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Original article

Outcomes for patients in the RESTORE registry with spinal muscular atrophy and four or more *SMN2* gene copies treated with onasemnogene abeparvovec

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ABSTRACT

Objective: We describe outcomes following onasemnogene abeparvovec monotherapy for patients with ≥four *survival motor neuron 2* (*SMN2*) gene copies in RESTORE, a noninterventional spinal muscular atrophy patient registry.
Methods: We evaluated baseline characteristics, motor milestone achievement, post-treatment motor function, use of ventilatory/nutritional support, and adverse events as of December 22, 2022.
Results: At data cutoff, 19 patients in RESTORE had ≥four *SMN2* copies and were treated with onasemnogene abeparvovec monotherapy (n=12 [63.2%] four copies; n=7 [36.8%] >four copies). All patients were identified by newborn screening and were reported as asymptomatic at diagnosis. Median age at onasemnogene abeparvovec administration was 3.0 months. Median time from treatment to last recorded visit was 15.4 months, with a range of post-treatment follow-up of 0.03–39.4 months. All 12 children who were assessed for motor development achieved new milestones, including standing alone (n=2) and walking alone (n=5). Five children reported one or more treatment-emergent adverse events (one Grade 3 or greater). No deaths or use of ventilatory/nutritional support were reported.
Conclusions: Real-world findings from the RESTORE registry indicate that patients with ≥four *SMN2* gene copies treated with onasemnogene abeparvovec monotherapy demonstrated improvements in motor function. Adverse events experienced by these patients were consistent with previously reported findings.

1. Introduction

Spinal muscular atrophy (SMA), a hereditary, neurodegenerative disease characterized by progressive muscle atrophy, weakness, and paralysis, is caused by biallelic *survival motor neuron 1* (*SMN1*) gene deletion or mutation [1–9]. SMA phenotype is highly variable, historically described as a range of clinical types (0–4), defined by maximal motor function achieved and age at symptom onset [10]. Typically, patients with SMA types 0 or 1 have the most severe symptoms if untreated, and patients with SMA type 4 have the least severe symptoms [11]. However, disease-modifying treatments and newborn screening are changing the way SMA is classified and described [12,13].

Patients with SMA are diagnosed based on *SMN1* alteration; the number of copies of the homologous *SMN2* gene is correlated with SMA

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disease severity and symptom onset [2–10,14–17]. However, despite the relationship between SMA disease severity and *SMN2* copy number, symptoms can be highly variable between patients who have the same number of *SMN2* copies [14,15,18–22]. While patients with four *SMN2* copies are most likely to develop SMA type 3, up to 19% will develop SMA type 2, and some may develop SMA type 1. Indeed, a number of reports have described symptom onset (e.g., proximal weakness) within the first year of life [13,14,18,19,23–26]. Further, laboratory testing for *SMN2* copies can vary widely within and between testing centers, which may contribute to the discrepancy observed between patients with the same number of *SMN2* copies and differing symptoms [23].

Regardless of phenotype, SMA manifestations indicate an irreversible loss of motor neurons [14,18,19,26,27], which may be prevented or mitigated with early intervention. This preventability, coupled with the unpredictable potential for development of life-threatening disease and the prevalence of SMA patients with four or more *SMN2* copies (found in up to 40% of patients with SMA identified by newborn screening), highlights the need for additional data and treatment recommendations for these patients [13,14,18,19,23,24,28,29].

Onasemnogene abeparvovec (OA) is a one-time, intravenous, adeno-associated virus 9 (AAV9) vector–based gene replacement therapy that delivers a functional copy of the human *SMN* cDNA into target cells [30,31]. Efficacy and safety of OA have been demonstrated in clinical trials for patients with SMA type 1 and for presymptomatic patients with two or three *SMN2* copies [30,32–37]. Although these trials included only patients with two or three *SMN2* copies, patients with four or more copies may be treated in clinical practice [38].

RESTORE is an ongoing, prospective, multicenter, multinational, observational disease registry assessing real-world treatment patterns and outcomes for patients with SMA, with the goal of informing treatment decisions and improving patient outcomes in the context of disease-modifying therapies and evolving treatment paradigms [38,39]. Here, we describe SMA patients with four or more *SMN2* copies treated with OA monotherapy from the RESTORE registry.

2. Methods

The RESTORE registry is a global, prospective, noninterventional registry representing a collaboration between Novartis Gene Therapies, Inc., and an international team of SMA treatment experts [38,39]. Detailed methodology, including registry study design, ethical considerations, patient eligibility, data acquisition, and variables assessed, has been published (Figure S1) [39]. As an observational registry, clinical care is not dictated by a research protocol [39].

In the current analysis, patient characteristics, post-treatment changes in motor function, motor milestone achievement, use of ventilatory/nutritional support, and safety of OA were assessed for children with four or more *SMN2* gene copies in RESTORE. Data cutoff was December 22, 2022.

2.1. Patient characteristics

Real-world effectiveness and safety outcomes were assessed for all SMA patients with four or more *SMN2* copies who received OA monotherapy (i.e., patients who received only OA gene therapy and had not received any dose of another disease-modifying treatment [i.e., nusinersen and/or risdiplam]) [40]. Patient variables collected include sociodemographic characteristics (e.g., age and sex), history of SMA (e.g., age at SMA diagnosis, genetic status), *SMN2* copy number (collected as "4" or ">4" for patients with >four copies), other medical history, and age at OA administration [39]. *SMN2* copy number was evaluated locally and not verified at a central location.

2.2. Effectiveness

2.2.1. Motor milestones

Motor milestones were assessed using criteria from the World Health Organization (WHO) [41,42] and Bayley Scales of Infant and Toddler Development, Third Edition (BSID) [43]. Ten select performance criteria were used to define the achievement of developmental milestones on the case report form, specifically: holds head erect 3 s; rolls from back to sides; sits independently without support for >10 s (WHO); sits independently without support for ≥30 s (BSID); stands with assistance; crawls forward ≥5 feet; pulls to stand; walks with assistance; stands alone; and walks alone five or more steps (WHO). The interval for each collection was dependent on routine follow-up visits [39]. Because no predetermined follow-up was scheduled, motor milestones may not have been recorded at every visit, and age of first recorded milestone achievement may not reflect true age at first achievement.

2.2.2. Motor function

Patient scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Infant Neurological Examination – Section 2 (HINE-2), and Hammersmith Functional Motor Scale – Expanded (HFMSE) were collected (Figure S1) [38,39]. Because clinical care is not dictated by a research protocol in RESTORE, if CHOP INTEND, HINE-2, and HFMSE were assessed, the interval between assessments was at the discretion of the treating clinician [39] and motor function assessments may not have been recorded at every visit. Changes in motor function were assessed for evaluable patients (i.e., patients having two or more assessments, with at least one assessment after OA administration). No pretreatment testing was required. Not all participating sites had clinical evaluators, mainly trained physical therapists, to perform these motor function tests.

2.3. Safety

Safety data (treatment-emergent adverse events [TEAEs]) collected in the RESTORE registry included pulmonary assessments, ventilatory support, use of non-oral feeding support, safety laboratories including liver function tests, and start and stop dates of serious adverse events (SAEs) and adverse events of special interest (AESI), including dates and primary causes of death [38,39]. Adverse events (AEs) were coded using MedDRA®, Version 25.0, with patients counted only once at each level of summarization.

RESTORE investigators reported AEs at their discretion [38]. Any reported AEs matching the prespecified definitions of AESI were counted as an AESI (i.e., hepatotoxicity, transient thrombocytopenia, cardiac AEs, and thrombotic microangiopathy) [38]. Hepatotoxicity was defined per protocol as having clinically significant laboratory values (i.e., alanine aminotransferase or aspartate aminotransferase >3 × upper limit of normal [ULN], and with associated bilirubin >2 × ULN), hepatic failure, fibrosis, cirrhosis or other liver damage-related conditions, or hepatic disorders (it should be noted that bilirubin may not have been measured as it is of secondary interest) [38]. Thrombocytopenia was defined as having an AE identified as hematopoietic thrombocytopenia, hemorrhages, or platelet disorders [38]. Cardiac AESI included ischemic heart disease, cardiomyopathy, cardiac arrhythmias, myocardial infarction, or embolic and thrombotic events [38].

2.4. Descriptive statistics

Descriptive statistics were used to assess demographic, clinical, and treatment characteristics, with means (±standard deviation [SD]), median and range, or percentages, as applicable [39]. The relationships of the endpoints were investigated qualitatively. Minimal clinically

Table 1
Demographics and baseline clinical characteristics.

Patient demographics/characteristics	Total patients (N=19)
Sex, n (%)	
Male	11 (57.9)
Female	8 (42.1)
Race, n (%)	
White	14 (73.7)
Black	2 (10.5)
Not available	3 (15.8)
Number of *SMN2* gene copies, n (%)	
Four	12 (63.2)
More than four	7 (36.8)
Identified by newborn screening, n (%)	19 (100)
Asymptomatic at diagnosis, n (%)	19 (100)
Functional status prior to OA administration, n (%)	
Non-sitter	15 (78.9)
Sitter	2 (10.5)
Standing	1 (5.3)
Missing	1 (5.3)
Age at initial SMA genetic diagnosis, months	
Median (min, max)	0 (0, 8)
IQR	0–1
Mean (SD)	0.95 (1.96)
Weight at OA administration, kg	
Median (min, max)	5.5 (3.4, 9.4)
IQR	4.4–7.6
Mean (SD)	6.01 (1.94)
Age at OA administration, months	
Median (min, max)	3.0 (1, 11)
IQR	2–7
Mean (SD)	4.58 (3.34)
Duration of follow-up after OA administration, months	
Median (min, max)	15.4 (0.03, 39.4)
IQR	1.1–23.5
Mean (SD)	13.81 (11.76)
Time between diagnosis and treatment, months	
Median (min, max)	3.0 (0, 10)
IQR	1–5
Mean (SD)	3.63 (3.09)

IQR, interquartile range; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2*.

important differences were defined for CHOP INTEND (≥4-point change), HFMSE, (≥3-point change), and HINE-2 (≥2-point change) [38].

3. Results

3.1. Patients

Recruitment started in September 2018, and as of the December 22, 2022 data cutoff, the RESTORE registry included data for a total of 449 patients (Figure S2). Forty patients had four or more *SMN2* gene copies, 19 of whom were treated with OA monotherapy (United States n=18 [94.7%]; Israel n=1 [5.3%]) (Figure S2). Twelve of these patients (63.2%) had four *SMN2* copies, and seven (36.8%) had more than four *SMN2* copies (Table 1; Figure S2). Median age of enrollment was 3.0 (range: 1.0–36.0) months. Median age at OA infusion was 3.0 (range: 1.0–11.0) months, with six patients ≥6 months of age at OA administration. Median weight at OA infusion was 5.5 kg. Median time from OA infusion to the last recorded visit was 15.4 months, with a range of post-treatment follow-up of 0.03–39.4 months. The majority of patients were male (57.9%). All 19 OA monotherapy patients were identified by newborn screening, and all were classified as asymptomatic at diagnosis.

3.2. Effectiveness

3.2.1. Motor milestones

Twelve patients had motor milestones recorded, seven of whom had four *SMN2* copies and five of whom had >four *SMN2* copies (Table 2 and Fig. 1). Though ages for enrollment and follow-up varied, median age at last recorded milestone for the 12 patients with available assessments was 14.6 (range: 4.1–24.5) months (Table 2). All 12 patients achieved new motor milestones during the observation period. No patient "lost" previously gained motor milestones (Fig. 1 illustrates the highest achieved motor milestones at each assessment). For most patients, newly achieved motor milestones were reported only after OA (n=8). One patient had achieved a new motor milestone before OA only, and three patients had recorded motor milestones both before and after OA.

The youngest patients by age at the last recorded milestone were able hold their heads erect for 3 s at a median of 4.1 months of age (Patient 10, who received OA at 5 months of age, and Patient 16, who received OA at 4 months of age). Rolling from back to side was noted for six patients at a visit performed at a median age of 5.6 (range: 4.3–17.9) months (n=4 with four copies [Patients 1–4]; n=2 with >four copies [Patients 11 and 14]). One of these patients achieved rolling ability at 4.3 months, prior to OA administration (Patient 1), and for two cases, this milestone was the last one reported during follow-up (at 6.6 and 17.9 months of age, Patients 14 and 2, respectively). Sitting independently without support for ≥30 s was noted for four infants at a median age of 8.15 (range: 7.5–10.8) months at follow-up (n=2 with four copies [Patients 1 and 4]; n=2 with >four copies [Patients 11 and 12]).

A majority of patients achieved either standing alone or walking alone for ≥five steps. Two children demonstrated independent standing at a visit performed at a median age of 19.9 months, one at 16.4 months (Patient 11; >four *SMN2* copies) and the other at 23.4 months (Patient 6; four *SMN2* copies). Five children demonstrated the ability to walk alone for ≥five steps at a visit performed at a median age of 15.1 (range: 10.1–24.5) months (n=4 with four copies [Patients 1, 3, 4, 9]; n=1 with ≥four copies [Patient 12]). Patient 13 (>four *SMN2* copies) achieved their highest recorded milestone of raising self to stand at age 9.3 months after demonstrating no milestones at two previous visits (OA administration at 2.5 months).

3.2.2. Motor function

Thirteen patients had one or more CHOP INTEND scores recorded, seven of whom maintained (n=3) or achieved (n=4) the maximum score of 64 points (Fig. 1; Table S1). Five patients who reached the maximum score had four *SMN2* copies and two had >four copies. Out of the seven patients with the maximum CHOP INTEND score, three patients were female and four were male, with a median age of 3 (range: 1–11) months. Median weight at OA infusion for these patients was 5.4 (range: 4.4–7.9) kg. Four patients (30.8% [n=2 four copies; n=2 ≥four copies]) had two or more evaluable CHOP INTEND assessments, with one or more assessment after OA administration. One patient maintained the maximum score of 64, and the remaining three patients had clinically meaningful improvements ranging from 8- to 18-point increases (Table S1).

Six patients had one or more HFMSE scores recorded. Although one patient achieved a score of 63 points, no patients achieved the maximum score of 66 points (Fig. 1; Table S1). Seven children had at least one HINE-2 score recorded; three (42.8%) achieved the maximum score of 26. One patient had subsequent scores and showed a clinically meaningful improvement from 0 to 6 (Fig. 1; Table S1).

3.3. Safety

All 19 patients were assessed for safety, five of whom (26.3%) had one or more recorded TEAEs (Table 3). SAEs of seizure and dehydration secondary to adenovirus infection were reported for two patients (10.5%), but none were determined by the investigator to be treatment-related. A TEAE of Grade 4 (seizure, which recovered/resolved) was reported for one patient (5.3%). No patients experienced treatment-related SAEs, as determined by the investigator. No deaths or use of ventilatory or nutritional support were reported.

Reported AESI included elevated transaminases, transient

Table 2
Age at last recorded milestone for the 12 patients with motor milestone assessments.

Patient	Number of *SMN2* gene copies	Age at OA administration, months	Age at last recorded milestone, months[a]	Last recorded milestone
Patient 1	Four	11	15.1	Walks alone ≥5 steps
Patient 2	Four	3	17.9	Rolls from back to sides
Patient 3	Four	3	10.1	Walks alone ≥5 steps
Patient 4	Four	6	12.0	Walks alone ≥5 steps
Patient 6	Four	3	23.4	Stands alone
Patient 9	Four	7	16.0	Walks alone ≥5 steps
Patient 10	Four	5	4.1	Holds head erect for 3 s
Patient 11	>Four	2	16.4	Stands alone
Patient 12	>Four	1	24.5	Walks alone ≥5 steps
Patient 13	>Four	2	9.3	Raises self to stand with support
Patient 14	>Four	3	6.6	Rolls from back to sides
Patient 16	>Four	4	4.1	Holds head erect for 3 s

OA, onasemnogene abeparvovec; *SMN2*, *survival motor neuron 2* gene.
[a]Age at last recorded milestone achievement may not reflect true age the milestone was first attained because there was no predetermined follow-up schedule and motor milestones were not recorded at every visit in the RESTORE registry.

thrombocytopenia, and elevated troponin (Table 3). Transaminase elevations over three times the normal values were reported for 21% (n=4/19) of patients. No cases of acute liver failure or acute serious liver injury were reported. Thrombocytopenic events comprised isolated decreases in platelet counts without clinical significance or sequelae. Troponin elevation without clinical significance or sequelae was recorded for one patient (5.3%).

4. Discussion

Children with four or more *SMN2* copies who had available data in the RESTORE registry achieved or maintained motor milestones, attained improvements in motor function, and remained free from nutritional or ventilatory support following OA treatment. Patients achieved milestones of sitting without support, standing with assistance, and standing alone at ages within or close to the appropriate age ranges for these milestones determined by the WHO Multicentre Growth Reference Study; however, milestones may have been achieved at other time points not captured [42]. Observed AEs were consistent with the established OA safety profile in patients with two or three *SMN2* gene copies [30,33–37]. This is the first study to follow patients with SMA and four or more *SMN2* copies treated with OA; ongoing follow-up of these patients will provide extended long-term data on the effectiveness and safety of gene replacement therapy for SMA in this understudied patient population.

While natural history data are limited for patients with four or more *SMN2* gene copies versus data for other patient populations, the phenotypic variability and risk for progressive decline and development of a more serious phenotype over time is evident [26,44–47]. For example, out of 268 patients with four *SMN2* copies from a retrospective analysis of patients in Germany, Austria, and Switzerland, 55% experienced symptoms before the age of 36 months, 3% never sat unaided, 13% never gained the ability to walk independently, and 33% of ambulatory patients lost this ability during the course of disease [47]. An Italian study of 169 patients confirmed this phenotypic heterogeneity, and overall reduction of motor function with increasing age [26]. Similarly, case studies have demonstrated that patients with four or more *SMN2* copies can exhibit severe weakness as early as 8 months of age. Moreover, some patients who were treated after symptom onset did not regain lost motor abilities, underscoring the importance of timely intervention before widespread permanent loss of motor neurons [18,19].

There is still no worldwide consensus recommendation for presymptomatic treatment for patients with four or more *SMN2* copies. The initial "wait-and-see" recommendation has been revised by experts in some countries, including the United States, to advocate early treatment of all infants with four *SMN2* copies to prevent the likelihood of serious manifestations of SMA [18,19,25,28,48]. In other regions of the world, watchful waiting remains the recommendation for screened newborns with more than four *SMN2* copies [18,19,25,28,48].

Though *SMN2* gene copy number typically correlates to SMA disease severity, there is considerable individual variation in symptom presentation and disease course regardless of *SMN2* copy number [14,15,18–23]. Potential difficulty in assessing accurate test results for patients with *SMN2* gene copies further compounds the discordant relationship between genotype and phenotype in these patients. Structural variations (e.g., partial deletions, modifier variants) or technical issues with *SMN2* quantitation could interfere with accurate detection of *SMN2* copy number, particularly in patients with four or more *SMN2* copies [23,49]. Improved understanding of the molecular genetics of SMA, including the

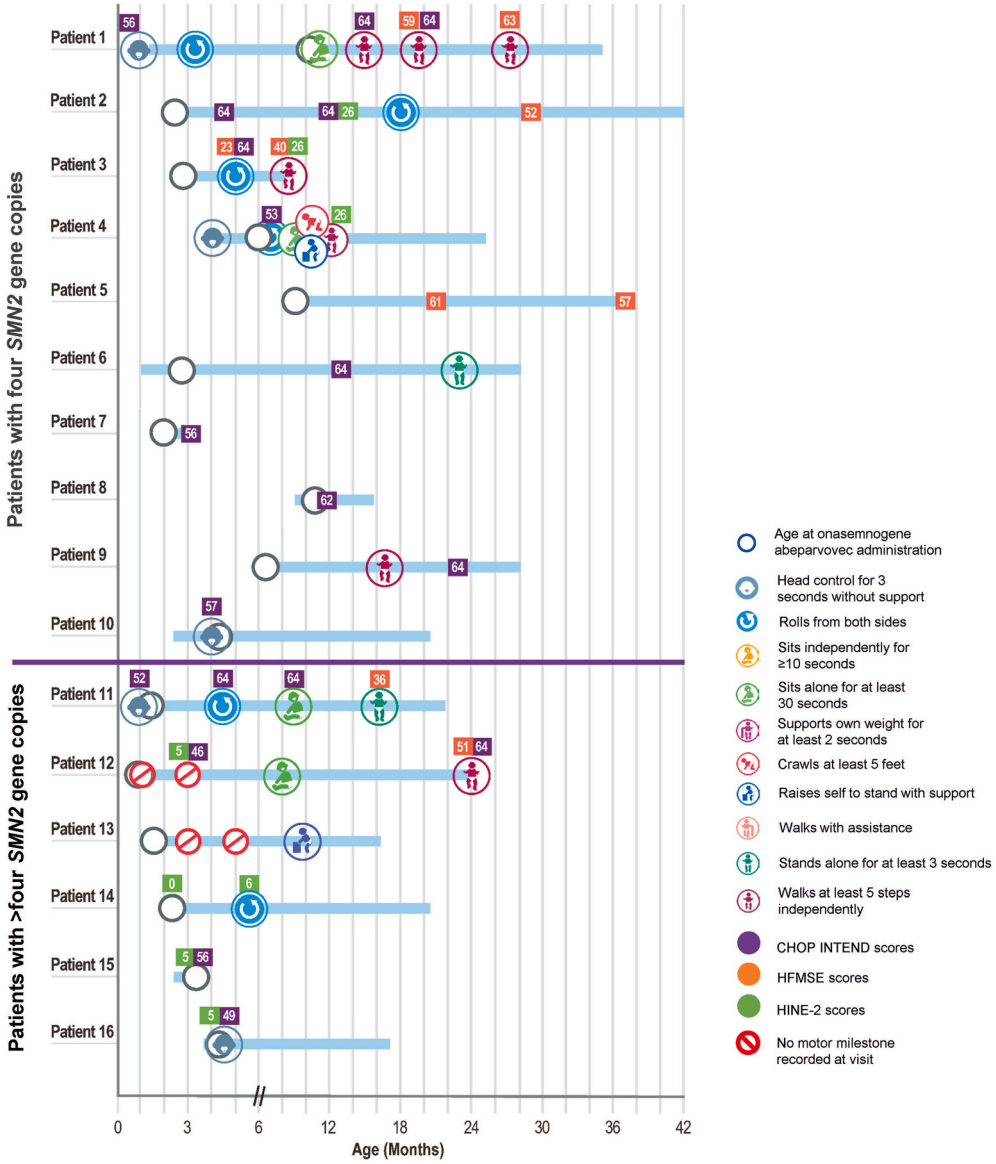

Fig. 1. Motor function scores and first recorded achievement of motor milestones by age.[a]
Note: Although data collection is ongoing, three patients do not yet have motor function scores or motor milestones recorded in the RESTORE registry database.
CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination – Section 2; HFMSE, Hammersmith Functional Motor Scale – Expanded; *SMN2*, *survival motor neuron 2*.
[a]All achieved milestones were maintained. Age of first recorded milestone achievement may not reflect true age at first achievement. There was no predetermined follow-up schedule, and motor function and/or motor milestones were not recorded at every visit. Some centers may have considered milestone and functional assessments to be redundant for some patients.

presence of other genetic variants that influence SMA severity, is needed [15,16,27,49,50]. Studies are underway to identify biomarkers for SMA to provide information about the underlying mechanisms of disease and to help in identifying those presymptomatic children who will present with early and rapid disease progression [51,52].

Our analysis has some noteworthy limitations, largely related to sample size, longitudinal data collection, and wholeness of real-world registry data. A small number of patients meeting analysis criteria were identified from only two countries. And, while duration of follow-up after OA administration was variable, the maximum follow-up time in this data set (39.4 months) warrants caution in attributing outcomes to treatment effect. Pertinent baseline data (e.g., SMA symptom status at time of OA infusion) were not always captured [39]. With respect to motor milestones, the earliest date/age of achievement recorded in the registry does not necessarily reflect true age at first achievement, and all milestone achievements may not have been recorded [8]. In addition, as data collection in RESTORE is mainly prospective, AEs occurring before enrollment may not have been recorded, and TEAEs occurring soon after administration of OA may not have been captured for patients enrolled post-administration [38]. Taken as a whole, these factors (essentially, the descriptive nature of the registry and limited longitudinal evaluation of functional assessments) preclude robust statistical hypothesis testing [39]. Lastly, quantification of *SMN2* gene copy number relied on variable testing methods and was not confirmed by a central laboratory. *SMN2* copy number ">4" was captured in the RESTORE electronic data capture tool, but specific copy number for patients with more than four copies is unknown.

Table 3
Treatment-emergent adverse events.

	Total patients (N=19)
Any grade TEAE, n (%)	5 (26.3)
≥Grade 3 TEAE, n (%)	1 (5.3)[a]
SAE,[b] n (%)	2 (10.5)
Related AE, n (%)	3 (15.8)
Serious related AE, n (%)	0 (0)
AESI	
Raised transaminases,[c] n (%)	4 (21.0)
Transient thrombocytopenia, n (%)	1 (5.3)
Cardiac AEs, n (%)	1 (5.3)

AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Grade 4 seizure reported in one patient.
[b]SAEs included seizure and dehydration secondary to adenovirus infection.
[c]Transaminase elevations over three times normal values.

5. Conclusions

Real-world data from the RESTORE registry indicate favorable safety and effectiveness of OA gene replacement therapy in clinical practice in the United States and Israel for children with four or more *SMN2* gene copies treated after newborn screening. Though patients in this analysis were asymptomatic at the time of diagnosis, their status at time of treatment was unknown. It is possible that patients may have demonstrated symptoms prior to treatment initiation. Indeed, the possibility of early disease onset in this patient population is well documented. Individual disease severity remains to be unpredictable in patients with four or more *SMN2* gene copies; however, identification of 'early-onset four-copy' patients may improve the benefit-risk calculus of early, pre-symptomatic treatment for patients with ≥four *SMN2* gene copies.

Author contributions

As stipulated in the RESTORE bylaws, all publication topics were approved by the members of the steering committee, and analyses were performed by statisticians employed by Novartis Gene Therapies, Inc. or the CRO that manages the registry data. All authors had access to and analyzed and interpreted the data, participated in the development and critical review of the manuscript, approved the final version of the manuscript submission for publication, and are accountable for the accuracy and integrity of the work.

Data-sharing statement

The data sets generated and analyzed during the study are available from the RESTORE registry. These data sets are not publicly available, but are available from the corresponding author/RESTORE Steering Committee on reasonable request.

Declaration of competing interest

EFT received personal compensation for consultancy from Novartis Gene Therapies, Inc., Biogen, Biologiz, Cytokinetics, Novartis, and Roche, and research funding from Biogen/Ionis and Roche. **SQ-R** has participated in clinical trials sponsored by Roche, Novartis and Biogen, and has received speaker and/or consulting fees from Biogen, Novartis Gene Therapies, Inc. (AveXis), Sanofi, UCB, and Roche. She has received research support from the European Commission, INSERM-Health Ministry, and the Association Française des Myopathies (AFM). She is the scientific coordinator of the Registre SMA FRANCE for the French neuromuscular network (FILNEMUS) (http://filnemus.fr) and coordinator of the Garches-Necker-Creteil Health Care Provider for the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD). **LS** has received personal compensation from Novartis Gene Therapies, Inc., Biogen, Inc., Cytokinetics, Scholar Rock, Biohaven, Akros Pharma, Roche, and Illumina, and research funding from Novartis Gene Therapies, Inc., Biogen, Dynacure, and Roche. **JAP** has received clinical trial funding from AveXis/Novartis, Biogen, PTC Therapeutics, Sarepta Therapeutics, Biohaven, Genentech, and Scholar Rock, and served as advisor/consultant for AveXis, Biogen, Genentech, and Scholar Rock. **SA** is a site principal investigator for clinical trials of Biogen, Novartis Gene Therapies, Inc., and Roche; has participated on advisory boards for Novartis Gene Therapies, Inc./Novartis, and Roche; received speaker's fees from Biogen, Novartis, and Roche; and received a research grant from Novartis Gene Therapies, Inc. **AL** has served on advisory boards for AveXis and Biogen and received research funding from Novartis and Genentech. **RSF** has received personal compensation for advisory board/data safety monitoring board participation from Novartis Gene Therapies, Inc., Biogen, Catabasis, Ionis, ReveraGen, Roche/Genentech, and Scholar Rock; editorial fees from Elsevier for co-editing a neurology textbook; license fees from the Children's Hospital of Philadelphia; and research funding from Novartis Gene Therapies, Inc., Biogen, Catabasis, ReveraGen, Roche/Genentech, and Scholar Rock.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2024.08.006.

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