AVXS-101 and Nusinersen for Spinal Muscular Atrophy: Effectiveness and Value

Final Background and Scope
September 19, 2018

Background

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease with the most severe cases affecting infants and young children.[1,2] SMA incidence is approximately 1 in 10,000 live births or about 500 new SMA cases per year.[3] The most common cause of SMA is the homozygous deletion or deletion and mutation of the alleles of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.[4-6] *SMN1* creates SMN protein, a protein essential for motor neuron development. Although the survival motor neuron 2 (*SMN2*) gene also produces SMN protein, only a small amount of the protein it creates is functional. Hence, while the number of *SMN2* copies modulates the severity of SMA, patients without *SMN1* have an insufficient level of SMN protein regardless of the number of *SMN2* copies.[7] This deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor functions.[1]

SMA subtypes are related to age of onset and number of motor milestones achieved (see Table 1 below).[2,8]

Table 1. Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death
0	Prenatal/ Fetal	None	<6 months
I	<6 months	Sit with support only	<2 years
II	6–18 months	Sit independently	>2 years
III	>18 months	Walk independently	Adulthood
IV	Adult (2nd or 3rd decade)	Walk during adulthood	Adult

Adapted from Table 1 of Verhaart *et al*. 2017.[2]

Type 0 SMA, the most severe subtype, affects individuals before birth and is very rare. Newborns with Type 0 have severe hypotonia (low muscle tone), need respiratory support, and have a life expectancy of minutes to weeks after birth. Type I SMA (infant-onset SMA) represents approximately 60% of all diagnosed SMA cases.[3] These patients typically have two or three copies

of *SMN2*, present with symptoms before six months of age, do not reach key motor milestones (e.g., sitting without support), and lose motor functions over time. Pulmonary complications are common, often leading to respiratory support. Patients may die or need permanent respiratory support within two years of life.[3] Approximately 40% of patients diagnosed with SMA have Type II or Type III.[3] Type II SMA presents between 6 to 18 months of age with patients typically having three copies of *SMN2*. These patients cannot walk independently, and most patients survive to adulthood with aggressive supportive care.[3] Type III SMA presents in patients aged 18 months to 18 years, and patients typically have three or four copies of *SMN2*. Patients have a normal life expectancy and can walk independently, although they may lose this ability over time. Type IV SMA, a very rare and the least severe subtype, presents in adults. Adults with Type IV SMA typically retain the ability to walk independently, do not suffer from respiratory issues, and have a normal life expectancy.[2,8]

Patients with SMA may need intensive care and support, especially those with SMA Type I. To maintain mobility and function as long as possible, multidisciplinary, supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed.[9-11] Nevertheless, supportive care does not modify disease progression and patients may be entirely dependent on family members and caregivers. The intense care and physical effort involved with caring for a patient with SMA may cause loss of sleep, stress, anxiety, and emotional distress for caregivers.[12,13] Hence, SMA may affect the health-related quality of life of patients as well as their families and caregivers.

Currently, only one disease-modifying therapy (nusinersen, Spinraza®, Biogen Idec) has been approved to treat SMA.[14] Nusinersen, an antisense oligonucleotide, targets the *SMN2* gene so that it creates more functional SMN protein. It is administered via intrathecal injection with four loading doses (day 0, day 14, day 28, and day 63) and every four months thereafter. Nusinersen has been studied in patients with or likely to develop SMA Types I-III,[15-17] with several studies on-going.[15,18-20] In December 2016, the Food and Drug Administration (FDA) approved nusinersen for the treatment of SMA (any subtype).[14]

A new, systemic gene therapy (AVXS-101, Novartis/AveXis) is currently in development to treat patients with SMA. AVXS-101 uses the adeno-associated virus serotype 9 vector to deliver a copy of the *SMN* gene to replace or correct the defective *SMN1* gene.[21] AVXS-101 is being studied as a one-time, intravenous administration. The FDA granted AVXS-101 a Breakthrough Therapy Designation and Fast Track Designation, with an FDA decision expected in early 2019.[22] The potential use of AVXS-101 has generated interest from clinicians, patients, and their families especially since SMA was recently added to the list of conditions for which to screen all newborns in the US.[23] Nevertheless, uncertainties remain regarding the effectiveness of AVXS-101 and nusinersen compared with supportive care and with each other, and how well the potential cost of these interventions aligns with potential patient benefits. Therefore, stakeholders will benefit from a

comprehensive review of the clinical evidence on both drugs and an analysis of their long-term cost-effectiveness and potential budget impact.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and their families, patient advocates, clinicians, researchers, and manufacturers of the agents of focus in this review. The draft scoping document incorporated feedback gathered during preliminary calls with stakeholders and open input submissions from the public. Based on feedback from the draft scope, the document has been revised to include bulbar function (e.g., speaking, swallowing) as an outcome of interest and to add clarity to the population and comparators for this review.

From patient advocates and caregivers, we heard how devastating the diagnosis of Type I SMA can be and how difficult it is to watch the disease progress in a child. Parents and caregivers feel helpless and fearful while also needing to be vigilant and constantly providing care. Care entails approaches to preserve respiratory and muscle function, including physical therapy, nutritional support, and extensive medical equipment. From adults with SMA, we also heard how frustrating it is that new interventions have not been commonly studied in adults and that more data are needed in this population, including data on appropriate dosages. Patients and caregivers reported wanting treatments that improve strength and ability to live more independently. We also heard extensively about the importance of early identification of and treatment for SMA.

While many of the above comments have been incorporated into this scoping document, the Evidence Report will provide additional details of these considerations. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of these agents.

Report Aim

This project will evaluate the health and economic outcomes of AVXS-101 and nusinersen for patients with SMA. We will assess AVXS-101 and nusinersen under an adaptation of the ICER value framework focused on treatments for serious, ultra-rare conditions because the assessment meets the following criteria:

- The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.[2,3]
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals

Stakeholder comments on the draft scope aligned with the selection of this approach. The ICER value framework for ultra-rare conditions includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

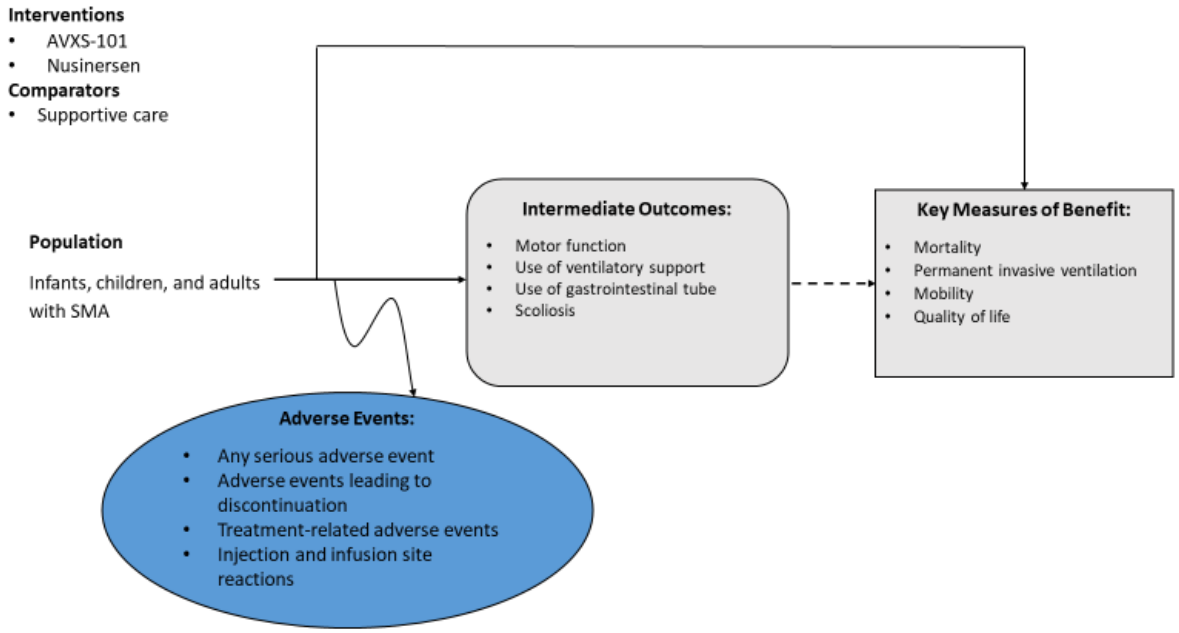
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials and non-randomized studies as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of AVXS-101 and nusinersen is depicted in Figure 1 on the following page.

Figure 1. Analytic Framework: Treatments for Spinal Muscular Atrophy



SMA: spinal muscular atrophy

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., use of ventilatory support), and those within the squared-off boxes are key measures of benefit (e.g., mortality). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[24]

Populations

The population of focus for the review is infants, children, and adults with SMA. Where data are available, we will look at subpopulations defined by age of onset (including presymptomatic SMA, infant-onset SMA, later-onset SMA), SMA subtype (0-IV), or number of *SMN2* copies. It is unlikely that data will be available for all populations and subpopulations, and we will note where gaps in evidence exist.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Nusinersen
- AVXS-101

We will work further with clinical experts to define likely pathways of care with these agents, including the possibility of sequential use.

Comparators

Where data permit, we intend to compare the agents to each other and to supportive care (with or without sham injections). Since its approval for use in the US in December 2016, nusinersen has been used by approximately 20-30% of patients with SMA.[25] In part due to the large portion of the population continuing to use supportive care, supportive care is a comparator of interest at this time. As noted in the population section above, it is unlikely that all comparisons will be available for all populations and subpopulations, and we will note where gaps in evidence exist.

Outcomes

The outcomes of interest are described below.

Efficacy:

- Mortality
- Permanent invasive ventilatory support
- Motor function, including:
    - Hammersmith Functional Motor Scale-Expanded (HFMSE)
    - Hammersmith Infant Neurological Examination-Section 2 (HINE-2)

    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
    - Revised Upper Limb Module (RULM)
    - World Health Organization motor development milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing along, walking alone)
- Mobility (e.g., 6-Minute Walk Test)
- Bulbar function (e.g., swallowing, speaking)
- Use of respiratory or gastrointestinal support (e.g., gastrointestinal tube)
- Other complications of SMA (e.g., scoliosis)
- Quality of Life (e.g., PedsQoL)

Safety:

- Treatment-related adverse events
    - Injection or infusion site reactions
    - Thrombocytopenia and low platelets
    - Renal toxicity
    - Liver function (e.g., elevated aminotransferase)
    - Complications of lumbar puncture (e.g., back pain, vomiting, headache)
- Serious adverse events
- Adverse events leading to discontinuation

Timing

Evidence on intervention effectiveness and safety will be derived from studies of any duration.

Settings

All settings will be considered, with a focus on settings in the United States.

Potential Other Benefits and Contextual Considerations

Our review seeks to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Table 2 below.

Table 2. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving the patient's ability to return to work and/or their overall productivity.
This intervention will have a significant positive impact outside the family, including communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to best supportive treatment, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

During the open input and draft scope review period, we received input from stakeholders on many of these aspects, which will be elaborated in the draft Evidence Report. ICER encourages stakeholders to continue providing input on these elements in their public comment submissions throughout the review process.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of each treatment of interest relative to comparator interventions. We plan to evaluate AVXS-101 and nusinersen versus supportive care in infants, children, and adults (pending data availability) with SMA. Where possible, we will look at cost-effectiveness by subgroups defined by SMA subtype, symptomatic status (i.e. pre-symptomatic or symptomatic) and disease onset (i.e. early or late onset).

We will develop a Markov or microsimulation model, pending data availability, which will be based in part on a literature review of prior published models of SMA and health technology assessment reports of SMA in other jurisdictions such as England,[12] Canada,[26] Ireland,[27] Scotland,[28] and Australia.[29] Following the ICER methodology for treatments of ultra-rare conditions, we will present a dual base case, where the health sector and modified societal perspectives will be presented concurrently.

The model will consist of health states based on motor function milestones, a health state for permanent ventilatory support, and an absorbing state, death. A cohort of patients will transition between the health states over a lifetime horizon, i.e., the patients will be modeled from treatment initiation until death. A 3% annual discount rate will be applied to both costs and outcomes.

Key model inputs will include clinical transition probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs may differ between the interventions to reflect the effectiveness between interventions. Treatment effects will be estimated using results from relevant trials identified in the clinical review. Uncertainty in the model parameters will be captured using one-way sensitivity analyses and parametric distributions which will inform probabilistic analyses. We will also include relevant scenario analyses as applicable.

Health outcomes will be dependent on time spent in each health state, clinical events, and adverse events (AEs). Quality of life weights will be applied to each health state, including quality of life decrements for serious AEs. The health outcome of each intervention will be evaluated in terms of life-years and quality-adjusted life years (QALYs) gained. The model will include direct medical costs, including but not limited to costs related to intervention administration, monitoring, SMA-related care, and serious AEs. Additionally, patient and caregiver productivity losses will also be included in the societal analysis. Given the known caregiver burden associated with SMA, we will attempt to model caregiver-related quality of life in addition to costs in the societal analysis, pending data availability. For all analyses, relevant pairwise comparisons will be made between treatments, and fully incremental analysis will be performed. Results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per selected clinical outcomes, such as cost per death prevented, cost per case of permanent ventilatory support

avoided, or cost per selected milestone achieved (such as sitting independently, standing independently, or walking independently).

In separate analyses, we will explore the potential health system budgetary impact of treatment with both agents over a five-year time horizon. We will analyze the potential budget impact of AVXS-101 versus nusinersen, and the impact of both agents (if prices are known) versus best supportive care. We will utilize published or otherwise publicly-available information on the potential population eligible for treatment and the results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by nusinersen or AVXS-101 (e.g., less need for respiratory support), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of SMA beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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