex in patients who are pre-symptomatic.[41] In patients with SMA Type 1 treated with onasemnogene abeparvovec, while an increase in motor function is observed in all age groups,[2,22,31,33,36,38,41,43,46] the level of improvement is best predicted by baseline CHOP-INTEND score and age at treatment initiation.[24] For patients who have been previously treated with a disease-modifying therapy, onasemnogene abeparvovec infusion can lead to further respiratory function improvement or stabilisation, and/or achievement of new motor milestones.[2,22-24,27,29,31,33-36,38-41,43-47]

From data gathered in the RWE data, Haberlová concluded that, further to clinical trial data, onasemnogene abeparvovec shows efficacy in patients with SMA in terms of symptom stabilisation and improvement.

Adeno-Associated Virus-Based Gene Therapy Benefit/Risk Profile

Francesco Muntoni

Although the benefits of viral vector therapy include how targeted it can be to the cause of a disease (in this case, onasemnogene abeparvovec replaces the missing *SMN1* gene and boosts SMN production),[1] there are potential treatment-associated, but manageable, adverse events. An immune response to the vector can arise as, while the virus itself is not pathogenic, a high viral load is needed for AAV-based gene therapies.[49] Due to such potential adverse events, close monitoring is required for a number of weeks pre- and post-onasemnogene abeparvovec infusion.[25,30,50,51] With this in mind, Muntoni discussed how knowing and understanding the overall benefit/risk profile of onasemnogene abeparvovec can help healthcare professionals when making treatment decisions for patients with SMA. Muntoni also stressed the necessity prior to and during an onasemnogene abeparvovec infusion of having a network of colleagues that have been educated with regard to gene therapy, and pre-warned prior to the infusion. “It is critical,” Muntoni said, “that other colleagues, such as physicians and nurses, are aware of what you are doing, because not everyone necessarily has expertise in this field.” Muntoni highlighted the need to “prepare the hospital team, even if 99% of the time they are not involved.”

To aid in identifying typical events following onasemnogene abeparvovec infusion, Muntoni highlighted how, in the first week, events indicative of activation of innate or adaptive immunity includes flu-like symptoms, such as malaise, loss of appetite, and fever, along with vomiting and troponin increase.[30] In the first 2 weeks, an early humoral response and/or an innate immune response against the viral capsid proteins is observed in some patients. This can cause complement activation consistent with thrombotic microangiopathy (TMA), low platelets, troponin release from cardiac muscle and platelets, and kidney and liver injury. Cardiogenic shock has been reported with other AAV therapies;[25,50,51] however, Muntoni reported that they had not personally seen this with onasemnogene abeparvovec. In the first month, liver toxicity and inflammation may be indicative

of a T cell-mediated immune response against the viral capsid.[51] In the following months, heart muscle inflammation, which can be indicative of a humoral and T cell-mediated immune response against the transgene protein, has been reported with other AAV therapies, but has not been observed with onasemnogene abeparvovec.[51]

Where safety and tolerability was assessed in onasemnogene abeparvovec RWE settings, TEAEs were reported fairly frequently, but with different degrees of severity.[2,22,23,28,30,31,36,40-43,46,47] The most common risk associated with AAV-based gene therapies is hepatotoxicity,[52] as evidenced by liver enzyme elevation.[2,22,23,28,30,31,36,40-42,46,47] This may be due to the AAV9 vector in onasemnogene abeparvovec having tissue tropism to the liver, as well as to skeletal muscle, the heart, and the brain.[53] It may also be due to an immune system primed by prior exposure to wild-type AAV, which can result in T cell and humoral immunity against the vector in the liver.[49,53] With onasemnogene abeparvovec, there appears to be a lower risk of liver transaminase elevation in patients who are younger and/or have a lower body weight, and a higher risk in older, previously treated patients.[2,23,24,40,41,44,45] According to Muntoni: "More severe liver involvement than usual may be observed in some patients who experience quite significant elevation of transaminases. Although liver failure is exceptional, it can potentially occur."[28]

Corticosteroids are used prior to and following onasemnogene abeparvovec infusion, as they can block the T cell response to capsid-derived peptides presented by transduced hepatocytes, and have a role in protecting hepatocytes against apoptosis and preventing cytolysis of ballooned hepatocytes.[54,55] According to Muntoni: "Corticosteroids appear to be effective in removing the most significant peaks of transaminitis." Indeed, studies show that elevations in liver enzymes resolve in most cases following such treatment,[2,23,36,37,40,41,44] and that most patients do not require corticosteroid treatment long term.[24,30,40,41,44]

Scheduling of corticosteroid administration is detailed in onasemnogene abeparvovec prescribing guidelines.[1] This includes starting oral prednisolone (or equivalent) at 1 mg/kg/day 24 hours prior to infusion, then continuing this dose for 30 days, followed by 28 days' tapering if liver enzyme values are below two-times the upper limit of normal.[1,56] Where liver-related AEs have occurred, short-term treatment with high-dose corticosteroids is advised in the prescribing information of a number of gene therapies, including onasemnogene abeparvovec.[1,49,57,58] Muntoni confirmed that, "if the patient is having bigger liver problems than you expect, there are protocols for using high doses of steroids, including intravenous administration." During the panel discussion, when asked if the initial dose should be 2 mg/kg/day prednisolone (or equivalent), Muntoni noted how, in their centre's experience, this higher starting dose did not make a difference, although it can be used if liver enzymes increase. Mercuri commented how the higher dose may also lead to liver complications; hence, not being suitable for every patient.

Other TEAEs reported following onasemnogene abeparvovec infusion are transient, mild increases in troponin I levels with no aberrant cardiac assessment report;[2,23,36,41] pyrexia;[2,23,28,30,36,41,42,47] vomiting; loss of appetite; and diarrhoea.[2,23,28,30,41-43,47] RWE evidences showed transient thrombocytopenia (where this was assessed) in 16–100% of patients, which generally normalised without intervention.[2,23,36,37,40,41,44] Also observed, though rare, is TMA.[42,43] "This is the adverse event that is most important in terms of morbidity," said Muntoni, "but only exceptionally is it very significant, and it is not difficult to monitor for." During the panel discussion, Muntoni explained how TMA usually occurs in the first 2 weeks after infusion, but stressed that a patient needs to be monitored very carefully for a potential TMA in the first 3 months.

Due to potential TEAE, patients should be followed-up every 6 months to a year following the initial infusion and have liver function tests as, said Muntoni: "We have an obligation to follow these patients clinically." Muntoni discussed how vital it is that the family of the patient understand the immediate post-infusion time. "When you describe and discuss [the treatment], managing expectations with the family is important, so they do not receive an AAV gene therapy then disappear for 6 months." Haberlová confirmed that, in their practice, even cases identified via newborn screening, so treated while pre-symptomatic, are followed up for at least 10 years.

Understanding and Discussing Long-Term Outcomes with Onasemnogene Abeparvovec Across Different Spinal Muscular Atrophy Patient Populations

Eugenio Mercuri

The final objective of this symposium was to explore treatment expectations ,and which outcomes are most meaningful for patients and their families. Mercuri discussed how improving understanding of gene therapy predictors and outcomes can aid treatment decisions, and help with expectation management.[13,24] Mercuri utilised the results of the recent RWE publication from the Italian experience in treating patients with SMA with onasemnogene abeparvovec in a clinical setting, which they had been involved in Italy to discuss.

In this paper, predictors of the efficacy and safety of onasemnogene abeparvovec were investigated in both treatment-naïve patients (n=19) and those switched from nusinersen (n=46) or risdiplam (n=2). All 67 patients had at least 6 months' follow-up and an available safety profile, with 46 followed up for 12 months. Patients varied with respect to age (22 days–58 months, with one child of 72 months), weight (3.2–13.5 kg, with the older child being 17.0 kg), and disease severity.[24] Mercuri highlighted how these ranges, especially at the higher end, were much broader than those in clinical trials.[12-21,59] Most (63 out of 67) patients were symptomatic with SMA Type 1 (94.0%), and four were identified through neonatal screening and were pre-symptomatic. Just over two-thirds (68.7%) of the patients had a CHOP-INTEND assessment at the time of treatment, and at 12 months from first infusion.[24]

As can be seen from Table 2, independent sitting after onasemnogene abeparvovec infusion was achieved by all patients who were pre-symptomatic, and most of those who were symptomatic but had received another treatment prior to onasemnogene abeparvovec, even if they had not achieved this functional milestone with such treatment. Of the four patients who achieved standing, two were pre-symptomatic and also acquired independent walking at 16 and 17 months; one was symptomatic and treatment-naïve and stood independently at 12 months; while the other was symptomatic and pre-treated, and achieved this motor milestone at 34 months.[24]

For many patients, their CHOP-INTEND scores did not fall from baseline over the follow-up period, and for some there was an increase from baseline at 12 months. For example, most patients with a baseline CHOP-INTEND score <40 achieved a 12-month score ≥40, with some achieving a score ≥60. The best predictor of change in CHOP-INTEND scores was patient age, with the greatest change in those aged <6 months and the least change in those aged >24 months.[24]

"It is very important when we counsel families to try to keep their expectations under control," said Mercuri. In regard to these findings and treatment expectations, Mercuri discussed how "it is important to look at the variability of responses because, while a number of patients did achieve sitting at the time they were taking onasemnogene abeparvovec, some, though very few, never achieved sitting, even if they had been on both [onasemnogene abeparvovec and another] therapies." Conversely, Muntoni commented in the panel discussion that while the baseline CHOP-INTEND score is useful, these results show that "you could have a low CHOP-INTEND score in a [young] child with a very short disease duration, and significant improvement is still possible."

Safety findings in this RWE publication reflected those shown in clinical trials[12-21,59] with TEAEs within 7 days of onasemnogene abeparvovec infusion, including pyrexia (22.4%), vomiting (20.9%), a two-fold increase in aspartate transferase (AST; 39%), and a two-fold increase in alanine transaminase (ALT; 29.9%). The risk of elevated liver enzymes increased with age and weight, with a 5.76x greater risk of abnormal AST and a 11.08x greater risk of abnormal ALT in patients aged >24 months compared to those aged <6 months (where 'abnormal' is defined as two-times the upper limit of normal). No major serious TEAEs were observed.[24] Mercuri stressed how the age stratification regarding tolerability and safety results "does not mean we should not treat patients if they are aged over 24 months, but we should be extra careful."

While shorter term clinical trial and RWE results are promising for onasemnogene abeparvovec, Mercuri commented that "one concern is whether

Table 2: Achievement of motor milestones following onasemnogene abeparvovec infusion according to patient subgroup (n=66*).[24]

	Independent sitting†	Independent standing	Independent walking
Subgroup	**% (n/N)**		
Pre-symptomatic	100.00% (4/4)	75.00% (3/4)	50.00% (2/4)
Symptomatic, treatment naïve	37.50% (6/16)	6.25% (1/16)	N/A
Symptomatic, pre-treated*	82.60% (38/46)	2.17% (1/46)	N/A
Before onasemnogene abeparvovec	36.80% (14/38)	N/A	N/A
After onasemnogene abeparvovec	63.20% (24/38)	N/A	N/A

*One patient is not included due to non-treatment related fatality.

†Ability to sit without support and without a brace for at least 3 seconds.

N/A: not applicable.

these children are going to lose what they have acquired in the first year." LT-001[59] and LT-002[18] are two long-term follow-up studies of patients treated with onasemnogene abeparvovec across five clinical trials. LT-001 includes 13 patients with SMA Type 1 enrolled in the START clinical trial, which was carried out between May 2014–December 2017.[12,13] Participants are planned to be followed up for 15 years with annual visits for 5 years, then annual phone contact for 10 years. The current data cut-off is up to 7.5 years post-dosing.[60] LT-002 includes 25 patients with pre-symptomatic SMA with two or three copies of *SMN2* (from the SPR1NT trial),[59] and 38 patients with symptomatic SMA Type 1 (from the STR1VE-US, n=12;[14] STR1VE-EU, n=24;[15] and STR1VE-AP, n=2,[16,17] trials, run up to February 2020), with the 15-year follow-up consisting of biannual visits (years 0–2), then annual visits (years 3–5), then annual phone contact for up to 10 years. The current data cut-off is up to 4.3 years post-dosing.[18]

Interim data from these studies show the efficacy of onasemnogene abeparvovec up to 7.5 years post-treatment.[18,60] In LT-001, all included patients who received a therapeutic dose of this drug (n=10), achieved or maintained head control and independent sitting (sitting up straight with their head erect for ≥10 seconds without using arms or hands for balance or support), and two out of 10 (20%) maintained independent walking.[60] In LT-002, 32 out of 36 (89%) patients with SMA Type 1 and two *SMN2* copies achieved or maintained unsupported sitting. All four patients who did not achieve the motor milestone of independent walking in the parent study achieved this at follow-up.[18]

"When we have long-term follow-up, it is also possible to see whether there are additional [safety] concerns which were not addressed in the clinical trial," said Mercuri. "During the 90 days is when we really focus on adverse events," they continued, "but past this time frame, there was no evidence of any new safety signals, even up to 7.5 years post-dosing." In LT-002, two TEAEs

(bronchiolitis and pneumonia) occurring in one patient were deemed potentially treatment-related, but in both studies there were no serious TEAEs that led to study discontinuation, and there were no adverse events of special interest.[18,60]

In conclusion, Mercuri discussed how RWE[24] and long-term follow-up[18,60] data may help clinicians to work with caregivers to set appropriate expectations around gene therapy outcomes in children of different ages. "These data are important," Mercuri said, "as we all face families who want to switch therapy and the expectations are generally based on the clinical trials, so RWE and long-term evidence help us, as clinicians, to communicate and set up best expectations." Muntoni also, during the panel discussion, stressed that when counselling parents with a child who has noticeable motor dysfunction, including a low CHOP-INTEND score, bulbar involvement, and respiratory dysfunction, it is important to explain that while they may improve, it may not be to the same extent as a child without this baseline. However, they said, "any outcome is meaningful when it's different from progression and death, so it's just a matter of having the right expectations."

Conclusion

RWE data of onasemnogene abeparvovec[2,22-47] support the clinical trial data[6,7,12-17] and suggest that a wide range of patients with SMA can gain motor and respiratory function stabilisation or improvement following a single infusion. While TEAEs appear to be mostly transient, careful monitoring and long-term follow-up are needed.[2,22-47] These findings may help healthcare professionals with the treatment decision-making process for patients with SMA.

References

1. Electronic Medicines Compendium. Zolgensma 2 × 10Exp13 vector genomes/mL solution for infusion. Summary of Product Characteristics. 2023. Available at: https://www.medicines.org.uk/emc/product/11572/smpc#gref. Last accessed:
2. Bitetti I et al. Onasemnogene abeparvovec gene replacement therapy for the treatment of spinal muscular atrophy: a real-world observational study. Gene Ther. 2022;DOI:10.1038/s41434-022-00341-6.
3. Verhaart IEC et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017;12(1):124.
4. Mercuri E et al. Spinal muscular atrophy. Nat Rev Dis Primers. 2022;8(1):52.
5. De Vivo DC et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: interim efficacy and safety results from the phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-56.
6. Strauss KA et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the phase III SPR1NT trial. Nat Med. 2022;28(7):1381-9.
7. Strauss KA et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the phase III SPR1NT trial. Nature Medicine. 2022;28(7):1390-7.
8. Chen I. An antisense oligonucleotide splicing modulator to treat spinal muscular atrophy. Nat Res. 2019;20:490-507.
9. Kwon JM et al. An expanded access program of risdiplam for patients with Type 1 or 2 spinal muscular atrophy. Ann Clin Transl Neurol. 2022;9(6):810-8.
10. Novartis. Zolgensma®▼ (onasemnogene abeparvovec) receives NICE final draft guidance in presymptomatic babies up to 12 months with spinal muscular atrophy (SMA). 2023. Available at: https://www.novartis.com/uk-en/news/media-releases/zolgensmav-onasemnogene-abeparvovec-receives-nice-final-draft-guidance-presymptomatic-babies-12-months-spinal-muscular-atrophy-sma. Last accessed: .
11. Novartis. Novartis shares Zolgensma long-term data demonstrating sustained durability up to 7.5 years post-dosing; 100% achievement of all assessed milestones in children treated prior to SMA symptom onset. 2023. Available at: https://www.novartis.com/news/media-releases/novartis-shares-zolgensma-long-term-data-demonstrating-sustained-durability-75-years-post-dosing-100-achievement-all-assessed-milestones-children--treated-prior-sma-symptom-onset. Last accessed:
12. Mendell JR et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(18):1713-22.
13. Mendell JR et al. Five-year extension results of the phase 1 START trial of onasemnogene abeparvovec in spinal muscular atrophy. JAMA Neurol. 2021;78(7):834-41.
14. Day JW et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(4):284-93.
15. Mercuri E et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(10):832-41.
16. Novartis Gene Therapies. Single-dose gene replacement therapy using for patients with spinal muscular atrophy type 1 with one or two SMN2 copies. NCT03837184. https://clinicaltrials.

gov/ct2/show/NCT03837184.

17. Mercuri E et al. Onasemnogene abeparvovec gene-replacement therapy (GRT) for spinal muscular atrophy type 1 (SMA1): global pivotal phase 3 study program (STR1VE-US, STR1VE-EU, STR1VE-AP). Journal of the Neurological Sciences. 2019;405S:277-8.
18. Connolly AM et al. Intravenous and intrathecal onasemnogene abeparvovec gene therapy in symptomatic and presymptomatic spinal muscular atrophy: long-term follow-up study. Poster P153. MDA Clinical and Scientific Congress, 19-22 March, 2023.
19. Novartis Pharmaceuticals. Safety and efficacy of intravenous OAV101 (AVXS-101) in pediatric patients with spinal muscular atrophy (SMA) (OFELIA) (OFELIA). NCT05073133. https://clinicaltrials.gov/ct2/show/NCT05073133.
20. Novartis Pharmaceuticals. Safety and efficacy of intravenous OAV101 (AVXS-101) in pediatric patients with spinal muscular atrophy (SMA) (SMART). NCT04851873. https://clinicaltrials.gov/ct2/show/NCT04851873.
21. Finkel RS et al. RESTORE: a prospective multinational registry of patients with genetically confirmed spinal muscular atrophy - rationale and study design. J Neuromuscul Dis. 2020;7(2):145-52.
22. Ali HG et al. Gene therapy for spinal muscular atrophy: the Qatari experience. Gene Ther. 2021;28(10-11):676-80.
23. Artemyeva SB et al. Experience of using gene replacement therapy with Zolgensma® (onasemnogene abeparvovec) in real clinical practice in Russia. Neuromuscular Diseases. 2022;12(1):29-38.
24. Pane M et al. Onasemnogene abeparvovec in spinal muscular atrophy: predictors of efficacy and safety in naïve patients with spinal muscular atrophy and following switch from other therapies. eClinicalMedicine. 2023;59:101997.
25. Chand DH et al. Thrombotic microangiopathy following onasemnogene abeparvovec for spinal muscular atrophy: a case series. J Pediatr. 2021;231:265-8.
26. Dosi C et al. acute benign myositis following onasemnogene abeparvovec therapy in type 1 spinal muscular atrophy. Pediatr Neurol. 2022;131:23-4.
27. D'Silva AM et al. Onasemnogene abeparvovec in spinal muscular atrophy: an Australian experience of safety and efficacy. Ann Clin Transl Neurol. 2022;9(3):339-50.
28. Feldman AG et al. Subacute liver failure following gene replacement therapy for spinal muscular atrophy type 1. J Pediatr. 2020;225:252-8.e1.
29. Ferrante L et al. Novel use of nusinersen as a therapeutic bridge to onasemnogene abeparvovec-xioi in a premature neonate with type 1 spinal muscular atrophy. Muscle Nerve. 2022;66(2):E8-10.
30. Friese J et al. Safety monitoring of gene therapy for spinal muscular atrophy with onasemnogene abeparvovec - a single centre experience. J Neuromuscul Dis. 2021;8(2):209-16.
31. Harada Y et al. Combination molecular therapies for type 1 spinal muscular atrophy. Muscle Nerve. 2020;62(4):550-4.
32. Kay DM et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genet Med. 2020;22(8):1296-302.
33. Lee S et al. Short-term clinical outcomes of onasemnogene abeparvovec treatment for spinal muscular atrophy. Brain Dev. 2022;44(4):287-93.
34. Matesanz SE et al. Clinical experience with gene therapy in older patients with spinal muscular atrophy. Pediatr Neurol. 2021;118:1-5.
35. Matesanz SE et al. Clinical course in a patient with spinal muscular atrophy type 0 treated with nusinersen and onasemnogene abeparvovec. J Child Neurol. 2020;35(11):717-23.
36. Mikos B et al. Onasemnogene abeparvovec therapy following nusinersen treatment in eight patients with spinal muscular atrophy type 1. J Neurol Neurosurg. 2021;16(3):555940.
37. Stettner GM et al. Treatment of spinal muscular atrophy with onasemnogene abeparvovec in Switzerland: a prospective observational case series study. BMC Neurol. 2023;23(1):88.
38. Tosi M et al. Switching therapies: safety profile of onasemnogene abeparvovec-xioi in a SMA1 patient previously treated with risdiplam. Acta Myol. 2022;41(3):117-20.
39. Waldrop MA, Elsheikh BH. Spinal muscular atrophy in the treatment era. Neurol Clin. 2020;38(3):505-18.
40. Waldrop MA et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. Pediatrics. 2020;146(3):e20200729.
41. Weiß C et al. Gene replacement therapy with onasemnogene abeparvovec in children with spinal muscular atrophy aged 24 months or younger and bodyweight up to 15 kg: an observational cohort study. Lancet Child Adolesc Health. 2022;6(1):17-27.
42. Witte D et al. [Thrombotic microangiopathy (TMA) after gene replacemant therapy (GRT) due to spinal muscular atrophy: case summary and recommendations for treatment]. Klin Padiatr. 2022;234(1):42-7. (In German).
43. Yazaki K et al. Child neurology: pathologically confirmed thrombotic microangiopathy caused by onasemnogene abeparvovec treatment for SMA. Neurology. 2022;98(19):808-13.
44. Gowda V et al. Real-world experience of delivering gene-therapy with onasemnogene abeparvovec (Zolgensma®) for children with spinal muscular atrophy (SMA) type-1 in the UK. J Neurol Neurosurg Psychiatry. 2022;93:e2.
45. Servais L et al. Onasemnogene abeparvovec (OA) treatment outcomes by patient weight at infusion: initial findings from the RESTORE registry. Neuromuscul Disord. 2022;32(Suppl 1):S87.
46. Khoshnood M et al. Onasemnogene abeparvovec (Zolgensma) decreases ventilator/bi-pap support in 3 infants with SMA 1. Ann Case Report. 2021;6:583.
47. Matesanz SE, Kichula EA. Early clinical experience with onasemnogene abeparvovec in spinal muscular atrophy (SMA) type 2 patients at a single center. Neurology. 2020;94(Suppl 15):4855.
48. Glanzman AM et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010;20(3):155-61.
49. Mingozzi F, High KA. Immune responses to AAV vectors: overcoming barriers to successful gene therapy. Blood. 2013;122(1):23-36.
50. Guillou J et al. Fatal thrombotic microangiopathy case following adeno-associated viral SMN gene therapy. Blood Adv. 2022;6(14):4266-70.

51. Ertl HCJ. Immunogenicity and toxicity of AAV gene therapy. Front Immunol. 2022;13:975803.
52. U.S. Food and Drug Administration (FDA). Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT). 2021. Available at: https://www.fda.gov/media/151599/download. Last accessed: 4 August 2023.
53. Verdera HC et al. AAV vector immunogenicity in humans: a long journey to successful gene transfer. Mol Ther. 2020;28(3):723-46.
54. Hinderer C et al. Severe toxicity in nonhuman primates and piglets following high-dose intravenous administration of an adeno-associated virus vector expressing human SMN. Hum Gene Ther. 2018;29(3):285-98.
55. Zhao B et al. Evaluation of the efficacy of steroid therapy on acute liver failure. Exp Ther Med. 2016;12(5):3121-9.
56. Chai Z et al. Optimization of dexamethasone administration for maintaining global transduction efficacy of adeno-associated virus serotype 9. Hum Gene Ther. 2019;30(7):829-40.
57. European Medicines Agency (EMA). Luxturna (voretigene neparvovec) summary of product characteristics. 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf. Last accessed: 4 August 2023.
58. European Medicine Agency (EMA). Hemgenix (etranacogene dezaparvovec) summary of product characteristics. 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/hemgenix-epar-product-information_en.pdf. Last accessed: 4 August 2023.
59. Novartis Gene Therapies. Pre-symptomatic study of intravenous onasemnogene abeparvovec-xioi in spinal muscular atrophy (SMA) for patients with multiple copies of SMN2 (SPR1NT). NCT03505099. https://clinicaltrials.gov/ct2/show/study/NCT03505099.
60. Mendell JR. Muscular Dystrophy Association Clinical and Scientific Congress, 19-22 March, 2023.