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Safety and Efficacy of IV Onasemnogene Abeparvovec for Pediatric Patients With Spinal Muscular Atrophy

The Phase 3b SMART Study

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Abstract

Background and Objectives

Safety and efficacy of IV onasemnogene abeparvovec has been demonstrated for patients with spinal muscular atrophy (SMA) weighing <8.5 kg. SMART was the first clinical trial to evaluate onasemnogene abeparvovec for participants weighing 8.5–21 kg.

Methods

SMART was an open-label, multicenter, phase 3b study conducted across 13 sites in 9 countries (NCT04851873). Symptomatic pediatric participants with SMA (any type; treatment-naïve or had discontinued prior treatment) were stratified into 3 weight cohorts (≥8.5–13, >13–17, and >17–21 kg), administered onasemnogene abeparvovec, and followed for 52 weeks. Corticosteroids were initiated 24 hours before infusion with dose increases in response to adverse events (AEs) and subsequent tapering at investigator discretion. The primary objective was safety. Secondary objective was efficacy (motor function/motor milestones).

Results

Twenty-four participants were enrolled; the majority had SMA type 2 (n = 11), 3 *SMN2* copies (n = 18), and prior treatment (n = 21). All participants completed the study; no deaths occurred. All participants had ≥1 treatment-related AE(s), 7 of 24 (29%) had serious treatment-related AEs, and 23 of 24 (96%) had ≥1 AE of special interest. Twenty of 24 participants (83%) had asymptomatic hepatotoxicity events, which were primarily transaminase elevations. No participant had bilirubin elevations >2× upper limit of normal, developed symptomatic hepatotoxicity, or met Hy law criteria. Transient asymptomatic thrombocytopenia events were reported in 17 of 24 participants (71%); all resolved spontaneously with no related bleeding events reported. Three of 24 participants (13%) had cardiac AEs (all unrelated to treatment). No thrombotic microangiopathy or dorsal root ganglionopathy-related AEs were reported. AE frequency and severity were similar across weight groups, although corticosteroid exposure was greater for the 2 heavier cohorts (median 135.0, 201.0, and 194.0 days, respectively) with 37% and 33% still on corticosteroids at the study end. By week 52, most participants maintained or

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Glossary

AAV = adeno-associated virus; **AE** = adverse event; **AESI** = adverse event of special interest; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **Bayley-III** = Bayley Scales of Infant and Toddler Development, Third Edition; **HFMSE** = Hammersmith Functional Motor Scale–Expanded; **RULM** = Revised Upper Limb Module; **SAE** = serious adverse event; **SMA** = spinal muscular atrophy; **SMN** = survival motor neuron; ***SMN1*** = *survival motor neuron 1*; ***SMN2*** = *survival motor neuron 2*; **TEAE** = treatment-emergent adverse event; **ULN** = upper limit of normal; **vg** = vector genomes.

improved motor function (Hammersmith Functional Motor Scale–Expanded 16/18; Revised Upper Limb Module 15/17); 4 participants (all 3 *SMN2* copies) achieved new motor milestones.

Discussion

Onasemnogene abeparvovec safety profile was similar across weight groups in this heterogenous participant population. Frequency and duration of asymptomatic aminotransferase elevations and thrombocytopenia are notable findings. Most participants demonstrated maintenance or improvement of motor function, suggesting clinical benefit for patients with SMA weighing up to 21 kg.

Trial Registration Information

ClinicalTrials.gov identifier (NCT04851873, clinicaltrials.gov/study/NCT04851873) submitted April 19, 2021. First participant enrolled on September 8, 2021.

Classification of Evidence

This study provides Class IV evidence that intravenous onasemnogene abeparvovec is safe in pediatric patients with SMA who weigh 8.5–21 kg.

Introduction

Spinal muscular atrophy (SMA) is a rare, progressive, neuromuscular disease caused by the biallelic deletion or variation of the essential *survival motor neuron 1* (*SMN1*) gene. Loss of *SMN1* gene function leads to deficiency of survival motor neuron (SMN) protein, which is critical for motor neuron survival. SMA treatments include the *survival motor neuron 2* (*SMN2*) splicing modifiers nusinersen and risdiplam, as well as onasemnogene abeparvovec, an adeno-associated virus (AAV) gene therapy.

IV onasemnogene abeparvovec has demonstrated efficacy and safety across 5 clinical trials of participants with SMA type 1[1-4] or presymptomatic SMA with 2[5] or 3[6] *SMN2* gene copies. Compared with natural history, patients with symptomatic SMA treated with onasemnogene abeparvovec demonstrated substantial improvements in event-free survival and motor function, achievement of developmental motor milestones, and independence from respiratory and nutritional support.[1-6] Long-term safety and sustained efficacy has been demonstrated for more than 5 years post dosing.[7]

Previous completed trials investigating the efficacy and safety of IV onasemnogene abeparvovec enrolled only treatment-naïve participants weighing less than 8.5 kg at the time of treatment.[1-6] Additional clinical trial data were required to confirm safety and efficacy for participants up to 21 kg. The SMART study (NCT04851873) was a phase 3b, open-label, single-arm, multinational study undertaken to determine the safety, tolerability, and efficacy of IV onasemnogene abeparvovec for participants with SMA (any *SMN2* copy number) weighing 8.5–21 kg, some of whom had discontinued another approved disease-modifying treatment. These data will help support informed treatment decision-making by health care professionals and caregivers and complement published real-world evidence.[8-13]

Methods

Study Design

SMART was an open-label, single-arm, multicenter, phase 3b study to evaluate the safety, tolerability, and efficacy of IV onasemnogene abeparvovec for participants with SMA weighing 8.5–21 kg (eFigure 1). The SMART study aimed to enroll 24–30 participants evenly across 3 weight groups (weight determined at dosing): ≥8.5–13, >13–17, and >17–21 kg.

Participants who met eligibility criteria at screening and baseline visits received a single dose of IV onasemnogene abeparvovec (1.1×10^{14} vector genomes [vg]/kg) on day 1 (treatment period), followed by inpatient safety monitoring for 48 hours and a 12-month follow-up period. After study completion, participants were invited to enroll in a long-term follow-up study, SPECTRUM (NCT05335876).

Standard Protocol Approvals, Registrations, and Participant Consents

This clinical study was undertaken in accordance with the International Council for Harmonisation E6 Guidelines for Good Clinical Practice with the ethical principles laid down in the Declaration of Helsinki. The study was approved by institutional review boards at all participating institutions (Ethics Committee Research UZ/KU Leuven [S65529]; Institutional Review Board-II Kaohsiung Medical University Chung-Ho Memorial Hospital [KMUHIRB-F(II)-20210115]; McGill University Health Centre Research Ethics Board [#2022-7908]; North East – York Research Ethics Committee; Sydney Children's Hospital Network Human Research Ethics Committee [SCHN HREC 2021_ETH00694]). Written informed consent was obtained from parents or legal guardians of enrolled participants. The SMART study was registered at ClinicalTrials.gov (NCT04851873).

Participants

Full eligibility criteria are listed in the eMethods. Key inclusion criteria included a symptomatic SMA diagnosis confirmed by biallelic *SMN1* pathogenic variants (deletion or point variants) and any number of *SMN2* gene copies, weight ≥8.5–≤21 kg at the time of screening, and naïve to treatment or have discontinued an approved disease-modifying therapy according to the washout period recommended per treatment (>4 months for nusinersen and >15 days for risdiplam).

Key exclusion criteria included elevated anti-AAV9 antibody titer greater than 1:50; inability to take corticosteroids; requiring invasive ventilation, tracheostomy, or awake noninvasive ventilation; hepatic dysfunction (as defined in the eMethods); presence of a confirmed or suspected active infectious process; and if previously treated with disease-modifying treatment, participants were excluded if they received less than 3 doses of nusinersen, nusinersen within 4 months before screening, or risdiplam within 15 days before screening.

The first participant was enrolled on September 8, 2021, and treated on October 8, 2021. The last participant enrolled was treated on July 5, 2022.

Treatment

Participants received prophylactic prednisolone (or equivalent) 1 mg/kg/d approximately 24 hours before the infusion to mitigate the safety risks associated with immune response to the AAV9 capsid, as per onasemnogene abeparvovec administration guidelines. On day 1, participants received a single IV administration of onasemnogene abeparvovec (1.1×10^{14} vg/kg) for approximately 60 minutes followed by inpatient safety monitoring for 48 hours. Corticosteroids were continued at 1 mg/kg/d for at least 30-day postinfusion, followed by weekly tapering by 0.25 mg/kg/d reductions if serum transaminases had returned to within normal range. Dose changes and subsequent tapering were allowed as per investigator discretion.

Primary Objective

The primary objective was safety as measured by the incidence and severity of reported treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESI) (including hepatotoxicity, thrombocytopenia, cardiac adverse events [AEs], troponin I, clinical symptoms of dorsal root ganglia toxicity, and thrombotic microangiopathy). AESI were identified using predefined AE search terms that broadly summarize each umbrella term. Changes from baseline in vital signs, cardiac safety assessments (e.g., electrocardiogram and echocardiogram), and clinical laboratory assessments were also measured. Laboratory parameters included, but were not limited to, platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamate dehydrogenase, alkaline phosphatase, gamma-glutamyl transferase, and bilirubin (total, direct, and indirect). Safety was monitored on an ongoing basis by an external Data Monitoring Committee.

Secondary Objective

The secondary objective was to determine the efficacy of IV onasemnogene abeparvovec as measured by change from baseline in achieved developmental motor milestones according to the World Health Organization Multicentre Growth Reference Study and Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) criteria, Hammersmith Functional Motor Scale–Expanded (HFMSE), and Revised Upper Limb Module (RULM), as appropriate according to participant age. Change from baseline was reported in all participants who had data (all items) at baseline and at subsequent visit.

Data Analysis

Analysis sets included the full analysis set and the safety set both of which comprised all participants who received IV onasemnogene abeparvovec.

Data analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). To identify safety signals whose underlying incidence rate was approximately 10% or greater, the sample size of 24 participants was considered reasonable (R Statistical Software, Vienna, Austria) to provide descriptive safety information across 3 weight brackets from ≥8.5 to ≤21 kg, providing 90% probability to observe at least 1 event (any unspecified safety event) if the underlying incidence of the event was 9%.

Categorical data were presented as frequencies and percentages, and continuous data were presented using summary statistics. Incidence and severity for TEAEs, SAEs, and AESI were summarized overall and by weight bracket in the safety set. Changes from baseline in HFMSE and RULM, as well as developmental motor milestone achievements, were summarized overall and by weight bracket for the full analysis set.

Data Availability

A redacted version of the SMART study protocol and a redacted version of the statistical analysis plan are available

at ClinicalTrials.gov (NCT04851873) and within the supplementary materials (eSAP). Novartis is committed to sharing clinical trial data with external researchers and has been doing so voluntarily since 2014.

Novartis is committed to sharing, on requests from qualified external researchers and subsequent approval by an independent review panel based on scientific merit, anonymized patient-level and study-level clinical trial data, and redacted clinical study reports, for medicines and indications approved in the United States and Europe after the respective study is accepted for publication. All data provided are anonymized to respect the privacy of participants who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on clinicalstudydatarequest.com.

Results

Participant Disposition

The SMART study was initiated on September 8, 2021, and the last participant was treated on July 5, 2022. Twenty-nine participants with SMA were screened, and 5 participants did not meet eligibility because of the presence of an active infection during screening (Figure 1). No participant was excluded because of anti-AAV9 antibody titer >1:50. Twenty-four participants were enrolled across the 3 weight brackets: 8.5–13 kg (n = 7), >13–17 kg (n = 8), and >17–21 kg (n = 9) (eTable 1). All participants completed the 52-week study, and no participant discontinued the study.

Baseline Clinical Characteristics

The mean (SD) age of participants at baseline was 4.7 (1.82 [range 1.5–9.1]) years, with older participants generally in the higher weight group (Table 1). The study enrolled an equal number of male and female participants, and mean baseline body mass index values were similar across weight groups. The enrolled population was heterogeneous in SMA type, *SMN2* copy number, use of previous disease-modifying treatments, baseline HFMSE scores (range 0–55), and baseline RULM scores (range 4–37). Specifically, 3 participants were naïve to treatment, and 21 (88%) had received previous SMA disease-modifying treatment (nusinersen or risdiplam). Nineteen participants (79%) had received nusinersen for a median duration of 2.1 (range 0.17–4.81) years, and 2 participants (8%) had received risdiplam for a median duration of 0.48 (range 0.11–0.85) years. The majority of participants included in the SMART study had SMA type 2 (n = 11, 46% vs SMA type 1, n = 8; or SMA type 3, n = 5) and 3 copies of the *SMN2* gene (n = 18, 75% vs 2 *SMN2* copies, n = 5; or 4 or more *SMN2* copies, n = 1).

Primary Safety Analysis

All participants had at least 1 TEAE, and 1 AE was considered related to onasemnogene abeparvovec by the study investigator (Table 2 and eTable 2). No deaths and no AEs leading to discontinuation from the study were reported. The most frequently reported treatment-related AEs in the overall population (>20% of participants) were vomiting (63%; n = 15/24), pyrexia (33%; n = 8/24), nausea (33%; n = 8/24), hypertransaminasemia (29%; n = 7/24), and platelet count decreased (25%; n = 6/24).

Fifteen participants had SAEs, and 7 participants had SAEs considered related to treatment. The most frequent treatment-related SAEs were thrombocytopenia (13%; n = 3/24) and vomiting (8%; n = 2/24).

AESI were reported for 23 participants (96%), including hepatotoxicity (83%; n = 20/24), thrombocytopenia (71%; n = 17/24), and cardiac AEs (13%; n = 3/24) (Table 2).

Figure 1 CONSORT Diagram of Trial Profile

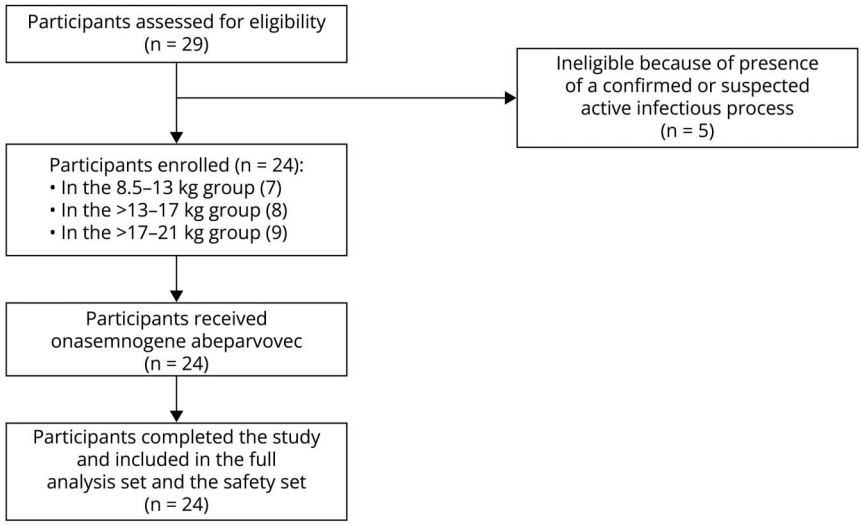


Table 1 Baseline Demographics and Clinical Characteristics

	≥8.5–13 kg (n = 7)	>13–17 kg (n = 8)	>17–21 kg (n = 9)	Overall (N = 24)
Age at dosing, y, mean (SD) [range]	3.03 (1.15) [1.51–4.68]	4.52 (1.18) [3.11–6.11]	6.14 (1.60) [4.37–9.13]	4.69 (1.82) [1.51–9.13]
Sex, n (%)				
Male	4 (57)	3 (38)	5 (56)	12 (50)
Female	3 (43)	5 (63)	4 (44)	12 (50)
Weight at baseline, kg, mean (SD)	11.8 (1.7)	15.4 (1.4)	19.2 (0.9)	15.8 (3.3)
BMI at baseline, kg/m^2, mean (SD)	15.0 (1.0)	15.2 (0.8)	15.4 (1.9)	15.2 (1.3)
SMA type, n (%)				
Type 1	3 (43)	3 (38)	2 (22)	8 (33)
Type 2	4 (57)	4 (50)	3 (33)	11 (46)
Type 3	0	1 (13)	4 (44)	5 (21)
Age at first symptom onset, y, mean (SD)	0.34 (0.37)	0.70 (0.68)	1.54 (1.67)	0.91 (1.19)
Age at diagnosis, y, mean (SD)	1.04 (0.93)	1.48 (0.99)	1.54 (1.25)	1.37 (1.06)
Previous SMA DMT, n (%)				
Risdiplam	1 (14)	0	1 (11)	2 (8)
Nusinersen	5 (71)	7 (88)	7 (78)	19 (79)
None	1 (14)	1 (13)	1 (11)	3 (13)
***SMN2* copy number, n (%)**				
2	3 (43)	2 (25)	0	5 (21)
3	4 (57)	6 (75)	8 (89)	18 (75)
4 or more	0	0	1 (11)	1 (4)
HFMSE, median (range)[a]	20.0 (6–40) n = 5	29.5 (0–55) n = 6	39.0 (4–51) n = 9	29.5 (0–55) n = 20
RULM, median (range)[a]	14.0 (7–30) n = 4	24.0 (4–35) n = 6	26.5 (8–37) n = 8	22.0 (4–37) n = 18

Abbreviations: DMT = disease-modifying treatment; HFMSE = Hammersmith Functional Motor Scale–Expanded; RULM = Revised Upper Limb Module; SMA = spinal muscular atrophy; *SMN2* = *survival motor neuron 2*.
[a] A total score was not derived if any item score was missing or "cannot test."

Of the hepatotoxicity events, the most frequently reported preferred terms were hypertransaminasemia and transaminases increased. Most of the events were mild or moderate in intensity, with severe events reported in 17% (n = 4/24) of participants. All participants remained asymptomatic (eTable 3).

Increases in transaminases (ALT or AST) as measured by clinical chemistry laboratory analysis were observed in the majority of participants, with 88% (n = 21/24) having an increase in ALT or AST >3× upper limit of normal (ULN), 58% (n = 14/24) having an increase >10× ULN, and 21% (n = 5/24) having an increase >20× ULN at any time during the study (Figure 2, A and B). As indicated in Figure 2C, ALT elevations were similar across weight groups. None of the participants had an increase in total bilirubin to >2× ULN, and none met the biochemical criteria for Hy law any time during the study. Hy law is defined by 3 criteria: (1) evidence of hepatocellular injury defined by serum ALT or AST >3× ULN; (2) serum total bilirubin >2× ULN without cholestasis; and (3) the absence of another etiology, such as viral hepatitis.

The time course of ALT and AST elevations varied between individual participants, with the peak elevations primarily occurring between week 1 and week 10 postdosing. The percentage of participants with elevations in ALT >3× ULN increased from 29% (n = 7/24) at week 1 to 61% (n = 14/23) at week 6, decreasing to 24% (n = 5/21) at week 26, and 0% (n = 0/23) with ALT >3× ULN at weeks 39 and 52. At the end of study, 67% (n = 16/24) of participants had an ALT value greater than ULN (but less than 3× ULN) and 8% (n = 2/24) of participants had an AST value greater than ULN.

AESI in the transient thrombocytopenia category were reported for 17 participants (71%). Most events were mild or

Table 2 Summary of Safety Findings (Primary Endpoint)

	≥8.5–13 kg (n = 7)	>13–17 kg (n = 8)	>17–21 kg (n = 9)	Overall (N = 24)
Any TEAE	7 (100)	8 (100)	9 (100)	24 (100)
Any TEAE related to onasemnogene abeparvovec	7 (100)	8 (100)	9 (100)	24 (100)
Any serious TEAE	3 (43)	7 (88)	5 (56)	15 (63)
Any serious TEAE related to onasemnogene abeparvovec	1 (14)	4 (50)	2 (22)	7 (29)
AESI	7 (100)	7 (88)	9 (100)	23 (96)
Cardiac AEs	0	2 (25)	1 (11)	3 (13)
Hepatotoxicity	6 (86)	5 (63)	9 (100)	20 (83)
Transient thrombocytopenia	4 (57)	6 (75)	7 (78)	17 (71)
Dorsal root ganglia toxicity	0	0	0	0
TMA	0	0	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; TEAE = treatment-emergent adverse event; TMA = thrombotic microangiopathy.

moderate decreases in platelet counts or thrombocytopenia (n = 7 each), and all participants remained asymptomatic with no observed related bleeding events (eTable 4). Three participants had thrombocytopenia that were reported as SAEs all of which spontaneously resolved without intervention.

Three participants had reported cardiac AESI, including bradycardia, nocturnal dyspnea, and electrocardiogram evidence of T wave inversion (n = 1 each) (eTable 5). All were mild, and none were considered related to treatment.

No events suggestive of possible dorsal root ganglia cell inflammation or overt thrombotic microangiopathy were reported.

Prednisolone Exposure

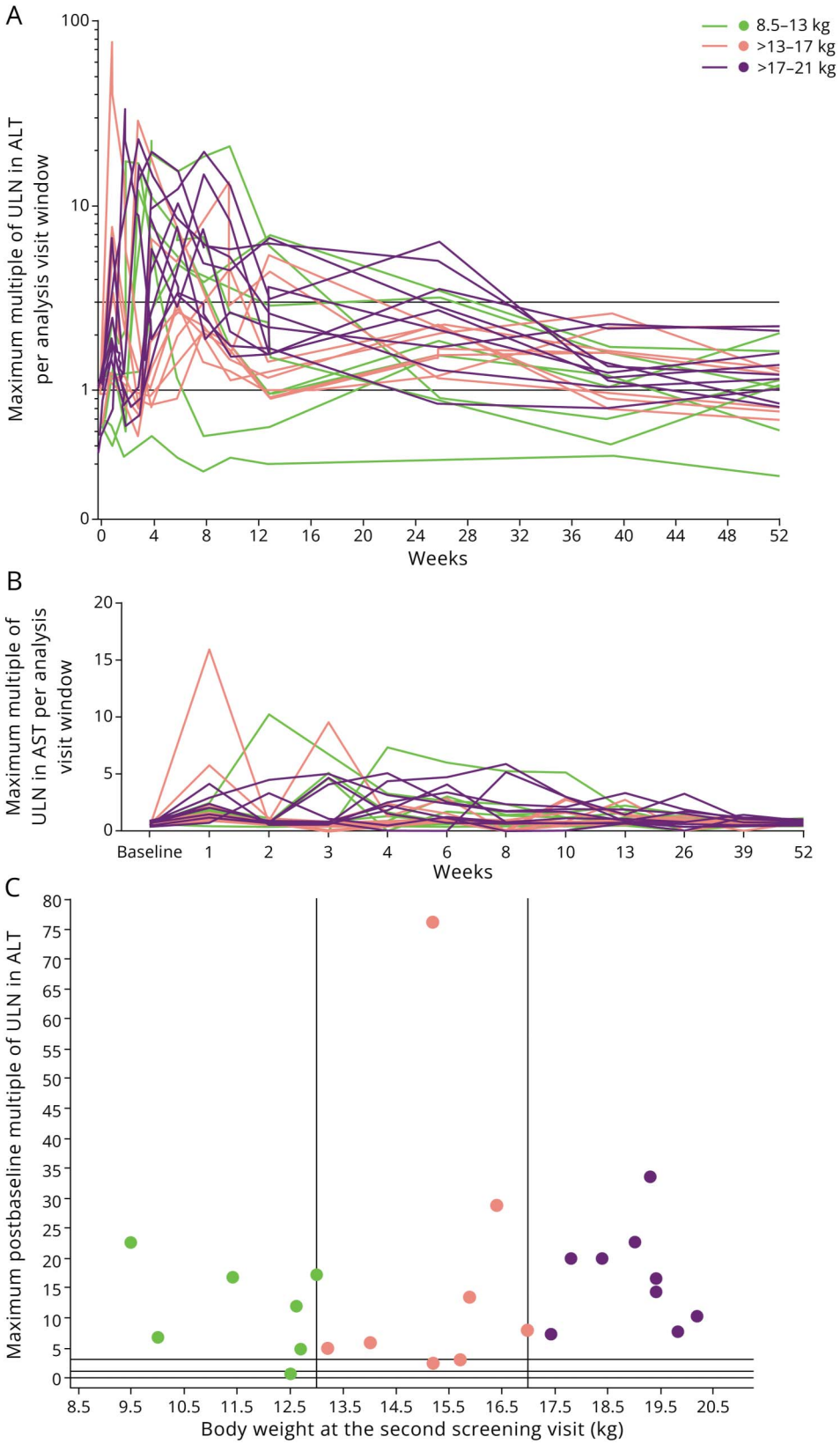
As per the protocol, all participants received prophylactic prednisolone (or equivalent) starting at day −1. The dose and duration of prednisolone to mitigate risk of immune response to the AAV9 capsid was greater than anticipated based on experience in previous trials.[1-6] The protocol stipulated that all participants would receive 1 mg/kg/d prednisolone (or equivalent) beginning the day before onasemnogene abeparvovec infusion and then continued for a minimum of 30 days. After 30 days, the protocol stipulated that prednisolone could be tapered weekly at increments of 0.25 mg/kg/d provided that serum ALT concentrations were normal. Investigators were permitted to increase prednisolone above 1 mg/kg/d and to subsequently taper back down to 1 mg/kg/d, at their discretion in response to the observed AEs. The mean (SD) total number of weeks of prednisolone administration was 31.2 (15.5) weeks for all 3 cohorts (range 80–444 days), with greater corticosteroid exposure in the 2 heavier cohorts (median 135.0, 201.0, and 194.0 days, respectively) (eTable 6). Twenty-one participants (88%) received a daily dose of prednisolone that was >1 mg/kg at any time (related to elevations in aminotransferases), and 9 participants (38%) received a daily dose >2 mg/kg. Four participants (17%) received at least 1 IV dose of corticosteroid during the study. Dose changes and the use of IV corticosteroids were investigator decisions and were not related to the magnitude of transaminase increases.

All participants continued prednisolone until at least week 10. Seventeen participants (71%) at week 26, and 6 participants (25%) at week 52 were still receiving prednisolone (with 1 participant still receiving prednisolone at day 440). AEs suggestive of hypercortisolism (i.e., Cushing syndrome and cushingoid features) were reported in 5 participants, attributable to corticosteroid use, which had resolved in all cases by end of study.

Secondary Efficacy Analyses

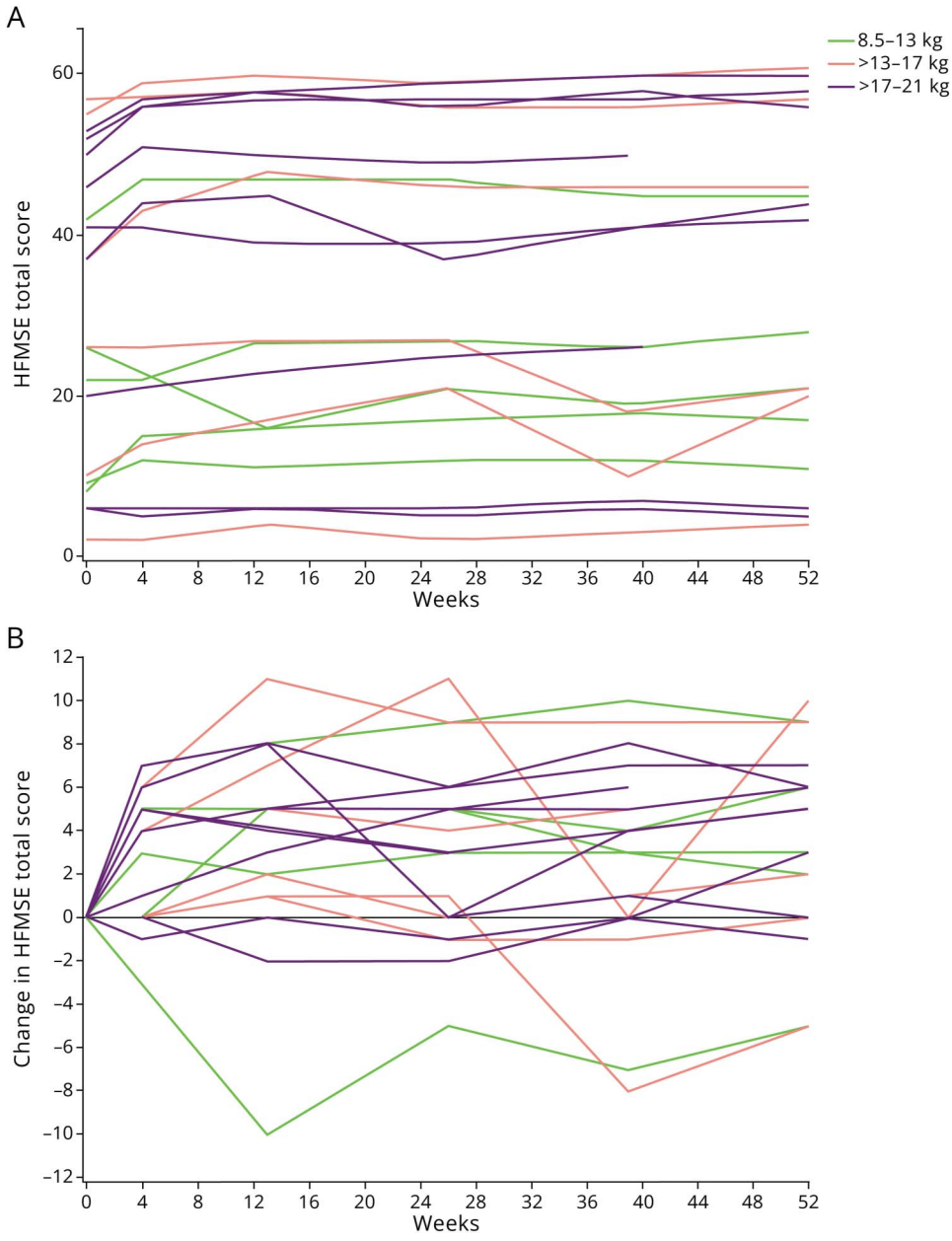
The analysis of HFMSE change from baseline included 20 participants who were ≥24 months of age at study start and who had available HFMSE total score data at baseline and postbaseline. As presented in Table 1, the wide variability in baseline HFMSE scores, ranging from 0 to 55 (total HFMSE score ranges from 0 to 66), reflects the heterogeneity of the enrolled population. The majority of the participants in all 3 weight groups achieved improvements from baseline in their HFMSE score during the study (Figure 3) with median (range) increases in HFMSE total score of 4.0 (−5 to 11) at week 26 and 4.0 (−5 to 11) at week 52 overall. Of the 20 participants with baseline and postbaseline HFMSE data, 18 had an increase in HFMSE score and 2 participants had a decrease in score. At week 52, 11 of 18 participants (61%) had a clinically meaningful increase of ≥3 points in HFMSE total score (n = 3, 8.5–13 kg; n = 3, >13–17 kg; n = 5, >17–21 kg),[14,15] 8 of 18 participants (44%) had an increase of ≥6 points (n = 2, 8.5–13 kg; n = 3, >13–17 kg; n = 3, >17–21 kg), and 2 of 18 participants (11%) had an increase of ≥10 points (n = 1, >13–17 kg; n = 1, >17–21 kg). Two participants (11%) had a decrease in HFMSE total score of ≤3 points at week 52 (n = 1, 8.5–13 kg; n = 1, >13–17 kg).

Figure 2 ALT and AST Elevations During the SMART Study (Primary Endpoint)



(A) Multiple of ULN in ALT per participant over time (log scale). (B) Multiple of ULN in AST per participant over time (log scale). (C) Maximum postbaseline multiple of ULN in ALT by body weight at screening per participant. Gray lines indicate 1× ULN and 3× ULN. ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Figure 3 HFMSE Total Score Over Time (Secondary Endpoint)

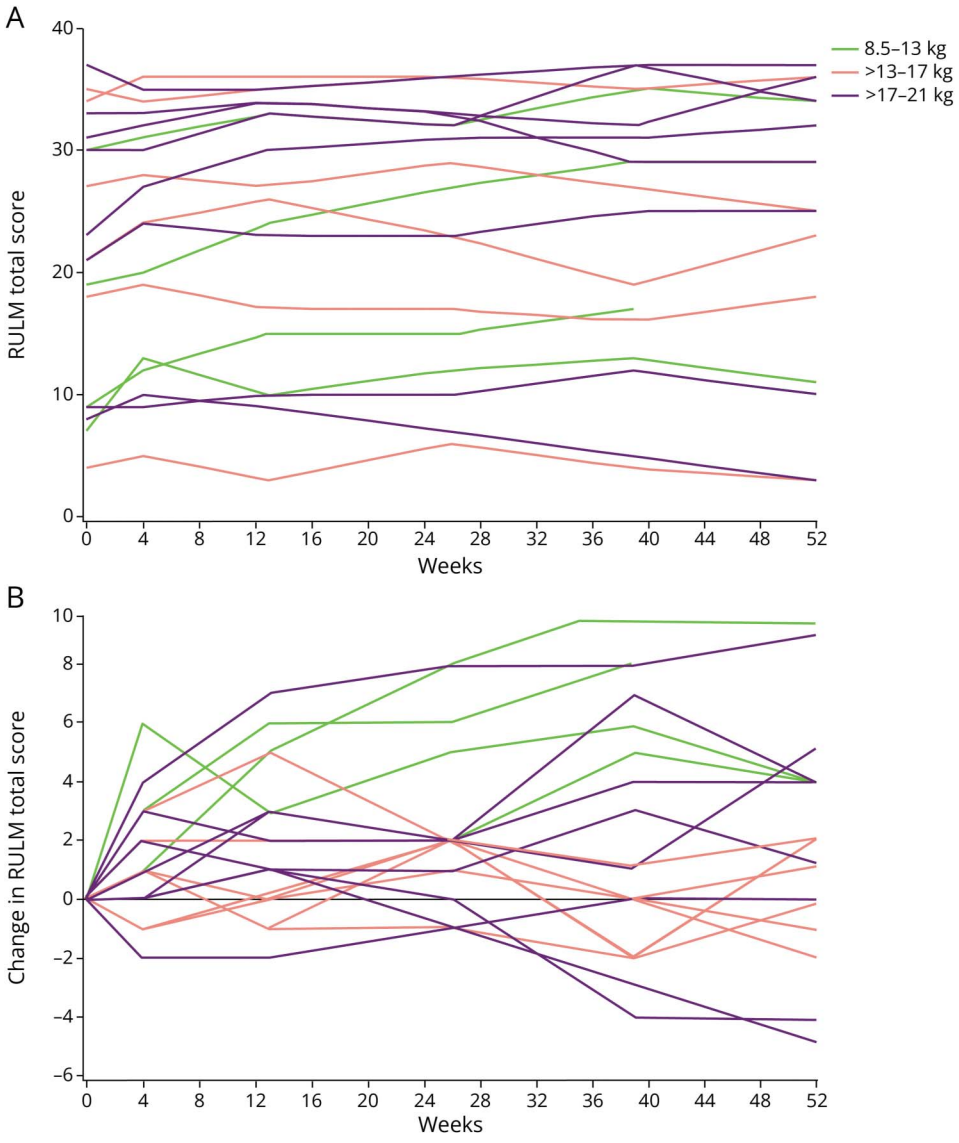


(A) Total score changes over time and (B) change from baseline. Green lines, ≥8.5–13 kg; blue lines, >13–17 kg; red lines, >17–21 kg. Gray line indicates maximum score for HFMSE of 66 points. HFMSE = Hammersmith Functional Motor Scale–Expanded.

Analysis of RULM change from baseline was performed for 18 participants who were ≥30 months of age at study initiation and who had available RULM total score data at baseline and postbaseline. Baseline RULM scores ranged from 4 to 37 (Table 1). As displayed in Figure 4, the majority of participants had stable or improved RULM total scores during the study, with median (range) increases in RULM total score of 2.0 (−1 to 8) points at week 26 and 2.0 (−5 to 10) at week 52 overall. At week 52, 7 of 17 participants (41%) had a clinically meaningful increase of ≥3 points in RULM total score (n = 3, 8.5–13 kg; n = 4, >17–21 kg),[16] 2 of 17 participants (12%) had an increase of ≥6 points (n = 1, 8.5–13 kg; n = 1, >17–21 kg), and 1 participant (6%) had an increase of ≥10 points (n = 1, 8.5–13 kg). Two participants (12%) had a decrease in RULM total score of ≤3 points at week 52 (n = 2, >17–21 kg).

Analysis of developmental motor milestones at baseline indicated that all participants demonstrated head control and sitting with support (Table 3 and eTable 7). In the overall population, 21 participants (88%) sat without support, 10 (42%) demonstrated hands-and-knees crawling, and 9 (38%) demonstrated pulls to stand. Seven participants (29%) stood with assistance and walked with assistance; 6 participants (25%) stood alone; and 6 (25%) walked alone. The majority of participants maintained their developmental milestones at week 52. Three participants lost a previously demonstrated

Figure 4 RULM Total Score Over Time (Secondary Endpoint)



(A) Total score changes over time and (B) change from baseline. Green lines, ≥8.5–13 kg; blue lines, >13–17 kg; red lines, >17–21 kg. Gray line indicates maximum score for RULM of 37 points. RULM = Revised Upper Limb Module.

developmental milestone during the study. One participant (baseline age and weight group, 5.1 years and >13–17 kg; baseline HFMSE and RULM, 8 and 18) who demonstrated sitting without support for 30 seconds at baseline, 1 participant (baseline age and weight group, 3.1 years and >13–17 kg; baseline HFMSE and RULM, 0 and 4) who demonstrated sitting with support for 30 seconds, and another participant (baseline age and weight group, 5.4 years and >17–21 kg; baseline HFMSE and RULM, 35 and 21) who demonstrated walking with assistance, did not demonstrate these milestones at 52 weeks. Four participants achieved new developmental milestones during the study (n = 2, 8.5–13 kg; n = 1, >13–17 kg; n = 1, >17–21 kg). These new milestones included higher milestones, such as standing with assistance (3 new participants), with 2 also demonstrating walking with assistance at week 52; 1 participant also demonstrated standing alone.

Classification of Evidence

This study provides Class IV evidence that intravenous onasemnogene abeparvovec is safe in pediatric patients with SMA weighing 8.5–21 kg.

Discussion

Unlike previous onasemnogene abeparvovec clinical trials, the SMART study enrolled a heterogeneous population of participants (≥8.5–≤21 kg) across a broad range of ages and SMA phenotypes, most of whom were previously treated with another disease-modifying treatment. Although the occurrence of AESI (hepatotoxicity and thrombocytopenia) was consistent with previously reported published clinical studies of patients with SMA type 1 or presymptomatic patients,[1-6] prolonged aminotransferase elevations in the SMART study were observed in the majority of participants, with 67% still having elevated

Table 3 Percentage of Participants Demonstrating Developmental Milestones (Full-Analysis Set): Bayley-III (Secondary Endpoint)

Developmental milestone, n (%)	Time point	≥8.5–13 kg (n = 7)	>13–17 kg (n = 8)	>17–21 kg (n = 9)	Overall (N = 24)
Head control (Bayley-III #4)	Baseline	7 (100)	8 (100)	9 (100)	24 (100)
	Week 26	7 (100)	8 (100)	9 (100)	24 (100)
	Week 52	7 (100)	8 (100)	9 (100)	24 (100)
Sits with support (Bayley-III #19)	Baseline	7 (100)	8 (100)	9 (100)	24 (100)
	Week 26	7 (100)	8 (100)	9 (100)	24 (100)
	Week 52	7 (100)	7 (88)[a]	9 (100)	23 (96)
Sits without support (30 s) (Bayley-III #26)	Baseline	6 (86)	7 (88)	8 (89)	21 (88)
	Week 26	7 (100)	5 (63)	8 (89)	20 (83)
	Week 52	7 (100)	6 (75)[b]	8 (89)	21 (88)
Pulls to stand (Bayley-III #35)	Baseline	1 (14)	3 (38)	5 (56)	9 (38)
	Week 26	2 (29)	3 (38)	5 (56)	10 (42)
	Week 52	2 (29)	3 (38)	5 (63)[c]	10 (44)[d]

Abbreviation: Bayley-III = Bayley Scales of Infant and Toddler Development, Third Edition.
[a] Participant who did not demonstrate this milestone was 3.11 months of age at dosing, in the >13–17 kg cohort, and previously treated with nusinersen.
[b] Participant who did not demonstrate this milestone was 5.14 months of age at dosing, in the >13–17 kg cohort, and previously treated with nusinersen.
[c] n = 8.
[d] n = 23.

concentrations at week 52. All cases were asymptomatic and managed with corticosteroid treatment. Many participants received greater dosages and longer duration of corticosteroid dosing than anticipated, with the median duration of corticosteroid being 175 days. The duration of corticosteroid exposure for participants in the 8.5–13 kg cohort was similar to that observed in previous studies, while participants in the 2 heaviest categories required more prolonged use of corticosteroids. As weaning of prednisolone below 1 mg/kg/d was recommended after serum ALT had returned to normal values, this may have contributed to the longer duration of corticosteroid dosing in some cases. Transient asymptomatic thrombocytopenia events were reported in 71% of participants, and all resolved with no related bleeding events or need to intervene (Table 2).

Data compiled from 100 participants with SMA treated with onasemnogene abeparvovec (mean [range] weight at baseline, 5.2 [3.0–8.4] kg) in 5 previous clinical trials demonstrated that most transaminase elevations began at week 1, with a second peak at month 1 that coincided with prednisolone tapering.[17] In addition, most cases with moderate or severe elevations (≥5× ULN ALT or AST) resolved within 3–6 months.[17] Although most participants in the SMART study also had transaminase elevations beginning at week 1, 80% of participants continued to have mild, asymptomatic transaminase elevations at 6 months post dosing. No Hy law cases were observed in any of the treated participants.

In the SMART study, transaminase increases were similar across weight groups. The increased occurrence of transaminase elevations observed in this study was consistent with previous real-world analyses of heavier patients, some of whom were previously treated with another disease-modifying treatment.[8,13] In an observational cohort study that examined onasemnogene abeparvovec treatment in 76 patients with SMA, some of whom were older than 24 months, weighed >8.5 kg, or were previously treated with nusinersen, maximum AST and ALT elevations were associated with older age and heavier weight.[8] In a separate cohort analysis of 67 onasemnogene abeparvovec-treated patients with SMA, increased risk for elevated serum transaminase was also observed for older and heavier patients.[18] In a recent report describing real-world safety and efficacy data for onasemnogene abeparvovec in 99 patients with SMA (54 receiving prior treatment) with weights ranging from 3.2 to 20.2 (median 7.86) kg, each 5 kg increase in weight was associated with 2.4-fold higher ALT peak and 46% longer duration of corticosteroid therapy.[19] Similarly, in a case series, AST and/or ALT elevations (≥2× ULN) were identified in 67% of older (≥8 months of age) patients and 83% of heavier (weight ≥8 kg) patients.[13] As with the SMART study, no indication of symptomatic liver dysfunction was observed.[13] However, the contribution of prior treatment on the safety findings observed in this study is unclear.

In the SMART study, most participants (88%) received greater prednisolone dosages and for longer periods of time than anticipated in the protocol guidance and reported for previous clinical trials.[1-6] For some participants, transaminase concentrations increased 2 or 3 times, which coincided with

tapering of corticosteroids in some cases, but not all. This is consistent with real-world evidence describing longer periods of prednisolone exposure for older and/or heavier patients.[8,9] Because most participants required greater dosages of corticosteroids compared with what was described in the protocol, corticosteroid tapering after dose increases in this study was based on investigator discretion using their clinical assessment, which led to different slopes of reduction. In addition, there was not necessarily a relationship between increased corticosteroid dosage and resolution of transaminase elevation. In some cases, investigators discontinued corticosteroid treatment at their own discretion when slight transaminase elevations (<2× ULN) were still present, based on individual benefit-risk evaluations of corticosteroid treatment. ALT concentrations did not exceed >3× ULN at end of study in any of those cases. Other studies have also reported that although most patients heavier than 8 kg with significant transaminitis responded well to doubling of prednisolone, IV methylprednisolone was required in individual cases.[19] These findings highlight the importance of evaluating the individual benefit-risk of prolonged corticosteroid use with expertise from a multidisciplinary team (e.g., gastroenterology and hepatology consultations).

Efficacy results demonstrated that the majority of participants across all weight cohorts maintained or improved baseline motor function during the study. This is particularly important given the overall heterogeneity of the participant population that included chronic participants who had already been exposed to another SMN-enhancing drug. Thus, while most participants had stable or improved motor function at week 52, a few participants had changes in individual scales, which is not completely unexpected given this older, more chronic patient population in whom contractures and other orthopedic complications might affect motor function. Specifically, most participants had improved or maintained changes from baseline in HFMSE and RULM at week 52, which is consistent with other real-world studies.[8,18] The majority of participants also maintained their developmental milestones during the study, with 4 participants demonstrating new developmental milestones at week 52. Of note, 6 participants had already achieved the highest milestone assessed in the study (walking alone) at baseline. Although some participants had decreases in individual scores and 3 lost a milestone, these were not universally observed across all efficacy endpoints. For example, some participants exhibited a decline of >10 points in HFMSE without a similar decrease in RULM or developmental motor milestones. Similarly, 3 participants demonstrated a developmental motor milestone at week 52 that was lower than the one demonstrated at baseline (sitting without support for 10 seconds vs 30 seconds for 1 participant, head control vs sitting with support for another participant, and standing with assistance vs walking with assistance for another participant); however, these changes did not coincide with changes in HFMSE or RULM total scores. These findings demonstrate the sometimes-nonlinear motor milestone achievement that may be observed for some patients with SMA. Furthermore, contributing factor(s) (e.g., change in evaluator, fracture, or other AE) may contribute to variability in scores in some cases but could not be identified for all participants. For the participant who sustained an upper limb fracture, this occurred after a fall from a stationary bicycle (the ability to pedal a bicycle was a new activity for this child). This participant had just completed a 5-month course of prednisolone before the fracture, which required open reduction and internal fixation and affected their mobilization, because they had been using a walker (putting weight on their upper limbs) before the fall and fracture occurrence. In this instance, we believe that this participant's fracture occurred as a consequence of SMA-related weakness, which may have been exacerbated by prednisolone use. In addition, functional outcomes may have been affected by SMA type. Finally, the effect of prior treatment on the efficacy findings is also unclear.

The small number of participants in each cohort, heterogeneity of the patient population, and lack of a comparator group represent study limitations, especially given that the trajectory of SMA is affected by age, weight, and comorbidities.[20] In addition, further studies are required to better understand the underlying pathophysiology involved in the prolonged aminotransferase elevations, which will guide future management strategies.

The safety profile for onasemnogene abeparvovec was similar across weight groups in this heterogeneous population of participants weighing up to 21 kg, although this required a more prolonged exposure to corticosteroids and demonstrated thrombocytopenia more often than expected, especially for those participants heavier than 13 kg. In addition, the nature of the AEs was consistent with the existing clinical evidence. Compared with previous clinical trials including participants weighing <8.5 kg, there was increased frequency of asymptomatic aminotransferase elevations and thrombocytopenia, as well as longer duration of transaminase elevation and related corticosteroid treatment in this study. Transaminase elevations were manageable with the adequate use of corticosteroids adapted on a case-by-case basis per the discretion of the treating physician. No participants developed symptomatic liver involvement or met the Hy law criteria, although mild transaminase elevations (ALT) above ULN were present in 67% of participants at study end. Maintenance or improvement of motor function was observed for most participants, suggesting a clinical benefit of IV onasemnogene abeparvovec for heavier patients with SMA. These findings from the SMART study complement the increasing real-world evidence of onasemnogene abeparvovec safety and efficacy for patients with different SMA types, those who are treatment-naïve or were previously treated with another disease-modifying therapy, and those with a wider range of ages and weights at baseline vs the previous onasemnogene abeparvovec trial populations.

Author Contributions

H.J. McMillan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. G. Baranello: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M.A. Farrar: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. C.M. Zaidman: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. T. Moreno: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L. De Waele: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Y.-J. Jong: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. V. Laugel: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Quijano-Roy: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E. Mercuri: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Y.-H. Chien: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. V. Straub: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B.T. Darras: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Seibert: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R. Bernardo Escudero: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. I. Alecu: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. F. Freischläger: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. F. Muntoni: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data.

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H.J. McMillan has participated in clinical trials with Roche, PTC Therapeutics, ReveraGen, Catabasis, Novartis, and Sarepta, and has been a consultant for and received honoraria from Novartis Gene Therapies Inc. and Hoffman La-Roche Ltd. G. Baranello has participated in clinical trials sponsored by Roche, Novartis, Sarepta, Pfizer, NS Pharma, ReveraGen, and Scholar Rock, and has received speaker and/or consulting fees from Sarepta, PTC Therapeutics, Pfizer, Biogen, Novartis Gene Therapies Inc. (AveXis), and Roche and grants from Sarepta, Roche, and Novartis Gene Therapies Inc. M.A. Farrar has received honoraria for scientific advisory boards from Novartis Gene Therapies Inc., Biogen, and Roche and research grants from Biogen. C.M. Zaidman has received research support from Biogen and Novartis and speaking fees from Sarepta, Chugai, and the France Foundation. T. Moreno received speaker and consulting fees for scientific advisory boards from Biogen, Novartis Gene Therapies Inc. (AveXis), Pfizer, and Roche. L. De Waele has received speaker and consulting fees from Novartis Gene Therapies Inc. (AveXis), Biogen, and Roche; has worked as a principal investigator of SMA studies sponsored by Novartis Gene Therapies Inc., Roche, Scholar Rock, and Biohaven; has received research grants from Novartis Gene Therapies Inc., Roche, and Biogen; and is a member of the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD). Y.-J. Jong has participated in clinical trials with Biogen, Novartis, Roche, PTC, Sarepta, Pfizer; received speaker and/or consulting fees from Biogen, Novartis, Roche, and Pfizer; and received research grants from Biogen. V. Laugel has participated in clinical trials with Roche, Novartis, Wave Life Sciences, FibroGen, and Genethon, and reports consulting honoraria from Roche, Biogen, Novartis, Sarepta, Alexion, PTC Therapeutics, Genethon, Pfizer, and Italfarmaco. S. Quijano-Roy 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; has received research support from the European Commission, INSERM-Health Ministry, and the Association Française des Myopathies (AFM); is the scientific coordinator of the Registre SMA FRANCE for the French neuromuscular network (FILNEMUS) (filnemus.fr); and is coordinator of the Garches-Necker-Creteil Health Care Provider for the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD). E. Mercuri has participated in SMA clinical trials sponsored by Roche, Novartis, Biogen Epirium, and Scholar Rock and has received speaker and/or consulting fees from Biogen, Novartis Gene Therapies Inc. (AveXis), and Roche, and has received grants to the institution from Biogen, Roche, and Novartis Gene Therapies Inc. Y.-H. Chien has served in an advisory role for Sanofi and Amicus Therapeutics, has received consulting fees from Sanofi, BioMarin, Amicus Therapeutics, Biogen, Novartis, PTC Therapeutics, DHKS, Pfizer, Regeneron, Recordati, and Takeda, and has received research funding from Sanofi and Biogen. V. Straub has served

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Appendix Coinvestigators

Coinvestigators are listed at Neurology.org.

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