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CLINICAL RESEARCH ARTICLE

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Early experiences of nusinersen for the treatment of spinal muscular atrophy: Results from a large survey of patients and caregivers

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Abstract

Background: This study aimed to examine the early experience of nusinersen for spinal muscular atrophy (SMA) from the patient and caregiver perspective.

Methods: A 54-item online survey was administered to adult patients and caregivers of pediatric patients diagnosed with SMA.

Results: Overall, respondents (56 patients and 45 caregivers) were satisfied with nusinersen. Satisfaction was highest on changes in energy, stamina, and motor function and lowest on treatment administration and overall time commitment. Differences were noted for treatment effect sustained over time as reported by adult patients vs caregivers reporting on behalf of pediatric patients. Respondents reported insurance approval as a key barrier to access, particularly among adult patients.

Conclusions: Despite therapeutic advances, there remain significant unmet needs for SMA. Challenges with administration and barriers to access potentially limit the number of patients treated or delay treatment. Continued efforts are needed to develop more treatment options and to improve access to treatments.

KEYWORDS

patient reported outcome, spinal muscular atrophy, unmet need, burden, nusinersen, SMA

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is a progressive, genetic, motor neuron disease with an estimated incidence of 9.4 per 100 000 live births in the United States.[1] Until recently, the management of SMA was limited to supportive pulmonary, gastrointestinal, nutrition, orthopedic, and rehabilitative care, usually requiring coordination by a multidisciplinary team.[2,3] In December 2016, nusinersen, an SMN2 targeting anti-sense oligonucleotide (ASO), became the first disease-modifying therapy approved by the United States Food and Drug Administration (FDA) for pediatric and adult patients with SMA, and was subsequently approved in May 2017 by the European Medicines Agency. Nusinersen is administered intrathecally, with four loading

Abbreviations: ASO, anti-sense oligonucleotide; FDA, United States Food and Drug Administration; IV, intravenous; SMA, spinal muscular atrophy.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

doses in the first 2 mo followed by maintenance doses every 4 mo.[4] In May 2019, onasemnogene abeparvovec-xioi, an intravenous (IV) gene therapy that delivers the *SMN1*cDNA encoding full length SMN protein, received FDA approval for the treatment of pediatric patients with SMA who are younger than 2 y of age.[5,6] In addition, several other SMA therapies are in different stages of development.

The availability of nusinersen, along with the more recent advances in gene therapy, has significantly changed the SMA treatment landscape. However, little is known about patients' and caregivers' perspectives of SMA treatment and how these newly approved treatments met their needs and what new challenges they may be facing in the era of disease-modifying treatments. An earlier report from Cure SMA, the largest patient organization for SMA, characterized the perspectives of people living with SMA, its impact on their daily lives and their expectations and priorities for treatments; however, the research was conducted prior to the approval of any disease-modifying treatments.[7] The purpose of the current study was to gain greater insight into the early experience with nusinersen treatment from a patient's perspective and to qualitatively assess areas of unmet need from clinical, logistical, and an access perspective in the United States. Nusinersen was the only FDA approved treatment at the time this study.

2 | METHODS

The current study was part of a broader effort to characterize and explore perceptions of SMA, its associated disease burden, and clinical, logistical, and access experience among patients, caregivers, and physicians, and to explore remaining unmet need in the SMA community after availability of treatment. The current work describes the survey results of patients (self-report, if a patient is 18 y or older) and caregivers (proxy-report, if a patient is less than 18 y of age). Studies examining the impact associated with providing care in the context of SMA and the perspective of physicians involved in the care of SMA have been published elsewhere.[8]

2.1 | Data sources and survey design

Data were collected from surveys administered to adult patients with SMA (aged 18 y or older) and caregivers of pediatric patients with SMA (younger than 18 y of age). To recruit participants, an email containing the research objectives and an invitation to participate in the research was sent in February 2019 to a mailing list of 1251 individuals registered in the database of a large SMA patient organization (Cure SMA). After 3 wk, an email reminder was sent to the same group. Inclusion criteria for patients included a diagnosis of type 1–4 SMA and age 18 y or older for adult patients. For patients with SMA under the age of 18 y, caregivers responding to the survey were required to be over the age of 18 y, unpaid, and routinely involved in the care of the patient (eg, attending medical appointments, engaged in medical care decision making). Respondents provided informed consent and were reimbursed $40 for participating in the study. An Institutional Review Board (Pearl IRB) reviewed and approved the study.

2.2 | Survey questionnaire

A 54-item survey was developed to assess patient's early experiences with treatment and their perceptions about current and future SMA treatments. Specifically, the survey assessed demographics, health and treatment history, current medical treatments, assessment of motor function, satisfaction with treatment, barriers to receiving care, and important attributes of a new theoretical SMA medication. The survey was designed to take less than 20 min to complete. Detailed accounts for a few measures are included below. A complete copy of the survey is available as Supporting Informatio Appendix S1, which is available online.

2.3 | Assessment of motor function

Two questions were included in the survey to assess respondents' highest motor function ever achieved and the current level of motor function. For ease of reporting, the eight response options were collapsed into three categories: walking alone/walking with assistance/standing alone/standing with assistance were collapsed into standing or greater category; sitting without support/hands and knees crawling were collapsed into sitting; and none of the above; they have some motor function/no motor function were collapsed into minimal function.

2.4 | Experience with current treatment

Patients or caregivers of patients receiving nusinersen were asked to rate their overall satisfaction with nusinersen, as well as satisfaction with specific attributes of this treatment using a five-point scale. For ease of understanding and reporting, the response options of very satisfied/extremely satisfied were referred to as high satisfaction; somewhat satisfied was referred to as medium satisfaction; and a little satisfied/not at all satisfied was referred to as low satisfaction.

Patients or caregivers of patients were asked about the time commitment for treatment, including travel to the administration center and administration and dosing (including time meeting with the medical team, waiting to receive treatment, length of the procedure, and post procedure recovery). Patients were asked to rate the level of comfort or discomfort experienced during administration on a scale of 0-10 (no discomfort - extreme discomfort). Additional questions assessed the amount of time associated with overall care and support for their day-to-day management of their disease.

2.5 | Reasons for not receiving treatment

For patients who had never received or had discontinued nusinersen treatment, the reason(s) for such a decision was asked. Respondents

were provided a list of options regarding possible reasons and could choose multiple responses.

2.6 | Data analysis

Descriptive analyses (frequencies, mean [SD]/median) were conducted to assess the study objectives. All analyses were conducted for either the entire patient population or in sub-groups specified within the results section. The analysis was conducted in SAS version 9.4 and R version 3.3.

3 | RESULTS

3.1 | Patient demographics and clinical characteristics

Within a month, an enrollment goal of 100 patients and caregivers was reached and recruitment was discontinued. Of the 142 survey attempts, 101 patients with SMA were eligible and completed the study, of whom nearly half had type 2 SMA, while most of the remaining patients had type 1 or type 3; only one patient had type

TABLE 1 Demographic information [Color table can be viewed at wileyonlinelibrary.com]

	All (n = 101)		Adult (n = 56)		Pediatric (n = 45)	
Type of SMA						
	n	%	n	%	n	%
Type 1	21	21	4	7	17	38
Type 2	49	49	23	41	26	58
Type 3	30	30	28	50	2	4
Type 4	1	1	1	2	0	0
Age (in y)						
	Mean		SD		Median	
Adult (n = 56)	35.38		13.20		32.50	
Pediatric (n = 45)	6.58		5.37		5.00	
Highest motor function						
	n	%	n	%	n	%
Walking alone	33	33	30	54	3	7
Walking with assistance	6	6	2	4	4	9
Standing alone	1	1	0	0	1	2
Standing with assistance	8	8	4	7	4	9
Hands and knee crawling	9	9	4	7	5	11
Sitting without support	29	29	14	25	15	33
None of the above; I had some motor function	13	13	2	4	11	24
No motor function	2	2	0	0	2	4
Current motor function						
	n	%	n	%	n	%
Walking alone	8	8	7	13	1	2
Walking with assistance	7	7	6	11	1	2
Standing alone	0	0	0	0	0	0
Standing with assistance	7	7	1	2	6	13
Hands and knee crawling	1	1	0	0	1	2
Sitting without support	41	41	21	38	20	44
None of the above; I had some motor function	35	35	21	38	14	31
No motor function	2	2	0	0	2	4
Insurance coverage[a]						
	n	%	n	%	n	%
Medicare	18	18	13	23	5	11
Medicaid	57	57	28	50	29	64
Private insurance (HMO)	29	29	18	32	11	24
Private insurance (PPO)	38	38	17	30	21	47
Other[a]	5	5	4	7	3	7

[a]Insurance categories are not mutually exclusive; patient may have multiple insurance coverage.

4. Forty-one respondents did not meet the study entry criteria. The most common reasons respondents were disqualified was because the respondent with SMA was below the age of 18 y or because the caregiver was either a paid caregiver or was not directly involved in the care and treatment decisions for their patient. The majority of patients were female and privately insured, with an average age of 35.38 y among adults and 6.58 y among pediatric patients. Only 21% of patients were able to maintain a "standing or greater" level of function at the time of the survey, with more than three-quarters of patients currently receiving nusinersen. Full details are provided in Table 1.

3.2 | Patient and caregiver reported experience with nusinersen

Patients and caregivers reported overall high satisfaction with nusinersen. With regard to specific attributes of treatment, adult patients considered changes in "energy and stamina" (58%), "respiratory function" (56%), and "motor function" (47%) to be their top three areas of satisfaction. Caregivers of pediatric patients reported the highest rates of satisfaction with regard to changes in "energy and stamina" (73%), "motor function" (61%), and "social functioning" (61%) (Figure 1).

Adult patients reported the lowest level of satisfaction with the following attributes, "treatment effect sustained over time" (50%), changes in "other symptoms (eg, pain, constipation)" (44%), and "medication administration" (39%). Caregivers of pediatric patients reported lowest satisfaction with changes in "activities of daily living" (37%), "time commitment to treatment" (34%), and "medication administration" (29%). Contrary to adult patients, a higher proportion of caregivers of pediatric patients (54%) reported high satisfaction with treatment effect being sustained over time compared to adult patients (22%) (Figure 1, Table 2).

About half of the respondents reported that they had to drive more than 1 h to a treatment center to receive nusinersen, and about 20% reported a drive time of greater than 2 h. On the day of nusinersen administration, the average time associated with treatment for all patients was more than 8 h, with longer mean administration times reported by caregivers of pediatric patients compared to adult patients (Table 3).

Patients reported a substantial level of discomfort during their treatment administration. With adult patients reporting a higher average discomfort compared to caregivers of pediatric patients.

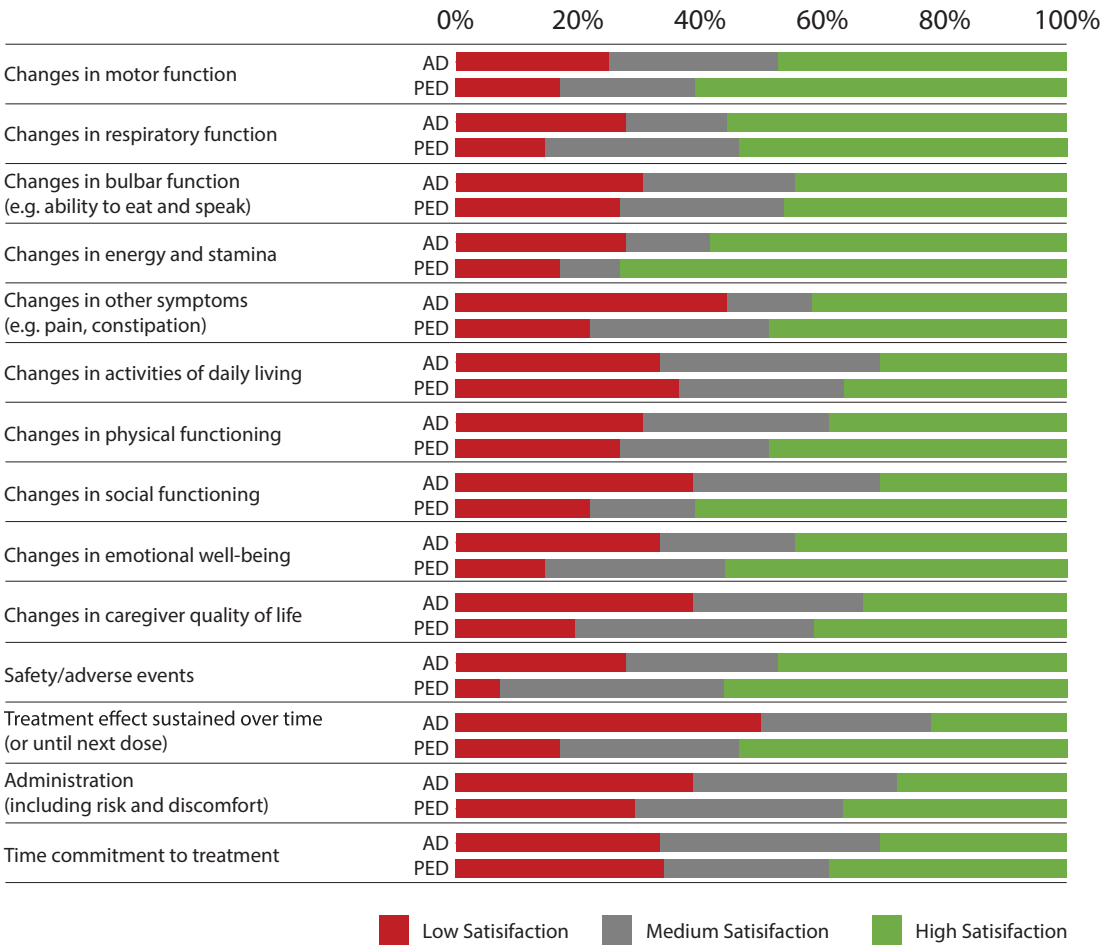

FIGURE 1 Adult and pediatric patient satisfaction with nusinersen (n = 77) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Patient satisfaction with nusinersen[a]

	Low satisfaction		Medium satisfaction		High satisfaction	
	n	%	n	%	n	%
Type 1						
Adult (n = 3)	1	33	1	33	1	33
Pediatric (n = 16)	1	6	8	50	7	44
Total (n = 19)	2	11	9	47	8	42
Type 2						
Adult (n = 12)	8	67	2	17	2	17
Pediatric (n = 23)	5	22	4	17	14	61
Total (n = 35)	13	37	6	17	16	46
Type 3						
Adult (n = 21)	9	43	7	33	5	24
Pediatric (n = 2)	1	50	0	0	1	50
Total (n = 23)	10	43	7	30	6	26

[a]Patients could select multiple responses.

TABLE 3 Patient and caregiver reported time associated with administration of nusinersen

Driving time to SMA treatment center[a]						
	All (n = 77)		Adult (n = 36)		Pediatric (n = 41)	
	n	%	n	%	n	%
Less than 1-h	38	49	20	56	18	44
1–2 h	25	33	11	31	14	34
Greater than 2-h	14	18	5	14	9	22
	Mean		SD		Median	
Average time driving to treatment center						
All (n = 77)	3.52		11.31		2.00	
Adult (n = 36)	1.94		1.84		1.00	
Pediatric (n = 41)[a]	4.90		15.35		2.00	
Hours spent on activities on the day of administration						
All (n = 77)	8.26		11.29		5.00	
Adult (n = 36)	4.78		2.15		4.00	
Pediatric (n = 41)[a]	11.32		14.75		6.00	
Level of discomfort while receiving nusinersen treatment (scale 0–10)						
All (n = 77)	4.51		2.58		5.00	
Adult (n = 36)	5.14		2.44		5.00	
Pediatric (n = 41)[a]	3.95		2.61		4.00	

[a]As reported by caregiver respondent.

3.3 | Reasons for not receiving nusinersen

At the time of survey administration, 24 patients were not receiving nusinersen. The first and second most frequent reason for not receiving treatment included "challenging route of administration" (58%) and "waiting for new treatment options" (46%). Other commonly reported reasons for not receiving nusinersen are listed in Figure 2.

3.4 | Experience with insurance approval and coverage

Among patients receiving nusinersen, a large variation in the length of time required for insurance approval was reported. Nearly a third of patients receiving nusinersen reported that their insurance provider approved the use of the treatment in less than 1 mo while nearly half reported an approval time between 1 and 6 mo (Figure 3A). Analyses of

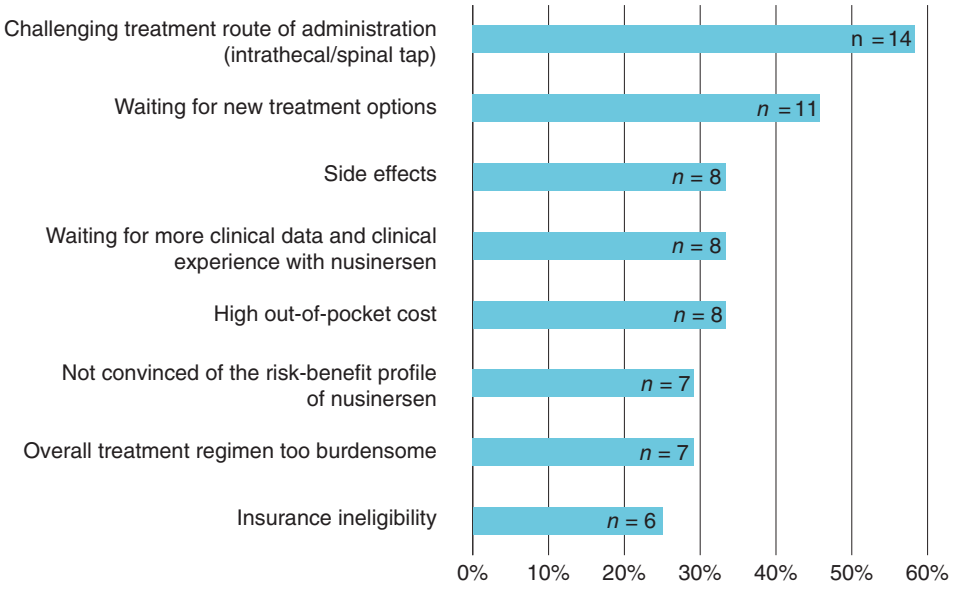

FIGURE 2 Patient/caregiver reported reasons for not receiving nusinersen (n = 24) [Color figure can be viewed at wileyonlinelibrary.com]

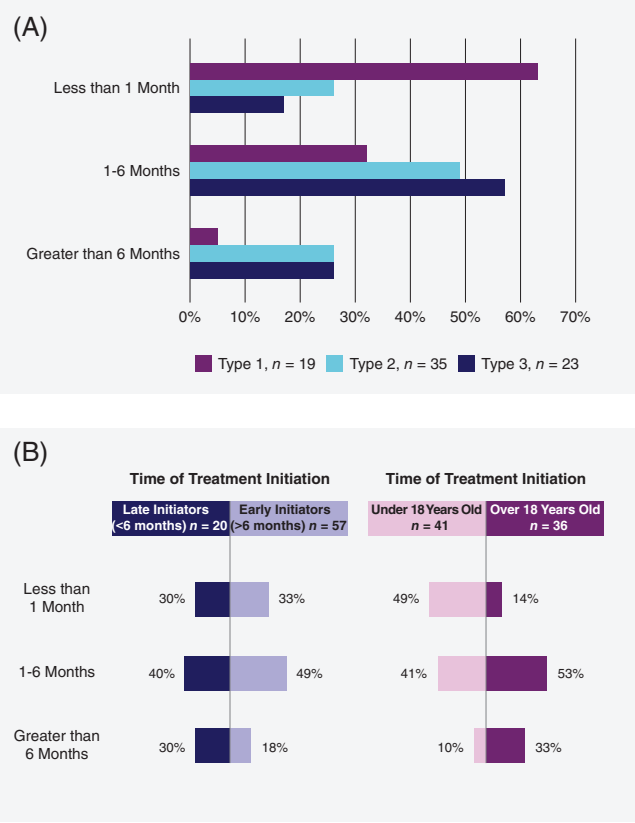

FIGURE 3 A, Time to insurance approval by SMA type. B, Proportion of patients with SMA treated by time of treatment initiation and age (n = 77) [Color figure can be viewed at wileyonlinelibrary.com]

time to insurance approval by SMA type indicated that a higher proportion of type 1 patients received approval in less than 1 mo compared to type 2 and 3 patients (Figure 3A). Time to insurance approval was longer among adult patients compared to pediatric patients (Figure 3B).

Of the 77 patients receiving nusinersen, 57 patients had received therapy for longer than 6 mo ("early initiators"), and 20 patients had started treatment within the 6 mo prior to the survey (ie, "late initiators"). Similar delays in approval time were reported by late and early initiators, suggesting insurance approval continues to be a barrier to treatment initiation, despite growing experience with nusinersen over time (Figure 3B).

3.5 | Attributes of future SMA treatments

Patients ranked safety (88%, n = 89), efficacy (87%, n = 88), and route of administration (59%, n = 60) as the most important attributes when considering future SMA treatments. While safety and efficacy were consistently ranked as top considerations, adult patients ranked efficacy as the number one factor, while caregivers ranked safety as the most important factor for their younger patients. In addition, ease of insurance approval process (54%, n = 55) and robust clinical data (45%, n = 45) were considered as important attributes when considering future treatments.

4 | DISCUSSION

Several clinical trials have demonstrated safety and efficacy of nusinersen as a treatment option for SMA patients, with ongoing clinical trials and real-world studies providing further understanding of long-term functional and subjective impacts of treatment across SMA types.[9-18] Recent studies in older patients with SMA have implied real-world benefits with nusinersen treatment in motor milestone achievement, functional assessments, and caregiver burden.[9,10,16-18] A real-world safety study concluded that the administration of nusinersen was well tolerated, including in patients that required fluoroscopy guidance, anxiolytics, or general sedation.[12] The results of

this study add to the early experiences of treatment with nusinersen from a patient and caregivers perspective. Study results indicated that satisfaction was highest among patients with type 1 SMA. Type 1 patients, due to the severity of the disease and early treatment, may have observed larger treatment benefit compared to patients with type 2 or 3 SMA. Risk tolerance and treatment commitment may also be higher in the more severe type 1 patients due to poor prognosis in the absence of treatment. The sense of optimism and hope in caregivers of type 1 patients, where treatment improves survival and breathing and leads to marked improvement in strength and function, may have played a role in the high level of treatment satisfaction observed in the survey.

As such, not surprisingly, caregivers of pediatric patients indicated high satisfaction with enhanced energy, motor function, and improvements in social functioning. However, they reported low satisfaction with improvements in activities of daily living. The desire for further gains in patients' functional ability was consistent with an earlier report that small changes that provide greater independence in activities of daily living are of vital importance to children and adolescents.[7] Adult patients indicated a high level of satisfaction with treatment-related improvements in energy levels, respiratory functioning, and motor function; however, they were less satisfied with the treatment effect over time. Although initial pharmacokinetic and pharmacodynamics studies support the approved dosing regimen for nusinersen,[19] it is possible that higher doses may provide improved or sustained responses.

Both caregivers and patients expressed concerns about medication administration. Intrathecal administration can be particularly challenging for patients with SMA. For patients with type 1 SMA, life-threatening respiratory symptoms, often requiring the presence of a multi-disciplinary care team at the time of treatment administration, frequent sedation, and radiation exposure could cause concern. Spinal complications may limit the ability for a patient to receive nusinersen, although recent research has indicated that individuals with complicated spines can receive nusinersen injections using fluoroscopic guidance[20] In our study, however, the route of administration was noted as the primary reason for not being able to receive nusinersen treatment among both adult and pediatric patients.

Similar findings were reported by Pechman and colleagues who reported that, while intrathecal administration of nusinersen could be performed in all children with type I SMA, lumbar punctures were unsuccessful in 33% of children on the first attempt. In addition, 35% required non-invasive mechanical ventilation, and 24% required sedation during the lumbar procedure.[21] Furthermore, Mousa and colleagues reported that, given the frequency of spinal deformities among patients with SMA, the intended treatment protocol for nusinersen had to be adapted for a number of patients to include pre-procedural imaging.[22]

Results of this study also indicated that patient satisfaction with nusinersen treatment was higher than physician satisfaction with treatment. In a survey of 51 physicians treating patients with SMA, lower satisfaction was reported by treating physicians, with 20% of physicians reporting overall high satisfaction with nusinersen compared to 56% of adult patients and 66% caregivers reporting overall high satisfaction with nusinersen.[8] This observation could be accounted for by many factors that may include physicians reporting on behalf of the overall patient population (ie, including both pediatric and adult patients), high level of requirement for setting treatment infrastructure of administration, high level of effort involved to secure insurance approval and recertification, and lack of clinical data in a real-world patient population, limiting physicians' ability to make treatment recommendations for patients not in nusinersen clinical trials.

The current study also identified several barriers associated with SMA treatment, with insurance approval and amount of time associated with traveling to receive treatment reported as key barriers to access to treatment. The key reasons reported by patients in this study for not receiving nusinersen treatment were similar to those reported by Pacione et al[23] They noted that key factors influencing patient's treatment decisions were concerns about risk factors and side effects, high cost, insurance coverage, time involvement, and lack of efficacy data.

It is important to note the barriers to access and attributes of treatment that are challenging for patients as these might potentially delay or limit treatment for some patients diagnosed with SMA. As the SMA treatment landscape evolves, it is critical to address these unmet needs, as early diagnosis and treatment of SMA are necessary to maximize effectiveness of the treatment and improve health outcomes in patients.[3] Indeed, when patients were asked about the most important attributes of a future treatment, improved route of administration was indicated as one of the most important aspects of treatment, following efficacy and safety.

4.1 | Limitations

It is important to interpret these results in light of the study's limitations. For example, patients who responded to this survey were recruited from a database of a patient organization and may not be representative of all individuals diagnosed with SMA. This is evident in that three out of four patients in the survey were, or had been, treated with nusinersen, whereas among all patients with SMA, approximately 20%-30% were receiving treatment during the same period.[24] In addition, clinical information, such as SMA type and highest and current motor function, was reported by the patients or their caregivers; no verification against clinical documentation was attempted.

Further research is needed to explore the needs and perspectives of patients who are not affiliated with the patient community or less active in research participation, in order to have a more complete picture of ongoing unmet need and challenges in the SMA community. Additionally, it is important to interpret these results with caution as they reflect early experiences of a new disease modifying treatment. For example, in this study, 20 patients had received treatment for less than 6 mo prior to the survey, limiting their exposure to the drug and likely treatment benefit. Furthermore, treatment effects reported are based on self-report and not clinically verified. Furthermore, the current survey was conducted prior to the approval of onasemnogene abeparvovec xioi and, thus, does not describe patients' experiences

with this new treatment; consequently, the results are reflective of only one available treatment. Last, there is likely a difference between self-reported satisfaction from patients vs satisfaction from caregivers of pediatric patients. Treatment benefit is based on observation from the caregiver and the responses of the pediatric caregiver may not be fully representative of the pediatric patients.

4.2 | Conclusions

Despite the availability of treatment options, there remain unmet needs and several barriers to access, potentially delaying or limiting treatment for some SMA patients. Efficacy, safety, and route of administration have been identified by patients as key attributes for future medications to treat SMA. As the SMA treatment landscape evolves, continued efforts are needed to improve timely access to treatments for patients and reduce barriers to care.

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CONFLICT OF INTEREST

Study funded by Genentech Inc., A member of the Roche Group. Er Chen is an employee of GNE. Rupali Naik is a contracting employee of GNE. Josh M Noone, Daniel Buchenberger, Sarah M Whitmire and Rosalina Mills received research funding from GNE for the design and conduct of the research and writing of the paper. Stacy Dixon was contracted with GNE as clinical advisor of this project, no financial compensation was provided. Previously served as a paid member for an advisory board for Genentech. Additionally, have served as a paid member on several advisory boards for Biogen. William Arnold was contracted with GNE as clinical advisor of this project, no financial compensation was provided. Previously served as a consultant to Genentech and F. Hoffmann-La Roche AG.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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