Biogen

27 January 2025

RE: ICER's Draft Scoping Document for updating evidence for SMA treatment

Biogen appreciates the opportunity to comment on ICER's draft scoping document for Spinal Muscular Atrophy (SMA). In this assessment, ICER proposes to update clinical evidence for the treatment of SMA types.

SMA is a devastating rare disease that affects infants, children, adults, parents, and caregivers. Individuals with SMA live with an uncertain future and are among society's most vulnerable individuals. Most untreated SMA Type I patients will die before the age of 24 months without respiratory support and nutritional intervention; and nearly a fifth (18%) of SMA Type II patients will die by the age of 10.[i,ii,iii,iv] Most SMA patients also face significant disability. This places incalculable burden on patients, their parents and care partners who often suffer loss of income from limited employment, and may experience higher levels of stress, worry, and mental and physical fatigue.[v]

Nevertheless, it is important to recognize that the clinical classification of SMA patients by type (I-IV) is imperfect and warrants further review and discussion. It is also important to understand how patient outcomes may differ based on factors like age of onset (e.g., early onset, late onset).

Spinraza® was the first approved treatment for infants, children and adults living with SMA. The body of evidence supporting its approval and use for treatment of SMA patients is substantiated by a rigorous and robust clinical development program. As the first manufacturer of a SMA treatment option, Biogen recognizes the importance of developing novel treatments, conducting research to understand how treatments meaningfully improve health outcomes for subpopulations of patients, and working with payers as well as other stakeholders to improve patient access.

We recognize the challenges and the many methodological choices that are necessary in cost-effectiveness analyses, including those related to the estimation of quality-adjusted life years (QALYs), patient survival, durability of treatment, and treatment pathways which may include combination therapy. Based on the conversation with ICER, Biogen welcomes the opportunity for sharing updated evidence since the previous ICER report and further discussion. Below is a summary of Biogen's detailed comments on the draft scoping document.

1. Recognize the unique challenges in SMA clinical trial programs and evidence generation.

Our experience is that SMA evidence cannot be evaluated in the same way as evidence for non-rare diseases. SMA is characterized by very small populations, fundamental unknowns in the epidemiology of the disease and unique challenges in clinical trial program design and execution.[vi] Biogen has sought to understand individual nuances of this disease by designing rigorous and robust trials that address the varied manifestations of SMA. This was necessitated by the fragility of this patient population and the need to ensure the greatest likelihood of treatment durability. ICER's Comparative Value Analysis should include sufficient sensitivity analyses and a thorough description of data constraints and assumptions to reflect existing uncertainties. Lastly, there are limitations of comparing Spinraza® trials to other trials including variations in study design, patient age, disease duration, disease severity and study endpoints; also, immunogenicity and durability issues must be accounted for in modeling.

2. Consider the unique impact of treatment for SMA subpopulations when assessing value.

SMA is clinically heterogeneous. Patients diverge significantly in a number of ways that determine prognosis, treatment response and durability. Biogen has worked extensively with the SMA community to better understand the impact of areas such as variations across the SMA phenotypic continuum, subtyping, ventilation support and the nature and timing of changes in physical functioning.[vii,viii] All of these factors are important to consider when selecting methods and reporting value across a range of patients with SMA. The value assessment methodology of treatment for infants will be different from that of adults.

3. Spinraza® Related long term clinical outcomes and safety profile

- SHINE: End of study data (more than 5 years follow-up) was published at CureSMA 2024.

  Finkel RS, et al. Final Safety and Efficacy Data From the SHINE Study in Participants With Infantile-Onset and Later-Onset SMA. Presented at Annual Cure SMA Research and Clinical Care Meeting, Austin, Texas, 5–7 June, 2024. P95.

- A meta-analysis of recent papers published 12/23/2016 through 07/01/2022 with ⩾ 5 individuals ⩾ 13 years of age and with ⩾ 6 months' data on ⩾ 1 selected motor function outcomes [Hammersmith Functional Motor Scale-Expanded (HFMSE), Revised Upper Limb Module (RULM), and Six-Minute Walk Test (6MWT)] was conducted to understand treatment effects by disease severity, subgroup meta-analysis by SMA type and ambulatory status.

  Hagenacker T, Maggi L, Coratti G, Youn B, Raynaud S, Paradis AD, Mercuri E. Effectiveness of Nusinersen in Adolescents and Adults with Spinal Muscular Atrophy: Systematic Review and Meta-analysis. Neurol Ther. 2024 Oct;13(5):1483-1504. doi: 10.1007/s40120-024-00653-2. Epub 2024 Sep 2. PMID: 39222296; PMCID: PMC11393259.

4. Spinraza® Related age-related and SMA stage data:

- Spinraza® in Adults with SMA Participating in the SMArtCARE Registry: Prospective, Observational, Multicenter Study

  In an analysis of the SMArtCARE registry in Germany, patients aged 16 to 65 years (N = 173; received at least one injection) with 5q SMA Types I-IV treated with Spinraza® for ≥ 6 months showed statistically significant improvements in motor function as measured by mean change in HFMSE score, RULM score, and 6MWT distance at 6, 10, and 14 months compared to baseline. AEs occurred in 47% (82 out of 173) of patients who received at least one injection, with the most common AEs being headache (35%), back pain (22%), and nausea (11%).

  Hagenacker T, Wurster CD, Günther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol. 2020;19(4):317-325.

  In an additional analysis of the SMArtCARE registry including patients aged 16 to 71 years (N = 389; received at least one injection) from Germany, Switzerland, and Austria, long-term efficacy and safety of Spinraza® was evaluated over 38 months. Significant increases from baseline in motor function outcomes including mean HFMSE scores, RULM scores, and 6MWT at 14 months, 26 months, and 38 months were observed. AEs occurred in 91% (353 out of 389) of patients who received at least 1 injection; the most common AEs included post-lumbar puncture syndrome, headache, backpain, and infections. No new safety signals were identified.

Günther R, Wurster CD, Brakemeier S, et al. Long-term efficacy and safety of nusinersen in adults with 5q spinal muscular atrophy: a prospective European multinational observational study. Lancet Reg Health Eur. 2024;39:100862.

- Spinraza® Safety and Effects on Motor Function in Adult SMA Type II and III. A retrospective, open-label, observational study in adults with SMA Type II or III found further RWE of Spinraza® safety and efficacy, with the efficacy benefits in SMA Type III appearing to be cumulative over time.

  Maggi L, Bello L, Bonanno S, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. J Neurol Neurosurg Psychiatry. 2020;91(11):1166-1174.

- The CS2/CS12/SHINE Study Showed Stable or Improved Motor Function in Young Adults with SMA Over 5.3 to 6.8 years of Follow-Up. Most young adults with later-onset SMA (Type II or III) who initiated treatment with Spinraza® at age ≥ 13 years to nearly 16 years in the CS2/CS12 study (N = 7; 1 Type II, 6 Type III) have demonstrated generally stable or improved motor function over 5.3 to 6.8 years of follow-up (aged 18.8 to 22.5 years as of 27 August 2019).

  Day J, Swoboda K, Darras B, et al. Longer-term experience with nusinersen in young adults with spinal muscular atrophy: results from the CS2/CS12 and SHINE studies. Presented at: American Academy of Neurology (AAN) Annual Meeting; April 25th – May 1st, 2020; Toronto, Canada.

- This contrasts with the expected gradual decline in motor function seen in the natural history of SMA.

  Kaufmann P, McDermott MP, Darras BT, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology. 2012;79(18):1889-97.

  Mazzone E, Bianco F, Main M, et al. Six minute walk test in type III spinal muscular atrophy: a 12month longitudinal study. Neuromuscul Disord. 2013;23(8):624-8.

  Mercuri E, Finkel R, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. Neuromuscul Disord. 2016;26(2):126-31.

  Sivo S, Mazzone E, Antonaci L, et al. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. Neuromuscul Disord. 2015;25(3):212-5.

  Montes J, McDermott MP, Mirek E, et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. PLoS One. 2018;13(6):e0199657.

  Wadman RI, Wijngaarde CA, Stam M, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol. 2018;25(3):512-518.

  Pera MC, Coratti G, Mazzone ES, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle Nerve. 2019;59(4):426-430.

- CS2 was a Phase 1b/2a multicenter, open-label, dose-escalation study designed to assess the safety and tolerability of multiple doses of Spinraza® delivered intrathecally to patients aged 2 to 15 years with later-onset SMA.

  Darras BT, Chiriboga CA, Iannaccone ST, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. Neurology. 2019;92(21):e2492-e2506.

- Analyses which focus on United States SMA patients including adult ambulatory and non-ambulatory cohorts:

Elsheikh B, Severyn S, Zhao S, Kline D, Linsenmayer M, Kelly K, Tellez M, Bartlett A, Heintzman S, Reynolds J, Sterling G, Weaver T, Rajneesh K, Kolb SJ, Arnold WD. Safety, Tolerability, and Effect of Nusinersen Treatment in Ambulatory Adults With 5q-SMA. Front Neurol. 2021 May 20;12:650535. doi: 10.3389/fneur.2021.650535. PMID: 34093395; PMCID: PMC8174580.

Elsheikh B, Severyn S, Zhao S, Kline D, Linsenmayer M, Kelly K, Tellez M, Bartlett A, Heintzman S, Reynolds J, Sterling G, Weaver T, Rajneesh K, Kolb SJ, Arnold WD. Safety, Tolerability, and Effect of Nusinersen in Non-ambulatory Adults With Spinal Muscular Atrophy. Front Neurol. 2021 Apr 16;12:650532. doi: 10.3389/fneur.2021.650532. PMID: 33935949; PMCID: PMC8085528.

- A critical review of the literature reporting real-world data on motor function in type 2 and 3 patients treated with Nusinersen. Results were subdivided according to SMA type, age and type of assessment and performing a meta-analysis of the available results.

Coratti G, Cutrona C, Pera MC, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis. 2021;16:430

5. Comparative effectiveness analyses:

- Published a manuscript in 2023: A Critical Appraisal of Matching-Adjusted Indirect Comparisons in Spinal Muscular Atrophy - PMC.

Jiang T, Youn B, Paradis AD, Beckerman R, Barnieh L, Johnson NB. A Critical Appraisal of Matching-Adjusted Indirect Comparisons in Spinal Muscular Atrophy. Adv Ther. 2023 Jul;40(7):2985-3005. doi: 10.1007/s12325-023-02520-2. Epub 2023 Jun 5. PMID: 37277563; PMCID: PMC10271880.

- Zolgensma then Spinraza treatment in infantile (Type I) patient population:
  - A small published real-world study showed patients switched from Zolgensma back to Spinraza.

Combination molecular therapies for type 1 spinal muscular atrophy. Y Harada, V K Rao, K Arya, et al. Muscle Nerve. 2020 Oct;62(4):550-554.doi: 10.1002/mus.27034. Epub 2020 Aug 10.

  - The ongoing Phase IV RESPOND study has had no emerging safety concerns which have been identified in enrolled participants who received Spinraza® after onasemnogene abeparvovec.

Brandsema JF, et al. Baseline Characteristics and Interim Safety in RESPOND: A Phase 4 Study in Children With Spinal Muscular Atrophy Treated With Nusinersen After Onasemnogene Abeparvovec. MDA 2023.

6. Information regarding motor scales used in different trials and challenges/limitations for use in the updated economic models.

- Hammersmith Infant Neurological Examination Section (HINE-2) motor milestones and general motor function as measured by the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP-INTEND) are motor function scales for infantile-onset SMA patients. (Apitegromab study patient cohorts did not include infantile patients with their cohorts ranging from 2-12 and 13-21 years of age). HFMSE and RULM are motor function scales for later-onset SMA patients.
- Considering the unique impact of treatment for SMA subpopulations, conversion of motor scales for comparative purposes is limited and conclusions should be interpreted with caution.

Conclusion

Biogen acknowledges the complexity of this disease; like many rare diseases, although much progress has been made in SMA, it is still not yet fully understood or well-defined. We encourage ICER to communicate and collaborate with the SMA community, and we welcome the opportunity to work with ICER to ensure patients have access to therapies that provide the very best chance at improved motor function and survival from this devastating disease.

Dr. Boyang Bian, PhD

Head of Evidence Generation, North America Medical

Medical Evidence Generation

[i] SMA Foundation. SMA Overview. SMA Varies in Severity. p. 4. Link.
[ii] Lally C, Jones C, Farwell W, Reyna S P, Cook S F, Flanders W D.. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet Journal of Rare Diseases. 2017; 12(1), 175. Link.
[iii] Ogino S, Wilson RB, Gold B. New insights on the evolution of the SMN1 and SMN2 region: simulation and meta-analysis for allele and haplotype frequency calculations. European Journal of Human Genetics. 2004 Dec;12(12):1015. Link
[iv] SMA Foundation. SMA Overview. SMA Incidence and Prevalence are Different. p. 5. Link.
[v] Farrar MA, Carey KA, Paguinto SG, Chambers G, Kasparian NA. Financial, opportunity and psychosocial costs of spinal muscular atrophy: an exploratory qualitative analysis of Australian carer perspectives. BMJ open. 2018 May 1;8(5):e020907. Link

[vi] Wästfelt M, Fadeel B, Henter JI. A journey of hope: lessons learned from studies on rare diseases and orphan drugs. Journal of Internal Medicine. 2006 Jul 1;260(1):1-0. Link

[vii] Darras BT. Spinal muscular atrophies. Pediatr Clin North Am. 2015 Jun;62(3):743-66.
[viii] Long WD III, Smith BG. A review: the use of growing rods to treat scoliosis in patients with spinal muscular atrophy. Semin Spine Surg. 2012 Sep;24(3):164-8.

Genentech
A Member of the Roche Group

January 24, 2025

Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on *Therapies for the Treatment of Spinal Muscular Atrophy: Draft Background and Scope* [1]. Recently approved disease-modifying therapies (DMTs) have transformed the natural course of spinal muscular atrophy (SMA). DMTs have improved life expectancy, prevented ventilator dependence, supported the achievement of key motor milestones, and enabled individuals with later-onset SMA to preserve crucial motor functions [2]. Evrysdi® (risdiplam), the first and only oral, non-invasive, at-home DMT for SMA, has demonstrated proven safety and efficacy in heterogeneous populations of adults, adolescents, children, and infants with SMA [3-9]. We are confident in the value risdiplam has provided to the SMA community and remain committed to ensuring individuals with SMA have access to therapies that best meet their needs.

We present three recommendations to ensure that the report remains patient-centered and reflects the realities of SMA:

1. **Comprehensive assessments of comparative clinical effectiveness must account for significant clinical and patient heterogeneity, such as age, SMA type, *SMN2* copy number, disease duration, baseline function, and presence of scoliosis or joint contractures.**
2. **All emerging clinical evidence surrounding post-gene therapy treatment sequencing should be evaluated.**
3. **ICER's base case evaluation of long-term value should fully incorporate a societal perspective, accounting for broad impacts to family spillover effects, time burden, and the full range of treatment benefits.**

We further expand on these recommendations with supporting references and rationale below:

1. **Comprehensive assessments of comparative clinical effectiveness must account for significant clinical and patient heterogeneity, such as age, SMA type, *SMN2* copy number, disease duration, baseline function, and presence of scoliosis or joint contractures.**

Recommendation: SMA indirect treatment comparisons (ITCs) must use all available evidence and appropriate statistical methods to account for intra- and inter-trial population heterogeneity. Important treatment effect modifiers to consider include age, SMA type, *SMN2* copy number, disease duration at time of treatment, pre-treatment function level, and presence of scoliosis or joint contractures [10].

Rationale: Several ITCs have been conducted in the absence of head-to-head studies across SMA DMTs. Ribero et al. conducted the first population-adjusted ITC comparing the three available DMTs for SMA: risdiplam, nusinersen, and onasemnogene abeparvovec (OA) [11]. A matching-adjusted indirect comparison (MAIC) was used to minimize bias from baseline differences across the SUNFISH, FIREFISH, ENDEAR, CHERISH, and STR1VE-US trials, adjusting for factors such as age at first dose, disease duration, and baseline motor function by SMA type [11, 12]. Results from this MAIC analysis suggest that Type 1 SMA patients treated with risdiplam had improved outcomes compared to nusinersen. Differences in prognostic factors and small sample sizes prevented definitive conclusions between risdiplam vs. OA in Type 1 and risdiplam vs. nusinersen in Types 2 and 3, highlighting the need for more evidence. Similar to Ribero et al., Kokaliaris et al. and Sideris et al. found risdiplam had improved outcomes over nusinersen in Type 1 SMA based on three and four years of follow-up data, respectively [13, 14]. Key treatment effect modifiers in SMA, such as age at treatment start, baseline

motor function scores, or ventilation dependence at baseline, differ across trial populations. Therefore, any unadjusted ITC results should be interpreted with caution [10, 13-16].

Implications: Failure to account for cross-trial heterogeneity in the assessment of comparative clinical evidence will introduce significant bias and risk misleading conclusions that are not generalizable to the wider SMA population.

2. **All emerging clinical evidence surrounding post-gene therapy treatment sequencing should be evaluated.**

Recommendation: As stated in the 2019 ICER *Spinal Muscular Atrophy Final Evidence Report*, there remains significant uncertainty on the durability of gene therapy [17]. ICER should consider all available evidence, including studies with small sample sizes and descriptive observational data, that investigates the durability of gene therapy and ongoing treatment patterns in the evolving SMA treatment landscape.

Rationale: Patients who respond incompletely to gene therapy could potentially benefit from follow-on therapy. Evidence to support additional treatment following gene therapy is summarized below:

- Administration of risdiplam to patients previously treated with OA has been reported in a Phase 2, open-label clinical trial (JEWELFISH, NCT03032172) [7, 8]. At 24 months of treatment with risdiplam, patients experienced increases in motor function scores (using the MFM32, RULM, and HFMSE scales) and in SMN protein levels. Additionally, three Phase 4 open-label studies are underway to assess the effectiveness and safety of risdiplam (HINALEA 1, NCT05861986 and HINALEA 2, NCT05861999) and nusinersen (RESPOND, NCT04488133), when administered following gene therapy [18-20].
- A multicenter retrospective cohort analysis included 66 infants with SMA [21]. Of these, 62 (93%) received OA. After a median of 10 months following OA treatment, 16 of these children (26%) added nusinersen (n=6) or risdiplam (n=10) due to SMA findings or suboptimal outcomes.
- A retrospective cohort analysis of the Cure SMA Clinical Data Registry described real-world outcomes for 49 patients treated with risdiplam [22]. Ten of those children received risdiplam treatment 12.2 [7.8, 20.3] (median [IQR]) months post-OA and experienced improvements in motor function scores.
- A recent case series of 19 children with SMA from six United States centers reported on risdiplam treatment after OA, given at a mean of 16.1 months later (range: 7–63 months) [23]. The main reasons for adding risdiplam were inadequate or plateaued improvements. Following risdiplam treatment, many children showed improvements in motor skills, bulbar function, and respiratory function with no significant adverse events reported. Other case series have also reported on the use of follow-on treatment after gene therapy [24-26].

Implications: The 2019 ICER *Spinal Muscular Atrophy Final Evidence Report* highlighted uncertainty about the duration of OA's effects [17]. Ignoring subsequent treatments could misrepresent the treatment landscape, overlook the cumulative benefits of additional therapies, and provide an incomplete view of potential stabilization or improvement.

3. **ICER's base case evaluation of long-term value should fully incorporate a societal perspective, accounting for broad impacts to family spillover effects, time burden, and the full range of treatment benefits.**

Recommendation: Assessments of SMA treatments should capture the comprehensive impacts for patients and their family members, inclusive of health-related quality of life (HRQoL), productivity, time burden and a broad set of clinical outcomes.

Rationale: We recommend implementing the following into ICER's value assessment and public meetings:

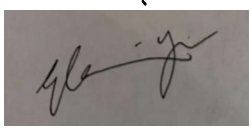
- *Include family spillover effects in the economic evaluation.* We recommend including: (1) published estimates on the utility values for caregivers of SMA patients [27-30]; and (2) productivity impacts for informal caregivers, as Cure SMA surveys found caregivers spend nearly 64 hours a week providing care and experience significant productivity losses [31, 32]. This evidence is also supported by previous evidence of SMA caregivers worldwide [33].
- *Account for bereavement impact on HRQoL and productivity*. Published literature indicates long-term HRQoL and productivity declines for informal caregivers after loss of a child with SMA that persist for more than 10 years [34, 35]. Health utility losses compared to population norms were 0.22 during the first 5 years after the loss of a child, 0.14 between years 5 and 10, and 0.09 for years beyond 10 [34].
- *Incorporate patient preferences on administration route.* Studies have shown that an oral medication or a one-time infusion are strongly preferred within the SMA community over repeated intrathecal injections, underscoring the importance of ease of administration and reduced time commitment [36-39]. Unlike other DMTs, risdiplam is the only oral formulation and does not require frequent clinic visits, hospitalizations, anesthesia, specialized care centers, or invasive procedures, such as complex spinal punctures [39-41]. This significantly reduces the time, travel, and recovery burdens associated with repeated intrathecal injections or an intravenous infusion [39-41].
- *Expand and account for a broader set of outcomes such as bulbar function*. Following 24 months of risdiplam treatment, most infants in the FIREFISH study could swallow and feed orally, defying the typical progression of the disease [4]. Additionally, a retrospective analysis using CEDAS indicated that most infants maintained or improved their bulbar function scores over 24 months of risdiplam treatment [42].

The impact of SMA extends beyond the individual living with the condition, greatly affecting caregivers, families, and communities. It is essential to adopt a societal perspective that is inclusive of the impacts to those that provide care to individuals with a lifelong condition, such as SMA. It is also imperative to account for functional outcomes that reflect meaningful benefits. Assessing bulbar function, which encompasses speech, swallowing, and feeding difficulties for all SMA types, is vital for determining functional improvements meaningful to patients and caregivers [43].

Implications: Excluding the societal perspective and key outcomes will result in an incomplete analysis that fails to capture the full scope of SMA's impacts, including family spillover effects, time burdens, and the full range of treatment outcomes.

Genentech is confident in the value risdiplam has provided to the SMA community. Most importantly, we are committed to ensuring individuals with SMA have access to therapies that best meet their needs. We encourage ICER to partner closely with the SMA community to ensure their perspectives are central to this review. We appreciate the opportunity to provide feedback and look forward to continued engagement with ICER.

Sincerely,



Elaine Yu, PharmD, MS
Head of Evidence for Access, Genentech

References

1. Institute for Clinical and Economic Review. Therapies for the Treatment of Spinal Muscular Atrophy: Draft Background and Scope. January 6, 2025; Available at: www.icer.org. Accessed on January 20, 2025.
2. Moultrie F, Chiverton L, Hatami I, Lilien C, Servais L. Pushing the boundaries: future directions in the management of spinal muscular atrophy. *Trends in Molecular Medicine*. 2025;0(0). doi:10.1016/j.molmed.2024.12.006
3. Genentech USA, Inc., A Member of the Roche Group. Evrysdi® (risdiplam) for oral solution prescribing information. January 2025; Available at: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf
4. Darras B, Baranello G, Boespflug-Tanguy O, et al. FIREFISH Parts 1 and 2: 36-month safety and efficacy of risdiplam in Type 1 spinal muscular atrophy (SMA) (P7-9.009). *Neurology*. 2023;100(17_supplement_2):3928. doi:10.1212/WNL.0000000000203624
5. Mercuri E, Baranello G, Boespflug-Tanguy O, et al. Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. *Eur J Neurol*. 2023;30(7):1945-1956. doi:10.1111/ene.15499
6. Mercuri E, Deconinck N, Mazzone ES, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2022;21(1):42-52. doi:10.1016/S1474-4422(21)00367-7
7. Chiriboga CA, Bruno C, Duong T, et al. Risdiplam in Patients Previously Treated with Other Therapies for Spinal Muscular Atrophy: An Interim Analysis from the JEWELFISH Study. *Neurol Ther*. 2023;12(2):543-557. doi:10.1007/s40120-023-00444-1
8. Chiriboga CA, Bruno C, Duong T, et al. JEWELFISH: 24-month results from an open-label study in non-treatment-naïve patients with SMA receiving treatment with risdiplam. *J Neurol*. 2024;271(8):4871-4884. doi:10.1007/s00415-024-12318-z
9. Servais L, Farrar M, Finkel R, et al. RAINBOWFISH: Primary Efficacy and Safety Data in Risdiplam-treated Infants with Presymptomatic Spinal Muscular Atrophy (SMA) (S37.006). *Neurology*. 2024;102(17_supplement_1):5269. doi:10.1212/WNL.0000000000205694
10. Baranello G, Gorni K, Daigl M, et al. Prognostic Factors and Treatment-Effect Modifiers in Spinal Muscular Atrophy. *Clin Pharmacol Ther*. 2021;110(6):1435-1454. doi:10.1002/cpt.2247
11. Ribero VA, Daigl M, Martí Y, et al. How does risdiplam compare with other treatments for Types 1–3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. *Journal of Comparative Effectiveness Research*. 2022;11(5):347-370. doi:10.2217/cer-2021-0216
12. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. *NICE DSU Technical Support Document 18: Methods for Population-Adjusted Indirect Comparisons in Submissions to NICE*. Vol 18. NICE Decision Support Unit; 2016.
13. Kokaliaris C, Evans R, Hawkins N, et al. Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy. *Adv Ther*. 2024;41(6):2414-2434. doi:10.1007/s12325-024-02845-6
14. Sideris E, Hawkins N, Evans R, et al. Long-Term Comparative Efficacy and Safety of Risdiplam versus Nusinersen in Children with Type 1 Spinal Muscular Atrophy. Poster presented at: International Congress of Neuromuscular Diseases; October 25-29, 2024; Perth, Australia. Available at: https://medically.roche.com/global/en/neuroscience/icnmd-2024/medical-material/ICNMD-2024-poster-sideris-long-term-comparative-efficacy-pdf.html

15. Finkel RS, Dabbous O, Arjunji R et al. P.060 Time to treatment effect in spinal muscular atrophy Type 1 (SMA1): an indirect comparison of treatments. Can. J. Neurologic. Sci. 46, S30 (2019).
16. Dabbous O, Maru B, Jansen JP, et al. Survival, Motor Function, and Motor Milestones: Comparison of AVXS-101 Relative to Nusinersen for the Treatment of Infants with Spinal Muscular Atrophy Type 1. *Adv Ther*. 2019;36(5):1164-1176. doi:10.1007/s12325-019-00923-8
17. Institute for Clinical and Economic Review. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value: Final Evidence Report. April 3, 2019; Available at: www.icer.org. Accessed on January 20, 2025.
18. Hoffmann-La Roche. *A Phase IV Open-Label Study Evaluating the Effectiveness and Safety of Risdiplam Administered as an Early Intervention in Pediatric Patients With Spinal Muscular Atrophy After Gene Therapy*. clinicaltrials.gov; 2024. Accessed January 20, 2025. https://clinicaltrials.gov/study/NCT05861986
19. Hoffmann-La Roche. *A Phase IV Open-Label Study Evaluating the Effectiveness and Safety of Risdiplam Administered in Pediatric Patients With Spinal Muscular Atrophy Who Experienced a Plateau or Decline in Function After Gene Therapy*. clinicaltrials.gov; 2025. Accessed January 20, 2025. https://clinicaltrials.gov/study/NCT05861999
20. Biogen. *A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec*. clinicaltrials.gov; 2023. Accessed January 20, 2025. https://clinicaltrials.gov/study/NCT04488133
21. Goedeker NL, Rogers A, Fisher M, et al. Outcomes of early-treated infants with spinal muscular atrophy: A multicenter, retrospective cohort study. *Muscle Nerve*. 2024;70(6):1247-1256. doi:10.1002/mus.28267
22. Shapouri S, To T, Whitmire S, et al. Clinical Outcomes Among Risdiplam-Treated Patients with Spinal Muscular Atrophy (SMA) in the Cure SMA Clinical Data Registry. Poster presented at: Academy of Managed Care Pharmacy Nexus; October 14-17, 2024; Las Vegas, NV. Available at: https://medically.gene.com/global/en/unrestricted/oncology/AMCP-NEXUS-2024/amcp-nexus-2024-poster-shapouri-clinical-outcomes-among.html
23. Kuntz N, Svoboda MD, Leon-Astudillo C, et al. Risdiplam Experience Following Onasemnogene Abeparvovec In Individuals With Spinal Muscular Atrophy (Sma): A Multicenter Case Series. Poster presented at: Muscular Dystrophy Association Clinical and Scientific Conference; March 3-6, 2024; Orlando, FL. Available at: https://medically.gene.com/global/en/unrestricted/neuroscience/MDA-2024/mda-2024-poster-kuntz-risdiplam-experience-following-on.html
24. Oechsel KF, Cartwright MS. Combination therapy with onasemnogene and risdiplam in spinal muscular atrophy type 1. *Muscle & Nerve*. 2021;64(4):487-490. doi:10.1002/mus.27375
25. Matesanz SE, Brigatti KW, Young M, Yum SW, Strauss KA. Preemptive dual therapy for children at risk for infantile-onset spinal muscular atrophy. *Ann Clin Transl Neurol*. 2024;11(7):1868-1878. doi:10.1002/acn3.52093
26. Leon-Astudillo C, Brooks O, Salabarria SM, et al. Longitudinal changes of swallowing safety and efficiency in infants with spinal muscular atrophy who received disease modifying therapies. *Pediatric Pulmonology*. 2024;59(5):1364-1371. doi:10.1002/ppul.26919
27. National Institute for Health Care Excellence. TA588 Single Technology Appraisal. Nusinersin for treating spinal muscular atrophy [ID1069]. 2019. Accessed January 21, 2025. Available at: https://www.nice.org.uk/guidance/ta588/evidence/final-appraisal-determination-committee-papers-pdf-6842813869

28. Sutherland CS, Hudson P, Mitchell S, Paracha N. Systematic Literature Review to Identify Utility Values in Patients with Spinal Muscular Atrophy (SMA) and Their Caregivers. *PharmacoEconomics*. 2022;40(1):39-67. doi:10.1007/s40273-021-01115-5
29. Sutherland C, Aponte Ribero V, Hoffart J, Gravestock I, Servais L. EE421 Burden of Illness Related to Motor Function in Types 2 and 3 Spinal Muscular Atrophy (SMA). *Value in Health*. 2022;25(7, Supplement):S417. doi:10.1016/j.jval.2022.04.669
30. Wohnrade C, Velling AK, Mix L, et al. Health-Related Quality of Life in Spinal Muscular Atrophy Patients and Their Caregivers—A Prospective, Cross-Sectional, Multi-Center Analysis. *Brain Sciences*. 2023;13(1):110. doi:10.3390/brainsci13010110
31. Mulé CM, Riley A, Lerner D, Vesel T, Galea C, Song M, Truong S, Belter L, Kowal S, Fox D, Shapouri S, O'Toole CM, Lavelle TA. Qualitative Examination of Bereavement in Parents of Children with Spinal Muscular Atrophy Type 1: Impact on Health-Related Quality of Life, Productivity, and Social Connection. 2024. Publication details forthcoming.
32. Belter L, Curry M, Schroth M. Understanding the Caregiving Experience. Results from the Cure SMA Caregiver Experience Survey. Cure SMA Meeting. Elk Grove Village, IL.
33. Paracha N, Hudson P, Mitchell S, Sutherland CS. Systematic Literature Review to Assess the Cost and Resource Use Associated with Spinal Muscular Atrophy Management. *PharmacoEconomics*. 2022;40(1):11-38. doi:10.1007/s40273-021-01105-7
34. Should Health Technology Assessment Include the Bereavement Effect on Health-Related Quality of Life? What Difference Could It Make to Decisions About Life-Extending Treatments? ISPOR | International Society For Pharmacoeconomics and Outcomes Research. Accessed January 21, 2025. https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-europe-2024/program/program/session/euro2024-3973/18370
35. Pennington B and Wong R. Modelling Carer Health-Related Quality of Life in NICE Technology Appraisals and Highly Specialised Technologies. Report by the Decision Support Unit. University of Sheffield. 2019. Accessed January 21, 2025. Available at: https://www.sheffield.ac.uk/nice-dsu/methods-development/carer-health-related-quality-life.
36. Monnette A, Chen E, Hong D, et al. Treatment preference among patients with spinal muscular atrophy (SMA): a discrete choice experiment. *Orphanet J Rare Dis*. 2021;16(1):36. doi:10.1186/s13023-020-01667-3
37. Lo SH, Gorni K, Sutherland CS, Martí Y, Lloyd A, Paracha N. Preferences and Utilities for Treatment Attributes in Type 2 and Non-ambulatory Type 3 Spinal Muscular Atrophy in the United Kingdom. *PharmacoEconomics*. 2022;40(1):91-102. doi:10.1007/s40273-021-01092-9
38. Lo SH, Lawrence C, Martí Y, Café A, Lloyd AJ. Patient and Caregiver Treatment Preferences in Type 2 and Non-ambulatory Type 3 Spinal Muscular Atrophy: A Discrete Choice Experiment Survey in Five European Countries. *PharmacoEconomics*. 2022;40(1):103-115. doi:10.1007/s40273-021-01118-2
39. Chen E, Dixon S, Naik R, et al. Early experiences of nusinersen for the treatment of spinal muscular atrophy: Results from a large survey of patients and caregivers. *Muscle Nerve*. 2021;63(3):311-319. doi:10.1002/mus.27116
40. Novartis Gene Therapies, Inc. Zolgensma® (onasemnogene abeparvovec-xioi) suspension for intravenous infusion prescribing information. January 2025; Available at: https://www.fda.gov/media/126109/download?attachment
41. Biogen. Spinraza® (nusinersen) injection for intrathecal use prescribing information. January 2025; Available at:

https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf

42. Baranello G, Conway E, Li Y, et al. Retrospective Assessment Of Feeding And Nutrition After 2 Years Of Risdiplam Treatment In Children With Type 1 Spinal Muscular Atrophy (Sma) Using A Novel Scale (P: 126P). Poster presented at: 29th Annual Congress of the World Muscule Society; October 8-12, 2024; Prague, Czechia. Available at: https://medically.gene.com/global/en/unrestricted/neuroscience/WMS-2024/wms-2024-poster-baranello-retrospective-assessment-of-f.html
43. Martí Y, Aponte Ribero V, Batson S, et al. A Systematic Literature Review of the Natural History of Respiratory, Swallowing, Feeding, and Speech Functions in Spinal Muscular Atrophy (SMA). *J Neuromuscul Dis*. 2024;11(5):889-904. doi:10.3233/JND-230248

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

(857) 259-3860
scholarrock.com

January 27, 2025

Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review (ICER)
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Scoping Document for ICER Evaluation of Spinal Muscular Atrophy (SMA)

Dear Ms. Emond:

Scholar Rock is committed to discovering, developing, and delivering life-changing therapies by harnessing cutting-edge science to create new possibilities for people with serious diseases that have high unmet need including those with spinal muscular atrophy (SMA). For more than a decade, our company has been working to bring transformative medicines to patients, developing a unique, highly selective scientific approach.

The SMA community has been clear about its goal of providers, patients and their caregivers having access to new therapies to address unmet needs like increased muscle strength, improving daily activities, stabilizing or gaining new motor functions, and reducing fatigue. Scholar Rock shares this goal and has been working diligently to ensure patients have access to apitegromab upon approval by the U.S. Food and Drug Administration (FDA). We want to share important information about the substantial burden and unmet need in SMA and highlight key areas for consideration by ICER in its assessment.[1]

1. **Remaining Unmet Needs in SMA: Progressive Muscle Atrophy and Weakness Continue to be Persistent Clinical Hallmarks of SMA**

   SMA is a rare neuromuscular disease characterized by rapid motor neuron degeneration, progressive muscle weakness, atrophy, and loss of function.[2] SMA pathophysiology reflects two main challenges related to the motor unit, each of which requires distinct therapeutic approaches for effective disease management.[3] One challenge is rapid, irreversible degeneration of motor neurons. The survival motor neuron (SMN) protein is critical to the function and survival of motor neurons that control muscle function; consequently, when SMN protein levels are low, motor neurons irreversibly degenerate.[4] Another, equally important, challenge of SMA is the progressive muscle atrophy and weakness that arises not only from ongoing neuron degeneration, but also from a lack of sufficient muscular stimulation, leading to a cycle of disuse and further weakness. Together, both motor neuron degeneration and muscle atrophy drive the progression of SMA and ultimately contribute to disabilities such as limited mobility, ventilatory insufficiency, and potentially life-threatening complications.[5] Unaddressed progressive muscle atrophy and weakness can dramatically impact patients, leaving them fearful of losing ambulation or having their muscles give out while doing daily activities.[6] While currently approved SMN-targeted treatments help slow further degeneration of motor neurons, they do not directly address muscle atrophy and weakness.[5,7,8]

Several cross-sectional and longitudinal studies in treatment-naïve patients with SMA show muscle weakness is persistent and progressive, correlating with declines in motor function.[9,10,11] The decline of muscle strength, even with apparent motor function stability,[12] provides additional rationale for early treatment of SMA including treatment approaches targeting muscle.[5,13] SMN-targeted therapies have significantly improved patient outcomes; however, patients treated with these therapies continue to experience substantial impairment in motor function and progressive loss of motor function.[9,10,11] Patients on nusinersen typically experience improvement in motor function as assessed by Hammersmith Functional Motor Scale—Expanded (HFMSE), but this improvement can plateau after the initial phase, followed by progressive decline in motor function.[7] Available long-term data for risdiplam also indicate an initial improvement in HFMSE from baseline followed by a subsequent decline.[8] Further highlighting these unmet needs, patients with SMA currently on SMN-targeted therapies participating in recent and ongoing clinical studies continue to have substantial motor function deficit based on low baseline HFMSE scores.[14] For example, baseline HFMSE in our pivotal Phase 3 (SAPPHIRE) study was approximately 26, far below their healthy counterparts.[14] In short, despite current treatment with SMN-targeted therapies, the SMA community still needs additional improvement in and/or sustainment of motor function.[15]

2. High Remaining Patient Burden in SMA

As ICER has recognized in its Draft Scoping document, SMA imposes a substantial physical, emotional, and economic toll on patients, families, and caregivers.[1] Loss of motor function impairs an SMA patient's ability to perform activities of daily living (ADL), leading to a loss of independence and imposing significant clinical and psychosocial burden on patients and their caregivers.[16] Current SMN-targeted therapies are essential in addressing motor neuron loss, slowing the progression of neuronal degeneration.[5] However, as noted in the Draft Scoping document, lost nerve function is not regained and current therapies do not directly address the underlying muscle pathology and associated muscle function impairment in patients.[1] With access to SMN-targeted therapies, treatment goals for patients, families, and physicians are shifting from survival and early motor milestones to increased functionality and independence.[17] Adults with SMA, the majority of whom are treated with SMN-targeted therapies, report the following most significant unmet needs for future treatment(s) to address:[17]

- 97% report the need to gain muscle strength;
- 88% report the need to achieve new or stabilize motor function; and
- 85% report the need to reduce fatigue.

A muscle-targeted therapy that can improve muscle strength and motor function can provide additional functional gains to address these reported unmet needs. An effective therapeutic strategy for SMA should incorporate not only SMN-targeted therapies to address the motor neuron component of the disease, but also a muscle-targeted treatment that addresses muscle atrophy and weakness. These complementary approaches can work in concert to improve, sustain, and regain motor function, altering the clinical trajectory for individuals with SMA.

3. Role of Apitegromab as a Muscle-Targeted Therapy Designed to Address Muscle Atrophy and Weakness for People Living with SMA

Apitegromab is an investigational fully human monoclonal IgG4 antibody that selectively binds to promyostatin and latent myostatin and inhibits the activation of myostatin.[18] It is a selective muscle-targeted treatment designed to address muscle atrophy and weakness. In clinical trials, a

total of 232 patients with SMA were exposed to apitegromab for a median duration of more than 12 months with 145 patients receiving treatment for at least 1 year and 50 patients for at least 4 years.[14,19]

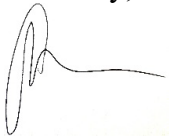
As the first and only muscle-targeted therapy with demonstrated Phase 3 (SAPPHIRE) clinical success in SMA, apitegromab significantly improves motor function with a clinically-meaningful, statistically significant increase in HFMSE compared with the observed decline with SMN-targeted therapies alone (+1.8 points, p=0.0192).[14] Importantly, in this trial, patients on average had been on nusinersen or risdiplam for approximately 5 and 3 years, respectively, at randomization. The observed HFMSE decline in the SMN-targeted treatment alone arm (1.2-point decline over 52 weeks) is similar to the decline observed in patients with similar duration of exposure to SMN-targeted therapy.[7,8] The odds of achieving a ≥3-point improvement in HFMSE vs. not achieving a ≥3-point improvement is 3 times more likely for apitegromab-treated patients than SMN-targeted therapy-alone (nominal p=0.0256).[14] Long-term data from the Phase 2 study of apitegromab (TOPAZ) demonstrated that motor function benefit by HFMSE were sustained over 4 years in apitegromab-treated patients.[19] Increases in HFMSE observed in both TOPAZ, where patients had on average ~2 years of prior exposure to nusinersen at entry, as well as SAPPHIRE, where patients had longer prior exposures to nusinersen and risdiplam, support the clinical benefit of apitegromab throughout an SMA patient's treatment journey, consistent with the biological role of myostatin and apitegromab's mechanism of action.[14,19] Favorable one-year apitegromab safety data from SAPPHIRE is similar to the SMN-targeted therapy-alone arm and is consistent with the established safety profile observed over 4 years of treatment in the TOPAZ trial.[14,19]

With no currently approved muscle-targeted therapies for SMA, apitegromab, if approved by the FDA, offers the potential to impact the disease trajectory in SMA.

We respectfully recommend ICER consider the following in their assessment:

- Recognize that while early diagnosis together with SMN-targeted therapies have significantly improved patient outcomes, patients continue to experience persistent motor function deficit, with many patients having a severe burden of illness and unmet need due to progressive muscle atrophy and weakness.
- Consider the unique muscle-targeted mechanism of apitegromab and its potential to improve and sustain motor function and address significant remaining unmet needs in SMA.
- Incorporate real-world evidence, disease trajectory, and long-term clinical trial data to contextualize the impact of progressive motor function decline despite treatment with SMN-targeted therapies while also considering the long-term benefits of sustaining or improving motor function.

Sincerely,



Allen Su
Vice President, Value and Access
Scholar Rock

References:

1. Institute for Clinical and Economic Review. Draft Scoping Document for "Therapies for the Treatment of Spinal Muscular Atrophy". Available at: https://icer.org/wp-content/uploads/2025/01/ICER_SMA_Draft-Scope_For-Publication_010625.pdf. Accessed January 14, 2025.
2. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2000 [cited 2024 Aug 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1352/
3. Le Verche V, Sunshine SS, Hammers D, Sweeney HL, Paushkin S. Chapter 21 - Skeletal Muscle in Spinal Muscular Atrophy As an Opportunity for Therapeutic Intervention. In: Sumner CJ, Paushkin S, Ko CP, editors. Spinal Muscular Atrophy [Internet]. Academic Press; 2017 [cited 2024 Nov 8]. p. 341–56. Available from: https://www.sciencedirect.com/science/article/pii/B9780128036853000215
4. Ting LH, Chiel HJ. Muscle, Biomechanics, and Implications for Neural Control. In: Neurobiology of Motor Control [Internet]. John Wiley & Sons, Ltd; 2017 [cited 2024 Aug 1]. p. 365–416. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118873397.ch12
5. Day JW, Howell K, Place A, Long K, Rossello J, Kertesz N, Nomikos G. Advances and limitations for the treatment of spinal muscular atrophy. BMC Pediatrics. 2022;22:632. Available from: https://bmcpediatr.biomedcentral.com/counter/pdf/10.1186/s12887-022-03671-x.pdf
6. Cruz R, Lenz M, Belter L, et al. The Voice of the Patient Report for Spinal Muscular Atrophy. 2018. Accessed April 4, 2024. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf
7. Finkel R, Farrar M, Krosschell K, Saito K, Mercuri E, Castro D, et al. Final Safety and Efficacy Data from the SHINE Study in Participants With Infantile-Onset and Later-Onset SMA. In 2024.
8. Oskoui M, Day J, Deconinck N, Mazzone E, Nascimento A, Saito K, et al. SUNFISH Parts 1 and 2: 4-year efficacy and safety of risdiplam in Types 2 and 3 spinal muscular atrophy (SMA). In Dallas, TX, USA; 2023.
9. Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto L a. M, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c–4. Eur J Neurol. 2018;25(3):512–8.
10. Annoussamy M, Seferian AM, Daron A, Péréon Y, Cances C, Vuillerot C, et al. Natural history of Type 2 and 3 spinal muscular atrophy: 2-year NatHis-SMA study. Ann Clin Transl Neurol. 2021 Feb;8(2):359–73.
11. Werlauff U, Vissing J, Steffensen BF. Change in muscle strength over time in spinal muscular atrophy types II and III. A long-term follow-up study. Neuromuscul Disord NMD. 2012 Dec;22(12):1069–74.
12. Wijngaarde CA, Stam M, Otto LAM, Bartels B, Asselman FL, van Eijk RPA, et al. Muscle strength and motor function in adolescents and adults with spinal muscular atrophy. Neurology. 2020 Oct 6;95(14):e1988–98.
13. Aragon-Gawinska K, Mouraux C, Dangouloff T, Servais L. Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening—A Systematic Review. Genes. 2023 Jul;14(7):1377.

14. Scholar Rock. SAPPHIRE Phase 3 study. Data on File.
15. Pera MC, Coratti G, Forcina N, Mazzone ES, Scoto M, Montes J, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. BMC Neurol. 2017 Feb 23;17:39.
16. Cure SMA. Spinal Muscular Atrophy Treatment [Internet]. https://www.curesma.org/. [cited 2024 Aug 30]. Available from: https://www.curesma.org/spinal-muscular-atrophy-treatment/
17. Cure SMA. State of SMA 2023 Report [Internet]. 2024 May [cited 2024 Aug 2]. Available from: https://www.curesma.org/wp-content/uploads/2024/06/9042024_State-of-SMA_vWeb.pdf
18. Long KK, O'Shea KM, Khairallah RJ, Howell K, Paushkin S, Chen KS, et al. Specific inhibition of myostatin activation is beneficial in mouse models of SMA therapy. Hum Mol Genet. 2019 Apr 1;28(7):1076–89.
19. Crawford TO, Day JW, De Vivo DC, Krueger JM, Mercuri E, Nascimento A, et al. Long-term efficacy, safety, and patient-reported outcomes of apitegromab in patients with spinal muscular atrophy: results from the 36-month TOPAZ study. Front Neurol [Internet]. 2024 Jul 22 [cited 2024 Dec 2];15. Available from: https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2024.1419791/full