Real-World Outcomes Following Onasemnogene Abeparvovec in Patients with Spinal Muscular Atrophy and Invasive Ventilatory Support: Findings from the RESTORE Registry

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Introduction

- Respiratory disease contributes to substantial morbidity and disability in patients with SMA, with respiratory failure representing a leading cause of infant and childhood mortality[1,2]
- Some patients with SMA receive insufficient pulmonary support with noninvasive ventilatory approaches (e.g., BiPAP) and require invasive ventilatory approaches such as tracheostomies[2]
- OA is a one-time gene replacement therapy approved for patients with SMA and has demonstrated safety and efficacy in several clinical trials[3–8]
- However, patients requiring invasive ventilatory support were excluded from OA clinical trials, so relatively little is known about treatment outcomes in these patients[4–8]
- The RESTORE registry (NCT04174157) is a prospective, multicenter, multinational, non-interventional, treatment-neutral registry of patients with SMA designed to build on existing real-world data on treatment patterns and long-term outcomes[9,10]
- Thus, RESTORE provides an opportunity to evaluate outcomes with OA treatment for patients with SMA who require ventilation support in real-world practice

Objective

- We sought to describe outcomes and safety following OA infusion for patients with SMA and tracheostomy in RESTORE, a multinational, noninterventional SMA registry

Methods

- RESTORE target enrollment was reached after a 5-year enrollment period and has a follow-up duration up to 15 years (**Figure 1**)[9]
- As of May 2023, 519 patients with SMA were enrolled in RESTORE
- In addition to demographics and clinical characteristics, outcomes assessed included:
  - Use of ventilatory support, including tracheostomies
  - Motor milestone achievement measured by performance criteria from the WHO MGRS[11,12] and the Bayley Scales of Infant and Toddler Development III[13]
  - Motor function measured by CHOP INTEND, HFMSE, and HINE-2, with clinically meaningful improvements defined as follows:
    - CHOP INTEND, ≥4-point change[14–16]
    - HFMSE, ≥3 point change[14,17]
    - HINE-2, ≥2-point change[18,19]
  - Safety (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

RESTORE Global SMA Registry

Patients	Prospective, multicenter, multinational, observational study
≥500 patients with genetically confirmed 5q SMA • With appropriate consent/assent to participate • Not enrolled in any interventional clinical trial involving an investigational medicinal product for SMA	Rolling enrollment over a 5-year period → Followed for up to 15 years or until early termination Patient care will follow usual SMA treatment practices in each country and participating clinical sites
Study objectives	**Enrollment sources**
• Primary objective is to assess the effectiveness of treatments for SMA, short- and long-term safety, and overall patient survival • Secondary objectives include the assessment of HCRU, caregiver burden, and changes in patient functional independence over time	• Individual *de novo* clinical sites • MAP: patients from the US MAP cohort and patients from the single-patient IND program are included in the registry. The US MAP provided onasemnogene abeparvovec access to eligible patients with a genetic diagnosis of SMA, which ended with US FDA approval of onasemnogene abeparvovec.

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

- As of May 23, 2023, 31 OA-treated patients in RESTORE had received tracheostomies (**Table 1**)
- Twelve patients (38.7%) received tracheostomies prior to OA infusion
- Most patients were from the United States (67.7%) and had two *SMN2* copies (96.8%)
- Four patients (12.9%) were identified by newborn screening and 27 patients (87.1%) were diagnosed clinically
- Eight patients (25.8%) received OA monotherapy; 23 patients (74.2%) received other treatments(s) before and/or after OA
- Median (range) age at diagnosis, initial treatment, and tracheostomy were 4.0 (0.0–14.0) months, 5.0 (1.0–21.0) months, and 8.1 (2.2–28.3) months, respectively

Table 1. Demographics and clinical characteristics

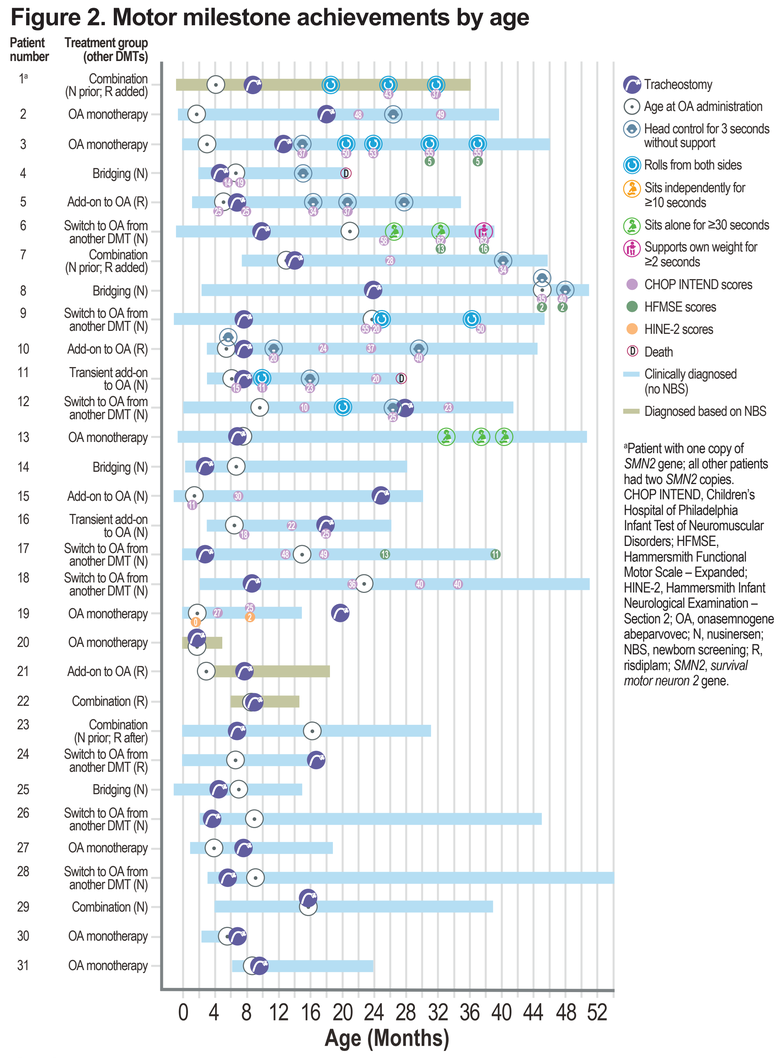
Characteristics	Patients with tracheostomy N=31
Sex, n (%)	
Male	18 (58.1)
Female	13 (41.9)
Number of *SMN2* gene copies, n (%)	
One copy	1 (3.2)
Two copies	30 (96.8)
Country, n (%)	
Greece	3 (9.7)
Japan	7 (22.6)
United States	21 (67.7)
Treatment, n (%)[a]	
OA monotherapy	8 (25.8)
Switch to OA from another DMT	8 (25.8)
Add-on to OA	4 (12.9)
Bridging	4 (12.9)
Combination	5 (16.1)
Transient add-on to OA	2 (6.5)
NBS, n (%)	4 (12.9)
Clinically diagnosed, n (%)	27 (87.1)
Symptomatic at diagnosis, n (%)	31 (100.0)
SMA type, n (%)	
0	1 (3.2)
1	29 (93.5)
Missing	1 (3.2)
Age at SMA diagnosis, months	
Median (min, max)	4.0 (0.0, 14.0)
IQR	2.0–5.0
Mean (SD)	4.2 (3.4)
Age at initial SMA treatment, months	
Median (min, max)	5.0 (1.0, 21.0)
IQR	2.0–8.0
Mean (SD)	5.6 (4.5)
Age at OA infusion, months	
Median (min, max)	7.0 (2.0, 45.0)
IQR	4.0–13.0
Mean (SD)	9.9 (8.9)
Age at tracheostomy, months	
Median (min, max)	8.1 (2.2, 28.3)
IQR	6.3–14.3
Mean (SD)	10.5 (6.6)
Time from diagnosis to first treatment, months	
Median (min, max)	0.7 (–0.7, 19.8)
IQR	0.3–1.2
Mean (SD)	1.5 (3.5)
Duration of follow-up from first treatment to last known visit, months	
Median (min, max)	6.0 (1.0, 8.0)
IQR	4.0–7.0
Mean (SD)	5.5 (1.8)

DMT, disease-modifying treatment; IQR, interquartile range; OA, onasemnogene abeparvovec; SD, standard deviation; SMA, spinal muscular atrophy; *SMN*, *survival motor neuron*; *SMN2*, *survival motor neuron 2* gene.
[a]OA monotherapy: received only OA infusion; Switch to OA from another DMT: longer-duration treatment >3 months with nusinersen or risdiplam which was then discontinued prior to receiving OA; Add-on to OA: any *SMN*-targeting DMT administered after infusion with OA; Bridging: short-duration treatment with nusinersen or risdiplam (loading doses only or ≤3 months, respectively) serving as a bridge to gene therapy with OA; Combination: initial treatment with nusinersen and/or risdiplam with ongoing or added treatment after infusion with OA; Transient add-on to OA: add-on treatment to OA that is discontinued.[20]

Motor function

- Sixteen of 18 patients (88.9%; Patients 2–13, 15, 16, 18, 19) with recorded motor milestone data achieved or maintained motor milestones based on any assessment during the observation period (**Figure 2**)
- Thirteen of 17 (76.5%) patients with CHOP INTEND score recorded demonstrated clinically meaningful improvements (Patients 3–12, 15, 16, 18) in CHOP INTEND scores:
  - OA monotherapy: n=1, Patient 3
  - Switch to OA from another DMT: n=4, Patients 6, 9, 12, and 18
  - Add-on to OA: n=3, Patients 5, 10, and 15
  - Bridging: n=2, Patients 4 and 8
  - Combination: n=1, Patient 7
  - Transient add-on to OA: n=2, Patients 11 and 16
- Median (range) change in CHOP INTEND scores per month across treatment groups was 0.43 (–1.0–4.0)
- Three of four patients (75.0%) with HMFSE scores recorded experienced clinically meaningful improvements (Patient 6) or maintenance (Patients 3 and 8) in HMFSE scores
- The patient with HINE-2 scores recorded (Patient 19) achieved a clinically meaningful HINE-2 score improvement

Figure 2. Motor milestone achievements by age



[a]Patient with one copy of *SMN2* gene; all other patients had two *SMN2* copies. CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale – Expanded; HINE-2, Hammersmith Infant Neurological Examination – Section 2; OA, onasemnogene abeparvovec; N, nusinersen; NBS, newborn screening; R, risdiplam; *SMN2*, *survival motor neuron 2* gene.

Safety

- TEAEs of any grade and ≥Grade 3 were reported in 74.1% and 70.9% of patients, respectively
- Of the 19 serious TEAEs reported, four (12.9%) were considered OA treatment-related
- Two deaths were recorded (one each due to respiratory failure [Patient 11] and respiratory failure post tracheostomy removal [Patient 4]); neither were considered related to OA treatment
- TEAEs are summarized in **Table 2**

Table 2. Treatment-emergent adverse events

Characteristics, n (%)	Patients with tracheostomy N=31
TEAEs	
Any grade	23 (74.1)
≥Grade 3	22 (70.9)
OA treatment-related	14 (45.1)
Serious TEAEs	19 (61.2)
OA treatment-related	4 (12.9)
TEAEs of special interest	
Hepatotoxicity	8 (25.8)
Transient thrombocytopenia	12 (38.7)
Cardiac AEs	9 (29.0)
Thrombotic microangiopathy	1 (3.2)

AE, adverse event; OA, onasemnogene abeparvovec; TEAE, treatment-emergent adverse event.

Limitations

- The patient population was limited based on enrollment in the RESTORE registry
- Most patients in this analysis were from the United States
- Baseline data obtained prior to OA infusion were incomplete
- Data on the reasons for tracheostomy use (e.g., disease progression) and changes in ventilatory support following OA infusion were not collected
- This analysis included a limited follow-up period

Conclusions

- In this analysis of the RESTORE registry, improvements in motor function after OA treatment were observed for patients who received tracheostomies in the real-world settings
- Clinically meaningful motor function improvements were observed independent of DMT types received before or after OA administration and most patients were still alive at the end of follow-up in this analysis
- TEAEs were consistent with the established safety profile of OA suggesting that, unlike previously reported, a greater risk of TEAEs was not observed in this small sample of patients with tracheostomies
- Cumulatively, these data support the DMT administration can provide improvements in motor function for patients with SMA who received tracheostomies

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Abbreviations

AE, adverse event; BiPAP, bi-level positive airway pressure; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DMT, disease-modifying treatment; HFMSE, Hammersmith Functional Motor Scale – Expanded; HINE-2, Hammersmith Infant Neurological Examination – Section 2; OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy; *SMN*, *survival motor neuron* genes; *SMN2*, *survival motor neuron 2 gene*; TEAE, treatment-emergent adverse event; WHO MGRS, World Health Organization Multicentre Growth Reference Study.

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