Received: 22 June 2018 | Accepted: 4 November 2018
DOI: 10.1002/ppul.24203

ORIGINAL ARTICLE: PCD, PIG, NEHI, CHILD, AND RARE DISEASES

WILEY PEDIATRIC PULMONOLOGY

# Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy

Samiah Al-Zaidy MD[1,2] | A. Simon Pickard PhD[3] | Kavitha Kotha MD[2] | Lindsay N. Alfano PT[1,2] | Linda Lowes PhD[1,2] | Grace Paul MD[2] | Kathleen Church MSW[1,2] | Kelly Lehman FNP[2] | Douglas M. Sproule MD[4] | Omar Dabbous MD/MPH[4] | Benit Maru MD/PhD[4] | Katherine Berry PT[1,2] | W. David Arnold MD[5] | John T. Kissel MD[1] | Jerry R. Mendell MD[1,2,5] | Richard Shell MD[1]

[1] Department of Pediatrics, Ohio State University, Columbus, Ohio

[2] Center for Gene Therapy Nationwide Children's Hospital, Columbus, Ohio

[3] Department of Pharmacy Systems, Outcomes, and Policy, University of Illinois, Chicago, Illinois

[4] AveXis, Inc., Bannockburn, Illinois

[5] Department of Neurology, Ohio State University, Columbus, Ohio

**Correspondence**
Samiah Al-Zaidy, MD and Richard Shell, MD, Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205.
Email: samiah.alzaidy@gmail.com (SA-Z) and richard.shell@nationwidechildrens.org (RS)

**Funding information**
Supported by AveXis, Inc.

## Abstract

**Background:** Spinal Muscular Atrophy type 1 (SMA1) is a rare genetic neuromuscular disease where 75% of SMA1 patients die/require permanent-ventilation by 13.6 months. This study assessed the health outcomes of SMA1 infants treated with AVXS-101 gene replacement therapy.

**Methods:** Twelve genetically confirmed SMA1 infants with homozygous deletions of the *SMN1* gene and two *SMN2* gene copies received a one-time intravenous proposed therapeutic dose of AVXS-101 in an open label study conducted between December 2014 and 2017. Patients were followed for 2-years post-treatment for outcomes including (1) pulmonary interventions; (2) nutritional interventions; (3) swallow function; (4) hospitalization rates; and (5) motor function.

**Results:** All 12 patients completed the study. Seven infants did not require noninvasive ventilation (NIV) by study completion. Eleven patients had stable or improved swallow function, demonstrated by the ability to feed orally; 11 patients were able to speak. The mean proportion of time hospitalized was 4.4%; the mean unadjusted annualized hospitalization rate was 2.1 (range = 0, 7.6), with a mean length of stay/hospitalization of 6.7 (range = 3, 12.1) days. Eleven patients achieved full head control and sitting unassisted and two patients were walking independently.

**Conclusions:** AVXS-101 treatment in SMA1 was associated with reduced pulmonary and nutritional support requirements, improved motor function, and decreased

**Abbreviations:** AAV, adeno-associated virus; LOS, length of stay; NIV, noninvasive ventilation; QoL, quality of life; SMA, spinal muscular atrophy; SMA1, spinal muscular atrophy type 1; WHO, World Health Organization.

This data, in part or whole, has also been presented at the following international meetings: AMCP Managed Care & Specialty Pharmacy (Boston, MA; April 23–26), American Academy of Neurology (Los Angeles, CA; April 21–27), American Society of Gene and Cell Therapy (Chicago, IL; May 16–19), and American Thoracic Society (San Diego, CA; May 18–23).

hospitalization rate over the follow-up period. This contrasts with the natural history of progressive respiratory failure and reduced survival. The reduced healthcare utilization could potentially alleviate patient and caregiver burden, suggesting an overall improved quality of life following gene replacement therapy.

**Trial registration:** ClinicalTrials.gov number, NCT02122952.

**KEYWORDS**

AVXS-101, gene therapy, gene replacement, health outcomes, quality of life, SMA1, spinal muscular atrophy

## 1 | INTRODUCTION

Spinal muscular atrophy (SMA), an autosomal recessive neurodegenerative disorder, is caused by biallelic loss or dysfunction of the survival motor neuron 1 (*SMN1*) gene. Insufficient levels of the survival motor neuron (SMN) protein result in loss of motor neurons of the brainstem and spinal cord, progressive muscular atrophy, and weakness. With an incidence of approximately 1 in 10 000 live births and a carrier frequency of approximately 1 in 54,[1] SMA is classified into four subtypes (1-4) on the basis of age of onset of symptoms and motor milestone achievement. This variability in the clinical phenotype is largely a result of the number of copies of the survival motor neuron 2 (*SMN2*) gene, a modifier gene nearly identical to *SMN1* that produces a small, insufficient fraction of SMN protein. The SMA type 1 (SMA1) phenotype is the most severe and accounts for 60% of SMA patients; it is the most common genetic cause of death in infants.[2] The onset of symptoms for SMA1 occurs shortly after birth and prior to six months of age with a clinical hallmark of the inability to achieve independent sitting.[3,4] Infants with SMA1 rapidly lose motor function and ultimately succumb to respiratory complications often within the first year of life. Longitudinal observational studies of SMA1 infants with two *SMN2* copies who were offered standard of care[5] showed a median age of death or permanent ventilation (≥16 h/day for at least 14 consecutive days) that ranged from 8 months[6] to 10.5 months.[3] Based on the published consensus statements for the standard of care of SMA,[7,8] many centers have adopted the use of non-invasive ventilation (NIV) and aggressive chest clearance to help manage the respiratory complications of SMA1. These standards also include guidance to provide enteral nutritional support early due to the loss of bulbar function in the natural history of the disease.

Most SMA1 patients experience the complications of respiratory failure and dysphagia that necessitate interventions (eg, nasogastric tube or gastrostomy tube placement and initiation of NIV or intubation leading to tracheostomy, respectively) to prolong patient survival.[3] Natural history studies show that in patients older than 12 months, 100% required nutritional or combined nutritional and ventilation support,[3] and 61% of SMA1 patients required ≥1 intubation within the first year of life.[9] Despite supportive care, SMA patients have high hospitalization rates; infants with SMA1 were reported to have 4.2[10] to 7.6[11] hospitalizations/year compared to 1.7 hospitalizations/year in non-SMA patients.[10] In a review of healthcare resource utilization over the past two decades, younger SMA patients (mean age, 1.2 years) had ≥1 inpatient hospitalization with a mean length of stay (LOS) of 13 days (maximum, 183 days).[12] The average follow up period for this cohort of subjects was 22.7 months with an average of 3.1 inpatient visits per patient and 3.7 emergency room visits per patient over this time period.

The devastating nature of this disease significantly reduces health-related quality of life (HRQoL) for SMA patients compared to healthy children.[13,14] Compared to patients with SMA type 3 (SMA3), which is a less severe form of SMA with onset at >18 months and achievement of independent walking,[5] SMA1 patients had lower HRQoL in terms of "problems with neuromuscular disease," "communication," and "family resources."[15] Although the disease has clear implications for QoL, the evaluation of QoL in SMA1 infants is limited by the nature of the condition, given that QoL is inherently subjective and relies on self-report and proxies, such as parents or health outcome indicators, due to the patients' age. Given the importance SMA patients place on small changes in motor function and maintenance of function on QoL,[16] management of symptoms and treatment may also improve QoL in patients as well as caregivers.

Promising therapies have recently been shown to alter the natural history of infants with SMA1.[17,18] Based on pre-clinical data,[19] we hypothesized that a single intravenous infusion of an adeno-associated viral (AAV) vector containing the human *survival motor neuron* gene (*hSMN*) under control of the chicken beta-actin promoter, AVXS-101 (Bannockburn, IL) would result in increased survival and improved motor function in a cohort of 12 SMA1 infants as reported previously[18] compared to historical cohorts.[3,6] In this report, we aim to describe and expand upon the health outcomes of SMA1 patients treated with AVXS-101, including pulmonary support, swallow function, nutritional outcomes, hospitalization rate, and motor function.

## 2 | MATERIALS AND METHODS

### 2.1 | Study participants

As previously reported,[18] 12 patients (Cohort 2) with a genetically confirmed diagnosis of SMA1 with homozygous *SMN1* exon 7

deletions and two copies of *SMN2* were enrolled in an open-label study (ClinicalTrials.gov: NCT02122952) and treated with the proposed therapeutic dose of AVXS-101 between December 2014 and December 2015.

With safety as a primary objective, time to death or permanent ventilation, defined as either ≥16 h/day for at least 14 consecutive days without an acute reversible illness or perioperative use, or tracheostomy placement, was a secondary objective and primary efficacy endpoint.[18]

The study was approved by the Institutional Review Board of Nationwide Children's Hospital (no. IRB00000568), and written informed consent was obtained from parents or legal guardians.

### 2.2 | Follow-up

Follow-up was conducted on days 7, 14, 21, and 30 followed by monthly visits through 12 months post-dosing, and then every three months through two years post-dosing. The last study visit was conducted in December 2017. Outcomes described in this report include data from the full 24-month post-treatment follow-up period, including data previously published.

### 2.3 | Outcomes

The outcomes of interest included (1) pulmonary support; (2) nutritional support; (3) swallow function; (4) hospitalization rate; and (5) motor function. As part of the pulmonary assessment, the parent(s)/legal guardian(s) reported the number of hours per day the patient required ventilation support over the two weeks prior to the visit if support was being used. All patients who failed a video-fluoroscopic swallow test were required to use non-oral modes of feeding, such as a surgically placed gastrostomy tube or a nasojejunal tube, prior to dosing.[5] Swallow function, determined through video-fluoroscopic swallow studies, was assessed at baseline and every 6 months during the follow-up period. In addition, details and outcomes of all inpatient hospitalizations, planned or unplanned, were captured during the follow-up period. The percent of time hospitalized for each patient was determined by dividing the total time hospitalized by the total number of days in the study and expressed as a percent. The annualized hospitalization rate for each patient was calculated by dividing the number of hospitalizations by the number of days in the study and standardizing to 365 days. Respiratory hospitalization was defined as any hospitalization containing a description with any of the following: pneumonia, bronchiolitis, upper respiratory infection (URI), upper respiratory tract infection (URTI), hypoxia, adenovirus, rhinovirus, or hypoventilation. For motor functioning, sitting unassisted was assessed by physical therapists as follows: (i) ≥5 s as per item 22 of the Bayley Scales of Infant and Toddler Development gross motor subtest; (ii) ≥10 s as per the World Health Organization (WHO) criteria[20]; and (iii) ≥30 s as per item 26 of the Bayley Scales mentioned previously.[21] Major motor milestones captured by video recording during visits were verified by an independent reviewer.

### 2.4 | Statistical analysis

Because statistical analysis was limited by the small sample size which is typical of rare diseases, descriptive statistics, such as frequencies and percentages, and means with ranges and/or standard deviations, were reported for the outcomes of interest.

## 3 | RESULTS

### 3.1 | Assessment of pulmonary support

At baseline (mean age 3.4 months, range [0.9-7.9]), 10 of 12 (83%) patients did not require NIV, and no patient required a tracheostomy at any time throughout the 2-year study period (Table 1).[18] As of their final study visit, 7 of the 10 patients who did not require ventilatory support before dosing completed the study without any ventilatory support. All three patients who did not require NIV at baseline but required it postdosing had an early onset of symptoms in the first month of life and a rapid disease progression characterized by diffuse muscle weakness, respiratory insufficiency, and inability to swallow. The NIV was required in the context of viral illnesses and was maintained thereafter. All five infants who required NIV at the final study visit remained stable post-dosing, as none reached the pulmonary endpoint.

### 3.2 | Evaluation of nutritional support, swallow function, and speech

At baseline, 7 of 12 (58%) patients were able to feed orally and did not require supplemental nutritional support, defined as enteral feeding (Figure 1).[18] At the end of the follow-up period, 6 of those 7 (86%) patients continued to eat exclusively by mouth.

Video-fluoroscopic swallow studies showed that the number of patients who achieved safe swallow function using thin liquids increased from 4 (33%) patients pre-treatment to 10 (83%) patients at the end of the follow-up period (Figure 1). The number of patients able to safely swallow to allow for at least partial oral feeding increased from 7 (58%) patients at baseline to 11 (92%) patients at the end of the follow-up period (Figure 1).

Because bulbar-innervated muscle function deterioration can negatively influence the ability of SMA1 patients to speak,[22] we also analyzed speech following AVXS-101 treatment. As shown in Table 2, 11 of 12 (92%) patients were able to speak by the end of the study.

### 3.3 | Respiratory infections, hospitalization, and LOS

Participants treated with the proposed therapeutic dose of AVXS-101 experienced, on average 1.4 respiratory hospitalizations per year (SD = 0.41, range 0-4.8). Ten patients (83%) required at least one hospitalization for respiratory illness during the trial. Some of these patients required an increased number of hours per day of NIV during the acute phase of the illness, but none exceeded 8 days, and all survived without reaching the pulmonary endpoint. This includes three

**TABLE 1** Decreased pulmonary support in SMA1 patients following AVXS-101 treatment

| Patients | BiPAP use prior to dosing | Age at last pulmonary assessment (months) | BiPAP use post dose | Pulmonary event reached |
|---|---|---|---|---|
| E.04 | Yes | 31.1 | Yes | No |
| E.05 | No | 28.5 | No | No |
| E.06 | No | 26.1 | No | No |
| E.07 | No | 28.1 | No | No |
| E.08 | Yes | 26.3 | Yes | No |
| E.09 | No | 28.9 | No | No |
| E.10 | No | 25.3 | No | No |
| E.11 | No | 27.7 | Yes | No |
| E.12 | No | 26.8 | No | No |
| E.13 | No | 25.4 | Yes[a] | No |
| E.14 | No | 27.9 | No | No |
| E.15 | No | 26.3 | Yes[a] | No |

BiPAP use is parent reported (for the most part, parents report hours used per night and hours used for naps).
[a]BiPAP was needed in these children because of hospitalizations for respiratory infections.

patients who were not using NIV at baseline, but required this support during their hospitalization for acute illness. All three patients returned to requiring no support at discharge.

The mean proportion of study time hospitalized was 4.4% (range = 0, 18.3%) for patients treated with AVXS-101; 10 (83%) patients were hospitalized <10% of the time, and none were hospitalized ≥20% of the time. In addition, the mean unadjusted annualized rate of hospitalizations (total hospitalizations/total number of subject-years followed) was 2.1 (range = 0, 7.6), and the mean LOS per hospitalization was 6.7 days (range = 3, 12.1) for the 10 patients who were hospitalized after treatment with AVXS-101.

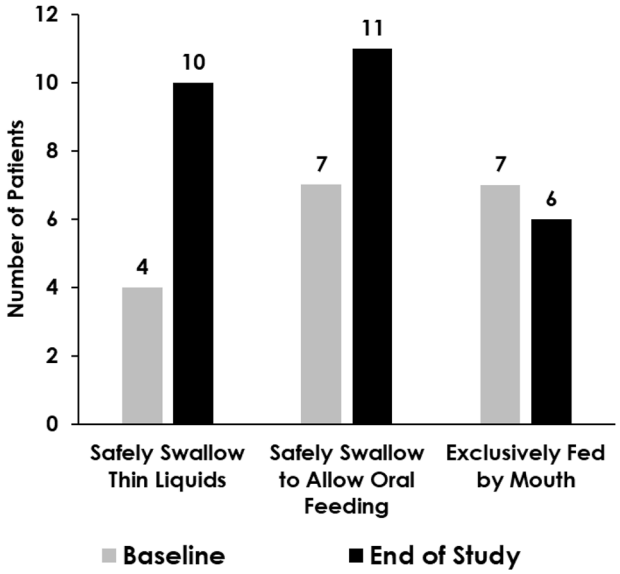


**FIGURE 1** Stabilization or improvement in swallow function in the AVXS-101 proposed therapeutic dose group ($n$ = 12). Swallow function was determined by a video-fluoroscopic swallowing test at baseline and every 6 months during the follow-up period. *In one patient, a gastrostomy placement was performed to enhance nutrition to improve wound healing and recovery from a difficult postoperative course after scoliosis surgery

### 3.4 | Motor milestone assessments

Following AVXS-101 treatment, 11 of the 12 (92%) infants achieved full head control and were able to sit unassisted. All 11 sat for ≥5 s, 10 (83%) sat unassisted for ≥10 s, and 9 (75%) could sit unassisted for ≥30 s during the 2-year follow-up period (Table 2). During the study, 9 (75%) patients were able to roll and 2 (17%) were able to crawl, pull to stand, and stand and walk independently. Continued long-term follow-up of the patients beyond the 2-year period revealed ongoing motor milestone achievements; two additional children developed the ability to sit unassisted for ≥30 s (11 [92%] total), and two additional children were able to stand with support (4 [33%] total; Table 2).

## 4 | DISCUSSION

AVXS-101, a one-time gene replacement therapy that crosses the blood-brain barrier[19] and treats the root cause of SMA (ie, deletion or loss of function of the *SMN1* gene), is designed for immediate and sustained expression of SMN protein, allowing for rapid onset and durable therapeutic effect and sustained SMN protein expression in motor neurons. To understand the impact of AVXS-101 gene replacement therapy in the absence of a standard care comparator group, the outcomes must be compared to those reported in natural history studies of SMA1 patients treated with the standard of care. In these studies, 100% of patients older than 12 months required either feeding or combined feeding and ventilatory support, and also lacked motor milestone achievement.[3,6] AVXS-101 one time gene

**TABLE 2** Motor milestone achievements impacting QoL

| | | Motor milestone achievement | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Sitting unassisted | | | |
| Patients | Age at GT (mos) | Brings hand to mouth | Head control | Roll[a] | Sitting with assistance | ≥5 s[b] | ≥10 s[c] | ≥30 s[d] | Standing assisted |
| E.04 | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* | ✓* | |
| E.05 | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| E.06 | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.07 | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* | |
| E.08 | 8 | ✓ | | | | | | | |
| E.09 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| E.10 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E.11 | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* |
| E.12 | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| E.13 | 1 | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| E.14 | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* |
| E.15 | 2 | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| Total (%) | N/A | 100 | 92 | 75 | 92 | 92 | 92 | 92 | 33 |

Single checks, 24-month follow-up; *Long-term follow-up.

[a]According to item 20 on the Bayley Scales of Infant and Toddler Development, rolling over is defined as movement of at least 180 degrees both left and right from a position of lying on the back.

[b–d]Sitting unassisted was determined as follows: (a) ≥5 s as per item 22 of the Bayley Scales of Infant and Toddler Development gross motor subtest, (b) ≥10 s as per the World Health Organization (WHO) criteria,[17] and (c) ≥30 s as per item 26 of the Bayley Scales.[18] GT, gene transfer

replacement therapy was able to preserve respiratory function in a cohort of symptomatic SMA1 infants with two copies of the *SMN2* gene; 70% of patients who did not require assisted ventilation prior to treatment were able to continue without such support for >2 years following treatment.[3] Remarkably, 92% of patients experienced stabilization or improvement in swallowing function and nutritional support. Compared to previous natural history studies of SMA1 patients, the present study had a lower mean number of annual inpatient admissions (2.1 versus 4.2[10] to 7.6[11] hospitalizations/year, respectively) and mean LOS (6.7 versus 13 days,[12] respectively). Participants also experienced only 1.4 respiratory hospitalizations per year, and no patients hospitalized for respiratory illnesses required a tracheostomy or prolonged invasive ventilation greater than 8 days. Regarding indicators of motor function, 92% of patients achieved full head control and the ability to sit independently for ≥5 s and were able to speak. As previously reported,[18] the only adverse event believed to be related to the viral vector gene therapy is a transient asymptomatic elevation of liver enzymes that was managed with a brief course of steroids. Taken together, AVXS-101 appears to transform the disease course with regard to respiratory and nutritional complications, hospitalizations, and motor functioning and raises the possibility of subsequent functional independence for SMA1 patients.

Along with reductions in the average number of hospitalizations and LOS compared to natural history, patients treated with AVXS-101 also spent less time hospitalized compared to the control group in the ENDEAR study (mean proportion of study time hospitalized, 4.4% versus 18.5%, respectively).[23] This randomized, sham-controlled, Phase 3 trial evaluating the clinical efficacy and safety of nusinersen had closely comparable study criteria and populations compared to the current study (ie, genetically confirmed SMA1 patients with homozygous *SMN1* exon 7 deletions and two *SMN2* copies). In addition, 83% (10/12) of the patients treated with AVXS-101 were hospitalized <10%, and none were hospitalized ≥20% of the 2-year follow-up period in contrast to the that observed in the control group of SMA1 patients who were enrolled as part of the ENDEAR study (41% were hospitalized <10% of the time and 37% were hospitalized ≥20% of the time; Figure 2).[23]

Qualitative studies have shown that SMA patients and their caregivers view small changes in motor function and maintenance of function as highly impacting patients' QoL.[16] In the context of treatment development, SMA patients reported that the functional activity they would most like to be preserved or improved was "respiratory functions (improvement or stabilization, including coughing and swallowing)."[24] Given that management of symptoms can improve[25] or maintain QoL in SMA patients even in those with disease progression,[26] the drastic reduction in respiratory and nutritional complications and continued achievement of motor milestones even beyond the follow-up period in the present study strongly suggest improved QoL. There are also potential QoL benefits to the family caregivers, who spend >8 h/day providing active care and have substantially lower QoL than the general population.[14] Reducing care requirements may also positively impact caregivers' productivity[27] as well as social and emotional well-being by allowing more time for leisure activities.

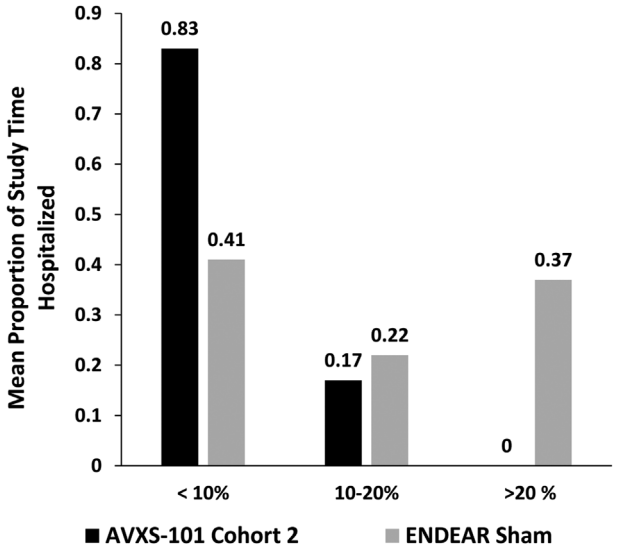


**FIGURE 2** Proportion of time hospitalized ($n$ = 12). The mean proportion of time hospitalized (<10%, 10-20%, and >20%) was determined during the 2-year follow-up period. The mean proportion of time hospitalized for the control group of the ENDEAR study[17] was also shown

One area of particular relevance to QoL assessment conferred by gene replacement therapy relates to speech development in infants and children. Patients with SMA1 often fail to develop speech as a result of bulbar-innervated muscle function deterioration.[22] In contrast, 92% of the patients in this report were able to speak following AVXS-101 treatment. Because speech is important for social interactions, including crucial early social interactions with their caregiver,[28] disruption of this function may negatively impact QoL. Thus, the development of speech in the majority of SMA1 patients has the potential to not only improve their social interaction, which may potentially enhance their cognitive function,[29] but also QoL.

Although results suggest that QoL of patients may be greatly improved with AVXS-101 gene replacement therapy and may even extend to improvements in caregiver QoL, the study did not directly assess QoL outcome in SMA1 patients or their caregivers. Previous studies have shown associations between motor function[30,31] and recurrent respiratory infections and QoL in other patient populations,[32] reinforcing the notion that reduced nutritional and pulmonary support requirements with the improved motor function may result in enhanced QoL in SMA patients.

Improved functioning in SMA patients may also have positive economic effects. Our recent retrospective analysis of the Kids' Inpatient Database (KID) database showed that the admission charges for SMA1 children were an average of $150 921 per hospitalization ($11 143 per day).[33] The decreased frequency of respiratory infections and hospitalizations observed following treatment with AVXS-101 compared to untreated SMA1 patients, are likely to result in concomitant reductions in healthcare costs associated with treating SMA1 children. However, further studies (ie, net benefit/cost-effectiveness analysis) are warranted.

In summary, successful treatment of SMA1 with AVXS-101 gene replacement therapy has the potential to transform the disease course of SMA1 along with improving patient and caregiver QoL due to decreased respiratory and nutritional complications, motor milestone achievements, and reduced hospitalizations. Reduction in the use of ventilation and nutritional support as well as the decreased hospitalization rate after AVXS-101 therapy could significantly decrease overall health care utilization related to this patient population and subsequently increase functional independence. Future studies will include direct QoL assessments in patients and their caregivers, expansion to SMA2, SMA3, and pre-symptomatic patients as well as cost-effectiveness analysis.

## ACKNOWLEDGMENTS

The authors thank Dr Marjet Heitzer for writing assistance in preparation of this manuscript and Monique Ryan and the staff at Royal Children's Hospital in Melbourne, Australia for care and monitoring of a study subject local to Australia.

## ORCID

*Richard Shell* http://orcid.org/0000-0002-4938-9075

## REFERENCES

1. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet*. 2012;20:27–32.
2. Hoyert DL, Xu J. Deaths: preliminary data for 2011. *Natl Vital Stat Rep*. 2012;61:1–51.
3. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014;83:810–817.
4. Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy—a literature review. *Orphanet J Rare Dis*. 2017;12:124.
5. Wang J, Xie J, Lu H, et al. Existence of transient functional double-stranded DNA intermediates during recombinant AAV transduction. *Proc Natl Acad Sci USA*. 2007;104:13104–13109.
6. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol*. 2017;82:883–891.
7. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*. 2018;28:197–207.
8. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018;28:103–115.
9. Bach JR, Baird JS, Plosky D, Navado J, Weaver B. Spinal muscular atrophy type 1: management and outcomes. *Pediatr Pulmonol*. 2002;34:16–22.
10. Shieh PB, Gu T, Chen E, Punekar RS, Tan H. Treatment patterns and cost of care among patients with spinal muscular atrophy. Paper presented at: Cure SMA 2017 Orlando, FL.
11. Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. *Arch Dis Child*. 2011;96:426–432.

12. Teynor M, Zhou J, Hou Q, Wells W, Hall E, Avendano J. Retrospective analysis of healthcare resource utilization (HRU) in patients with spinal muscular atrophy (SMA) in MarketScan®. Paper presented at: American Academy of Neurology 2017 Boston, MA.
13. Iannaccone ST, Hynan LS, Morton A, et al. The PedsQL in pediatric patients with spinal muscular atrophy: feasibility, reliability, and validity of the pediatric quality of life inventory generic core scales and neuromuscular module. *Neuromuscul Disord*. 2009;19:805–812.
14. Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. *Orphanet J Rare Dis*. 2017;12:141.
15. Klug C, Schreiber-Katz O, Thiele S, et al. Disease burden of spinal muscular atrophy in Germany. *Orphanet J Rare Dis*. 2016;11:58.
16. McGraw S, Qian Y, Henne J, Jarecki J, Hobby K, Yeh WS. A qualitative study of perceptions of meaningful change in spinal muscular atrophy. *BMC Neurol*. 2017;17:68.
17. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377:1723–1732.
18. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377:1713–1722.
19. Foust KD, Wang X, McGovern VL, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. *Nat Biotechnol*. 2010;28:271–274.
20. Wijnhoven TM, de Onis M, Onyango AW, et al. Assessment of gross motor development in the WHO multicentre growth reference study. *Food Nutr Bull*. 2004;25:S37–S45.
21. Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment Inc; 2006.
22. Bach JR. POINT: is noninvasive ventilation always the most appropriate manner of long-term ventilation for infants with spinal muscular atrophy type 1? Yes, almost always. *Chest*. 2017;151:962–965.
23. Salmon F, Grosios K, Petry H. Safety profile of recombinant adeno-associated viral vectors: focus on alipogene tiparvovec (Glybera(R)). *Expert Rev Clin Pharmacol*. 2014;7:53–65.
24. Rouault F, Christie-Brown V, Broekgaarden R, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. *Neuromuscul Disord*. 2017;27:428–438.
25. Simonds AK. Recent advances in respiratory care for neuromuscular disease. *Chest*. 2006;130:1879–1886.
26. Young HK, Lowe A, Fitzgerald DA, et al. Outcome of noninvasive ventilation in children with neuromuscular disease. *Neurology*. 2007;68:198–201.
27. Yoshida M, Claypool SM, Wagner JS, et al. Human neonatal Fc receptor mediates transport of IgG into luminal secretions for delivery of antigens to mucosal dendritic cells. *Immunity*. 2004;20:769–783.
28. Robbins KL, Glascock JJ, Osman EY, Miller MR, Lorson CL. Defining the therapeutic window in a severe animal model of spinal muscular atrophy. *Hum Mol Genet*. 2014;23:4559–4568.
29. Polido GJ, Barbosa AF, Morimoto CH, et al. Matching pairs difficulty in children with spinal muscular atrophy type I. *Neuromuscul Disord*. 2017;27:419–427.
30. Husby IM, Stray KM, Olsen A, et al. Long-term follow-up of mental health, health-related quality of life and associations with motor skills in young adults born preterm with very low birth weight. *Health Qual Life Outcomes*. 2016;14:56.
31. Surender S, Gowda VK, Sanjay KS, Basavaraja GV, Benakappa N, Benakappa A. Caregiver-reported health-related quality of life of children with cerebral palsy and their families and its association with gross motor function: a South Indian study. *J Neurosci Rural Pract*. 2016;7:223–227.
32. Jiang X, Sun L, Wang B, Yang X, Shang L, Zhang Y. Health-related quality of life among children with recurrent respiratory tract infections in Xi'an, China. *PLoS ONE*. 2013;8:e56945.
33. Cardenas J, Menier M, Heitzer MD, Sproule DM. High healthcare resource use in hospitalized patients with a diagnosis of spinal muscular atrophy type 1 (SMA1): retrospective analysis of the kids' inpatient database (KID). *Pharmacoecon Open*. 2018; [Epub ahead of print].

**How to cite this article:** Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatric Pulmonology*. 2019;54:179–185.
https://doi.org/10.1002/ppul.24203