Real-world Outcomes of Nusinersen or Onasemnogene Abeparvovec Monotherapy, or Switching to Onasemnogene Abeparvovec from Nusinersen in SMA Patients Aged ≥6 Months

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Introduction

- SMA is a rare, genetic neuromuscular disease caused by a deletion or mutation of the *SMN1* gene associated with loss of voluntary motor function and bulbar function, which are essential for breathing and swallowing[1–3]
- DMTs have substantially improved the prognosis of SMA with US FDA approval of targeted and gene therapies[4–12]
  - Onasemnogene abeparvovec is a single-dose, AAV9-based gene replacement therapy that delivers a fully functional copy of the *SMN* transgene into target motor neurons via intravenous infusion[5,10–11]
  - Nusinersen, an *SMN2* gene splicing modifier, is an antisense oligonucleotide administered via intrathecal injection every 4 months after a series of loading doses[4]
  - Almost all patients in clinical trials for onasemnogene abeparvovec were <6 months of age and none had received a prior DMT[10,11]
  - In real-world practice however, patients ≥6 months of age may be treated, and patients may receive other DMTs before switching to onasemnogene abeparvovec
- Real-world data on treatment outcomes and HCRU associated with FDA-approved SMA therapies are limited, particularly for patients who have received more than one treatment or for patients who were excluded from interventional clinical trials (e.g., patients ≥6 months of age at treatment)

Objective

- We aimed to describe real-world outcomes and HCRU for patients in the United States with SMA who received nusinersen or onasemnogene abeparvovec monotherapy, or switched to onasemnogene abeparvovec from nusinersen at ≥6 months of age

Methods

- A retrospective chart review was conducted to describe real-world outcomes and HCRU data for patients with genetically confirmed SMA aged ≥6 months when treated with nusinersen monotherapy, onasemnogene abeparvovec monotherapy, or switching to onasemnogene abeparvovec from nusinersen
- Chart data were collected retrospectively from 15 sites/health care providers across the United States
- Patients with prior enrollment in a clinical trial of investigational SMA therapy were excluded
- Outcomes were summarized for patients at/before the index date (date of monotherapy initiation or switch to onasemnogene abeparvovec) who had medical information available for ≥1 follow-up visit
  - Developmental (motor) milestones (sitting, standing, walking)
  - Bulbar function measures (crying, speaking, eating)
- HCRU was summarized PPY during baseline period (time from onset of SMA symptoms or time of diagnosis [whichever came earlier]) and follow-up period (time from the index date until the end of chart data availability)
  - SMA-related inpatient admissions
  - SMA-related emergency room visits
- All analyses were descriptive, with no statistical comparisons between treatment groups performed

Results

Patients

- This chart review included 55 patients (19 nusinersen monotherapy; 21 onasemnogene abeparvovec monotherapy; 15 nusinersen switching to onasemnogene abeparvovec) (**Table 1**)
- SMA phenotypes were type 1, type 2, type 3, and undetermined (**Table 1**)
- On the index date, most patients (84.2% treated with nusinersen monotherapy, 61.9% treated with onasemnogene abeparvovec monotherapy, and 80.0% patients switching to onasemnogene abeparvovec from nusinersen) weighed ≥8.5 kg (**Table 1**)
- Most patients were not screened for SMA as newborns

Table 1. Demographics and baseline clinical characteristics

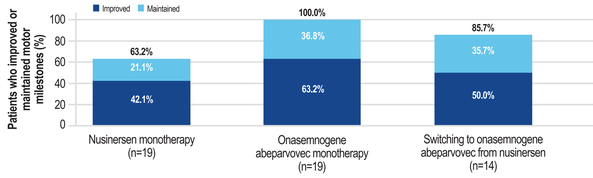
Characteristic	Nusinersen monotherapy (n=19)	Onasemnogene abeparvovec monotherapy (n=21)	Switching to onasemnogene abeparvovec from nusinersen (n=15)
Age at SMA diagnosis, months			
Median	12.0	13.0	2.0
Mean (SD)	17.7 (14.1)	12.2 (7.9)	3.2 (3.0)
Range	2.0, 53.0	0.0, 22.0	0.0, 9.0
Age at treatment initiation, months[a]			
Median	35.0	14.0	4.0
Mean (SD)	33.2 (15.8)	14.7 (6.2)	4.1 (3.4)
Range	8.0, 57.0	6.0, 23.0	0.0, 10.0
Weight at monotherapy initiation or switch to onasemnogene abeparvovec administration			
Median, kg	12.1	9.5	9.2
Mean (SD), kg	13.1 (4.3)	9.7 (2.1)	9.5 (2.3)
Range	7.6, 21.8	6.9, 13.8	5.1, 15.0
≥8.5 kg, n (%)	16 (84.2)	13 (61.9)	12 (80.0)
Sex, n (%)			
Male	11 (57.9)	11 (52.4)	9 (60.0)
Female	8 (42.1)	10 (47.6)	6 (40.0)
SMA type, n (%)			
1	8 (42.1)	4 (19.0)	12 (80.0)
2	8 (42.1)	9 (42.9)	1 (6.7)
3	3 (15.8)	5 (23.8)	0 (0)
Undetermined	0 (0)	3 (14.3)	2 (13.3)
***SMN2* copy number, n (%)**			
Two	9 (47.4)	3 (14.3)	12 (80.0)
Three	9 (47.4)	14 (66.7)	2 (13.3)
Four or more	1 (5.3)	4 (19.0)	1 (6.7)
Newborn screening performed, n (%)			
No	19 (100.0)	16 (76.2)	11 (73.3)
Age at SMA symptom onset, months			
Median	7.0	7.0	2.0
Mean (SD)	11.5 (11.3)	9.1 (6.0)	3.3 (2.1)
Range	0.0, 35.0	0.0, 19.0	1.0, 8.0

SMA, spinal muscular atrophy; *SMN2*, *survival motor neuron 2* gene.
[a]Table includes age at nusinersen treatment initiation for patients switching to onasemnogene abeparvovec from nusinersen (age at switch to onasemnogene abeparvovec: median, 4.0 months; mean [SD], 4.1 [3.4] months; range, 0.0, 10.0 months.

Motor milestones and motor function assessments

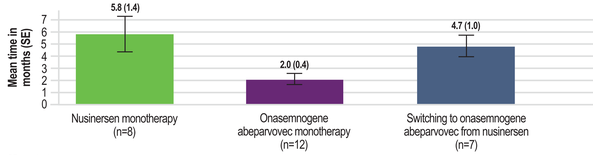
- Improvement of motor milestones from index was achieved by 63.2% (n=12/19) of patients who received onasemnogene abeparvovec monotherapy, 50% (n=7/14) of patients who switched to onasemnogene abeparvovec from nusinersen, and 42.1% (n=8/19) of patients who received nusinersen monotherapy (**Figure 1**)

Figure 1. Patients who improved or maintained developmental milestones by therapy type



- Mean (±SE) time to observed improvement was shorter for patients who received onasemnogene abeparvovec monotherapy (2.0 [0.4] months) than for patients who switched to onasemnogene abeparvovec from nusinersen (4.7 [1.0] months), or patients who received nusinersen monotherapy (5.8 [1.4] months) (**Figure 2**)

Figure 2. Time to improvement from baseline in developmental milestones[a]

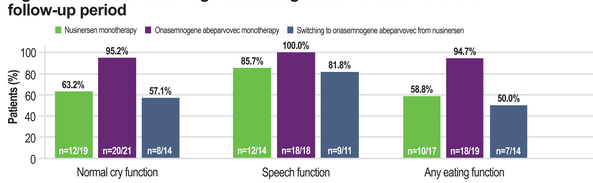


SE, standard error.
[a]Time to improvement in developmental milestones (e.g., sitting, standing, walking) was assessed for patients who achieved improvement in motor milestones following treatment.

Bulbar function

- At the end of the follow-up period, a greater percentage of patients who received onasemnogene abeparvovec monotherapy achieved/maintained normal cry function (95.2%, n=20/21), improved/maintained speech function (100%, n=18/18), and improved/maintained any eating function (e.g., thin liquids by mouth, some food consistency by mouth; 94.7%, n=18/19) compared with patients who received nusinersen monotherapy or who switched to onasemnogene abeparvovec from nusinersen (**Figure 3**)

Figure 3. Patients achieving/maintaining bulbar function[a] at end of follow-up period

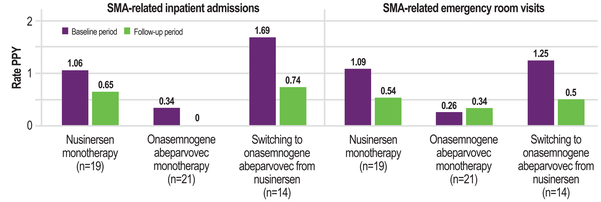


[a]Includes normal cry function, speech function, and any eating function (e.g., thin liquids by mouth, some food consistency by mouth).

Health care resource utilization

- HCRU, as measured by inpatient admission rates and emergency room visits, was generally reduced in the post-treatment follow-up period versus baseline period for patients in each treatment group (**Figure 4**)

Figure 4. SMA-related inpatient admission and emergency room visit rates at baseline vs. follow-up[a]



PPY, per patient-year.
[a]Emergency room visits were not related to treatment but general disease-related visits.

Limitations

- Small number of patients per treatment group
- Variable completeness of data across charts
- Results are descriptive and do not account for differences in patient characteristics or other potential confounders
- Duration of baseline and follow-up periods was variable across patients; however, rates were standardized PPY to account for this variation

Conclusions

- Patients with SMA improved or maintained function across multiple outcomes after receiving onasemnogene abeparvovec at ≥6 months of age, regardless of prior nusinersen therapy
- Time to improvement in developmental milestones was the shortest for patients who received onasemnogene abeparvovec monotherapy (within 2 months after treatment initiation)
- A greater percentage of patients who received onasemnogene abeparvovec monotherapy achieved/maintained normal cry and speech function and improved/maintained any eating function compared with patients who received nusinersen monotherapy or who switched to onasemnogene abeparvovec from nusinersen
- Inpatient admissions in the post-treatment follow-up period were reduced compared with baseline, with no admissions reported after onasemnogene abeparvovec monotherapy
- Rates of emergency room visits during follow-up were lowest for patients who received onasemnogene abeparvovec monotherapy; rates were comparable between patients who received nusinersen monotherapy and those who switched to onasemnogene abeparvovec from prior nusinersen

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Abbreviations

AAV9, adeno-associated virus vector 9; DMT, disease-modifying treatment; HCRU, health care resource utilization; PPY, per patient-year; SMA, spinal muscular atrophy; *SMN1*, *spinal motor neuron 1* gene; *SMN2*, *spinal motor neuron 2* gene; FDA, United States Food and Drug Administration.

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