Therapies for the Treatment of Spinal Muscular Atrophy

Revised Background and Scope

FEBRUARY 13, 2025

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 one in 15,000 live births or about 500 new SMA cases per year in the United States (US).[3] [4] 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.[5-7] *SMN1* creates survival motor neuron (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. 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.[8] 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 1.1 below).[2,9]

Table 1.1 Clinical Classification of SMA

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death
0	Prenatal/ Fetal	None	<6 months
1	<6 months	Sit with support only	<2 years
2	6–18 months	Sit independently	>2 years
3	>18 months	Walk independently	Adulthood
4	Adult (2nd or 3rd decade)	Walk during adulthood	Adult

Adapted from Table 1 of Verhaart, IEC, Robertson, A, Wilson, IJ, et al. 2017.[2]

SMA: spinal muscular atrophy

The natural history of SMA has been dramatically altered by the availability of disease modifying therapies. Figure 1 shows changes in SMA Type 1 outcomes in Italy since 2016. In the US, neonatal screening for SMA is now performed in all 50 states and allows for treatment prior to symptomatic diagnosis of disease.[10] The first two disease modifying therapies, nusinersen and onasemnogene abeparvovec, were reviewed in a 2019 ICER report.[11] Nusinersen (Spinraza®, Biogen), approved by the Food and Drug Administration (FDA) in 2016, is an antisense oligonucleotide that targets *SMN2* 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.[12]

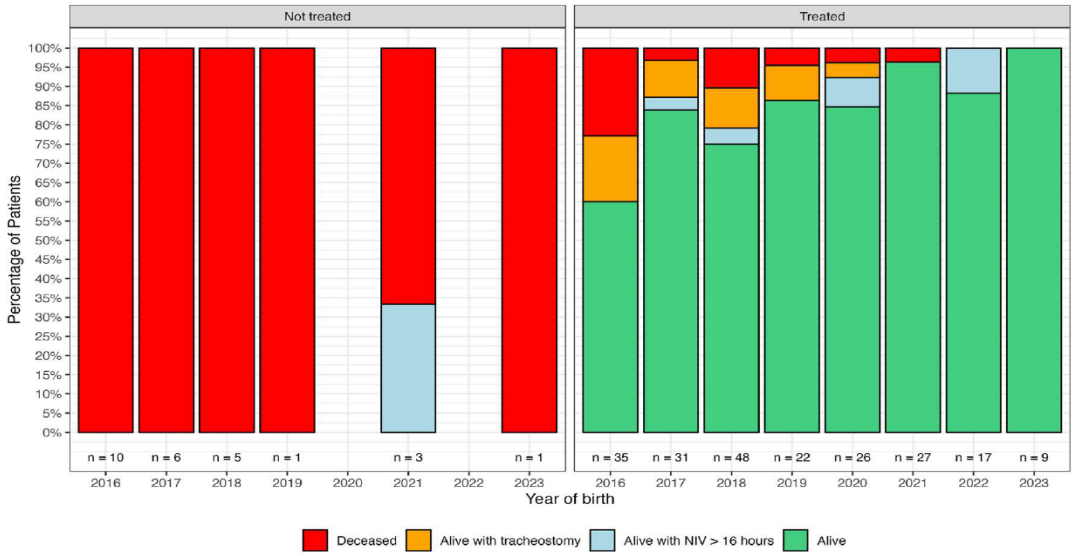
Onasemnogene abeparvovec (Zolgensma®, Novartis), approved by the FDA in 2019, is a gene therapy that uses the adeno-associated virus serotype 9 (AAV-9) vector to deliver a functional copy of the *SMN1* gene.[13] Onasemnogene abeparvovec is given as a one-time intravenous (IV) injection.

Risdiplam (Evrysdi®, Genentech), approved by the FDA in 2020, is a splicing modifier that, like nusinersen, targets *SMN2* to increase the production of SMN. Unlike nusinersen, it is an oral medication taken once daily. ICER did not review risdiplam in 2019.

During ICER's review in 2019, questions arose about whether patients who received onasemnogene abeparvovec were likely to also be treated with nusinersen and whether such treatment would be beneficial.

Despite improvements for patients with SMA with the above treatments, there are many individuals with Type 2 and Type 3 SMA who developed disease prior to newborn screening. While it is likely that the above therapies improve outcomes for these patients, lost nerve function is not regained. Apitegromab (Scholar Rock) is a new therapy that is being evaluated to improve muscle function in patients with symptomatic SMA. It is a selective inhibitor of a myostatin precursor. It is being studied in patients with Type 2 and Type 3 SMA and is given by IV infusion every four weeks.

Figure 1. SMA Type 1 Outcomes in Italy Stratified by Year of Birth and Treatment Status



Adapted from Figure 2 of Pera, MC, Coratti, G, Pane, M, et al. 2024.[14]
NIV: non-invasive ventilation, Tracheostomy: tracheostomy with continuous invasive ventilation

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, incorporates input received during the 2019 review, and includes input from patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document also incorporates additional feedback gathered during preliminary calls with stakeholders and open input submissions from the public. 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 preventive treatments.

We heard how frustrating it is that these new interventions have not been adequately studied in adults and that more data are needed for this population, including data on appropriate dosages. Patients and caregivers reported wanting treatments that improve strength and ability to live more independently. We heard that patients who have been treated with gene therapy and those who are receiving *SMN2*-directed therapies still experience fatigue and have functional deficits. We heard hope that myostatin-directed therapy could help to address these unmet needs.

We learned how devastating the diagnosis of Type 1 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. Multiple approaches are needed to preserve respiratory and muscle function, including physical therapy, nutritional support, and extensive medical equipment. Patients and caregivers reported wanting additional treatments that improve strength and the ability to live more independently.

Caregivers of patients with SMA have significantly worse quality of life compared with similar individuals in the community. This primarily reflects mental health (anxiety, depression, grief) rather than measures of physical health.

We updated our scope to include efficacy outcomes related to bulbar function (e.g., swallowing, speaking) to better reflect what is important to patients with SMA and their families. Comments about families' experiences with SMA provided patient-centered context for interpreting clinical trial outcomes by communicating the importance of independent functioning for older children and adults with SMA, and delay of disease progression for infants and younger children with SMA. Caregivers underscored the importance of not only improved mobility but also slowed progression and stabilization of current motor functions, including smiling and independent sitting, eating or feeding, toileting, and transferring from wheelchairs.

Report Aim

This project will evaluate the health and economic outcomes of apitegromab. It will also update the evidence base for nusinersen and onasemnogene abeparvovec and review the evidence base for risdiplam. The ICER value framework 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.

Applicable Framework Adaptations

We propose to assess apitegromab under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because we believe it 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.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

Following formal public comment and discussions with stakeholders, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

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.

Our review will include two components, each with a unique PICOTS structure: The first will assess apitegromab in its studied population. The other will be an evidence update on the approved disease modifying therapies previously reviewed in our 2019 SMA review, nusinersen and onasemnogene abeparvovec, with the addition of risdiplam. Our intention is to determine whether subsequent evidence exists that might alter our previous evidence ratings comparing nusinersen and onasemnogene abeparvovec against supportive care in SMA subpopulations, specifically those who are presymptomatic, and patients with Type 1, Type 2, and Type 3 SMA.

Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. We will also evaluate evidence from single-arm studies of disease-modifying therapies. 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 ICER's 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. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

PICOTS 1

Population

Individuals with SMA Type 2 or 3 on background disease modifying therapy (nusinersen or risdiplam).

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, race/ethnicity)
- Background therapy (nusinersen vs. risdiplam)
- SMA subtype
- Age at start of treatment
- Prior treatment with Onasemnogene abeparvovec

Interventions

Apitegromab (10 or 20 mg/kg IV every four weeks) as an add-on to nusinersen or risdiplam.

Comparators

Nusinersen or risdiplam alone.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Avoidance of permanent invasive ventilation
    - Measures of functional mobility
    - Bulbar function (e.g., swallowing, speaking)
    - Health-related quality of life
    - Impact on activities of daily living
    - Caregiver burden
    - Adverse events including
        - Any serious adverse event
        - Adverse events leading to discontinuation
        - Treatment-related adverse events
        - Injection and infusion site reactions

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least 12 months duration.

Settings

All relevant settings will be considered.

PICOTS 2

Population

Infants, children, and adults with SMA.

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, race/ethnicity)
- SMA subtype
- Presymptomatic or symptomatic at start of treatment
- Age at start of treatment

Interventions

The full list of interventions is as follows:

- Nusinersen (Spinraza®)
- Onasemnogene abeparvovec (Zolgensma®)
- Risdiplam (Evrysdi®)

Comparators

We intend to compare the interventions to each other and, for patients who previously received onasemnogene abeparvovec, to no additional disease-modifying treatment.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Avoidance of permanent invasive ventilation
    - Measures of functional mobility
    - Bulbar function (e.g., swallowing, speaking)
    - Health-related quality of life
    - Impact of activities of daily living
    - Caregiver burden
    - Adverse events including
        - Any serious adverse event
        - Adverse events leading to discontinuation
        - Treatment-related adverse events
        - Injection and infusion site reactions

Timing

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

Settings

All relevant settings will be considered.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities 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 general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on April 10, 2025. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of apitegromab + background therapy (nusinersen or risdiplam), relative to background therapy alone focusing on PICOTS 1 above. The model structure will be based, in part, on a previous ICER model for later-onset SMA (Types 2 and 3) from 2019 and publicly available literature.[15-17] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment

on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of apitegromab on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of SMA Type 2 or 3 patients on background therapies, nusinersen or risdiplam. The model will likely consist of health states based on motor milestones, changes in the Hammersmith Functional Motor Scale-Expanded, and death. A cohort of patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death. The model will be able to accommodate differential utility scores within each health state by treatment status. In addition, cost-effectiveness may be estimated for shorter time horizons (e.g., five years) in scenario analyses.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using data from Phase II and Phase III clinical trials and network meta-analyses where appropriate.[18,19]

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of life-years gained, QALYs gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, and cost per life-year gained. Costs and outcomes will be discounted at 3% per year.

In separate analyses, we will explore the potential health care system budgetary impact of apitegromab over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. The target population will consist of SMA Type 2 or 3 patients on a background disease-modifying therapy, either nusinersen or risdiplam. However, pending data availability and feedback from clinical experts on possible indications for apitegromab, we may expand the population to include early-onset SMA (Type 1) or to patients receiving background disease-modifying therapy after prior treatment with onasemnogene abeparvovec.

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 here.

Identification of Low-Value Services

ICER includes 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 ICER's Value Assessment Framework). These services are ones that would not be directly affected by apitegromab, such as need for an assistive device, 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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