REPORT AT A GLANCE: SPINAL MUSCULAR ATROPHY

KEY FINDINGS

Intervention	Comparators	Evidence Rating	Health-Benefit Price Benchmark
Apitegromab as an add-on to risdiplam or nusinersen	Risdiplam or nusinersen alone	**P/I** (promising but inconclusive)	$4,600 to $30,200 per year
Nusinersen in patients previously treated with onasemnogene abeparvovec	No additional treatment	**P/I** (promising but inconclusive)	Not applicable
Risdiplam in patients previously treated with onasemnogene abeparvovec	No additional treatment	**C++** (Comparable or better)	Not applicable

"SMA, in its most common forms, has been a devastating degenerative neurologic disease of infants and children. Disease modifying therapies and newborn screening have dramatically altered the course of disease and represent one of the great medical success stories in the past decade. However, as the votes of the independent appraisal committee recognized, we still have important uncertainties about how best to utilize these therapies to provide maximal benefits to those affected."

ICER's Chief Medical Officer, David Rind, MD, MSc

THEMES AND RECOMMENDATIONS

- The manufacturer should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. Given the small average improvement in motor function for patients treated with apitegromab and the uncertainty about serious adverse events, manufacturer pricing should reflect ICER's value-based price range in moderating launch pricing.
- The use of SMN-directed therapy after gene therapy or in combination should only be done in the context of research studies.
- A randomized trial should be performed of first-line therapy in asymptomatic patients identified through newborn screening to better understand the comparative advantages and disadvantages of each of the three SMN-directed therapies.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disease. SMA incidence is approximately one in 15,000 live births or about 500 new SMA cases per year in the United States (US). 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. 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. SMN protein deficiency causes the irreversible degeneration of motor neurons, which leads to progressive muscle weakness and prevents patients from reaching motor milestones or retaining motor function.

The natural history of SMA has been dramatically altered by the availability of disease-modifying therapies. In the US, neonatal screening for SMA is now performed in all 50 states and allows for treatment prior to symptomatic diagnosis of the disease. The mortality rate for patients with SMA has dropped by 77% from 2014 to 2024, likely due to the combination of newborn screening and the availability of SMN-targeted therapy.

The first two disease modifying therapies, nusinersen and onasemnogene abeparvovec, were reviewed in a 2019 ICER report. Nusinersen (Spinraza®, Biogen), approved by the Food and Drug Administration (FDA) in 2016, is an antisense oligonucleotide administered via intrathecal injection that targets SMN2 so that it creates more functional SMN protein. Onasemnogene abeparvovec (Zolgensma®, Novartis), approved by the FDA in 2019, is a gene therapy that uses an adeno-associated virus vector to deliver a functional copy of the SMN1 gene.

Risdiplam (Evrysdi®, Genentech), approved by the FDA in 2020, is a splicing modifier that, like nusinersen, targets SMN2 to increase the production of SMN protein. Unlike nusinersen, it is an oral medication taken once daily.

Despite improvements for patients with SMA with the above treatments, there are many individuals with SMA who have significant muscle weakness. Apitegromab (Scholar Rock) is a selective inhibitor of a myostatin precursor. Myostatin inhibits muscle growth and strength; inhibiting myostatin may increase muscle size and strength. Apitegromab is being studied in patients with Type 2 and Type 3 SMA and is given by IV infusion every four weeks.

Among patients ages 2 to 12 years old with Type 2 or 3 SMA already receiving treatment with risdiplam or nusinersen, the added benefit of apitegromab was small: a gain of 0.6 points on the Hammersmith Functional Motor Scale-Expanded (HFMSE) (from 25.5 to 26.1) after one year, compared with a drop of 1.2 points in patients who received placebo (p=0.019). This difference was less than the Minimal Clinically Important Difference (MCID) of three points, but more patients in the apitegromab group had an increase of at least three points at one year (30.4% versus 12.5%, p=0.016). Extended follow-up of patients participating in the Phase II trial suggests that the benefits remain steady through four years of follow-up. There were almost twice as many serious adverse events in patients treated with apitegromab (19.8% versus 10.0%). These were primarily pneumonia (6.6%) and dehydration (2.8%), neither of which occurred among patients who received the placebo. The net health benefit is based on one study and there were more serious adverse events in the apitegromab arm, so the level of certainty around net health benefit is modest at best. For this population, we judge

Clinical Analyses

that treatment with apitegromab likely provides comparable or incremental benefits compared with no additional therapy, but that there is some possibility of substantial benefit with long-term use as well as some possibility of net harm **("promising but inconclusive"; P/I)**. There are insufficient data to estimate the net health benefits of apitegromab in other populations **(I)**.

There is one unpublished, single-arm study of nusinersen in 29 patients with suboptimal response to onasemnogene abeparvovec. The addition of nusinersen was associated with an increase of about five points on the Hammersmith Infant Neurological Examination – Section 2 (HINE-2) score at six months and seven points at 10 months. No new harms were identified, but repeated intrathecal procedures are burdensome and have rare but serious potential adverse events. Given the substantial uncertainty, we judge that there is moderate certainty of comparable to substantial net benefit, with a small, but possible net harm from repeated intrathecal injections compared with no additional therapy **(P/I)**.

The JEWELFISH trial is an open-label study of risdiplam in patients previously treated with other spinal muscular atrophy therapies. Among the 14 patients who had previously received onasemnogene abeparvovec, nine showed a 4.7 point increase in the HFSME at one year and a 7.1 increase at two years. In a case series of 20 children treated with risdiplam, there were some improvements in swallowing and breathing function, but no summary data were reported. The safety profile was consistent with risdiplam's known adverse events (e.g., rash, constipation). The gains are potentially substantial and there do not appear to be important harms, but there is substantial uncertainty about the magnitude of the net benefits. We judge that there is moderate certainty of a comparable, small, or substantial net health benefit compared with no additional therapy **("comparable or better"; C++).**

There are no head-to-head trials comparing risdiplam, nusinersen, and onasemnogene abeparvovec to each other as first-line therapy in patients with SMA of any type, SMN2 copy number, or age. We qualitatively assessed the available clinical evidence of presymptomatic treatment with these three therapies and found all had strong evidence of benefits including increased survival, avoidance of permanent ventilation, and achievement of motor milestones. Given the lack of comparative data, we conclude that there is insufficient data to estimate the net health benefits of risdiplam, nusinersen, and onasemnogene abeparvovec compared to one another in patients with SMA of any type or age **(I)**.

Economic Analyses

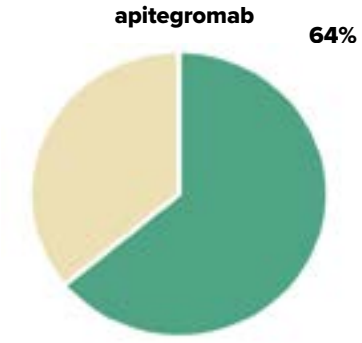
LONG-TERM COST EFFECTIVENESS

At a placeholder price of $350,000 per year, adding apitegromab to standard of care (nusinersen and risdiplam), resulted in higher incremental costs ($5.7 million) and gains of approximately 1.9 years of life and 2.0 evLYs (equal value life years) from health care system perspective, resulting in incremental cost-effectiveness ratios of more than $2.8 million per evLY gained. From the modified societal perspective—which includes family utilities—apitegromab provided a slightly higher gain of 3.30 evLYs, but the ICER remained high at $1.7 million per evLY gained. At the placeholder price, the incremental cost-effectiveness ratios remained above traditional willingness-to-pay thresholds in all sensitivity and scenario analyses, including a co-base case scenario using a modified societal perspective. After excluding non-intervention healthcare costs and standard of care costs so as to achieve positive threshold prices, the Health Benefit Price Benchmark (HBPB) for apitegromab is $4,600 to $30,200 annually.

At the placeholder price of $350,000, an estimated 64% of eligible patients could receive therapy over five years without exceeding ICER's budget impact threshold; all patients could be treated at the modified societal perspective $150,000 threshold price of $30,200. Given these numbers, and in the absence of a known price from the manufacturer, ICER is not issuing an access and affordability alert for apitegromab at this time.

POTENTIAL BUDGET IMPACT

Assuming a 20% uptake of apitegromab each year, 64% of eligible patients could be treated over five years at the placeholder price of $350,000 before reaching the ICER potential budget impact threshold of $880,000,000. All eligible patients could be treated at the $50,000, $100,000, and $150,000 per evLY gained threshold prices ($6,600, $13,800, and $21,100 from the health care system perspective and $9,600, $19,900, and $30,200 from the modified societal perspective) before reaching the ICER potential budget impact threshold.



Percent of eligible patients with spinal muscular atrophy that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

ICER's Virtual Public Meeting: Voting Results on Clinical Evidence

ICER assessed, and the independent appraisal committee voted on the evidence for effectiveness and value of therapies for spinal muscular atrophy:

- The majority of panelists (8-5) found that current evidence is **not adequate** to demonstrate a net health benefit of apitegromab in addition to standard of care (risdiplam or nusinersen) compared to the standard of care alone.
- The majority of panelists (12-1) found that current evidence is **not adequate** to demonstrate a net health benefit of using risdiplam after patients are treated with onasemnogene abeparvovec when compared to no additional treatment after receiving onasemnogene abeparvovec.
- The majority of panelists (12-1) found that current evidence is **not adequate** to demonstrate a net health benefit of using nusinersen after patients are treated with onasemnogene abeparvovec when compared to no additional treatment after receiving onasemnogene abeparvovec.
- The panelists unanimously (13-0) found that current evidence is **not adequate** to distinguish the net health benefit among nusinersen, onasemnogene abeparvovec, and risdiplam as first line therapy.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and weighed special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.

ICER's Virtual Public Meeting: Voting Results on Long-Term Value for Money

Apitegromab has not yet been approved by the FDA for SMA, and the manufacturer has not yet announced a US price for the therapy if approved. ICER did not perform a comparative value analysis for the disease-modifying therapies.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for the treatment, the panel did not take a vote on the treatment's long-term value for money.

ICER has calculated a health benefit price benchmark (HBPB) to be between **$4,600 and $30,200 per year.**

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.