

## RESPONSE TO ICER'S DRAFT SCOPING DOCUMENT REGARDING AVXS-101 AND NUSINERSEN FOR SPINAL MUSCULAR ATROPHY

### Executive summary

AveXis, a Novartis company, respectfully recommends the following be considered in the Institute for Clinical and Economic Review's (ICER's) review of treatments for spinal muscular atrophy (SMA):

- 1) At this time, any meaningful clinical and economic comparison between AVXS-101 and nusinersen can only be conducted in symptomatic SMA type I patients, given the available data from the AVXS-101 CL-101 phase I trial and the ENDEAR trial for nusinersen.
- 2) Separate evaluations should be conducted by SMA subtype and by symptomatic status.
- 3) The economic evaluation should use the societal perspective for the base case and incorporate treatment-related improvement in caregiver's utility and likely productivity gains and consider patients' ability to achieve developmental stages including entering the workforce.
- 4) Permanent ventilation should be considered as a health state in the cost-effectiveness analysis (CEA).

### Evaluations of AVXS-101 vs. nusinersen should only be conducted for symptomatic SMA type I

ICER implies that AVXS-101 and nusinersen will be compared to each other and to supportive care (SC) in all SMA subtypes. However, to date, peer reviewed published clinical evidence is only available from the ENDEAR trial for nusinersen<sup>1</sup> and the AVXS-101 CL-101 phase I trial.<sup>2,3</sup> Based on the eligibility criteria, the population of these trials include only symptomatic SMA Type I patients with 2 copies of *SMN2*.<sup>1,2,3</sup> Therefore, any meaningful comparative effectiveness and economic analyses can only be assessed in symptomatic SMA Type I patients. Additionally, enrolled patients were required to have the onset of symptoms at age  $\leq 6$  months and are symptomatic at baseline.<sup>1,2,3</sup>

Further, we believe SC is not an appropriate treatment for this population given the advancement in therapies for these patients and widespread payer coverage of nusinersen in the US.<sup>4</sup> While SC aims to minimize the impact of disability, address complications, and improve quality of life (QoL), it does not slow or halt disease progression. In the absence of effective therapies SC was previously used for the management of SMA Type I however, according to the 2018 treatment algorithm developed by experts from Cure SMA, infants with confirmed SMA type I who have only 2 or 3 copies of the *SMN2* gene should receive immediate treatment with an *SMN* up-regulating therapy, currently available only in the form of nusinersen.<sup>5</sup> Previous HTA submissions of nusinersen, which included SC as a comparator, were evaluated before the widespread use of nusinersen use.<sup>6-8</sup> Thus, AveXis recommends that nusinersen and AVXS-101 should be the only two therapies evaluated for symptomatic SMA type I patients because SC is no longer a realistic or ethical comparator in the US.

### Separate evaluations should be conducted by SMA subtype and by symptomatic status

ICER's draft scoping document indicates the population of interest includes infants, children, and adults with SMA. We respectfully recommend that ICER conduct separate evaluations for patients with each SMA subtype and by symptomatic status due to the following considerations:

- **Disease trajectory, available treatments and burden differ by SMA subtypes:** Each SMA subtype has dramatically different disease trajectories and prognosis. Patients with type I have the most serious form of the disease and generally die before adolescence due to respiratory failure, while patients with SMA types II-IV may survive to adulthood and achieve some level of independence.<sup>9</sup> Given this large heterogeneity and different life expectancies among patients with different SMA subtypes, each subtype should be evaluated separately to reflect: 1) its unique course of disease progression; 2) use of treatments with clinical evidence specific for the subtype; and 3) different lifetime economic burden and costs.
- **Clinically meaningful outcomes differ by SMA subtypes:** Health states in the CEA models of SMA patients are typically defined by different sets of motor milestones representing clinically meaningful functional achievements for patients with a particular SMA subtype. However, these differ by SMA types. For example, the milestone of "sitting without support" would be a clinically relevant and important endpoint for SMA type I patients; however, it would not be meaningful for SMA type II/III

patients. Another example is bulbar function, including the ability to eat or speak, which is one of the most significant functions impacting the daily life and QoL of SMA type I patients and caregivers, however it is not relevant for SMA type II/III patients.<sup>10</sup>

- **Efficacy differs between pre-symptomatic and symptomatic states within the same SMA subtype:** Therapeutic efficacy, as measured by milestones achieved, could vary significantly amongst patients treated after symptomatic onset and the pre-symptomatic stage in SMA, therefore separate CEA models should be developed for symptomatic and pre-symptomatic SMA patients. Typically, treatments are not initiated until clinical diagnosis of SMA, which occurs on average of 6.3 months of age in patients with SMA Type I,<sup>11</sup> at which point irreversible loss of motor function has already progressed significantly, with a precipitous loss of up to 95% of motor neurons occurring in the weeks following symptom onset in SMA type I patients.<sup>12</sup>
- As of now, there is no published clinical evidence of AVXS-101 for pre-symptomatic patients or for SMA type II-IV; nor is there any peer-reviewed, final results for pre-symptomatic treatment with nusinersen. Additionally, it is important to note that in pre-symptomatic SMA patients, distinguishing type I and type II patients is difficult as the recent National Institute for Health and Care Excellence (NICE) ACD highlights (114 of 206 or pdf page 207 (<https://www.nice.org.uk/guidance/gid-ta10281/documents/committee-papers>)). Therefore, we suggest that ICER conduct the review only among the treatments and SMA subtypes where clinical trial evidence are available – symptomatic SMA type I patients.
- Once data for AVXS-101 in pre-symptomatic patients become available, AveXis would be pleased to submit this evidence to ICER for future analysis.

#### **A societal perspective, including treatment-related improvement in caregiver utility and productivity gains, should be the base case and emphasized**

ICER states that patient and caregiver productivity losses will be included in what ICER has called a “modified societal perspective”, and that caregiver-related QoL may be considered.<sup>13</sup> Given the substantial QoL burden of SMA type I on caregivers, and the demonstrated efficacy of nusinersen and AVXS-101 in clinical trials, AveXis strongly recommends that ICER incorporate improvement in caregiver-related QoL and productivity gains in the evaluation. In addition, patients' ability to achieve developmental stages with the ability to enter the workforce should be considered in a model with a lifetime horizon.

- Caregiver disutilities (“family-spillovers”) should be included in the model to more fully capture the impact of SMA type I from a societal perspective. This perspective was well-accepted in previous HTA submissions in SMA.<sup>6-8,14</sup> The NICE agreed that “SMA has a substantial effect on [caregivers] and families”.<sup>6</sup> Caregivers of SMA type I patients not only experience physical burden and financial pressures, but also bear substantial emotional suffering. Caregivers and other family members of affected patients also experience emotional stress and effects on daily activities.<sup>6,10</sup> As stated by caregivers, any improvement in the patient’s health would, therefore, potentially have a very positive impact on the family and caregivers.<sup>6</sup> Thus, AveXis recommends that ICER include caregiver disutility in the CEA model of SMA type I. Furthermore, rather than simply acknowledging its existence, and including it as a qualitative checklist item under “Potential Other Benefits”, we would encourage ICER to break some new methodological ground here, and attempt to model its impact quantitatively.
- The productivity gain of caregivers and the ability of patients to achieve development stages with the possibility to enter the workforce should be considered in a lifetime horizon model. Given the efficacy of AVXS-101 and nusinersen based on milestones achieved in the respective clinical trials,<sup>1,3</sup> these treatments may reduce caregiver time needed, and perhaps allow some caregivers and potentially patients themselves to enter the workforce or return to work.

#### **Permanent ventilatory support should be included as a health state in the CEA model**

ICER’s scoping draft indicates that a Markov model will be developed based on prior published models of SMA and HTA assessment reports, and will consist of health states based on motor function milestones and the “dead” state. AveXis recommends that ICER includes a health state for permanent ventilatory support as

this is a key outcome evaluated in clinical trials of SMA<sup>1-3</sup> and the lack of such a state was critiqued by NICE in the nusinersen assessment.<sup>6</sup>

- In the natural progression of SMA type I, infants typically die or require ventilation by 2 years of age.<sup>15</sup> Children on mechanical ventilation require full-time care, placing immense stress on caregivers, and preventing most affected patients from being able to participate in daily childhood activities and gaining an education, which has substantial QoL and economic consequences.<sup>16,17</sup> Permanent ventilation also impairs speaking ability, which is one of the most significant symptoms of the disease<sup>10</sup> and further impacts QoL. Nusinersen and AVXS-101 have been shown to prevent or delay the use of permanent ventilation, making ventilation a key endpoint to be considered when evaluating the efficacy of treatments.<sup>1,3</sup>
- In England's NICE evaluation of nusinersen for SMA, the submitted nusinersen models were criticized for their lack of ventilation considerations in the model. NICE's committee papers stated that clinical advisors commented on other important outcomes besides motor function, noting "in particular, aspects of SMA relating to respiratory function, the explicit use of ventilation and the possibility of infections" were not explicitly captured in the model structures.<sup>6</sup>
- The nusinersen and AVXS-101 clinical trials used different definitions of permanent ventilatory support. The ENDEAR trial defined permanent assisted ventilation as "tracheostomy or ventilatory support for at least 16 hours per day for more than 21 continuous days in the absence of an acute reversible event, as determined by an independent end-point adjudication committee".<sup>1</sup> In the AVXS-101 CL-101 phase I trial, ventilatory support was defined as the need for tracheostomy or ventilation for at least 16 hours per day for at least 14 consecutive days based on the established definition commonly used in the literature.<sup>3,18</sup> Thus, these endpoints are not directly comparable, because the AVXS-101 trial applied more clinically conservative and more broadly accepted criteria<sup>18</sup> vs. the ENDEAR trial (14 vs. 21 consecutive days). Some patients in the ENDEAR trial may have met the endpoint based upon the conventional criteria (14 days) but not reached the adapted endpoint used in the ENDEAR trial, thus potentially overstating nusinersen's efficacy in terms of reducing needed "permanent assisted ventilation." Given the considerable costs for permanent ventilation<sup>17</sup> and the potential increased risk of complications and mortality related to ventilation, different definitions of permanent ventilation might also affect the average cost per ventilation occurrence and the overall cost-benefit profile for a treatment.

In summary, a patient's need for permanent ventilator support represents a distinct and significant progression of disease, has a substantial impact on patient and caregivers, and is associated with substantial cost and incremental mortality; thus, it should be considered as a separate distinct health state in the CEA model.

### **Comments on disease background and key measures of benefit**

- Please consider this revision on Page 1: "1 in 10,000 live births, or about 500 new SMA patients per year of which approximately 60% have SMA Type I"
- Page 2 of the draft scope states that "Patients with SMA may need intensive care and support, especially those with SMA type II." The statement should be revised to include both SMA Type I and SMA Type II because intensive care and support and high costs are also needed to manage patients with SMA type I as demonstrated in the literature.<sup>19</sup>
- AveXis recommends that bulbar function should be considered as a key measure of benefit for symptomatic SMA type I patients consistent with published literature and consensus statement for the standard of care for SMA.<sup>21, 22, 23</sup> Inability to breathe, eat, swallow, or communicate is one of the most significant symptoms of the disease and a source of concern and frustration for caregivers and the patient.<sup>10</sup> In Cohort 2 of the AVXS-101 clinical trial, 11/12 (92%) of patients were able to feed orally and 11/12 (92%) were able to speak versus natural history for SMA Type I in which most patients are not able to swallow or speak effectively.<sup>24</sup> While comparable data have not been disclosed as part of the nusinersen program, such data are almost assuredly available and can be provided by the sponsor. Bulbar function should be considered as a key measure of benefit for symptomatic SMA type I.

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12 September 2018

**RE: ICER's Draft Scoping Document for AVXS-101 and nusinersen (Spinraza®) for SMA**

Biogen appreciates the opportunity to comment on ICER's draft scoping document for AVXS-101 and nusinersen (Spinraza®) for Spinal Muscular Atrophy (SMA). In this assessment, ICER proposes to assess all SMA types to inform ICER's March 2019 CEPAC vote on comparative clinical effectiveness and value.

**SMA is a devastating rare disease that affects infants, children, adults, parents, and caregivers.** Individuals with SMA live with an uncertain future and are among society's most vulnerable patients. Most untreated SMA Type I patients will die before the age of 24 months without respiratory support and nutritional intervention; and nearly a fifth (18%) of SMA Type II patients will die by the age of 10.<sup>1,2,3,4</sup> Most SMA patients also face significant disability. This places incalculable burden on patients, their parents and caregivers who suffer loss of income from limited employment and experience higher levels of stress, worry, and mental and physical fatigue.<sup>5</sup>

Nevertheless, it is important to recognize that the clinical classification of SMA patients by type (I-IV) is imperfect and warrants further review and discussion. It is also important to understand how patient outcomes may differ based on factors like age of onset (e.g., early onset, late onset).

**Spinraza® is the first and only approved treatment for infants, children and adults living with SMA.** The body of evidence supporting its approval and use for treatment of SMA patients is substantiated by a rigorous and robust clinical development program. As the first manufacturer of a SMA treatment option, Biogen recognizes the importance of developing novel treatments, conducting research to understand how treatments meaningfully improve health outcomes for subpopulations of patients, and working with payers as well as other stakeholders to improve patient access.

**ICER's assessment of SMA medicines will need to be updated as new evidence becomes available.** Since SMA is a rare disease, there is a significant paucity of evidence. This is further complicated by the fact that pivotal clinical trials are still ongoing for Spinraza® and AVXS-101. Consequentially, ICER should plan to update its assessment of SMA medicines as new evidence is published.

We recognize the challenges and the many methodological choices that are necessary in cost-effectiveness analyses, including those related to the estimation of quality-adjusted life years (QALYs), patient survival, durability of treatment, and treatment pathways which may include combination therapy. Biogen welcomes the opportunity for further discussion. Below is a summary of Biogen's detailed comments on the draft scoping document.

**1. Include societal costs in a sole base-case and as part of the value-based price calculation.**

SMA costs to families are staggering and include out-of-pocket medical costs, informal care costs, non-health transportation expenses, as well as costs associated with assisted living devices, and housing and vehicle adaptation.<sup>6</sup> Parents and caregivers suffer lost earnings and underemployment because of the required need to care for their SMA-afflicted child, which can be a 24-hour job. Lost earnings are further incurred if patients are unable to reach their full employment potential and maintain work in the future due to premature death and significant lifetime disability. The total cost in the U.S. of SMA, including direct medical, non-medical and

indirect annual costs prior to an approved treatment, was estimated at \$957 million (2012). Patients, their families and employers bear a significant share of these costs -- between 37 and 60 percent of the total.<sup>7</sup>

**2. Include patient and caregiver outcomes and societal costs (e.g., productivity loss) as the sole base-case for CEPAC's vote on value.**

ICER's assessment should capture all major elements of value inclusive of all stakeholders in its sole base-case. This should include 1) full patient and caregiver costs; and 2) outcomes that encompass the devastating nature of this disease not only to patients but their caregivers as well. SMA has a significant impact on caregivers, including reduced quality of life and increased levels of co-morbidities when compared to the general population.<sup>8</sup> This more complete assessment should extend to the New England CEPAC's vote on value.

**3. Recognize the unique challenges in SMA clinical trial programs and evidence generation.**

Our experience is that SMA evidence cannot be evaluated in the same way as evidence for non-rare diseases. SMA is characterized by very small populations, fundamental unknowns in the epidemiology of the disease and unique challenges in clinical trial program design and execution.<sup>9</sup> Biogen has sought to understand individual nuances of this disease by designing rigorous and robust trials that address the varied manifestations of SMA. This was necessitated by the fragility of this patient population and the need to ensure the greatest likelihood of treatment durability. ICER's Comparative Value Analysis should include sufficient sensitivity analyses and a thorough description of data constraints and assumptions to reflect existing uncertainties. Lastly, there are limitations of comparing the Spinraza<sup>®</sup> ENDEAR or NURTURE trial to the AVXS-101 trial including variations in study design, patient age, disease duration, disease severity and study endpoints; also, immunogenicity and durability issues must be accounted for in modelling.

**4. Consider the unique impact of treatment for SMA subpopulations when assessing value.**

SMA is clinically heterogeneous. Patients diverge significantly in a number of ways that determine prognosis, treatment response and durability. Biogen has worked extensively with the SMA community to better understand the impact of areas such as variations across the SMA phenotypic continuum, subtyping, ventilation support and the nature and timing of changes in physical functioning.<sup>10,11</sup> All of these factors are important to consider when selecting methods and reporting value across a range of patients with SMA. The value assessment methodology of treatment for infants will be different from that of adults.

**5. Conduct appropriate sensitivity analyses to address uncertainties in QALY estimates for SMA.**

The collection of health utilities in young children presents a fundamental challenge in that they typically cannot speak, write or express themselves to the level required to understand how they may feel about a given state of health. This problem is further exacerbated for children with SMA who may require ventilation or have difficulties with every day activities (sitting up, moving their head) that the general population takes for granted. QALYs may not adequately capture improvements that are of monumental importance to patients with SMA; for example, the ability to move a finger to operate a wheelchair or computer mouse offers a patient with SMA the opportunity to maintain a level of independence that he/she would not have otherwise. Existing methods to estimate QALYs are unduly limited.

These challenges specific to SMA are compounded by well-acknowledged methodological issues in the QALY leading to high levels of variation and inconsistency over time and across respondents.<sup>12</sup> These challenges are further amplified where a sole reliance on the QALY and willingness-to-pay thresholds for decision-making fails to acknowledge individual SMA patients' rights to an equal chance for good health. ICER should consider enhancing the QALY with multi-criteria decision analysis, focusing on studies that demonstrate an alignment between QALYs and objective improvements in motor function and survival; and performing extensive sensitivity analyses to address the inherent uncertainty in this assessment.

**6. Model patient survival according to data from the ENDEAR and SHINE trials, which show SMA patients treated with nusinersen (Spinraza®) show improvements in motor function and increased event-free survival.**

The end-of-study results from ENDEAR show a significant treatment benefit with regard to event-free survival and overall survival in patients treated with nusinersen (Spinraza®). 84% of the nusinersen-treated infants were alive without the need for permanent ventilation at the end of ENDEAR, compared with 61% of controls. Among participants who received sham (note: the comparator should be referred to as 'sham injection' in the final scoping document, not 'placebo'), the median time to death or permanent ventilation was 22.6 weeks within ENDEAR.<sup>13,14</sup> Interim results as of June 30, 2017 from SHINE, the open-label extension study for patients with infantile-onset SMA (most likely to develop Type 1) who transitioned from the Phase 3 ENDEAR study (as well as others), illustrate longer-term benefits for infantile-onset SMA patients treated with nusinersen, including continuous improvements in motor function and increased event-free survival. SHINE participants who initiated nusinersen in ENDEAR, as well as those who received sham in ENDEAR and initiated nusinersen in SHINE, experienced improvements in specific Hammersmith Infant Neurological Examination Section (HINE-2) motor milestones and general motor function as measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP INTEND). The median time to death or permanent ventilation for participants who initiated Spinraza® in ENDEAR and continued in SHINE was 73 weeks. The majority (58%) of subjects who were alive and did not require permanent ventilation after they received sham in ENDEAR remained event-free after receiving nusinersen in SHINE for a median time of 9.2 months.<sup>15</sup>

*Note: In the clinical trial program, Spinraza® demonstrated a favorable benefit-risk profile. The most common adverse reactions that occurred in the Spinraza® group were respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in Spinraza®-treated patients.*

## **Conclusion**

In summary, ICER should consider enhancing its proposed approach to more fully reflect value relevant to patients and caregivers. Biogen acknowledges the complexity of this disease; like many rare diseases, although much progress has been made in SMA, it is still not yet fully understood or well-defined. We encourage ICER to communicate and collaborate with the SMA community, and we welcome the opportunity to work with ICER to ensure patients have access to therapies that provide the very best chance at improved motor function and survival from this devastating disease.

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September 12, 2018  
Institute for Clinical and Economic Review (ICER)  
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Dear ICER Review Panel,

Genentech Inc., a member of the Roche Group, is dedicated to bringing best-in-class therapies to patients with unmet medical need through scientific innovation and supporting access to these therapies through robust evidence generation. Genentech, in collaboration with PTC Therapeutics and the Spinal Muscular Atrophy Foundation (SMAF), is developing risdiplam, an investigational survival motor neuron 2 (SMN2) splicing modifier for the treatment of patients in all ages and stages of SMA.

SMA is a rare, progressive, and often fatal neuromuscular disease that can impact affected individuals' ability to walk, sit, swallow, and breathe, and perform other everyday activities most people take for granted. Nusinersen is the first approved treatment for SMA, signifying an important milestone for the clinical and patient community. The investigational gene therapy, AVXS-101, has also demonstrated initial promise in a subset of patients. Despite clinical advances, there remain significant unmet medical needs. Due to a number of clinical, logistical, and access challenges, only 20-30% of patients received nusinersen one year after its approval (CureSMA 2018).

We would like to highlight two key points for your consideration in the forthcoming review of AVXS-101 and nusinersen for the treatment of SMA.

1. ICER should consider capturing the full value of treatment to patients, caregivers, and society by utilizing the adapted value framework for ultra-rare diseases and highlighting additional contextual considerations.
2. ICER should consider expanding the assessment of treatment benefit beyond motor function milestones in order to holistically capture patient-relevant benefits.

**1. ICER should consider capturing the full value of treatment to patients, caregivers, and society by utilizing the adapted value framework for ultra-rare diseases and highlighting additional contextual considerations.**

Genentech appreciates ICER's proposal to assess nusinersen and AVXS-101 under the adapted value framework for ultra-rare conditions. A framework that hinges on traditional measures of

value, such as cost-effectiveness, frequently fails to capture the full spectrum of value. This results in an inadequate characterization of the benefit a treatment brings to patients, caregivers, and society. It is therefore critical that ICER conduct a comprehensive, patient-centered value assessment while highlighting additional contextual considerations.

**1a. SMA is an ultra-rare disease with a significant unmet medical need.**

The prevalence of SMA in the US ranges between 8,000 and 10,000 (Nally 2017) and the population eligible for treatment is expected to be even smaller. SMA is the leading genetic cause of death for infants (Farrar 2015). SMA affects people of all ages, although symptoms typically appear in infancy or early childhood. Patients with type 1 SMA, if left untreated, never achieve the ability to sit. With proactive care, they may live past 2 years of age (Wang 2007). Although patients with type 2 and 3 SMA may live to adulthood, the early onset of disease denies their ability to live a full life from a very early age (Iannaccone 2009). Prior to the approval of nusinersen, there were no effective treatments beyond supportive care.

**1b. The age of onset and the severity of SMA result in a significant disease burden not only on the lives of patients, but also on their families, caregivers and the broader society.**

Genentech recommends that ICER take a dual base case perspective for the economic evaluation that includes both health systems perspective as well as a broader societal perspective. In a survey commissioned by Muscular Dystrophy Association (MDA), 16-24 hours of daily care is needed for more than 80% of patients diagnosed before 3 years of age, and 50% of the rest of patients (Larkindale 2013). In addition, disability-related cost is significant for families with SMA. For example, families with patients diagnosed before 3 years of age were reported to have an annual cost of \$50,542 associated with moving or modifying homes, purchasing motor vehicles, professional caregiving and other non-medical costs (Larkindale 2013). SMA is also associated with substantial indirect costs. In a survey of adult patients with type 2 SMA, less than half were employed (Jeppesen 2010). Many of the parents of patients with SMA must stop working at some point in their lives to take care of the loved ones (Larkindale 2013).

**1c. Genentech believes that other benefits and contextual considerations should be a core component of the value assessment. The following elements should be considered:**

1. Advent of new treatments offering hope to the SMA community as well as profound effect on the wider discipline of neuromuscular disease research (Groen 2018).
2. Significant impact of treatment on care delivery (e.g., SMA has been added to the Recommended Uniform Screening Panel for newborns in the United States) and potentially on the course of the disease (Department of Health and Human Services 2018, Glascock 2018)

3. Uncertainty surrounding long-term benefits and risks, particularly the durability and reversibility of effect associated with delivery of a high dose of adeno-associated viral vector with AVXS-101 (Mendell 2017)
4. Despite therapeutic advances, a number of treatment related issues still exist:
  - Limited clinical data has created some disparity within the SMA population. For example, available treatment has not been studied in randomized, controlled clinical trials for patients aged 12 years and above (Biogen 2018).
  - There is varying level of coverage across health plans and across countries, causing potential socioeconomic and geographic inequality (CureSMA 2018).
  - Repeated intrathecal injections of nusinersen could create a potential barrier to access for some patients (Groen 2018).

**2. ICER should consider expanding the assessment of treatment benefit beyond motor function milestones in order to holistically capture patient-relevant benefits.**

In the current proposal, the cost-effectiveness analysis is based on a Markov model consisting of health states defined by motor function milestones. Motor function milestones reflect features of SMA and are often assessed in clinical trials as primary endpoints. However, they are a crude measure of a patient's health state that may not capture meaningful changes in a patient's day-to-day life. According to the 'Voice of Patients' workshop hosted by CureSMA, the significance of any therapeutic changes should be relative to where a patient is on the functional spectrum. Small losses or gains in functional ability may have a substantial impact on the patient and the family, particularly, when such changes have implications on patient's independence (CureSMA 2017). For example, a non-ambulatory patient may gain the ability to transfer between wheelchair, bed and toilet independently during the course of treatment. This gain in independence can be meaningful, despite his or her health state remaining 'non-ambulatory'.

In addition, other aspects of the disease, such as strength, fatigue/endurance, respiratory function, activities of daily living, and communication also have critical impact on patients' quality of life (CureSMA 2017). Genentech encourages ICER to explore ways to incorporate these aspects into the cost-effectiveness assessment.

In summary, Genentech remains committed to engaging with ICER on your continuous efforts to assess value of innovation. We appreciate the opportunity to comment and hope our comments will lead to a more comprehensive evaluation that represents the needs of all stakeholders.

Sincerely,



Jan Hansen, PhD  
Vice President, Evidence for Access

U.S. Medical Affairs, Genentech, Inc.

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Dear ICER,

I am a geneticist and medical director but not a statistician or economist so I'll try my best to make a couple of comments regarding your draft scoping document.

First of all, this is needed document. Thank you. Two items you might consider:

1. Look at whether the number of SMN2 copies changes the effect of nusinersen. I do not know if the same genotype correlation will affect AVXS-101 or not. There is some data in the supplementary appendices to ENDEAR.
2. I don't know if it is within the scope of your organization but a discussion of the ethical dilemmas of these sorts of coverage matters would be interesting. Articles on the topic already exist (Burgart, 2018) and could be informed by your economic analysis. Perhaps a comparison of how your cost/QALY analysis compares to more common treatments.

These opinions are my own and not those of Highmark Health.

Thank you,

Matt

Matt Fickie, MD, FACMG  
Assoc. Medical Director  
Health Plan CMO Organization  
Highmark, Inc

I was diagnosed with SMA type II at 18 months old. Despite this, I have gone on to live a fulfilling and successful life. Originally from Upstate New York, I earned a Bachelor's degree in Communications and Computer Science from The College of Saint Rose and a Master's degree in Information Technology from Rensselaer Polytechnic Institute. I now live with my beautiful wife, Laura, in Herndon, VA and work as a Software Engineer. When I was first diagnosed it was barely known what caused this disease. I always had hope for a cure, but it was always far in the future. Well, that future is now here. I know now that my generation may be the last to ever be affected by SMA. Having that happen in my lifetime is indescribably amazing. I know that, realistically, I'll probably never walk. Regardless, having a treatment that could give me more strength opens up so many possibilities that would drastically improve my quality of life. If I could go to the bathroom by myself, roll over in bed, unbuckle my own seat belt, or hold a baby then I could travel anywhere I want, never have to wake up anyone at night for assistance, drive to work by myself, and change my (future) child's diaper. These may sound like menial tasks to some, but to me it would be a dream come true. The greatest gift for me to come from a treatment for SMA is for everyone around me burdened with helping me. More than anything else I would love to be the one helping others rather than having to rely on that help.

**Kyle Derkowski**

**Ashburn, VA**

Imagine living with a disease that slowly paralyzes you. One that steals all of your muscle strength, your ability to walk stolen before you even had it. Now imagine that you are a bright and social little boy watching literally every child around you move effortlessly as they play tag, run up a ladder and slide down a slide, play soccer, and ride bikes. This is what children with Spinal Muscular Atrophy (SMA) live with.

My name is Esther and I am the mom to two very special little boys diagnosed with SMA type 2. SMA is a rare degenerative disease that affects the motor neurons needed for activities such as crawling, walking, head and neck control, lifting your arms, breathing, and swallowing.

Children with SMA are missing a gene that creates a protein the motor neurons need to live. As the motor neurons slowly die, a child with SMA slowly gets weaker and it robs the child of the ability to move. The brain's cognitive functions and the ability to feel objects and pain are not affected. These kids are bright and social and love to be doing what all the other kids are doing. Their cognitive abilities are just like any other kids their age.

Tanner was diagnosed when he was 20 months old after seeing several doctors to try to figure out why he never started to walk. At the time of Tanner's diagnosis, I was 7 weeks pregnant with Skyler. We had Skyler tested right after birth and sadly, he was also diagnosed with SMA when he was 10 days old. Just after Tanner turned 2, despite our constant fight to keep his strength, he lost his ability to crawl. He would slump over on the couch and not be able to sit up again, instead he called to us for help. He kept getting weaker and we felt helpless.

Just before Tanner turned 3 he was accepted in a clinical trial for the drug Isis-SMNRx. Since that time he not only stopped getting weaker, that alone would have made us celebrate, but he started getting stronger. He started to be able to go from laying down to sitting up on his own. He started crawling again. He started pulling up to his knees and even is able to stand without any support or bracing for a few seconds. His arms are so much stronger. It has been amazing to watch. He has gained so much confidence with gaining strength and getting this treatment has been a huge impact for good in his life. We would have been thrilled to just have this drug stop SMA from paralyzing him, but we love that it given back so much of his lost strength. All SMA kids need this treatment too.

Skyler is so much weaker than his brother. He has never been able to crawl. He cannot bear any weight on his legs at all. He can't stay sitting independently for very long. I wish so much he could have gotten this treatment soon after birth before the symptoms of SMA set in.

Time makes all the difference with a disease like SMA. Waiting for treatment versus getting it now is the difference between having a disability and a much, much more severe disability. It is so easy to feel frustrated right now when there is a treatment out there that works but that only a lucky few have access to. As with any parent who cares about their children, the desperation to keep whatever strength their children have starts to grow. It is hard to stand by and wait when time is not on these kids side. SMA kids do not have years to wait. Kids with type 1 SMA have a life expectancy of under 2 years from the time they are diagnosed. For stronger kids like Tanner and Skyler, muscles will be lost, contractures will set in, scoliosis will worsen, feeding tubes will be placed, breathing support will be required and many will die. All could be

prevented with access to this treatment. SMA is an unmerciful disease that causes paralysis and death and we need to have access to treatments.

**Esther Jensen**

**Layton, UT**

Back in 2006, I lost my grandson Gavin to SMA Type 1 at 5 months. At the time we had no idea it existed, let alone that we were carriers to the gene. To say the least, we were devastated. He was our first grandchild. We were robbed of so many firsts. No first birthdays, first Christmas, no first days of school. Even after all these years, I wonder what those would have been like to enjoy those or what he would look like today. To be robbed of a child is the most horrible thing that no one should have to face ever.

**Janice Kress**

**Carmichaels, PA**

Imagine looking at your perfectly healthy and strong baby and then, all of a sudden, noticing that something isn't quite right and being told that he has a very severe disease that is going to rob him from all of his strength before he even has the chance to enjoy life as a typical child and that his life might be cut short by making it too difficult for him to breathe on his own. This is our story, this is my son's prognosis.

As a parent, when you are told this, you immediately stop breathing and we have not taken a full breath since that day when we received the devastating news. Our son has SMA type 2, we were told he was strong being able to stand supported and crawl, but he quickly lost these abilities after his diagnosis. Never have we ever felt such an overwhelming feeling of helplessness and fear. Every day, we are consumed by the thoughts of what's going to happen and what IS happening to his little body that seems so perfect. We are constantly keeping an eye on him so he stays safe, doing his stretching exercises to prevent any contractures, assuring he has his time in his special equipment so his body stays in good shape for as long as it can, doing aqua therapy to keep him moving and strong and to alleviate some of the stress off his spine.

For us, it is constant worrying, constant researching and constant care. I can not imagine how the parents of the type I children manage every day having to assure around the clock that their child's oxygen is up, g-tube feedings, suctioning, etc.

What an awful, devastating disease...it NEEDS to stop, we need a CURE now! This is an URGENT matter. These kids deserve to play, to breathe, to smile on their own! They tell us to have hope that someday, there will be a cure...that day needs to be today! We try so hard to stay hopeful and we do have hope that SMA will someday be a thing of the past but what does this mean for our little boy who is deteriorating before our eyes and all of the others who are sick today? Time is of the essence and these children do not have time because their motor neurons are weakening every day and the treatments they will eventually receive will sadly not be able to erase some of the effects of this harsh disease because it'll be too late for them. These treatments mean the difference between being able to sit or stand, or even walk and for others it means being able to breathe without a machine or eat and actually taste and enjoy their food. It means independence for our children and well deserved quality of life! It's a chance to live a long, normal, healthy life!

For ourselves and for most, if not all, of the parents in the SMA community, these treatments are well worth many risks possibly associated to them long term in comparison to the effects of this disease. We want to see this generation fully benefit from treatment and better yet a cure!

**The Melanson Family**

**Norwell, MA**

"Why don't my legs work?"

This is a question that a 4 year old should not have to ask. After her 4 year annual checkup with vaccinations, she asked "Will those shots help my legs to work?" This is a question that I wish I did not have to come up with an answer for.

My name is Keanna Nichols, and my daughter Brooklyn has Spinal Muscular Atrophy Type II. Brooklyn was diagnosed a week after her first birthday. We feel blessed that we are now surrounded by good doctors, therapists, and family but we are still faced with many challenges.

Her inability to walk is the least of our concerns. Our main concerns are respiratory, as those muscles are weak. She will be unable to attend school on a full-time basis because she tires so easily. We have to give her body time to recoup and rest, or she will get sick. Intellectually, she is smart as a whip and very bright, however she is unable to write and color like other kids because of her low muscle tone. We have to be very careful of where and how we sit her as she easily loses balance and falls over. We are blessed to not be faced with this, but many SMA patients have feeding tubes and breathing tubes.

SMA patients are very bright and they deserve a chance to experience the things that "typical" children experience. SMA does not have to be a death sentence, but we need the opportunity to give our children the drugs that can help.

**Keanna Nichols**

**Athens, AL**

As the mother of a patient who has received AVXS-101, I can appreciate that there are many aspects of the clinical research and development of this treatment that are outside my scope of expertise. However, there is one aspect with which I am intimately aware. That is, the insurmountable benefit AVXS-101 has brought to my child and my family.

My son was diagnosed with SMA Type 1 at 5 weeks of age. He has two copies of SMN2 and even compared to others with his same diagnosis, he was very weak. By this time, he was dependent on a feeding tube and would soon need non-invasive ventilation to support his breathing as well. He could not hold his head up or tolerate being in a sitting position with support for more than a few minutes at a time. He was incredibly weak, and we did not expect him to be alive on his first birthday.

At 9 weeks of age he was the 15<sup>th</sup> child treated with AVXS-101 and today, at 35 months old, he bears no resemblance to the seriously ill baby he once was. Please consider my son, who has only 2 copies of SMN2 and developed symptoms in the first weeks of life, as he is among a class of SMA patients who have seen poorer results with Nusinersen and other available interventions.

I also ask you to consider my son, because though he will face challenges in life and may need support, his life is a most precious commodity. Just shy of his third birthday, he is advanced for his age in speech and cognition. He can read short sight words, identify dozens of shapes, colors, numbers, and letters. He has an interest in space and loves playing with other children.

Though he has had challenges, he has also had many successes. He can hold his head up and sit unsupported for hours at a time. He can roll from one end of the room to the other. He can sit and propel himself in a manual wheelchair. He can drink and eat independently. He has increasing strength in his legs and can stand with support. He only requires non-invasive ventilation during times of sickness.

I can confirm that he continues to grow stronger and gain more milestones. I believe that he will walk on his own two feet. But even if he does not, he will have the skills to live a full and independent life. He will get an education, he will work, and he will live. We can only imagine what his contribution to the world will be. If you have been given the incredible task of deciding if AVXS-101 will become widely available, I beg you to not only consider my son, but to also consider the generations that will come after him. What will their contributions to the world be? How much is that worth?

I appreciate that we need measures in place to determine fair pricing for healthcare, but AVXS-101 is in a class of its own. A baby born with SMA Type 1 will mostly likely die before their second birthday, if they do live beyond that age they will face a severely life limiting disability. AVXS-101 may not be a cure, but to me it is a miracle. It is a miracle to take an SMA Type 1 child and give them the chance to truly live. Keep an eye out for lucky number 15, his story has only just begun.