# Safety and Efficacy of Intravenous Onasemnogene Abeparvovec in Pediatric Patients with Spinal Muscular Atrophy: Findings from the Phase 3b SMART Study

Scan QR code to access the poster and supporting materials

3169

Hugh J. McMillan[1]; Giovanni Baranello[2,3]; Michelle A. Farrar[4,5]; Craig M. Zaidman[6]; Julia Seibert[7]; Roberto Bernardo[8]; Iulian Alecu[7]; Frank Freischläger[9]; Francesco Muntoni[2,3]

[1]Department of Pediatrics, Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada; [2]The Dubowitz Neuromuscular Centre, Developmental Neuroscience Research and Teaching Department, University College London, Great Ormond Street Institute of Child Health, London, UK; [3]NIHR Great Ormond Street Hospital Biomedical Research Centre & Great Ormond Street Hospital NHS Foundation Trust, London, UK; [4]School of Clinical Medicine, UNSW Medicine and Health, UNSW Sydney, Sydney, Australia; [5]Department of Neurology, Sydney Children's Hospital Network, Randwick, Australia; [6]Department of Neurology, Division of Pediatric Neurology, Washington University School of Medicine, St. Louis, MO, USA; [7]Novartis Pharmaceuticals, Basel, Switzerland; [8]Novartis Global Drug Development – Neuroscience & Gene Therapy, East Hanover, NJ, USA; [9]Freischläger Consulting, Nortmoor, Germany

## Introduction

- IV onasemnogene abeparvovec has demonstrated efficacy and safety across five clinical trials of patients with SMA type1[1–4] or presymptomatic SMA with two[5] or three copies of *SMN2*.[6] All trials enrolled only patients weighing <8.5 kg at the time of treatment.[1–6]
- In the United States, onasemnogene abeparvovec is approved by the FDA for patients younger than 2 years of age.[7] In Europe, it has been authorized for use without age limit, but its label provides dosing instructions only for patients weighing up to 21 kg.[8]
- SMART (NCT04851873) was a phase 3b, open-label, single-arm, multinational study to evaluate the safety, tolerability, and efficacy of IV onasemnogene abeparvovec for patients with SMA weighing 8.5 to ≤21 kg
- Findings from SMART will complement emerging real-world data for use of onasemnogene abeparvovec across different weight ranges and SMA populations and support informed treatment decision-making by health care professionals and caregivers
- SMART was the first clinical study assessing the safety and efficacy of IV onasemnogene abeparvovec in patients with SMA weighing ≥8.5 kg at time of treatment. SMART was also unique because it included patients who could have been treated with another approved DMT. Previous clinical studies have only included treatment-naïve patients.[1–6]

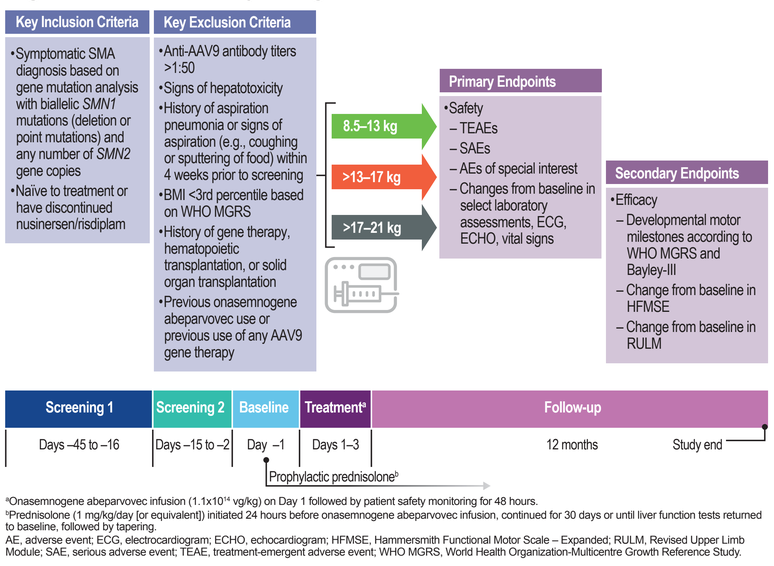
## Objective

- Here, we describe findings of the SMART study, reporting safety, tolerability, and efficacy of IV onasemnogene abeparvovec in patients with SMA weighing 8.5 to ≤21 kg.

## Methods

- SMART enrolled 24 patients distributed across three weight groups (**Figure 1**)

**Figure 1. SMART study design**




[a]Onasemnogene abeparvovec infusion ($1.1x10^{14}$ vg/kg) on Day 1 followed by patient safety monitoring for 48 hours.
[b]Prednisolone (1 mg/kg/day [or equivalent]) initiated 24 hours before onasemnogene abeparvovec infusion, continued for 30 days or until liver function tests returned to baseline, followed by tapering.
AE, adverse event; ECG, electrocardiogram; ECHO, echocardiogram; HFMSE, Hammersmith Functional Motor Scale – Expanded; RULM, Revised Upper Limb Module; SAE, serious adverse event; TEAE, treatment-emergent adverse event; WHO MGRS, World Health Organization-Multicentre Growth Reference Study.

- Changes from baseline are summarized descriptively: number, percentage, mean, standard deviation, median, minimum, and maximum are presented. No hypothesis testing was performed.

## Results

### Baseline characteristics

- 24 patients were enrolled in SMART (**Table 1**)
- Seven (29.2%) patients were in the lowest-weight group, eight (33.3%) in the middle-weight group, and nine (37.5%) in the highest-weight group
- Patients ranged in age from 1.5 to 9.1 years
- Nearly half (11/24 [45.8%]) of the patients had SMA type 2. The majority (18/24 [75.0%]) of patients had three *SMN2* gene copies.
- Most patients (21/24 [87.5%]) had received prior *SMN*-targeting therapies (nusinersen or risdiplam). Only three (12.5%) patients were treatment-naïve at study entry.
  - Nusinersen must have been discontinued at least 4 months prior to screening
  - Risdiplam must have been discontinued at least 15 days (washout period of at least five half-lives) prior to screening

**Table 1. Baseline demographics and clinical characteristics**

| | Weight group | | | |
|---|---|---|---|---|
| | 8.5–13 kg n=7 | >13–17 kg n=8 | >17–21 kg n=9 | Overall N=24 |
| **Age at dosing (years), mean (SD)** | 3.03 (1.15) | 4.52 (1.18) | 6.14 (1.60) | 4.69 (1.82) |
| **Sex, n (%)** | | | | |
| Male | 4 (57.1) | 3 (37.5) | 5 (55.6) | 12 (50.0) |
| Female | 3 (42.9) | 5 (62.5) | 4 (44.4) | 12 (50.0) |
| **SMA type, n (%)** | | | | |
| Type 1 | 3 (42.9) | 3 (37.5) | 2 (22.2) | 8 (33.3) |
| Type 2 | 4 (57.1) | 4 (50.0) | 3 (33.3) | 11 (45.8) |
| Type 3 | 0 | 1 (12.5) | 4 (44.4) | 5 (20.8) |
| **Age at first symptom onset (years), mean (SD)** | 0.34 (0.37) | 0.70 (0.68) | 1.54 (1.67) | 0.91 (1.19) |
| **Age at diagnosis (years), mean (SD)** | 1.04 (0.93) | 1.48 (0.99) | 1.54 (1.25) | 1.37 (1.06) |
| **Previous DMT, n (%)** | | | | |
| Risdiplam | 1 (14.3) | 0 | 1 (11.1) | 2 (8.3) |
| Nusinersen | 5 (71.4) | 7 (87.5) | 7 (77.8) | 19 (79.2) |
| None | 1 (14.3) | 1 (12.5) | 1 (11.1) | 3 (12.5) |
| ***SMN2* copy number, n (%)** | | | | |
| Two | 3 (42.9) | 2 (25.0) | 0 | 5 (20.8) |
| Three | 4 (57.1) | 6 (75.0) | 8 (88.9) | 18 (75.0) |
| Four or more | 0 | 0 | 1 (11.1) | 1 (4.2) |

DMT, disease-modifying treatment; SD, standard deviation; *SMN2*, *survival motor neuron 2* gene.

### Safety and tolerability

- The frequency and severity of AEs were similar across weight groups
- All 24 patients experienced ≥1 TEAE, and more than half (15/24 [62.5%]) experienced ≥1 serious TEAE. Seven patients (29.2%) experienced serious TEAEs related to onasemnogene abeparvovec (**Table 2**).
- Three (12.5%) patients experienced in total four cardiac AEs (bradycardia, ECG T-wave inversion, nocturnal dyspnea, tachycardia). All were considered unrelated to onasemnogene abeparvovec.
- Hepatotoxicity was observed in 20 (83.3%) patients (**Table 2**), the majority of which were transaminase increases (all were asymptomatic). One event was PT prolongation.
- Transient asymptomatic thrombocytopenia occurred in 17 (70.8%) patients
- No events of TMA or dorsal root ganglionopathy were observed

**Table 2. Summary of safety findings**

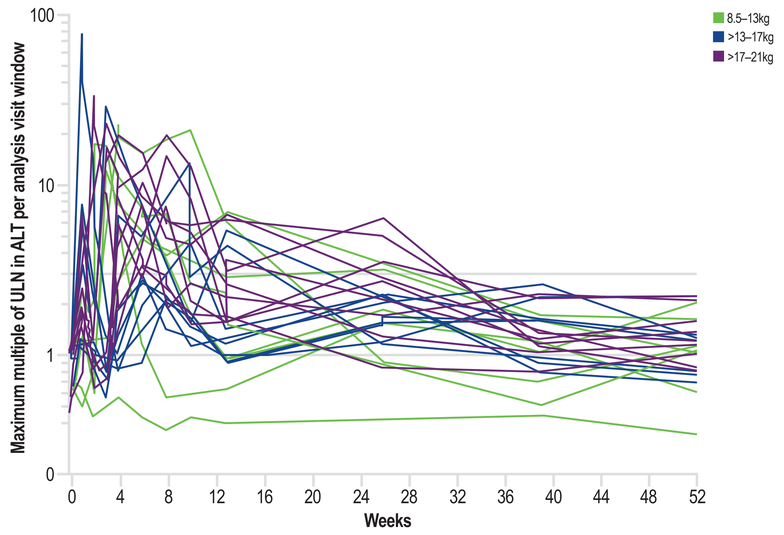
| | Weight group | | | |
|---|---|---|---|---|
| Category | 8.5–13 kg n=7 n (%) | >13–17 kg n=8 n (%) | >17–21 kg n=9 n (%) | Overall N=24 n (%) |
| **Any TEAE** | 7 (100) | 8 (100) | 9 (100) | 24 (100) |
| **Any TEAE related to onasemnogene abeparvovec** | 7 (100) | 8 (100) | 9 (100) | 24 (100) |
| **Any serious TEAE** | 3 (42.9) | 7 (87.5) | 5 (55.6) | 15 (62.5) |
| **Any serious TEAE related to onasemnogene abeparvovec** | 1 (14.3) | 4 (50.0) | 2 (22.2) | 7 (29.2) |
| **AESIs** | 7 (100) | 7 (87.5) | 9 (100) | 23 (95.8) |
| Cardiac AEs | 0 | 2 (25.0) | 1 (11.1) | 3 (12.5) |
| Hepatotoxicity | 6 (85.7) | 5 (62.5) | 9 (100) | 20 (83.3) |
| Transient thrombocytopenia | 4 (57.1) | 6 (75.0) | 7 (77.8) | 17 (70.8) |
| Dorsal root ganglia toxicity | 0 | 0 | 0 | 0 |
| TMA | 0 | 0 | 0 | 0 |

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

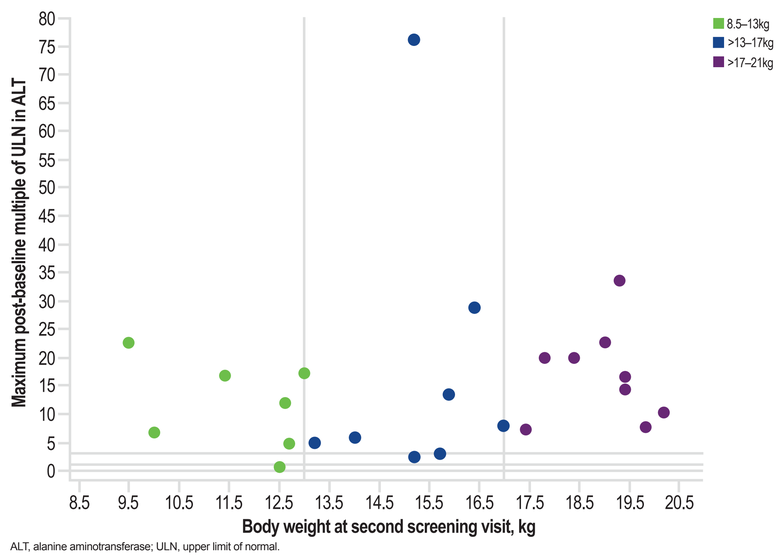
- In total, 21 (87.5%) patients presented ALT increases (two Grade 2; 14 Grade 3; five Grade 4) that were similar across weight groups (**Figure 2**)
  - In 21 (87.5%) patients, ALT increased to >3x ULN at any time during follow-up, with five (20.8%) patients experiencing increases to >20x ULN
  - At Week 52, no patient had ALT elevations of more than 3x ULN; in 14 of 22 patients (63.6%), ALT was above ULN
  - No bilirubin elevations or Hy's law cases were observed
  - Prophylactic steroid treatment was used over a median of 175 days. In 21 (87.5%) patients, doses >1 mg/kg/day were prescribed, and in 9 (37.5%) patients, doses >2 mg/kg/day were prescribed.
- Twenty (83.3%) patients experienced platelet count decreases. All platelet count decreases resolved, and no associated bleeding events were reported.
- No study withdrawals or deaths occurred

**Figure 2. ALT elevations during SMART study**

**a) Multiple of ULN in ALT per patient over time (log scale)**




**b) Maximum post-baseline multiple of ULN in ALT by body weight at screening per patient**




ALT, alanine aminotransferase; ULN, upper limit of normal.

### Efficacy

- Most patients maintained or improved motor milestones from baseline at Week 52 (**Figure 3**). Four patients demonstrated at least one new milestone at Week 52.
- Motor function, measured by RULM (**Figure 4**) and HFMSE (**Figure 5**), and motor milestone assessments were maintained or improved in most patients
- Mean (SD) change from baseline at Week 52 was 2.0 (4.0) points for RULM
- Mean (SD) change from baseline at Week 52 was 3.7 (4.3) points for HFMSE

**Figure 3. Motor milestones**

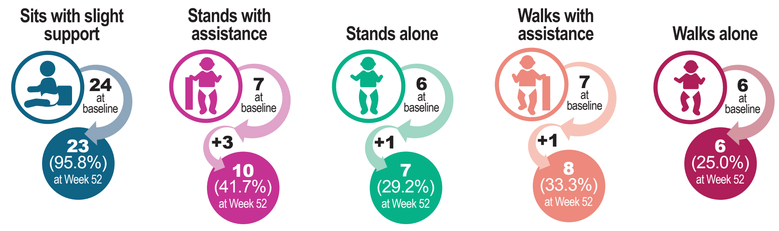
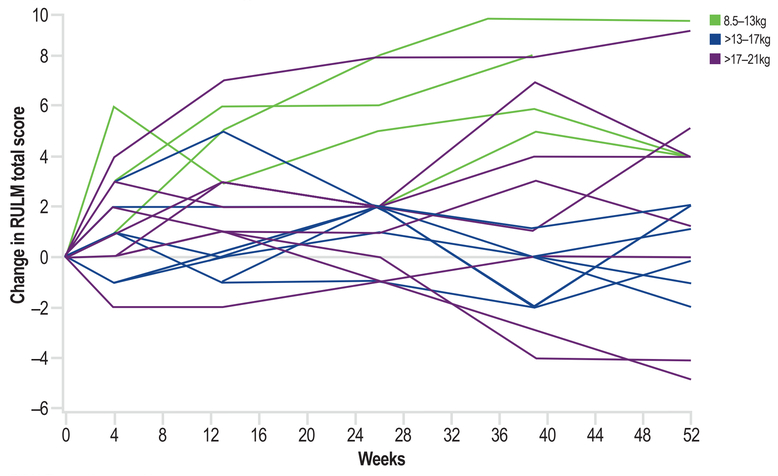
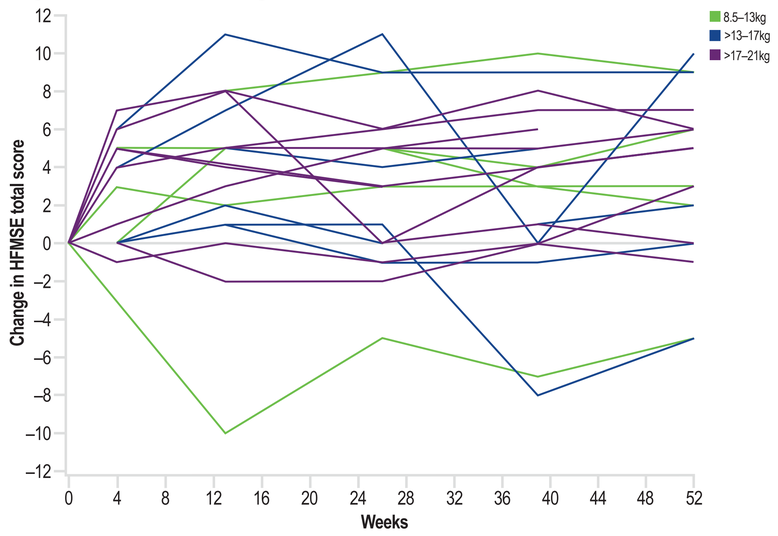



**Figure 4. RULM change from baseline**




RULM, Revised Upper Limb Module.

**Figure 5. HFMSE change from baseline**




## Conclusions

- SMART enrolled a heterogeneous population of patients who weighed more than patients included in previous clinical trials with onasemnogene abeparvovec, and most had been treated with another DMT for SMA before receiving onasemnogene abeparvovec
- The observed safety profile of onasemnogene abeparvovec was similar across the different weight groups and no new safety signals were observed
- The pattern of AE types was similar to previous reports, clinical evidence, and real-world experience. Aminotransferase elevations were observed in the majority of patients, but all cases were asymptomatic and managed with prophylactic prednisolone. Most patients received higher doses as prescribed in the protocol, with nine patients receiving doses >2 mg/kg. Serum transaminase elevations (all Grade 1) were ongoing for a majority of patients at Week 52.
- Across all assessed efficacy measures, most patients demonstrated maintenance or improvement of motor function at Week 52, suggesting clinical benefit of IV onasemnogene abeparvovec for heavier patients with SMA, and for patients switching from nusinersen or risdiplam

**References**

1. Day JW, et al. *Lancet Neurol*. 2021;20:284–93.
2. Mendell JR, et al. *N Engl J Med*. 2017;377:1713–22.
3. Al-Zaidy SA, et al. *J Neuromuscul Dis*. 2019;6:307–17.
4. Mercuri E, et al. *Lancet Neurol*. 2021;20:832–41.
5. Strauss K, et al. *Nat Med*. 2022;28:1381–9.
6. Strauss K, et al. *Nat Med*. 2022;28:1390–7.
7. Zolgensma. Prescribing information. 2023. https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf. Accessed November 16, 2023.
8. Zolgensma. Product information. https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf. Accessed November 16, 2023.

**Abbreviations**
AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; BMI, body mass index; DMT, disease-modifying treatment; ECG, electrocardiogram; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IV, intravenous; PT, prothrombin time; RULM, Revised Upper Limb Module; SAE, serious adverse event; SMA, spinal muscular atrophy; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene; SD, standard deviation; TEAE, treatment-emergent adverse event; TMA, thrombotic microangiopathy; WHO MGRS, World Health Organization-Multicentre Growth Reference Study.

**Acknowledgments and Disclosures**
This study was funded by Novartis Gene Therapies, Inc.
Medical writing and editorial support were provided by Jennifer Gibson, PharmD, Kay Square Scientific, Newtown Square, PA.
The authors wish to thank the investigators and, most importantly, all of the patients, families, and caregivers for their willingness to participate in this study, which is sponsored by Novartis Gene Therapies, Inc.

**Disclosures: HJM** has participated in clinical trials with Roche, PTC Therapeutics, ReveraGen, Catabasis, Novartis, and Sarepta; been a consultant for and received honoraria from Novartis Gene Therapies and received research support from Roche. **GB** has received speaker and consulting fees from Biogen, Novartis Gene Therapies, Inc. (AveXis), and Roche, and has worked as a principal investigator of SMA studies sponsored by Novartis Gene Therapies, Inc., and Roche. **MAF** has received honoraria for scientific advisory boards from Novartis Gene Therapies, Inc., Biogen, and Roche, and research grants from Biogen. **CMZ** has received research support from Biogen. **JS**, **RB**, and **IA** are employees of Novartis and hold stock/other equities. **FF** is a paid statistical consultant under contract with Novartis Gene Therapies, Inc. **FM** reports grants and personal fees from Novartis Gene Therapies, Inc., Biogen, Sarepta Therapeutics, and F. Hoffmann-La Roche. He has received honoraria for scientific advisory boards from Biogen, Novartis, Novartis Gene Therapies, Inc., PTC Therapeutics, F. Hoffmann-La Roche, and Sarepta Therapeutics, and is member of the Pfizer Rare Disease Advisory Board and of Dyne Therapeutic SAB.

Presented at the 2024 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, March 3–6, 2024, Orlando, FL, USA.