Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

February 22, 2019

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AveXis		
1.	1. We disagree with ICER's base case model assumption that 1/6 of sitting ZOLGENSMA patients return to the not-sitting state at the end of the short-term model, and with ICER's assumption that these patients "required" Spinraza. This assumption is not grounded in evidence and is inconsistent with those made for Spinraza. We acknowledge scenario analysis #6 reports results assuming no loss of milestones, and removing this assumption lowers the ICER by $17,000 to $230,000 per QALY for ZOLGENSMA vs. BSC. However, we request the modeling team remove this loss of sitting milestones assumption for ZOLGENSMA in the base case. We also request the removal of the word "required" when referencing patients who did receive Spinraza after ZOLGENSMA as there is no evidence to support this language. • There is no clinical evidence to support the milestone loss. Importantly, no patients who received the therapeutic dose in the ZOLGENSMA CL-101 24-month study, or the long-term study (maximum follow-up of 30 months) experienced any loss of milestones or worsening disease. • There is no evidence that Spinraza was "required" or beneficial for ZOLGENSMA patients in the trial. It is highly implausible that any ZOLGENSMA-treated patient would receive additional benefits by commencing chronic treatment with Spinraza. • Because there was no evidence of clinical deterioration in the CL-101 trial, it is our contention that the decision to initiate Spinraza post ZOLGENSMA was driven by parental desire, rather than by clinical indication or biological plausibility. It is understandable that parents would have considered additional options, regardless of the lack of scientific evidence to support the plausibility of additional effectiveness (see above). And, while the specific motivations that underlay the decision to initiate use of Spinraza is a private matter between patient's guardians and physician, these motivations should not be used as a foundational assumption that patients were deteriorating or that Spinraza was required.	Clinical expert opinion suggested that both rationales for seeking Spinraza were plausible (i.e. patients seeing benefit on Zolgensma but wanting to achieve additional benefit, and patients losing milestones who want the therapy to prevent further loss). As such, we assumed that half of the patients on Spinraza would lose a milestone. We have amended the text to state "apparently required" Spinraza. We note the new data presented the counterfactual is still unknown.
2.	• ICER's approach to ZOLGENSMA milestone persistence, which was modeled as a decline in the absence of evidence, is contradictory to ICER's approach to Spinraza milestone persistence, which was modeled as consistent despite published data showing a decline in the proportion of sitting patients. Table 4.2 (page 56) of the ICER report states: "In the short-term model for Spinraza, we assumed that the numbers of patients sitting cannot decrease over	We have updated the short-term data on the proportion sitting in Spinraza arm (please see Appendix E2), which does not include the persistence assumption in the short-term model.

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	time." This is explained in Table E2 and page 158: The numbers of patients sitting are monotonically increased with time, except for the last time point where the number of patients sitting is lower than the previous time point. It is not clear if this is due to administrative censoring or patients losing milestones. We assumed that this was due to administrative censoring, and in step three, the number of patients sitting at the last time point was set as equal to those in the previous time period." This assumption's importance can be observed in the one-way sensitivity analysis for Spinraza (Figure 4.4, page 72), Scenarios 7a-c for Spinraza vs BSC (Table 4.21, page 75), and where ICER reports 64% of Spinraza QALYs are from the sitting (Table E12, page 168).	
3.	• The loss of milestones assumption was not mentioned in the original model analysis plan. Based on the report, it is unclear whether clinical, SMA or gene therapy experts were consulted about this assumption, and a discussion with experts or AveXis may have benefitted this assumption. • If the assumption is not removed, for the purposes of balancing the analysis, we request the modeling team conduct a scenario analysis where responders are restored to full health.	The loss of milestones was discussed with a clinical expert. The observed data apparently shows that none of the patients who received Spinraza after Zolgensma achieved full health and thus this scenario analysis has not been conducted.
4.	2. We request the modeling team conduct a new value-based price (VBP) analysis for the threshold prices in Table 4.26 using the "no milestones lost" assumption for ZOLGENSMA.	The value-based price analyses for threshold prices will only be conducted for the base-case model.
5.	3. As discussed in earlier consultations, we recommend ICER's "Report at a Glance" should include all relevant thresholds including the VBP analysis using a willingness-to-pay of $500,000 per QALY. This short version report is more accessible for decision makers than long-form reports, and including this figure would be consistent with ICER's stated objectives for ultra-rare diseases. This request is also supported by a £100K- £300K per QALY threshold for ultra-orphan drugs by NICE.	While our threshold prices extend to the $500,000 per QALY threshold for reviews conducted under ICER's ultra-rare disease framework, our value-based price benchmarks are still the prices that would meet the $100,000 to $150,000 per QALY threshold. We always publish the value-based prices (and not the entire range for threshold prices) in the "Report at a Glance" document.
6.	4. We find the "ZOLGENSMA vs Spinraza" scenario (Pages 77-8, Tables 3, and 4.23-24) misleading. • We recommend this scenario should be removed given the lack of clinical and biologic plausibility for sequential treatment with Spinraza (Point 1), and an unaddressed uncertainty of whether Spinraza would be covered for ZOLGENSMA-treated patients by US insurers. • If this scenario is not removed, we request the scenario be relabeled as "ZOLGENSMA followed by Spinraza vs. Spinraza" for clarity, as this reflects the true comparison. • Further, it would be appropriate for ICER to modify the scenario and report the scenario where ZOLGENSMA	We believe this scenario addresses an important policy consideration and will help inform decision-making, so have not removed it from the revised report. In our description of this scenario, we have explicitly stated that Spinraza is added on to Zolgensma for a percentage of patients in the Zolgensma arm.

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	(monotherapy) is the comparator against the sequential treatment. The current ICER of $202,000 (Table 4.23, page 78) shows the incremental benefit of ZOLGENSMA as a bridging therapy to Spinraza treatment, an indication for which ZOLGENSMA has not been studied, nor follows clinical rationale. ZOLGENSMA as the comparator shows the incremental benefit of adding Spinraza post-ZOLGENSMA. Based on current values in the reports, we have calculated this ICER for ZOLGENSMA followed by Spinraza vs ZOLGENSMA to be $1,415,323/QALY (($5,240,000 - $3,485,000) / (12.57 – 11.33) = $1,755,000 / 1.24). Adding Spinraza to ZOLGENSMA-treated patients would not be clinically justified nor cost-effective. • We also request the modeling team report an additional scenario analysis of "ZOLGENSMA monotherapy (without milestone loss) vs. Spinraza monotherapy" so that the committee, and subsequent audiences, can more fully consider the long-term value for money. • In the event ZOLGENSMA followed by Spinraza vs. Spinraza scenario is not removed, based on recent data from the ZOLGENSMA managed access program (MAP) (16 out of 20 =80% MAP patients received Spinraza prior to ZOLGENSMA), we request ICER to conduct a switch strategy scenario (1 to 3 doses of Spinraza followed by ZOLGENSMA) and report the ICERs for switch strategy vs. BSC and Spinraza monotherapy."	
7.	5. To match current recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine, NICE, and HTA agencies in The Netherlands and Belgium, and given the long-term health benefits provided by ZOLGENSMA, we request the modeling team conduct additional scenario analyses using differential discounting (i.e., 3% for costs and varying utilities from 0% - 3%). Also, as recommended by the Second Panel, we request that the modeling team include discounting as part of the one-way sensitivity analysis for all treatments. There is broad agreement that in cost-effectiveness analysis (CEA), future outcomes should be discounted, and their present values calculated so that cost-effectiveness ratios will be appropriately adjusted for the differential timing of costs and consequences. However, there is disagreement over the appropriate discount rate to use. The Second Panel noted that the appropriate discount rates for costs and health will depend, among other things, on fixed health care budgets, the social objective of maximizing welfare vs health, and social time preferences (which may be different for health vs consumption). The Second Panel recognized the uncertainty around the	We have now included a scenario analysis using a 1.5% discount rate. We have also included undiscounted costs and outcomes for the base-case analysis in the appendix.

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	appropriate discount rates from societal and health care sector perspectives. The Panel noted that "since the goal of the Reference Cases is to promote comparability across studies, we recommend that a 3% interest rate be used for both costs and effectiveness from both the societal and the health care sector perspectives." We recognize this rate was used in the ICER model. However, the Second Panel stated it is always advisable to perform sensitivity analyses for any baseline discount rates used, especially when the costs and benefits are incurred at different times for different interventions. More recently, other have argued, based on theoretical and empirical evidence, that the Second Panel's recommended discount rate of 3% per annum is too high, resulting in systematic bias against health technologies with upfront costs and long-term health effects.	
8.	• We note ICER is preparing its framework for curative therapies and hope ICER will consider the merits of differential discounting in its assessment. As the standard practice in the US is to discount benefits at the same rate as costs, the benefit of potentially curative medicines may be severely misrepresented. In the meantime, given the considerable public attention to ICER reports beyond the field of health economics, it would be beneficial to patients and members of the public for an undiscounted survival benefit to be published, as well as a VBP based on undiscounted benefits. This is demonstrated well by an example from the published draft report. Table E10 (page 167) reports a gain of 32.4 undiscounted life years for the ZOLGENSMA cohort. To test the ICER per QALY, we multiplied the corresponding utility value for each health state (using 0.88 as an average for walking) by the undiscounted LYs (by health state) for ZOLGENSMA to yield the undiscounted QALYs. Our calculations show ZOLGENSMA yields 22.4 undiscounted QALYs; in the base case (3% discounting) ZOLGENSMA yields 11.33 QALYs. Removing discounting nearly doubles the QALYs. Using costs from Table 4.13 (page 70) shows the benefit of differential discounting (3% costs, 0% utilities), as the ICER for ZOLGENSMA vs. BSC lowers to $123,000 / QALY from the base case of $247,000 / QALY.	We are researching and evaluating the merits and disadvantages of differential and variable discounting in models that include curative therapies as part of our "valuing a cure" project. Since that effort is ongoing and is not complete yet, we feel it premature to include differential discounting in this assessment. We have, however, now included a scenario using a discount rate of 1.5% per annum, and included undiscounted outcomes and costs for all interventions assessed. Results of the latter can be found in the appendix of the report.
9.	6. We appreciate HTA bodies outside the US frequently use stopping rules in CEA. We disagree with the base case 24-month stopping rule assumption for Spinraza, as this is not likely to be indicative of US clinical practice. We request that the modeling team report the results from scenario analyses where different Spinraza stopping rules are tested (e.g. 36 months, 48 months). • Insurance guidelines for Spinraza suggest that Spinraza	Given the contradicting suggestions from the different stakeholders regarding this issue, we are keeping the 24 month stopping rule for the patients who do not achieve milestones.

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	can be continued if it helps to improve, maintain, or slow the disease progress. Spinraza is indicated for life-long treatment. Therefore, even if patients do not achieve a milestone (i.e., not sitting to sitting), it is expected that they would continue treatment. Understanding how the stopping rule affects the Spinraza vs. BSC ICER results will be important when assessing long-term value for money.	
10.	7. We request the modeling team remove the "Drug X" pre-symptomatic analysis. We enthusiastically agree that there is promise for treating SMA patients early. However, there is little clinical evidence to support these analyses, thus the "Drug X" analyses are premature and speculative. Also, as the results rely heavily on patient mix, they are not generalizable. The patient mix does not match the ongoing pre-symptomatic study AveXis is conducting which means ICER's results are unlikely to reflect how ZOLGENSMA will be used in practice. Further, it is unclear how SMA patients may be identified pre-symptomatically as not every US state has a compulsory newborn SMA screening program. Therefore, the source and validity of pre-symptomatic prevalence assumptions are unclear.	As SMA screening programs become increasingly prevalent, we anticipate that Zolgensma (and/or other gene therapies) will be used in pre-symptomatic SMA patients. Therefore, we found it necessary to model and understand the implications on the potential value of a therapy in this population if it were priced and had the same efficacy of Zolgensma in the SMA Type 1 population. We acknowledge that the trial for Zolgensma in this patient population is ongoing and there exists no other published evidence on its efficacy in this sub-population. We have thus named the potential therapy "Drug X" and not Zolgensma.
11.	8. We request optimistic versions of scenarios 7a-7c (i.e., assume 10/20/30% of sitting [or not sitting] patients transition to walking [or sitting] at the end of the short-term model) to test uncertainties.	We feel the base case model is already optimistic as we assume that the motor function milestones are sustained until death.
12.	9. We request the modeling team conduct a scenario analysis accounting for a blended Spinraza price: 60% with $127,500 (Table 4.7, page 66) and 40% with the hospital markup ranging from 8% to 60%. In Table 4.7, ICER assumes no hospital markups for Spinraza. However, in calculating the total administration cost for Spinraza, ICER assumes 40% of patients receive Spinraza in inpatient settings (Table 4.8, page 5). If 40% of patients receive Spinraza in inpatient settings, it would be reasonable to account for the hospital markup costs for Spinraza. Our range recommendation is from clinical experts who have advised hospital markups could range between 8%-60% per dose.	The base-case analysis already includes the hospital markups (please see Table 4.7).
13.	10. Intubation in the US is more common. We request ICER conduct a scenario using pooled survival curve of non-invasive and tracheostomy patients (PV to death) with a survival limit (e.g. 22 years).	We do not feel that conducting this scenario analysis is necessary.
14.	11. There are several important considerations for ZOLGENSMA that should be added to Section 5 – Potential Other Benefits and Contextual Considerations. We list these below. • ZOLGENSMA is a one-time, one-hour IV treatment that should eliminate patient and caregiver anxiety,	Thank you for noting these important considerations. They have been added to Section 5.

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	inconvenience, and complexity associated with repeated lumbar punctures needed for Spinraza while improving patient outcomes. • The benefits of ZOLGENSMA extend beyond improved patient survival and quality of life. These children will have the potential to attend school and require substantially reduced levels of care, allowing family to return to work, with subsequent mental health and financial benefits. • Due to its mode of action and its one-time dosing, ZOLGENSMA may reduce the existing burden on caregivers by helping to eliminate the need to continuously navigate complex and often-changing health insurance coverage policies.	
Biogen		
1.	(1) The rationale for ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in strength of evidence. ICER should strongly reconsider these ratings. • Page 51: The rationale for assigning investigational AVXS-101's uncontrolled, single-site, open-label Phase I CL-101 trial, which enrolled only 12 patients in the proposed therapeutic dose cohort, an evidence rating of an "A" is unsubstantiated. The ranking of CL-101 in infantile-onset SMA eliminates the large difference in evidence between investigational AVXS-101 and the robust Spinraza clinical trial data. As stated by ICER on Page 51: "Despite the limitations of the single-arm, open-label design in which 12 infants received the proposed therapeutic dose, we have high certainty that Zolgensma provides a substantial net health benefit, and rate the evidence base as "superior" to standard care (A)." According to ICER's evidence rating matrix, an "A" rating requires high certainty in level of evidence and a substantial comparative net benefit effect. In reference to investigational AVXS-101, we believe that the net health benefit is currently uncertain, particularly given lack of data on the durability of investigational AVXS-101. The long-term efficacy of investigational AVXS-101 is unknown, with data limited to a single-site, open-label, uncontrolled study of a small population of infants with SMA treated for just over 24 months as of the last report. Furthermore, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended. ENDEAR, a randomized, multi-center, international, double-blind, sham-controlled Phase III study, with a total of 121 participants, should not receive the same rating as an uncontrolled trial with only 12 participants. Furthermore, patients with infantile-onset SMA who were treated with Spinraza in ENDEAR have been followed for nearly 3 years	We have added a section to the report explaining the rationale behind the evidence ratings and the differences in the evidence bases for Spinraza and Zolgensma.

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	in the SHINE extension study, during which additional improvements in motor milestones and general motor function have been observed.	
2.	• There were two patients (N=2/12 or 17%) in the high dose cohort of CL-101 who were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]). This raises questions on the sponsor's ability to select appropriate patients for an SMA Type 1 study and why these two patients were included in the proposed therapeutic cohort. • Page 25-26: 17 out of 19 publications meeting PICOTS criteria were Spinraza studies, which points to its solid evidence base while also underscoring the prematurity of the ICER analysis of investigational AVXS-101. • An ICER report from October 2018 assigned a "C+" rating to the evidence for investigational inotersen for hereditary transthyretin amyloidosis (hATTR) based on NEURO-TTR, a Phase III, randomized, controlled trial with 172 total patients followed for over 15 months after treatment. Similarly, in a report from February 2018, ICER assigned a "B+" rating to voretigene neparvovec for biallelic RPE65-mediated retinal disease, based in part on a Phase III randomized control trial (Study 301) with 31 participants. This represents a large inconsistency in ICER evidence ratings across evaluations.	Both patients were genotyped and genetically confirmed to have SMA and two copies of *SMN2*. Both showed symptoms of disease onset prior to six months of age as required by the trial inclusion criteria.
3.	2. ICER's report makes no attempt to adjust the economic value comparison of Spinraza vs. investigational AVXS-101 despite significant and clinically relevant differences in baseline characteristics of populations and trial designs in ENDEAR and CL-101. • Although ICER did not assign an evidence rating comparing investigational AVXS-101 versus Spinraza for infantile-onset SMA in the Comparative Clinical Effectiveness section of its report (Section 3.5), the foundation of ICER's economic modeling in Section 4 is the clinical data, for which ICER makes no adjustments to account for differences in baseline characteristics between study populations, as recommended by ISPOR's Good Research Practices. • Page 51: ICER notes "Differences in trial populations related to age at treatment initiation and disease duration limit our ability to adequately distinguish the net health benefit of investigational AVXS-101 versus Spinraza for infantile-onset SMA. We therefore rate the evidence to be insufficient (I)." • Page 31: Key baseline characteristics of ENDEAR and CL-101 indicate that the patient populations have clinically	As explained in the draft report, adjusting for differences in baseline characteristics is not possible without access to individual patient data. We have requested this analysis from Biogen multiple times without success. As such, we have acknowledged this issue of naive comparison in our report (please see Table 4.2).

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	relevant differences, with patients in ENDEAR having a comparatively less favorable profile in terms of potential to respond to therapy: o Treatment with Spinraza was initiated later after disease onset compared to investigational AVXS-101: Patients treated with Spinraza in the ENDEAR study (mean age: ~5.3 months) were older at study initiation compared to investigational AVXS-101 patients in the high dose cohort of CL-101 (mean age: ~3.4 months). o Patients treated with Spinraza in the ENDEAR study had a longer disease duration (3.3. months) compared to patients treated with investigational AVXS-101 in the high-dose cohort of CL-101 (approximately 2.0 months). o There was a greater proportion of patients treated with nusinersen in the ENDEAR study (26%) who required respiratory intervention at baseline than those in the high-dose cohort of CL-101 (17%), which could have an important impact on clinical outcomes, such as event-free survival and respiratory outcomes. Table 3.1 incorrectly transposes numbers from those reported in Table 1 of the Mendell et al 2017 publication. Page 36: As noted in the previous point, two patients (N=2/12 or 17%) in the high dose cohort of CL-101 were treated soon after birth (0.9-1.9 months) and had CHOP INTEND scores at baseline (~46-50) that were similar to what would be expected for healthy infants as opposed to infants with SMA Type I (see Figure 1 from Mendell et al. [2017]). Due to early treatment and higher baseline motor function, these patients may have had more opportunity to respond compared to patients treated with Spinraza in ENDEAR who received initial treatment at a later age and had lower baseline motor function. Page 78: Of great concern, ICER estimates an incremental cost-effectiveness ratio comparing Spinraza and investigational AVXS-101 in the infantile onset patient population based on a naïve, unadjusted comparison of trial data. In contrast, HTA bodies such as NICE in the UK and the TLV in Sweden are cautious to conduct such cost-effectiveness evaluations based on naïve comparisons and ask for adjusted comparisons also in areas where such comparisons are challenging to conduct, as exemplified by their evaluations of CAR-T therapies such as Yescarta and Kymariah.	
4.	Lack of consensus exists on appropriate methods to assess the substantial uncertainty around long-term safety and effectiveness of gene therapies.	We agree that a lack of consensus exists in the appropriate methods to address the long-term effectiveness and safety of gene therapies. We

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	In the absence of a consensus on appropriate methodology, ICER should utilize durability assumptions for its evaluation of investigational AVXS-101. One consideration would be to use what was previously applied for durability assumptions for the gene therapy voretigene neparvovec for inherited retinal disease. In this previous assessment, treatment effect was assumed to be maintained for 10 years, followed by a 10-year waning of effect, after which the rate of decline in vision was the same as SOC. There are significant unknowns in the long-term efficacy of investigational AVXS-101, further amplified by the extremely limited number of patients who have received this treatment to date. In addition, public reports indicate that ~47% of investigational AVXS-101 treated patients in CL-101 received Spinraza after this trial ended.	have now included a scenario analysis using a shorter time horizon of 10 years.
5.	In either the base case analysis or in the scenario analyses, ICER should assume that SMA patients treated with Spinraza will continue to improve (e.g., increase motor function) as observed in clinical trials results, such as the ENDEAR/SHINE analysis, and reports from real-world practice. In ICER's current analysis, improvements observed in clinical trials and real-world practice are ignored and replaced with the incorrect assumption that patients do not improve from the health state they are in at the end of short-term clinical trials.	Strong evidence of continued improvement has not been presented. The base case, which uses differential utility between Spinraza and best supportive care, is deemed sufficient.
6.	The present ICER model fails to adequately capture clinically meaningful improvements and quality of life changes and relies on arbitrary assumptions about long-term efficacy. The proposed model health states are based on binary motor milestone achievements and are not sensitive enough to differentiate between changes in clinical or quality of life improvements that affect QALYs. ICER should alter its methods to allow for more sensitivity in QALY estimates for patients in different SMA health states reflecting 'no milestones,' 'mild milestones,' and 'moderate milestones.' For the long-term model, the base case analysis assumes that motor milestones achieved at the end of follow-up in clinical trials are sustained until death. This assumption is biased, as it conflicts with the trend of continuous improvement observed in patients treated with Spinraza and confers a durability of efficacy to investigational AVXS-101 that has yet to be proven.	The base-case analysis now includes utility benefit in the treatment arms for achieving interim milestones rather than being a scenario analysis. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details. Strong evidence of continued improvement has not been presented.
7.	Motor Milestones Achieved on Spinraza, Page 58: The estimated proportion of 'sitting' patients at different time points was based only on participants in SHINE who attended those study visits. Because the ENDEAR study was terminated early due to the favorable benefit/risk profile established at the interim analysis, not all patients were followed long enough to make it to latter study visit	We have used an alternative method to calculate the short term data for Spinraza (please see Appendix E2).

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	days in ENDEAR and SHINE. ICER disadvantages Spinraza in the multi-stage calculation process as shown in Table E2 and underestimates the proportion of patients in the 'sitting' health state by incorrectly using the number of patients at baseline as the denominator instead of the number of patients at the study visit (e.g. Day 698). ICER's current approach does not produce an accurate estimate of patients achieving the ability to sit in the SHINE study.	
8.	Long-term Assumptions, Page 61: ICER's assumptions on QALY weights for different health states inadvertently apply a downward bias in the value of Spinraza while also overstating the value of investigational AVXS-101. In ICER's current assessment, the 'not sitting' health state assumes the same overall survival of the ENDEAR sham control arm which recognized no treatment benefit. The 'walking' health state is also assumed to have the same overall survival of the US general population. Since a higher proportion of patients were in the 'walking' health state for the investigational AVXS-101 model, these optimistic assumptions were applied to benefit the incremental QALYs and cost-effectiveness ratio of investigational AVXS-101.	We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."
9.	Time Horizon of Long-Term Model, Page 55: ICER mentioned that the extrapolation of motor function milestones was conducted for the long-term model over a lifetime horizon. However, ICER excluded the exact number of years (e.g. 10 years, 20 years, etc.) that was defined as the lifetime horizon.	The time horizon used in the model was 110 years.
10.	Patient Utility Values, Page 64: The patient utility values for the different health states are key drivers of uncertainty and drastically impact the incremental QALY results. Patient utilities have the largest impact on cost-effectiveness results, especially for the later-onset model. ICER decided to use patient utility values from multiple references versus one study. ICER did not discuss or evaluate the key utility data (for Type I and II) from the Lloyd vignette study in its sensitivity analyses. Of the 3 available utility sources, the ERG preferred the vignette study according to the NICE committee papers August 2018.	In the original Biogen submission to NICE the ERG considered that the company's utility values had poor face validity. Alternative utilities from Bastida and Lloyd still have limited face validity. Although none of the datasets were ideal, of the three available utility sources the ERG preferred Lloyd (taken from the slides shown in public). There are two things to note on this: 1) The ERG is choosing between three options and are stating the one with the least lack of face validity, and 2) In the model submitted by Biogen (see page 120 of the first ERG report) in the long-term patients who were alive were either in the best or worse health state; in this model construct only these health states really matter and Lloyd was reasonable for this. Page 134 from the ERG report states, "Overall, the ERG considers that none of the sources are ideal,

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		but prefers the vignette study [Lloyd] as this broadly aligns with the final models' health states and is based on EQ-5D assessments of clinical experts in SMA. The ERG also notes that owing to the company's extrapolation assumptions regarding no deterioration in motor function for nusinersen-treated patients and no motor function improvement for patients receiving usual care, the utility values for the best and worst states have the greatest influence on the ICER in both the early and later onset models." When a different model was used (as described publicly in the second NICE appraisal committee) the intermediate steps were more important, which mean that the lack of face validity of Lloyd was more influential. In personal communication, the ERG for the NICE appraisal has stated that they are comfortable that the utilities used in the ICER report have more face validity than Lloyd and should be preferred.
11.	Treatment Costs, Page 65: Since investigational AVXS-101 is not yet approved by the FDA, its final market price is not yet available and remains highly uncertain. Many long-term costs of investigational AVXS-101 are unknown and sensitivity analyses should be conducted to understand the potential impact of downstream costs on treatment value. There is also large uncertainty regarding the long-term durability and safety of investigational AVXS-101. As there are limited data for investigational AVXS-101 with only 15 patients total, of which 7 have been reported to receive Spinraza post CL-101 trial, total treatment costs should consider inclusion of Spinraza as reported in the real-world.	We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."
12.	As suggested by ISPOR and NICE guidelines, robust methodologies include performing extensive sensitivity and scenario analyses to explore the impact of structural and input parameter uncertainty.	We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."
13.	Later-onset (Types II/III): Page 42-43: It is a failure and limitation of the ICER economic model to not capture any of the benefits of Spinraza versus SOC, as demonstrated in the CHERISH study, and acknowledged in ICER's own clinical assessment for later-onset SMA. These include a significant treatment difference of 5.9 points in total HFMSE score at 15 months in the interim analysis, and a clinically meaningful increase in RULM score from baseline to 15 months (4.2 vs. 0.5) for patients treated with Spinraza vs. SOC. These outcomes should be included in the ICER model as these assessments measure motor ability across	We have now included the utility benefit for achieving interim milestones in the base case analysis.

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	domains that are meaningful to patients and important for activities of daily living. The current ICER model is incomplete without including these outcomes.	
14.	Later-onset (Types II/III): Page 88: As mentioned by ICER and recognized by a key HTA body, the Type II/III model submitted by Biogen to NICE resulted in an incremental QALY difference for later-onset SMA: 16.88 and 14.52 QALYs for Spinraza and BSC, respectively, in the base case.	We note that the NICE committee that appraised Spinraza stated that several model assumptions used in deriving these results were overly optimistic, and have added language describing these considerations to the report section on comparisons to other economic models.
15.	Pre-symptomatic: Patients with genetically diagnosed pre-symptomatic SMA (most likely to develop Type I/II) have been studied in the ongoing Phase II, open-label, multi-center NURTURE trial. The study has been presented at three different sources/conference proceedings. Presymptomatic patients treated with Spinraza who were most likely to develop SMA Type I/II (median follow-up = 27.1 months) demonstrated unprecedented outcomes in the context of SMA natural history on event-free survival, motor function, and motor milestone endpoints. NURTURE, a Phase II, open-label, multi-center trial of N=25 pre-symptomatic infants, was determined as a "B+", a lower rating than open-label CL-101 for investigational AVXS-101.	We rated the evidence as B+ because trial results have not yet been published in a peer-reviewed journal.
16.	6. The ICER draft report contrasts sharply with the outcomes of numerous HTA assessments globally and does not capture the real-world value experienced by SMA patients. • Spinraza is used to treat over 6,000 patients worldwide and has become the foundation of care for individuals with SMA. Individuals with SMA live with an uncertain future and are among society's most vulnerable patients. Denying access to treatment can be life-threatening to patients. • Spinraza has been approved for use in over 40 markets worldwide as of January 2019. The clinical benefit of Spinraza has been rigorously evaluated and validated by numerous other HTA bodies. (Germany: First orphan drug ever with major added benefit & third product with major added benefit since AMNOG exists, out of 246 assessments. France: One of the few rare drugs to be recognized as bringing a high level of medical innovation, receiving an ASMR III for Type I and Type II.) • Economic modeling in rare disease is often challenging and frequently does not portray the full picture of the unmet medical needs of the community or adequately address how to objectively assign monetary value to quality of life. Many orphan medicines are not deemed cost-effective (determined by cost per quality of adjusted life year) based on standard accepted cost-effective thresholds. However, many key HTA markets (Germany,	We are unsure in what way the report contrasts with other HTA assessments and fails to capture the real-world experience of SMA patients. As noted, Spinraza was rated as providing substantial benefits compared with prior standard of care. We agree with the bullet points.

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	France, Australia, Sweden, Scotland, Canada/INESS) recognize Spinraza's value and have ensured access driven by clinical benefit and the robustness of the clinical data.	
Genentech		
1.	Infantile-Onset Model: • The current model is based on permanent ventilation, death, and motor milestone achievement. Unless 'sitting' or 'walking' were achieved, the utility and health-state cost are assumed to be the same. Given the majority of patients in the ENDEAR trial did not achieve 'sitting' or 'walking,' this model construct essentially ignores the benefits of delayed or circumvented permanent ventilation on patient and caregiver QoL. Literature has showed that patients requiring ventilation had a lower utility score than patients who did not, despite not achieving any motor milestones. • In the base case of infantile-onset model, improvements in bulbar function and minor motor function improvements (e.g., head control, rolling, crawling, and standing) are not reflected. In clinical trials, an increase of ≥4 points in the CHOP-INTEND score is considered clinically meaningful and this was achieved by a large majority of treated patients in the ENDEAR and START trials. Even when the 'sitting' or 'walking' milestone is not reached, improvements in other motor abilities (e.g., head control and rolling), bulbar function (e.g., eating and speaking) and activities of daily living (e.g., moving and dressing) are clinically meaningful and are associated with QoL improvements for both patients and caregivers. Genentech encourages ICER to adjust the health state cost and utility value in the base case model. Applying different assumptions for permanent ventilation and 'not sitting' will reflect the lower level of support required as well as the improved QoL for patients not requiring permanent ventilation. To the extent possible, ICER should also apply additional utility benefit for improved bulbar function, achieving interim milestones (e.g., head control, rolling), and other functional improvements due to treatment.	The base-case analyses now include utility benefit in the treatment arms for achieving interim milestones rather than being a scenario analysis. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details.
2.	Later-Onset model: • The model structure includes only three motor milestones: 'not sitting,' 'sitting,' and 'walking.' Although these milestones are convenient for linking to available data on health state utilities, these were not the primary endpoints in clinical trials. For example, none of the treated patients in the CHERISH trial achieved walking without assistance. However, an increase of ≥3 points in HFMSE is considered clinically meaningful and this was achieved in 57% of treated patients in the CHERISH trial.	We have now included the utility benefit for achieving interim milestones in the base-case analysis rather than as a scenario analyses.

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	Such improvements would translate into improved functional ability and QoL, thus should be captured in the model. In addition, the ICER report concludes that Spinraza (nusinersen) is dominated by best supportive care, with higher costs but no improvement in quality-adjusted life years (QALYs) or life years (LYs). This model result lacks clinical validity. Natural history suggests that as SMA progresses, patients lose motor functions and their ability to remain independent decreases over time. • Even in the absence of stark improvement in motor milestones such as 'walking,' disease stabilization or prevention of further deterioration are important improvements. A qualitative study demonstrated avoiding declines in function are important for patients and even small changes make a substantial difference for patients to function and thrive. As noted by a clinician in the study, "the difference between not being able to move a finger and being able to move a finger by half an inch can mean the difference between being able to operate a motorized vehicle or not, and that can make a huge impact on their quality of life and on their ability to be independent." • Additionally, the mean age of patients with later-onset SMA in the economic model was assumed to be 2 years. While this mean age was based on the CHERISH trial population, it is not representative of the population in the real world. The Cure SMA membership database may be a better source for the age used in the model. Genentech encourages ICER to explore an alternative model structure for later-onset SMA. The health states should be defined by patient functional levels that are meaningful to patients and caregivers (e.g., level of independence) and reflect the benefit of treatment. In addition, we also recommend revising the mean age of later-onset patients in this model to be more in line with the real-world population.	
3.	While it takes time for the long-term effects for any new therapy to emerge, the optimistic assumptions around the durability of effect have created bias in favor of Zolgensma (onasemnogene abeparvovec). This is likely due to the one-time administration frequency and the large magnitude of effect observed in a Phase I, single-arm study with a highly selected patient population (N=15). There are multiple key assumptions built into ICER's base case evaluation, given the "unknown duration of expression of the gene therapy." Most notably, ICER assumed motor function milestones achieved at the end of the trial period are sustained until death. Additionally, it was assumed that Type I patients who achieved 'sitting' or 'walking' had	These comments have been noted. A scenario analysis has been performed which restricted the time horizon to 10 years. There is considerable debate regarding the motive for the use of Spinraza after Zolgensma resulting in the base-case assuming that 50% of those who received Spinraza would have declined a milestone otherwise.

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	mortality similar to Type II and Type III patients, respectively. However, despite motor milestone improvements, 5 out of 12 (42%) patients in the START trial (cohort 2) still required ventilation, an intervention not common for Type II or Type III patients. Moreover, 5 out of 12 patients treated with Zolgensma also went on to receive Spinraza after the end of the study period indicating a need for additional therapy in some patients.	
4.	In ICER's model, key drivers of uncertainty are (1) monthly cost, (2) utility values for 'sitting,' 'non-sitting,' and 'walking,' and (3) the length of survival associated with the 'sitting' and 'walking' health states for infantile-onset patients. Of note, none of these estimates are from clinical trials or robust observational studies. In many cases, proxy estimates and assumptions were used. These may have led to a low level of precision in parameter estimates, leading to further uncertainties surrounding model results.	We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."
5.	Lastly, cost and disutility of treatment-related adverse events should be captured in the model as those events are well characterized and distinct from disease-related complications. Similarly, cost and disutility associated with intrathecal administration should be accounted for. Specifically, facility costs associated with intrathecal administration, in both inpatient and outpatient settings, should be included.	The costs of administration are described in detail in Table 4.8 in the section "Administration and Monitoring Costs." As explained in the draft evidence report, given the nature of SMA, it is difficult to disentangle the AEs due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, separate costs and disutilities for adverse events are not included in the model.
6.	The short-term and long-term model results would be more meaningful, if presented separately. For the long-term model, it would be more conservative to adopt a 5-year or 10-year model horizon as the base case rather than lifetime horizon. A shorter time horizon would also be in line with ICER's last evaluation of a gene therapy (Luxturna™ [voretigene neparvovec-rzyl]) which applied a 10-year model horizon as the base case. Additionally, the lack of nationalized healthcare in the US makes the shorter-term horizon more relevant in payer decision making.	We have now included a scenario analysis using a shorter time horizon of 10 years.
7.	Revise the base case to assume a proportion of Zolgensma patients lose motor function over time based on the fact that ~40% of patients from the START trial subsequently received Spinraza.	The base case analyses already assumes that 50% of the Zolgensma patients who receive Spinraza lose motor function milestones at the end of the short-term model. Scenario analyses were performed assuming a greater proportion lose their milestones at the end of the short term model (please see Table 4.22).
8.	Vary utility and cost parameter values by 20% instead of 10% in sensitivity analysis given the high level of uncertainty in the model.	We have now varied the parameter values by 20% in the sensitivity analyses.

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9.	Include the cost and disutility related to adverse events and the facility cost and disutility associated with intrathecal administration in the model.	The costs of administration are described in detail in Table 4.8 in the section "Administration and Monitoring Costs." As explained in the draft evidence report, given the nature of SMA, it is difficult to disentangle the AEs due to treatment from the complications associated with SMA, which are already accounted for in the health state costs and disutilities. As such, separate costs and disutilities for adverse events are not included in the model.
10.	We believe that caregiver burden should be included in any cost-effectiveness analysis determining societal value. The impact of SMA on caregiver productivity and QoL is well documented in published literature. In this draft report, caregiver burden is excluded because ICER believes its inclusion may "lead to counter-intuitive results due to prolonged negative productivity effects and unknown quality of life effects on caregivers when children who need substantial care live longer." However, in a cost-effectiveness assessment of pediatric interventions, incremental cost-effectiveness ratios on average decreased by 31% when family spillover effect was included. Genentech strongly recommends that ICER include caregiver burden by including productivity and QoL impact in the infantile-onset, later-onset, and pre-symptomatic models.	There are a considerable number of issues around including spillover utility effects that do not yet have consensus around methodology. Some of the key issues being the number of caregivers to account for, differentiating family effect from caregiver effect, accounting for relationship dynamics over time between patient and caregivers that affect health care decision making, and subsequently the patient and caregiver utility, and the trajectory of caregiver utility post-milestone outcomes such as death. We reviewed the literature to identify pertinent caregiver utilities in this population but found none that we deemed satisfactory to use. We are happy to consider any studies measuring caregiver utility for this population, for our analysis.
Clinicians and Health Economists		
Richard Finkel, MD		
1.	This detailed analysis relies on many assumptions and a very small sample size with limited duration of observation under treatment. The conclusions made in this report are fraught with uncertainty. While the goal of this ICER evidence report is certainly of high merit, it is premature to endorse the conclusions drawn by the authors. Later analysis of a larger sample of treated patients who are observed over a longer period of time will be of greater value.	We agree that there is a substantial degree of uncertainty in many of the report's conclusions, and have highlighted these areas in the report. However, these therapies are either already approved or nearing an FDA decision and despite the uncertainty present in the evidence base, patients and clinicians will need to make decisions about how to use these therapies, and payers will need to develop coverage policies. We believe ICER's independent analyses to be an important source of information that can inform these decisions.
Louis Garrison, PhD		
1.	With regard to this SMA report, these arguments would suggest that ICER is being too conservative in applying a cost-per-QALY threshold of $150,000 per QALY in projecting a "value-based price" (VBP) for onasemnogene abeparvovec. ICER does recognize a broader range for rare diseases of up to $500,000 per QALY, and should consider, in this instance, either not making a specific projection for a VBP based on $150,000 per QALY, or presenting it at a	While our threshold prices extend to the $500,000 per QALY threshold for reviews conducted under ICER's ultra-rare disease framework, our value-based price benchmarks are still the prices that would meet the $100,000 to $150,000 per QALY threshold. Regarding our modified societal perspective, we have we not included the family spillover utility affect in our analysis. While we

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	higher level or as a range with a higher upper bound. Given that onasemnogene abeparvovec has not been launched, the device of using "placeholder price" of $2,000,000 is understandable. However, it may create misleading benchmark: for example, the US Government values lives at closer to $10 million (https://www.transportation.gov/regulations/economic-values-used-in-analysis). Furthermore, given the grave, negative implications of having a child with SMA Type 1 for parents and caregivers, ICER should emphasize the societal perspective. It was not clear to me whether the "Modified Societal Perspective" alternative in the report captures the "family spillover" effect, e.g., on the (dis-)utility of parents and caregivers. Of course, as outlined in our ISPOR report, augmenting cost-effectiveness analysis—beyond the cost-per-QALY—affects the calculation and/or interpretation of the appropriate CET.	recognize capturing its effect in SMA, we have outlined reasons for not including it in the appendix of our report.
Patient Advocacy Groups		
Cure SMA		
1.	Within the report are multiple errors showing a lack of basic understanding of the disease. For instance, the report states that "there remains considerable uncertainty in the generalizability of the results" (page 48). However, Spinraza clinical trials were completed in patients with SMA types I-III. SMA types I-III represents approximately 95% of patients with SMA. Due to the genetic homogeneity of SMA, the mechanism of action for Spinraza and Zolgensma is the same across the disease spectrum.	While SMA is attributed to a specific gene, there is a spectrum of response to treatment that has been observed across patients in the trials.
2.	Additionally, this report does not seem to understand the basic biology of SMA stating on page 27 that "Overall, we noted some differences in baseline characteristics between the Spinraza and sham control arms of both ENDEAR and CHERISH that suggest more severe SMA symptoms in the Spinraza arm. The direction of potential bias in results is unclear as the patients receiving Spinraza may be at higher risk of death and other complications but may also have a greater potential to improve." The progressive loss of motor function is due to loss of motor neuron innervation. An important consideration for therapeutic efficacy is that motor neurons cannot be restored after being lost and this limits the time window allowing for maximal improvement.	We have updated the text to address your concern.
3.	The long-term extrapolation model for non-sitters is flawed. The long-term model utilizes a lower mean survival of 1.55 years for non-sitters compared to a mean survival of 5.3 years for permanent ventilation thus assuming significantly poorer survival for non-sitters compared to permanent ventilation, even though the non-sitter group	The base case analyses now assumes that the survival of patients on Spinraza is independent of permanent ventilation, however, the survival for patients not receiving permanent ventilation on best supportive care has remained the same. Furthermore, there is also utility benefit in the

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	has showed better outcomes and improvements following treatment with Spinraza. The ENDEAR trial demonstrated a 47% reduction in the risk of death or permanent ventilation in the Spinraza treated group compared to control (Finkel et al, NEJM, 2017). The life years for the SMA type I not sitting Spinraza treated model is severely underestimated.	treatment arms for achieving interim milestones. Please see Table 4.2 for more details.
4.	Throughout the report, clinical trial data is misinterpreted in the ICER models, which has a major impact on the determination of cost effectiveness of the therapies under evaluation. Table 3.4 of the report correctly indicates that maximally 29% of patients had the ability to sit independently towards the end of the SHINE extension study (Castro et al, NMD, 2018). However, in section 4 of the report a value of only 11% is used. This lower value appears to be calculated using the total number of patients receiving Spinraza in the ENDEAR trial (n=81, Finkel et al, NEJM, 2017), rather than the number of patients being assessed at that particular time point (n=31, Castro et al, NMD, 2018). By doing so, the model unfairly assumes unfavorable outcomes for the unassessed 50 patients, i.e., none would have sat if assessed. Meanwhile, the actual reason that many in the full cohort were not assessed at this time or beyond is that they had not yet reached this point in the study (meaning that they had been on drug less time than the actual timepoint under evaluation).	We have used an alternative method to calculate the short term data for Spinraza (please see Appendix E2).
5.	Furthermore, there are major flaws in framing the outcomes of pre-symptomatic treatment with Spinraza, which downplay the dramatic impact on survival and function in this situation compared to natural history. Trial data demonstrate that most infants treated proactively, when free of symptoms, achieve the motor milestones of walking and standing. In fact, 22 of 25 were able to walk with assistance and 17 of 25 were able to walk independently (Swoboda et al, WMS, 2018). To date, no pre-symptomatic SMA infant treated with Spinraza in this study has died or required permanent ventilator support. The assessment of pre-symptomatic treatment benefit is wrongly framed by a comparison to the development of healthy children. Natural history outcomes regarding individuals with the same SMN2 copy number should be used for comparison, not outcomes in unaffected children.	In Table 3.11, we include the 1st-99th percentiles of the windows of WHO milestones. These percentiles are also included in the manufacturer's presentation of results. See e.g., De Vivo's presentation of interim NURTURE results presented at the 2018 Cure SMA Annual Research Meeting (slide 8).
6.	Finally, as with any treatment whose approval is based on clinical trials of a feasible and ethical duration, there is always ongoing uncertainty about longer-term outcomes. However, the report has a lengthy section (3.4) about clinical trial controversies that seems unwarranted. These would be better framed as important issues that would ideally now be examined using real world data capture on drug efficacy and safety. We believe ICER should frame	Thank you for raising this concern. We have added text in Section 3.4 to note the potential for Zolgensma to provide a life-long benefit. We believe that the base case scenario has been "optimistic" where choices were made, which is reflected in the larger number of "conservative" scenarios.

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	long-term uncertainties in a more balanced manner, leaving open the possibilities of both pessimistic and optimistic scenarios for future results. Currently, for example in tables 4.21 and 4.22, there are only 2 and 3 positive scenarios modeled out of the total in each table.	
7.	ICER assigns benefit to the patient only if the drug allows for obtaining milestones such as sitting or walking. Meanwhile patients have reported, and the FDA has recognized, the great value in abilities that allow for more independence and activities of daily living (McGraw et al, BMC Neurol, 2017; and Rouault F et al, NMD, 2017). For some patients and their families, simply not getting worse is an improvement and a meaningful outcome. It should also be noted that even incremental increases in a patient's motor abilities may alleviate the stresses and challenges involved in caregiving by allowing patients greater ability for self-care. These meaningful and valued milestones are not factored into this analysis; however, the complete set of clinical trial data from the early open label studies to the pivotal ones demonstrates these improvements in SMA type I, II, and III participants.	The base-case analysis now include utility benefit in the treatment arms for achieving interim milestones. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details.
8.	We know that most patients show clinically meaningful improvement with Spinraza, yet ICER ignores these when constructing this analysis. This lack of patient perspective about the value of these milestones and incremental improvements seriously weakens ICER's models, and therefore, the analysis of value and efficacy is incomplete. It is a disservice to all with SMA that a report which could impact access to life saving treatments for some of the most vulnerable members of society does not include their perspective. The ICER models show that only 1% of SMA patients gain any meaningful benefit from Spinraza. This ignores and contrasts with: • 51%, vs 0% untreated, HINE Responders. • 45%, vs 0% untreated, with Head Control. • 71%, vs 3% untreated, CHOP Responders. • 57%, vs 26% untreated, HFMSE Responders. The process of determining QALYs for patients permanently on ventilators and those who are non-sitters appears arbitrary and does not take into account the wide range of patient outcomes in between these two statuses. The analysis also fails to take into account the advances in technology that have made it possible for physically limited individuals to meaningfully contribute to society in ways never before possible. Many patients who have not	The base case analysis now include utility benefits in the treatment arms for achieving interim milestones. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms but not for best supportive care. Please see Table 4.2 for more details. We have performed extensive scenario and sensitivity analyses to understand the impact of these assumptions. Please see the sections entitled "Sensitivity Analyses Results" and "Scenario Analyses Results."

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	achieved the arbitrary ICER chosen milestones are productively employed.	
9.	Moreover, incorrect assumption and subsequent erroneous modeling occurred around the fact that some subjects who received Zolgensma in the START trial were subsequently treated with Spinraza. The assumption that Spinraza was added after Zolgensma due to a deteriorating health status led to modeling that "half of the patients would lose a milestone in the absence of Spinraza. We therefore assumed that a sixth (33% * 50%) of the patients in the sitting health state at the end of the short-term model in the Zolgensma arm dropped a milestone (i.e., to not sitting) to reflect those patients who apparently required Spinraza after the study period." There is no evidence to support this assumption. The more likely explanation is that families' expectations are high for best outcomes and families will do everything possible to get their child every available treatment in order to eliminate as many symptoms as possible.	Our clinical expert suggested thought that both rationales for seeking Spinraza therapy were plausible (i.e., patients seeing benefit would want to achieve additional benefit and patients at risk of losing milestones would want the other therapy to prevent further loss). As such, we assumed that half of the patients would lose a milestone.
10.	For a pediatric and typically fatal disease such as SMA, now with transformative and impactful treatments, the ICER model of financially discounting life years has a significant effect. The controversial approach of using a financial model for discounting life years (prior to any utility discounting) should be clearly disclosed and have scenario analyses to indicate the impact on any conclusions.	Discounting costs and outcomes in health economic modeling is standard practice. We have now included undiscounted costs and outcomes of our base case analysis in the appendix of the report.
Muscular Dystrophy Association		
1.	With regard to the value of treatments for SMA as set out in the draft report, we would note that the evaluation of milestones may not fully reflect the experiences and needs of the patient community. For example, gains in mobility, such as the ability to sit or to reposition unassisted, can represent significant, positive change in the life of an individual living with SMA and their caregivers. Improvements in mobility, however small they may be deemed, often represent major improvements in quality of life and the value of these gains cannot be discounted. In addition to health improvements that may be associated with increased mobility, increases in mobility are directly related to independence, which is a critical factor for those living with neuromuscular disease. Similarly, respiratory function is also major concern for the SMA community. The significance of what one may consider even relatively small gains for SMA patients in this area must be reflected in any evaluation. Further, with SMA being classified as not only a rare disease, but as an ultra rare disease with a significant burden, the QALY applied in the report is likely insufficient. This is important as such determinations may impact access to treatment. Additionally, while the report	The base-case analyses now include utility benefits in the treatment arms for achieving interim milestones. Furthermore, we also included a survival benefit for patients in the "not sitting" health state of treatment arms. Please see Table 4.2 for more details.

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	notes that there are "common limitations" in applying the framework in rare diseases, there are further limitations in the draft report as Zolgensma has not yet received FDA approval. Thus, for example, it does not yet have a price. Similarly, and as noted in the report, there are no coverage policies associated with Zolgensma to evaluate.	
Patients Rising Now		
1.	As we've previously stated, "evaluating the clinical and market potential of medicines prior to approval – and by definition prior to the final FDA label of indications and warnings – is extremely difficult." In the Draft Report ICER has taken an additional leap to include a completely fictional construct. Therefore, we think it would be analytically and socially responsible for ICER to reissue an updated Draft Evidence Report that includes actual data for Zolgensma after FDA approval when its labelled indications and warning will be known, as well as the list price – and of course separately publish any fictional constructs of potential medicines in more appropriate publications.	Policymakers need to make decisions about appropriate pricing, coverage, and clinical use at the time a treatment is approved by the FDA despite the challenges in doing so, and our reports serve as an independent assessment that can inform these decisions. ICER has an established update process for revisiting reports when important new evidence emerges. We have also added additional language to the report describing the policy considerations the "Drug X" analysis is intended to inform.
2.	While the genetic cause of SMA is known, and tests for determining a patient's status are available, we share ICER's concern about the limited data available about Spinraza and Zolgensma. However, models or projections based on uncertain data is inherently an error prone process and a fundamental flaw in this Draft Report, as well as many other ICER activities. The 189-page Draft Report contains numerous references to this uncertainty, including the admission on page 183 that "the true uncertainty is likely to be more than that represented in our probabilistic analyses." Nevertheless, the Draft Report makes economic declarations that it clearly recognizes others will rely upon for decisions affecting patients and families.	Therapies such as Spinraza and Zolgensma may produce substantial long-term benefit, but at non-negligible costs to patients and the health system. Economic models such as ours serve to aid the decision-making process when choosing the right treatment for patients, especially in the absence of long-term data on their benefits. This absence of long-term data poses uncertainty regarding health and economic impacts of such treatments, which is why we include sensitivity and scenario analyses in an attempt to address these uncertainties.
3.	We also appreciate the complications of modeling based upon clinical trials that are single armed or limited in duration. However, for certain innovations, single arm trials are the appropriate structure and research methodology. As has been written, "Such comparisons [in a single arm study to the natural history of the disease] are meaningful only when the expected outcomes in the absence of the intervention are well-known, and the expected effect size from the intervention is large," which clearly is the situation with Zolgensma. Similarly, projecting long-term outcomes from trials of limited duration is a well-recognized issue in clinical research. However, this issue has largely been settled, since waiting for lifetime results (i.e., 60+ year trials) is impractical, would deny patients access to treatment that have demonstrated short or intermediate term benefits,	ICER's evidence rating for Zolgensma follows the rationale described here, and additional context regarding these ratings can be found in earlier responses. As noted in other responses, clinicians, patients, and payers must make decisions about how to use and cover these therapies at the time of their approval, regardless of the maturity of the evidence base. It is also important to note that drugmakers select the prices of their therapies despite these uncertainties. We also note that despite these uncertainties, both therapies have received highly favorable evidence ratings.

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	and would also effectively terminate any investments in such research. Overall, the objections ICER raises about the sparsity of data are due to the self-determined timing of ICER's activities (i.e., before or shortly after FDA approvals) rather than the realities of the data itself. This is akin to a paraphrase of the Heisenberg Uncertainty Principle, i.e., the sooner you get the data, the more uncertainty there will be, and conversely the more you demand certainty of data the longer you will have to wait - and more people and society will be denied the benefits of the resulting innovations. Thus, while families and patients with SMA would clearly benefit from better treatment options, we believe that ICER's Draft Report – both its technical aspects and overall approach – are counterproductive to that goal.	
4.	ICER's assumption filled process fundamentally risks incorrectly modeling the real world. For example, it is widely recognized that modeling of uptake and usage of new medicines can be very far off from what actually occurs once a treatment is approved by the FDA. This was evident from the actual usage of the first new medicines to treat hepatitis C (which had initial usage much greater than had been projected), and those to treat very high cholesterol because of PCSK9 protein variants (which had initial usage that was much less than projected). What is also interesting in both those cases was that over time, there was dramatic decline in the net prices paid by payers, although what patients paid may not have fallen to the same extent – which is of course an ongoing concern – and a factor ICER also does not address in its framework process. We would appreciate ICER's comments about how its methodology does not account for such real-world market dynamics that effect prices and overall costs to payers, patients, and society.	Real-world evidence on current drug market share is usually data that is confidential and even if shared with ICER, cannot be used in the public domain due to the sensitive nature of the data. As for market uptake, as you rightly state, it can be far off prediction, which is why we use extreme scenarios in our budget impact models, which are intended to serve as "plug-and-play" models for different payers based on the population they cover and their respective budgets.
5.	The Draft Report provides a link to the list the stakeholder from whom ICER requested input, but not those from whom it actually received input. That list should be provided.	This list includes organizations that have provided input as well as those that have been invited to provide input.
6.	The Draft Report only lists one "Expert Reviewer," and that individual appears to have only a few years of experience since finishing her doctorate.	Given that each ICER report is subject to a month-long public comment period, we do not believe this to be a limitation of our report. As can be seen in this document, we receive detailed feedback from stakeholders, and much of this feedback is written or informed by clinical expert input. We also note that the reviewer is an expert in SMA clinical outcomes measures and is also a

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		practicing therapist with highly relevant experience.
7.	The Draft Report states that "Harvard Pilgrim and UHC specify that the patient seeking coverage must have at least two copies of the SMN2 gene; Humana states that patients may have no more than two copies." Can you explain the rationale for why different insurers would have such opposite prior authorization criteria? Also, Humana appears to have updated their criteria so that individuals with Delayed Onset SMA can have "no more than three copies of SMN2."	This section is intended to describe how various payers cover the therapies of interest for a given review and does not address the rationale behind these decisions. Because we did not develop these policies, we cannot comment on the reasons why each payer chose such a policy. We expect to discuss these considerations during the policy roundtable at the upcoming public meeting.
8.	It seems the 100% survival rate for Zolgensma has now been reported at 24 months.	Thank you for your comment. We have added the longer-term follow-up data for Zolgensma.