Genentech
A Member of the Roche Group

June 20, 2025

Dear ICER Review Panel,

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report, 'Therapies for the Treatment of Spinal Muscular Atrophy' [1]. As highlighted in the report, Evrysdi® (risdiplam) and other disease-modifying therapies (DMTs), have fundamentally transformed the lives of individuals and families affected by spinal muscular atrophy (SMA) over the past decade. These innovative treatments have improved life expectancy, prevented ventilator dependence, facilitated the achievement of key motor milestones, and enabled individuals with later-onset SMA to preserve crucial motor functions. We recognize, as echoed in the Draft Evidence Report's Patient Community Insights, that a critical unmet need persists for therapies that enhance strength and the ability to live more independently. We are confident in the value Evrysdi provides to the SMA community and remain committed to ensuring that those living with SMA have access to the therapies, including innovative treatments, that best meet their unique needs.

SMA is a rare, progressive, and degenerative neuromuscular disease. Without treatment, symptoms can include severe disability and early mortality. However, with the introduction of Evrysdi and other DMTs, the progression of SMA has changed significantly from this natural history. These new disease phenotypes now transcend the historical SMA subtypes, leading to an evolution in the remaining needs of individuals living with SMA. To meet the ongoing unmet needs of SMA patients, robust and appropriate value assessment approaches are crucial for healthcare decision-making. Our comments highlight the limitations of the economic model, the inherent challenges of emerging data in rare diseases, and the significant qualitative and societal benefits that extend beyond current quantitative measures.

ICER's long term cost-effectiveness model underestimates the true value of myostatin inhibitors due to an oversimplified representation of the disease. While we recognize that ICER used the data available for the myostatin inhibitor treatment outcomes, anchoring to a simplified state-transition framework does not fully capture the nature of muscle preservation or weakening in individuals living with SMA. The impact of SMA extends far beyond motor function, encompassing pulmonary, swallowing, and nutritional challenges, all of which impose immense burdens on patients and their caregivers. The current model's health states and health utilities fail to value small, but clinically meaningful, improvements in motor milestones, or the prevention of further deterioration that are highly valued by patients and their families. As stated

in the Draft Evidence Report, patients and caregivers "desire treatments that improve strength and functional ability while also valuing treatments that stabilize the disease. Even small improvements, such as a gain in finger strength, can have a transformative impact, enabling activities like driving a power wheelchair." The transformative impact of seemingly minor functional gains and the maintenance of certain motor functions, which are profoundly valued by patients, are simply not captured by the current health economic model or typical clinical scales.

Rare disease research faces unique challenges, including small patient populations, limited trial durations, and a scarcity of long-term data. Compounded by high heterogeneity in SMA, these data limitations force value assessments to make assumptions and extrapolations that fail to capture the multifaceted benefits of myostatin inhibitor therapies. As seen in the Draft Evidence Report's scenario analyses, several key uncertainties, such as long-term progression impact and caregiver utilities, greatly impacted the results. The ICER results, spanning $32.7 million to $1.3 million per QALY in the base case and scenario analyses, show the conclusions are highly sensitive and underscore the considerable uncertainty caused by critical data gaps. Therefore, conducting a cost-effectiveness analysis is premature and consequently undervalues the benefit of myostatin inhibitors in SMA.

It is important to recognize the value of myostatin inhibitors projected by this assessment today does not reflect the full value patients and their families will ultimately realize. The current analysis falls short in capturing the complete impact of SMA, including qualitative patient improvements, ripple effects on family, and the full spectrum of treatment outcomes. As noted in the Draft Evidence Report, patients have a continued need for improvements in strength and function, even if these are not fully reflected on clinical trial scales due to the inherent limitations that can exist in such scales. Outcomes like reduced caregiver burden, increased employment for individuals living with SMA, and greater independence in daily living can vary more significantly than what the value framework for this cost-effectiveness analysis captures. These limitations in the cost-effectiveness analysis risk flawed justifications potentially leading to arbitrary access restrictions. This could deny patients access to myostatin inhibitor therapies that offer substantial benefits extending beyond the traditional framework.

Genentech remains committed to collaborating with ICER and all stakeholders to refine our understanding of the long-term value these therapies bring to SMA patients and society, always prioritizing insights directly from patients and caregivers. We urge ICER to reconsider the appropriateness of applying a traditional cost-effectiveness framework to rare diseases like SMA, especially given the lack of available data. With the limitations of the economic model, the final report should highlight patient and caregiver insights more prominently, recognize the emerging nature of the data, and consider the qualitative and societal benefits that extend beyond current utilized measures. Above all, after making transformative strides in SMA treatment over the past

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decade, it is paramount that the final assessment does not become a barrier to patient access and future innovation for essential SMA medicines.

Sincerely,

Elaine Yu

Head of Evidence for Access, Genentech

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Scholar Rock
301 Binney Street, 3rd Floor
Cambridge, MA 02142

(857) 259-3860
scholarrock.com

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Institute for Clinical and Economic Review (ICER)
One State Street, Suite 1050
Boston, MA 02109 USA

Re: Public Comment on ICER Draft Evidence Report: Therapies for Spinal Muscular Atrophy (Posted May 27, 2025)

Dear ICER Review Panel:

Please find below Scholar Rock's (SRRK) comments on ICER's Draft Evidence Report[1] evaluating apitegromab for the treatment of spinal muscular atrophy (SMA). We are concerned that the Draft Report contains serious methodological flaws, unsupported assumptions, and evidence interpretation issues that grossly misrepresent the value of apitegromab.

As ICER acknowledges, the report's model design is simplistic. It is apparent that several model assumptions lack the level of rigor needed to draw meaningful conclusions about the value of apitegromab, a potential innovative treatment that the SMA community has been eagerly awaiting since the 2020 Phase 2 TOPAZ study, due to substantial remaining unmet need for new treatments that address progressive motor function decline. It is imperative that the limitations of ICER's evaluation are appropriately acknowledged when the Final Report is released.

1. SMA Results in Progressive Muscle Degeneration, Leading to Loss of Motor Function and Diminished Independence

As noted in our previous public comments to ICER during the scoping process, SMA is a life-altering neuromuscular disease, which impacts both motor neurons and muscles. While current survival motor neuron (SMN)-targeted treatments address the motor neuron component of SMA, these treatments do not directly address the muscle component of the disease.[2,3,4] As ICER has appropriately acknowledged in the Draft Report, people living with SMA (PLwSMA) continue to experience persistent motor function loss despite ongoing SMN-targeted treatments. **In fact, 89% of adults with SMA report gaining muscle function as their greatest unmet need.**[5] Loss of motor function impairs the ability of PLwSMA to perform critical activities of daily living (e.g., feeding oneself, using the bathroom independently, or being able to make transfers successfully), leading to a loss of independence and imposing significant clinical and psychosocial burden on themselves and their caregivers. Given the high remaining burden of SMA and persistent unmet need voiced by the SMA community, there is a critical need for new treatments like apitegromab that have the potential to reverse or halt motor function decline.

2. ICER's Interpretation and Conclusions About the Evidence is Flawed and Inconsistent with Prior Evaluations of SMA and Other Rare Diseases

ICER's conclusion that apitegromab has limited clinical benefit due, in part, to the "small" SAPPHIRE study size is inconsistent with ICER's prior SMA evaluation.[6] SAPPHIRE (N=188) represents the largest successful, registrational, randomized-controlled study in SMA patients to

date.[7] The size and design of the SAPPHIRE trial support a reasonable interpretation of statistically and clinically meaningful outcomes—particularly given the historical precedent of similar or smaller trials that formed the evidentiary basis for ICER assessments and regulatory approvals in rare diseases like SMA.

Efficacy outcomes in two of the apitegromab studies—SAPPHIRE and TOPAZ—are clinically meaningful and directly address the SMA community's greatest voiced unmet needs. In SAPPHIRE, apitegromab has demonstrated the potential to reverse or halt motor function decline. The odds of achieving a ≥3-point improvement in HFMSE vs. not achieving a ≥3-point improvement is three times more likely for apitegromab-treated patients than SMN-targeted treatment alone (nominal p=0.0256). Currently available long-term data from TOPAZ demonstrated that motor function benefit by HFMSE was sustained for over four years in apitegromab-treated patients, and we continue to collect data on these patients in ONYX, our long-term extension study.

In addition, ICER's assessment that there is "some possibility of net harm" with apitegromab is unreasonable given ICER's own acknowledgement that "it is difficult to be certain whether these serious adverse events were caused by treatment with apitegromab and no patients dropped out of the study due to AEs".[1] No serious adverse events (SAEs), including pneumonia, in SAPPHIRE were attributed to apitegromab. No study-drug discontinuations were due to adverse events (AEs).[7] **An overwhelming 98% of patients from the SAPPHIRE trial elected to continue in ONYX, and 85% of TOPAZ participants enrolled and remain in ONYX on apitegromab treatment for over five years of exposure**. Across these trials, Scholar Rock has collected patient safety data for apitegromab that represents over 600 patient years of data showing that apitegromab was well tolerated.

Furthermore, pneumonia was classified under the broad category of respiratory infections. Respiratory tract infections are a common occurrence in PLwSMA with disease-related weakening of respiratory muscles regardless of treatment. Most participants in SAPPHIRE who were treated with apitegromab already had compromised respiratory function, which increased the risk of respiratory infections.

Rates of pneumonia in SAPPHIRE are generally consistent with the underlying disease. Similar clinical studies in SMA, such as CHERISH (nusinersen)[8] and SUNFISH Part 2 (risdiplam)[9], show similar numerical differences in rates of pneumonia between the treatment and control arms of pneumonia SAEs. The CHERISH study had a 2% incidence in the nusinersen group, and 14% in the control group. The SUNFISH study showed an incidence of 7.5% in the risdiplam group and 1.7% in the placebo group.[8,9] Despite some variability between the two studies, these results are generally comparable with the SAPPHIRE study.

In the Draft Report, ICER failed to consider the total published safety data for apitegromab, which indicate that the rates of pneumonia are consistent with other pivotal trials for SMN-targeted treatments[3,4,6] and that these events were not attributed to apitegromab by SAPPHIRE investigators. [10,11] ICER's failure to apply consistent evidentiary standards undercuts the credibility of ICER's conclusions in the Draft Report.

3. ICER's Simplified Model Structure Demonstrates a Lack of Understanding of the Unmet Needs in SMA

ICER's simplistic sitting/non-sitting/death model structure is clinically unrealistic and makes it impossible to capture the full value of apitegromab in PLwSMA. As ICER notes, the transition of worsening from sitting to non-sitting applies to zero percent of patients in the model. The WHO milestones represent static developmental categories that do not capture the value of maintaining function or the nuanced, incremental motor function improvements highly valued by patients, such as improved trunk control, head control, upper limb strength, and transfer ability—each of which can transform independence, caregiver burden, and quality of life (QoL).[12-14] By failing to recognize that both motor function improvement and stabilization are valuable to PLwSMA, ICER minimizes the significant unmet needs clearly stated by the SMA community,[5] as well as the potential value a new treatment like apitegromab brings to those living with this progressive and debilitating disease.

Specifically, ICER's model:

- Restricts health states to WHO milestones (e.g., "sitting" and "non-sitting"), creating an overly simplistic structure that eliminates any opportunity to adequately capture the value of improvements in motor function for non-ambulatory patients and minimizes the daily experience of PLwSMA and many life-essential motor functions reflected in HFMSE.
- Does not adequately reflect the natural history of SMA or expected motor function decline, despite published evidence.[15-17]
- Assumes no decline in motor function over time (in the base case) among PLwSMA taking SMN-targeted treatments alone, yet acknowledges that PLwSMA continue to experience persistent motor function loss despite ongoing SMN-targeted treatments. This is with compelling evidence from open-label extension studies showing decline with SMN-targeted treatments alone and SAPPHIRE control data confirming this progressive decline. [15-19]
- Fails to incorporate data from the published TOPAZ trial regarding the durability of apitegromab's motor function benefit as a dual modality approach,[11] despite acknowledging in the Draft Report that "Extended follow-up of patients participating in the Phase II trial suggests that the benefits remain steady through four years of follow-up."
- Limits the durability of benefit to patients achieving only a ≥3-point gain in HFMSE, assuming those with lesser gains cannot sustain improvements. There are no published data to support this assumption and in fact this assumption minimizes the value that PLwSMA voiced regarding the importance of maintaining or improving motor function.[5]
- Attributes minimal quality-adjusted life year (QALY) gains (0.01) for functional improvements in the base case. Apitegromab has demonstrated compelling outcomes needed by the SMA community in a large trial of a treated population—including the potential to reverse or halt motor function decline, complemented by long-term safety and efficacy data from TOPAZ. In addition, ICER has ignored real-world benefits in daily functioning, caregiver burden reduction, and health-related QoL in the base case. This minimal QALY gain also deviates from the model assumptions and inputs used during ICER's 2019 evaluation of other SMA treatments.[6] PLwSMA experience a spectrum of motor function gains (e.g., improved arm/hand function, transfers, and endurance) that

profoundly affect daily living, independence, and caregiver burden[12,13] but are not shown in ICER's model structure. ICER's 2019 SMA evaluation acknowledged these functional dimensions by assigning incremental utilities for milestone gains. By applying a dramatically lower utility gain (0.01) than previously used in its 2019 SMA model (0.05 to 0.10), ICER creates an internal inconsistency that materially distorts cost-effectiveness estimates.

4. ICER's Model Uses Outdated and Unsupported Clinical Thresholds

While apitegromab has compelling data at a ≥3-point HFMSE threshold in SMA, the model should consider maintenance or any improvement of motor function as meaningful to patients. ICER assumes that only a ≥3-point increase on the HFMSE scale constitutes clinically meaningful benefit, referencing a 2018 study that no longer reflects contemporary clinical understanding and was specific to untreated patients. **In fact, the most recent publication by Coratti and colleagues reported that a 1.5-point improvement in HFMSE total score was clinically meaningful for Type 2 and 3 SMA[20] untreated patients and direct input from the SMA patient and clinical communities emphasize that seemingly small functional improvements can have transformative impacts on independence and QoL.** Furthermore, additional research needs to be conducted to determine the incremental clinically meaningful benefit for patients treated with an SMN-targeted treatment. In the interim, the continued use of this outdated threshold biases the analysis against capturing the value of meaningful patient outcomes among patients who have already achieved some functional gains due to SMN-targeted treatments and are seeking additional gains or stabilization through a muscle-targeted treatment like apitegromab.

5. ICER's Model Includes Disproportionate Harm Assumptions

ICER's Draft Evidence Report assumes a disproportionately high value of harm associated with pneumonia for apitegromab. Specifically, the report inflates harm risks by:

- Attributing the risk of pneumonia* to apitegromab, despite no cases being causally related to apitegromab.[7,10] Moreover, ICER assumes that all pneumonia events last one month, which is for the worst/most severe cases, without supporting data from the SAPPHIRE trial to validate this assumption.
    - In the SAPPHIRE study, all SAEs of pneumonia resolved with continued treatment with apitegromab and without patient discontinuation of the study.
    - When looking at all lower respiratory tract infections (includes pneumonia) in SAPPHIRE, the placebo arm had a numerically higher percentage of participants than the apitegromab arm; this reflects the balance between the arms for this type of infection.[7,10]
- Assuming pneumonia has a disutility nearly 10-fold greater than improvements in motor function undervalues the importance of gains in motor function voiced by the SMA community. As a result, ICER introduces a disproportionate penalty for pneumonia and minimizes the QoL impact of motor function stabilization or gain, skewing the incremental cost-effectiveness ratios against apitegromab. This structural imbalance

artificially amplifies harm assumptions relative to benefit assumptions, creating systematic downward bias in ICER's economic conclusions.

Conclusion

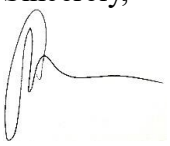
In summary, ICER's Draft Evidence Report raises concerns on three core dimensions:

1. **Evidence inconsistency:** ICER applies inconsistent standards and application of evidence to apitegromab compared to the prior SMA evaluation.
2. **Model invalidity:** ICER's oversimplified health state structure does not capture clinically meaningful gains in motor function for apitegromab reported in the SAPPHIRE trial.
3. **Unsupported assumptions:** ICER's model applies arbitrary utility values, AE penalties, and outdated clinical thresholds that render the cost-effectiveness estimates unreliable, collectively undervaluing apitegromab's clinical and economic benefit.

While disease-modifying treatments slow progression of SMA, they do not halt neuronal loss or motor function decline in many patients. Apitegromab's potential to change the standard of care in SMA and improve or sustain muscle function translates into major QoL gains over time, yet these are not reflected in the model's structure, utility projections or cost offsets. As a result, ICER's assessment leads to model outputs that are not robust, thereby limiting the credibility and reproducibility of results and raising questions about the validity of ICER's conclusions.

ICER's evaluation risks misinforming policy decisions by undervaluing a treatment with potential to address substantial unmet needs for, and identified by, patients and caregivers affected by SMA. We urge ICER to adopt a more clinically valid, evidence-aligned, and methodologically consistent approach that fully reflects the real-world value that apitegromab provides to PLwSMA, their caregivers, and the healthcare system, and to ensure analytic integrity that supports credible policy decisions.

Sincerely,



Allen Su
Vice President, Value & Access
Scholar Rock

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Public Comment on ICER Draft Evidence Report: "Therapies for Spinal Muscular Atrophy: Effectiveness and Value" (published on 27-May-2025)

23-Jun-2025

5q-Spinal Muscular Atrophy (SMA) is a rare, genetic, and progressive neuromuscular disorder that presents a wide spectrum of severity across children and adults. If untreated, SMA leads to muscle weakness, loss of motor function, and in severe cases, premature death. The advent of therapies—nusinersen, risdiplam, and onasemnogene abeparvovec—able to increase the levels of the lacking survival motor neuron (SMN) protein has tremendously improved outcomes for many people living with SMA, including those with severe symptoms and of older age.

Yet, as highlighted in the Draft Evidence Report and widely recognised by patient organisations, substantial challenges and unmet needs remain for individuals living with SMA and their caregivers.

While early treatment in asymptomatic or mildly symptomatic individuals, enabled by genetic diagnosis and newborn screening, is the most effective way to halt disease progression, a large portion of the current SMA population—particularly teenagers and adults—has already sustained significant and often irreversible damage.

Clinical symptoms and treatment response among the population is highly variable and depends on several factors, including age at treatment initiation and symptom severity at onset. For some individuals, residual muscle weakness, fatigue, respiratory and skeletal complications, and systemic effects persist under treatment. In fact, beyond the decline in motor function primarily caused by motor neuron degeneration, neuromuscular junction impairment and muscle weakness, people with SMA may experience several other symptoms, such as respiratory issues, skeletal deformities, feeding and swallowing difficulties, fatigue, joint contractures, and metabolic disorders. These manifestations are not always fully addressed by existing therapies.

Also, the disease progression within the SMA population is dynamic: an individual's response to treatment can change over time, and those who are currently stable may still experience gradual deterioration at some point, potentially followed by phases of stabilisation. None of the current therapies are curative, and no one therapy has consistently proven to be superior to others.

There is also insufficient understanding of how effectively current treatments reach all tissues, and whether the level of restored SMN is adequate for each tissue types and for each individual living with SMA, across all phases of life.

These realities underscore the need for next-generation treatments that extend beyond and might be combined to those that target SMN production alone.

In this context, apitegromab represents a potentially meaningful advancement. As a selective inhibitor of a myostatin precursor, apitegromab aims to increase muscle strength and size, potentially enhancing physical function in individuals already receiving SMN-targeted treatments.

The Draft Evidence Report has analysed the clinical data and rated apitegromab as "promising but inconclusive" (P/I) for the population ages two to 12 years old with Type 2 and Type 3 SMA. This rating reflects that "the net health benefit is based on one small, unpublished study, and that there were more serious adverse events in the apitegromab arm", and hence the authors evaluated "the level of certainty around net health benefit is modest at best".

While current evidence remains preliminary and peer-reviewed published data from the SAPPHIRE trial are pending, the signals of benefit are promising, as acknowledged in the Draft Report. Patients receiving apitegromab in combination with nusinersen or risdiplam showed improved outcomes on the Hammersmith Functional Motor Scale-Expanded (HFMSE), with more individuals achieving clinically meaningful gains compared to placebo. Importantly, follow-up data indicate that benefits may persist over multiple years. While these gains may appear modest in traditional clinical metrics (as the "Minimal Clinically Important Difference" of three points), real-world relevance must not be underestimated. In fact, current clinical outcome measures are often inadequate to capture the real-world experiences of people living with SMA, resulting in gaps in understanding the true impact of treatment. As the Draft Evidence Report notes, for individuals living with SMA, even small improvements—such as slight increases in strength or endurance—can profoundly impact daily function and independence. Moreover, stabilization of disease progression is itself a highly valued outcome. According to SMA Europe's EUPESMA 2019 survey, 96.5% of patients view stability as a meaningful therapeutic outcome (Gusset et al., 2021). In fact, stability helps manage other symptoms as well, as routine medical care is less frequently interrupted by hospital visits. SMA Europe strongly recognizes the importance of Patient Experience Data (PED) and consistently gathers it through both quantitative (such as the EUPESMA survey series) and qualitative methods (collected via real-life stories, e.g. OdySMA | Real-life-stories), using a rigorous scientific method.

Despite a higher rate of serious adverse events—particularly pneumonia and dehydration, which occurred only in the apitegromab group—none of these events led to treatment discontinuation. This aligns with existing experience in SMA, where individuals have shown a willingness to accept risks associated with treatment, if there is hope for improved quality of life or disease stabilisation. All currently available treatments carry some level of risk, so a comparable safety profile would generally be considered acceptable. However, potential side effects must be clearly communicated, and the overall risk–benefit profile should be transparent and benchmarked against existing therapies.

The Draft Evidence Report also states that "there are insufficient data to estimate the net health benefits of apitegromab in other populations" (beyond children aged two to 12 years with Type 2 and Type 3 SMA, enrolled in the SAPPHIRE study). In this context, it is important to underscore that SMA exists along a broad clinical spectrum. The traditional classification into "types" often fails to capture the real lived experiences of individuals. This limitation has become increasingly evident with the advent of disease-modifying therapies—particularly when initiated early through newborn screening—which have significantly altered the natural course of the disease. As a result, the conventional classification system is no longer adequate for describing the lived condition or long-term prognosis of individuals with SMA and can contribute to inequities in treatment access.

In conclusion, while more robust and long-term data on apitegromab are needed, early findings suggest it holds meaningful promise. Given the progressive nature of SMA and the limitations of existing therapies, additional treatments that can be safely combined with current standards of care may offer a critical step toward a more holistic and personalised approach, one that addresses also broader functional improvements and quality of life for individuals living with SMA.