Therapies for Spinal Muscular Atrophy
Response to Public Comments on Draft Evidence Report

JULY 17, 2025

Table of Contents

#	Comment	Response/Integration
Manufacturers		
Genentech		
1.	**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.	We acknowledge the use of a simple model structure to model myostatin inhibitors. We note that this model is similar to models used in the previous ICER report as well as in previous HTA submissions. Unfortunately, there are limited data available in the public domain or shared with ICER through its data sharing process related to motor milestone improvements, which necessitated the use of the simplified structure. However, the model does reflect the treatment effect observed in the available clinical trials and captures utility gains related to improvements in the validated and commonly used HFMSE score. The utility gains incorporated in the model are there to capture incremental functional gains like the ones you listed, that are not necessarily gains in milestones. Finally, we have revised our analysis to incorporate disease progression in the base case to capture a more complete picture of disease, and additional utility gains for the proportion of patients who experience a gain in motor milestone based on mean WHO milestone changes reported in SAPPHIRE.
2.	**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	We agree there is substantial uncertainty in the results of the model, however, this does not necessarily represent an underestimate of the value. It may overestimate the value—that is the nature of uncertainty. These analyses are performed to inform current decisions based on the best available data. While we acknowledge the inherent challenges in rare disease research, health technology assessment must still proceed to guide coverage and access decisions for patients who need

	uncertainty caused by critical data gaps. Therefore, conducting a cost-effectiveness analysis is premature and consequently undervalues the benefit of myostatin inhibitors in SMA.	these therapies today. The alternative of indefinitely delaying assessment until "perfect" data become available would deny patients access to potentially beneficial treatments. The uncertainty you highlight underscores why these results should be interpreted with appropriate caution rather than dismissed entirely. Specific suggestions around data sources or model structural changes that could reduce uncertainty are likely to provide more actionable input than general statements of concern about uncertainty.
3.	**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.	We agree that there is tremendous unmet need that remains for patients living with SMA and their caregivers. The value framework that is being used is able to capture reduced caregiver burden, increased employment, and greater independence in daily living. To ensure comprehensive capture of these broader impacts, we revised our report to include a modified societal perspective as a co-base case that incorporates caregiver utilities and bereavement disutilities. However, the product under review has not demonstrated an impact on these outcomes either directly or indirectly in their clinical trials or elsewhere. Further, the results of cost-effectiveness analyses are only one input into the deliberative process involved in coverage and reimbursement decisions.
Scholar Rock		
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	We agree with this characterization of SMA as a progressive disease that continues to impose significant burden despite current treatments. There is a critical need for new treatments that demonstrate robust evidence of reversing or slowing functional decline.

	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.	The assessment of limited clinical benefit has nothing to do with the size of the trial. The assessment of limited net clinical benefit comes from the gain at 1 year of 0.6 points on the HFMSE. For comparison, when nusinersen was added, there was a 7 point gain at 10 months. In addition, there are concerns about serious adverse events with apitegromab (19.8% versus 10.0% with placebo). We have removed "small" from the text, but still judge that data from one unpublished study of 156 patient for the primary outcome (not 188) at one year is consistent with moderate certainty in the net benefit at best. Some would consider this to be low certainty evidence.
3	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	We disagree. We feel that a 2-fold difference in serious adverse events with a 10% absolute difference is potentially concerning. This could be a chance finding, but it is concerning and adds

	out of the study due to AEs". 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.	uncertainty to the magnitude of the net clinical benefit.
4.	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 indicates 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.	As noted above, we find the differences in SAEs to be concerning. As you note, pneumonia is an illness related to weak respiratory muscles. A priori, we expected that apitegromab would improve respiratory muscle function and thus reduce the incidence of pneumonia. The opposite finding in a randomized comparison is surprising and concerning. Uncontrolled comparisons from different populations with different interventions do not alleviate the concern raised by these results of this randomized trial. Results from comparisons in randomized trials represent the highest evidentiary standard.
5.	**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,	We acknowledge the use of a simple model structure. We note that this model is similar to models used in the previous ICER report as well as in previous HTA submissions. Unfortunately, there are limited data available in the public domain and no motor milestone data was shared with ICER through our data sharing process despite our data request, which

	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.	necessitated the use of the simplified structure. We recognize the importance of motor function improvement and stabilization to patients, as we clearly highlighted in our patient community insight section where we noted that 89% of adults with SMA reported that gaining muscle strength was their greatest unmet need. Although the transition of worsening was not applied in the base case in our draft report, it was explored in scenario analyses. Additionally, we have revised the base case to include disease progression to capture a more complete picture of disease in our evidence report. Incremental utility gains were applied to patients to capture the incremental motor function improvements listed by Scholar Rock, despite patients not transitioning to higher milestones. Both motor function improvements and stabilization were explored in our draft report based on the current available evidence.
6.	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	**Regarding our model structure:** Changes in HFMSE that don't equate to milestone changes are incorporated through incremental utilities within states. Despite the simple model structure, the model does capture current evidence on clinical benefit. We requested data on patient WHO motor milestone distributions but did not receive any through our data sharing process, which necessitated the simplistic structure. It would be more helpful if Scholar Rock provided specific data to allow us to model a more intricate structure and help reduce the uncertainty. **Regarding disease progression:** Our revised base case now incorporates disease progression to provide a more complete picture of the disease. Data on decline is limited for disease-modifying standard of care treatments, and even more limited with add-on apitegromab, creating substantial uncertainty that

	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.	requires modeling assumptions. This uncertainty is why we initially explored progression in scenario analyses. In our updated base case, apitegromab patients do not progress during the first 4 years of treatment, with different periods of no-progression explored in scenario analyses. **Regarding durability assumptions and quality-adjusted life year gains:** We did not assume patients with lesser gains cannot sustain improvements. Rather, our utility mapping was constrained by the limited available evidence linking HFMSE changes to quality-of-life benefits. The only published reference we identified that mapped changes in motor function scores to utility changes showed no utility changes in minor improvements of < 3 points. Our model does not ignore real-world benefits in daily functioning – these are captured through the incremental utilities as described above. The value framework is able to capture a reduced caregiver burden, increased employment and greater independence in daily living when evidence supports these outcomes. However, apitegromab has not demonstrated direct nor indirect impact on these outcomes in clinical trials or elsewhere. **Regarding utility comparisons to 2019:** The utility gains differ from our 2019 SMA model because they are linked to different magnitudes of clinical benefit. For reference, apitegromab showed a gain of 0.6 points in HFMSE at 1 year, while nusinersen showed a 7-point gain at 10 months.
7.	**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	The ≥3-point threshold is the analysis highlighted by Scholar Rock in their topline press release and has been an accepted minimal clinically important difference (MCID) for the HFSME scale in this patient population. The utility study we referenced did not find a difference in

	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 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.	utilities for lower amounts of change, which may reflect some changes in HFMSE are more clinically meaningful than others. We want to highlight that we requested data on HFMSE changes and milestone changes from Scholar Rock to allow for alternative benefit estimations, but we did not receive any data through our data sharing process. The 1.5-point threshold referenced by Scholar Rock has not been reported by them in their clinical trial results for apitegromab. If a stabilization threshold (≥0 points on HFMSE) is used, this was met by 50.0% of patients in the placebo group and 62.7% of patients in the apitegromab group—a 12.7% difference that was not statistically significant. This suggests that even using a lower threshold does not demonstrate compelling evidence of clinical benefit.
8.	**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. 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	We disagree with the characterization that pneumonia disutility is "10-fold greater" than motor function improvements. The actual impact of pneumonia in our model was clearly demonstrated through a scenario analysis in our draft report that removed pneumonia completely – this resulted in a reduction in costs of $1,000 over the lifetime and no changes in QALYs. This analysis demonstrated that pneumonia assumptions had essentially no impact on the cost-effectiveness results, directly contradicting the assertion that pneumonia creates "systematic downward bias" in our economic model. While we acknowledge that individual pneumonia events resolved through the trial, economic models must still account for the temporary impact on quality of life during these episodes.

	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.	

#	Comment	Response/Integration
Patient/Patient Groups		
SMA Europe		
1.	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.	Thank you. It appears that you are agreeing with our assessment. The average gain in the treated population (0.6 points on the HFMSE) was much smaller than the gains observed with risdiplam and nusinersen when those therapies were added on to gene therapy. The reported results for apitegromab are unpublished and may change in the final analysis, which adds to the uncertainty. Finally, if we look at stability or improvement in the HFSME over one year, 62.7% of the apitegromab group had stability or better, compared with 50% of placebo group. Again, this represents a meaningful finding for patients, but not a large treatment effect.
2.	**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	We agree that even maintenance of muscle function is important to patients as the natural history appears to be a continued loss of motor neurons over time. However, even if we look at maintenance as an outcome (no decline in the HFSME), the difference in the proportion of patients meeting this outcome between the apitegromab group (62.7%) and the placebo group (50.0%) is modest and is not statistically significant ($p>0.1$).

	(collected via real-life stories, e.g. OdySMA | Real-life-stories), using a rigorous scientific method.	
3.	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.	We agree that most patients will accept these risks even for modest benefits, despite the requirement for an IV infusion every month.
4.	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.	We agree and we look forward to additional data demonstrating clinical benefits in patient population beyond those enrolled in the SAPPHIRE study. We hope that the manufacturer prices the drug in line with its clinical benefits (value based price) so that all patients who would like to use it have access to the therapy.