Real-World Outcomes Following Onasemnogene Abeparvovec in Patients with SMA and One *SMN2* Gene Copy: Findings from the RESTORE Registry

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Introduction

- SMA is a rare, debilitating neuromuscular disease characterized by motor neuron loss, resulting in progressive muscle weakness and atrophy caused by deletion or mutation of the *SMN1* gene[1,2]
- Severity of SMA generally correlates with the number of copies of the *SMN2* gene, which produces SMN protein with reduced function, partially compensating for *SMN1* gene mutation or deletion[3,4]
- Patients with only one *SMN2* gene copy are at risk to have SMA types 0 or 1, type 0 being the rarest and most severe SMA phenotype, characterized by prenatal onset of muscle weakness, joint contractures and no antigravity movement at birth, the requirement of mechanical ventilation support at birth, and death before 6 months of age.[1,2,5,6] Patients with SMA and one *SMN2* gene copy require early treatment with urgency because their expected lifespan is so short.
- There are three approved treatments for patients with SMA (nusinersen, risdiplam, and OA;[7–9] however, clinical trials have not included patients with SMA with one *SMN2* gene copy[10]
- Clinical trials of OA treatment have demonstrated improvements in motor function and survival of patients with two or three copies of the *SMN2* gene[11–15]
- The RESTORE registry (NCT04174157) includes real-world data on patients with SMA varying in *SMN2* gene copy number, clinical characteristics, and treatments, providing an opportunity to focus on patients with one *SMN2* gene copy[16,17]

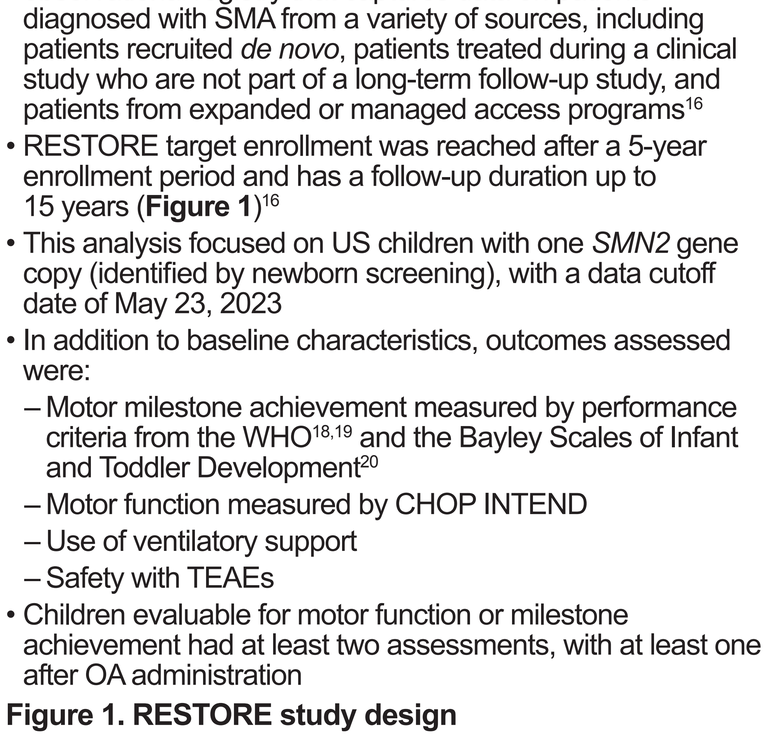
Objective

- We sought to describe clinical outcomes after OA treatment for patients with SMA enrolled in RESTORE who have one *SMN2* gene copy

Methods

- RESTORE is a prospective, multicenter, multinational, observational registry that captures data on patients diagnosed with SMA from a variety of sources, including patients recruited *de novo*, patients treated during a clinical study who are not part of a long-term follow-up study, and patients from expanded or managed access programs[16]
- RESTORE target enrollment was reached after a 5-year enrollment period and has a follow-up duration up to 15 years (**Figure 1**)[16]
- This analysis focused on US children with one *SMN2* gene copy (identified by newborn screening), with a data cutoff date of May 23, 2023
- In addition to baseline characteristics, outcomes assessed were:
  - Motor milestone achievement measured by performance criteria from the WHO[18,19] and the Bayley Scales of Infant and Toddler Development[20]
  - Motor function measured by CHOP INTEND
  - Use of ventilatory support
  - Safety with TEAEs
- Children evaluable for motor function or milestone achievement had at least two assessments, with at least one after OA administration

Figure 1. RESTORE study design



HCRU, health care resource utilization; IND, investigational new drug; MAP, managed access program; SMA, spinal muscular atrophy; US FDA, United States Food and Drug Administration.

Results

Patients

- Three patients with one *SMN2* gene copy were included for this RESTORE subanalysis, based on the May 23, 2023 data cutoff (**Table 1**)
  - One patient was male, and two female, all >30 weeks gestational age at birth
  - Patients had either SMA type 0 or 1
  - All but one received OA as their first treatment, occurring at 1 month of age
    - Patient 3 received nusinersen at 1 month of age before OA infusion at 4 months of age, and then risdiplam was initiated at 13 months of age
  - Patients 1 and 2 are twins diagnosed with SMA after newborn screening, who demonstrated normal tone and reflexes throughout hospitalization[21]

Table 1. Demographics and baseline clinical characteristics

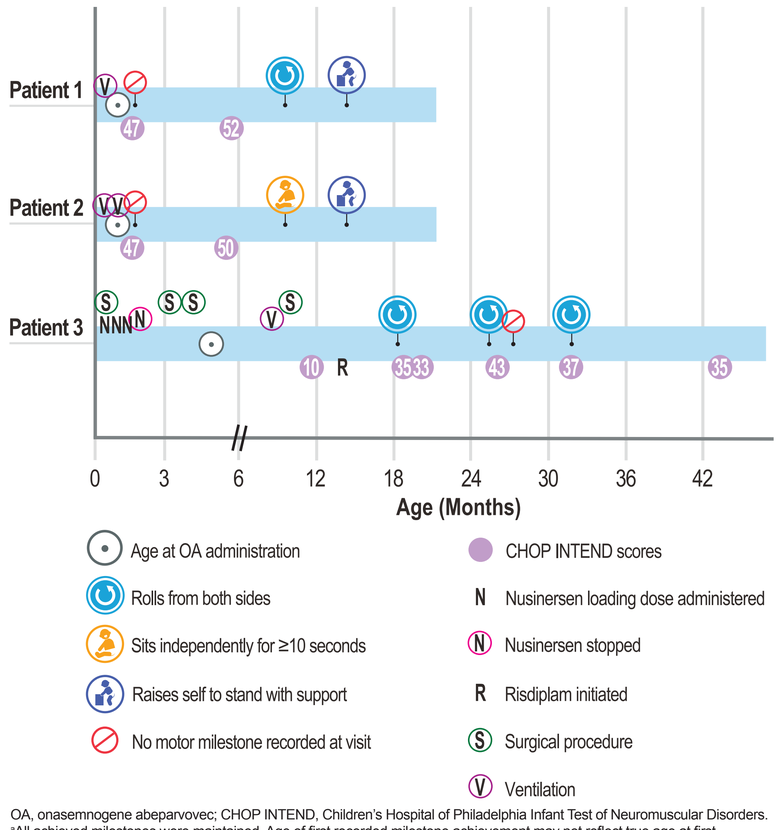
Characteristic	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Male
Gestational age at birth, weeks	30–32 weeks	30–32 weeks	>35 weeks
Race	Multiple	Multiple	White
Ethnicity	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino
Age at SMA diagnosis, months	1	1	0
SMA type	1	1	0
Age at first treatment, months	1	1	1
First treatment	OA	OA	Nusinersen
Age at OA treatment, months	1	1	4
Weight at OA treatment, kg	1.6	1.6	10.9
Follow-up time, months	19	19	44

OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy.

Motor milestones and motor function assessments

- All patients were alive at data cutoff
- All three patients received ventilatory support, before OA for Patients 1 and 2, and before and after OA for Patient 3
- All patients achieved motor milestones after OA treatment during the observation period (**Figure 2**), the greatest of which for each patient are below:
  - Patients 1 and 2 raised themselves to stand with support
  - Patient 3 rolled from side to side on three separate visits
- Post-OA CHOP INTEND scores were >40 for all three patients (**Figure 2**)

Figure 2. Motor milestone achievements by age[a]



OA, onasemnogene abeparvovec; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
[a]All achieved milestones were maintained. Age of first recorded milestone achievement may not reflect true age at first achievement. There is no predetermined follow-up schedule, and motor function and/or motor milestones are not recorded at every visit. Some centers may consider milestone and functional assessments to be redundant for some patients.

Safety

- One patient, Patient 1, reported TEAEs of a parainfluenza virus infection and respiratory distress, neither of which were considered to be treatment-related

Limitations

- A small number of evaluable patients with SMA and one *SMN2* gene copy receiving OA were identified among the large number of patients in RESTORE
- Patients who did not survive or were too ill to receive OA were not included
- Patients who were identified with newborn screening and treated within 1–2 months of diagnosis. Patient outcomes after treatment will differ dependent on diagnosis and treatment time, as well as symptom severity, among other variables.
- The data included variable follow-up durations, with longer follow ups in some increasing their likelihood of having a motor milestone achievement documented
- Additional genetic phenotypic modifiers were not investigated as part of the RESTORE protocol
- There may have been TEAEs that occurred after OA infusion but before patient enrollment dates that were not captured

Conclusions

These three cases demonstrate that in rare instances, patients with SMA with one *SMN2* gene copy can survive and achieve substantial motor improvements after OA treatment, indicating positive benefit:risk in these particularly vulnerable children

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Abbreviations

AE, adverse event; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HCRU, health care resource utilization; IND, investigational new drug; MAP, managed access program; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy; *SMN1*, *survival motor neuron 1* gene; *SMN2*, *survival motor neuron 2* gene; TEAE, treatment-emergent adverse events; US, United States; US FDA, United States Food and Drug Administration; WHO, World Health Organization.

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