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Introduction

- Spinal muscular atrophy (SMA) is a neuromuscular disorder resulting in progressive degeneration of motor neurons and muscle weakness<sup>1</sup> due to a deficiency of survival motor neuron (SMN) protein<sup>2</sup>
- Three SMN-targeted treatments that increase SMN protein levels and thereby preserve motor neurons are approved in the US: nusinersen, onasemnogene abeparvovec-xioi (OA), and risdiplam<sup>3</sup>
  - Nusinersen was approved first in 2016<sup>4</sup>
  - OA and risdiplam were approved in 2019 and 2020, respectively<sup>3</sup>
- While these treatments improve motor function, many individuals with SMA continue to experience persistent muscle weakness,<sup>5</sup> and longer-term data are limited
- We conducted a systematic literature review (SLR) to characterize the trajectory of longer-term outcomes for individuals receiving SMN-targeted treatment. Here, we present the results for nusinersen, which had the largest body of literature available

Methods

SLR eligibility criteria

- Interventions included nusinersen, OA, and risdiplam, focusing on studies reporting motor function endpoints
- English-language manuscripts, conference abstracts, and posters for clinical trials and observational studies published in PubMed and Embase between 2017 and July 29, 2024, were identified
- Studies were conducted in the US, Europe, and Australia
- Only studies with ≥5 individuals with types 1, 2, or nonambulatory type 3 SMA were included
  - Studies were included in the SLR that contained some ambulatory individuals in addition to those defined above. Alternatively, studies that only included ambulatory individuals were excluded
- The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

SLR primary outcomes

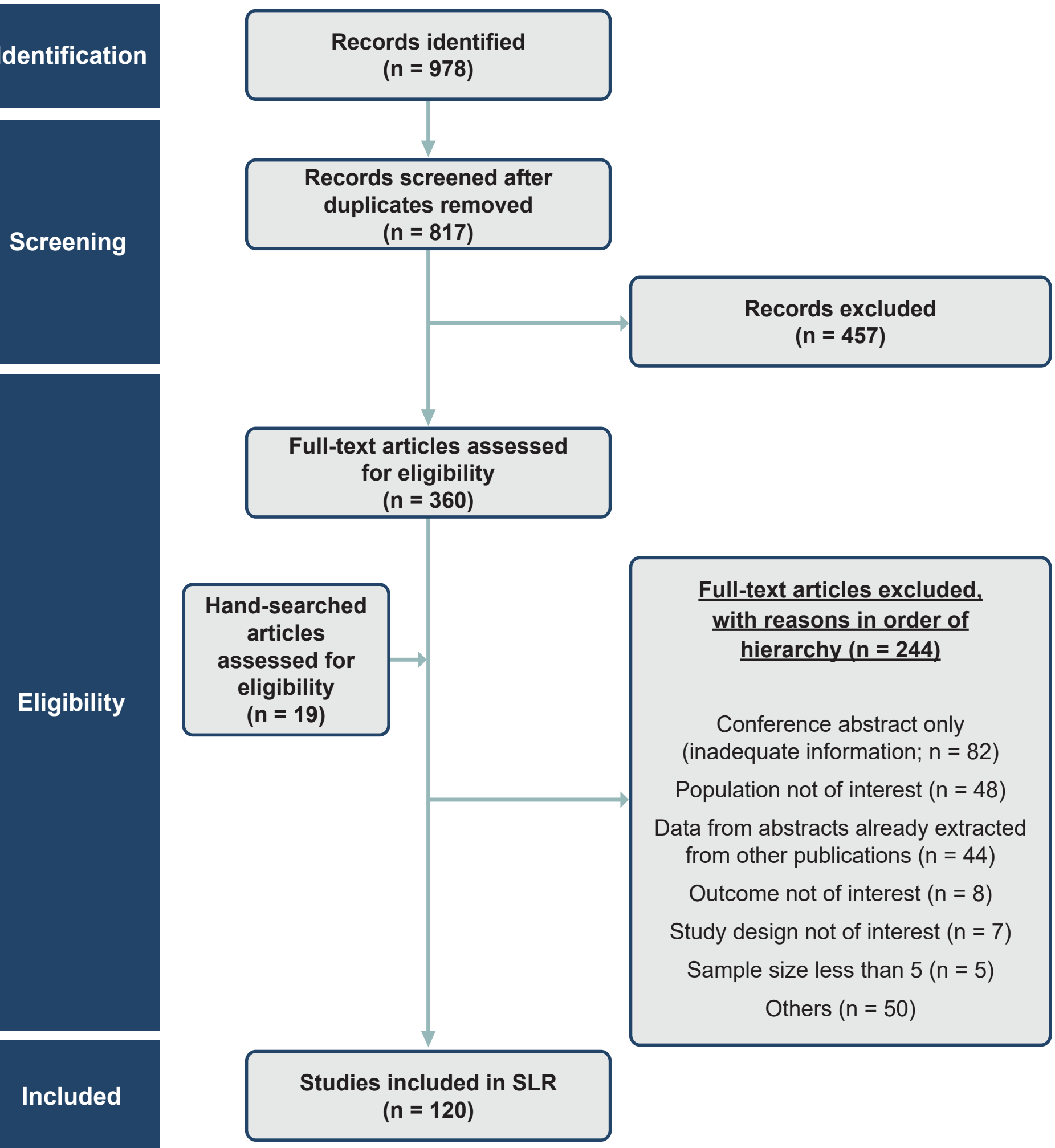
- Hammersmith Functional Motor Scale Expanded (HFMSE) scores
- Revised Upper Limb Module (RULM) scores

Results

SLR search

- Of the 978 identified articles, 120 met the search criteria for inclusion in the SLR (**Figure 1**)
  - Included studies comprised 18 clinical trials and 102 real-world studies
  - SMA types 2 and 3 were most frequently evaluated
- There were 44 publications with HFMSE scores and 36 publications with RULM scores

Figure 1. PRISMA flow diagram



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

References

1. Schroth M, et al. *Neural Clin Pract*. 2024;14(4):e003030. 2. Wertz MH, et al. *Ann NY Acad Sci*. 2016;1386(1):5-19. 3. Tosi M, et al. *Acta Myol*. 2022;41(3):117-20. 4. US Food and Drug Administration. FDA approves first drug for spinal muscular atrophy. December 23, 2016. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-spinal-muscular-atrophy>. 5. Bittel L, et al. *Orphanet J Rare Dis*. 2020;15(1):217. 6. Andrés-Benito P, et al. *Int J Mol Sci*. 2024;25(7):3810. 7. Belaric A, et al. *J Clin Med*. 2023;12(8):2818. 8. Bjelic B, et al. *J Neurol*. 2023;270(7):1816-22. 9. Bonanno S, et al. *J Neurol*. 2022;269(6):1264-75. 10. Coratti G, et al. *Eur J Neurol*. 2024;31(12):e16517. 11. Darras BT, et al. *Neurology*. 2019;92(21):e2492-4506. 12. Dunaway Young S, et al. *J Clin Med*. 2023;12(15):4901. 13. Elsheikh H, et al. *Front Neurol*. 2021;12:650532. 14. Günther R, et al. *Lancet Reg Health Eur*. 2024;38:100862. 15. Hagenacker T, et al. *Lancet Neurol*. 2020;19(4):317-25. 16. Lusakowska A, et al. *Orphanet J Rare Dis*. 2023;18(1):220. doi:10.1186/s13023-023-02769-4. 17. Maggi L, et al. *J Neurol Neurosurg Psychiatry*. 2020;91(11):1160-74. 18. Mercuri E, et al. *N Engl J Med*. 2018;378(25):35. 19. Pane M, et al. *Ann Clin Transl Neurol*. 2022;9(4):644-9. 20. Pechmann A, et al. *Orphanet J Rare Dis*. 2022;17(1):384. 21. Finkel RS, et al. Poster presented at: Core SMA Meeting; June 6-8, 2024. Szabo L, et al. *Eur J Paediatr Neurol*. 2020;27(3):42. 22. De Wei L, et al. *J Neuromuscul Dis*. 2021;8(suppl 1):S27. 24. Mercuri E, et al. *N Engl J Med*. 2018;378(7):625-35.

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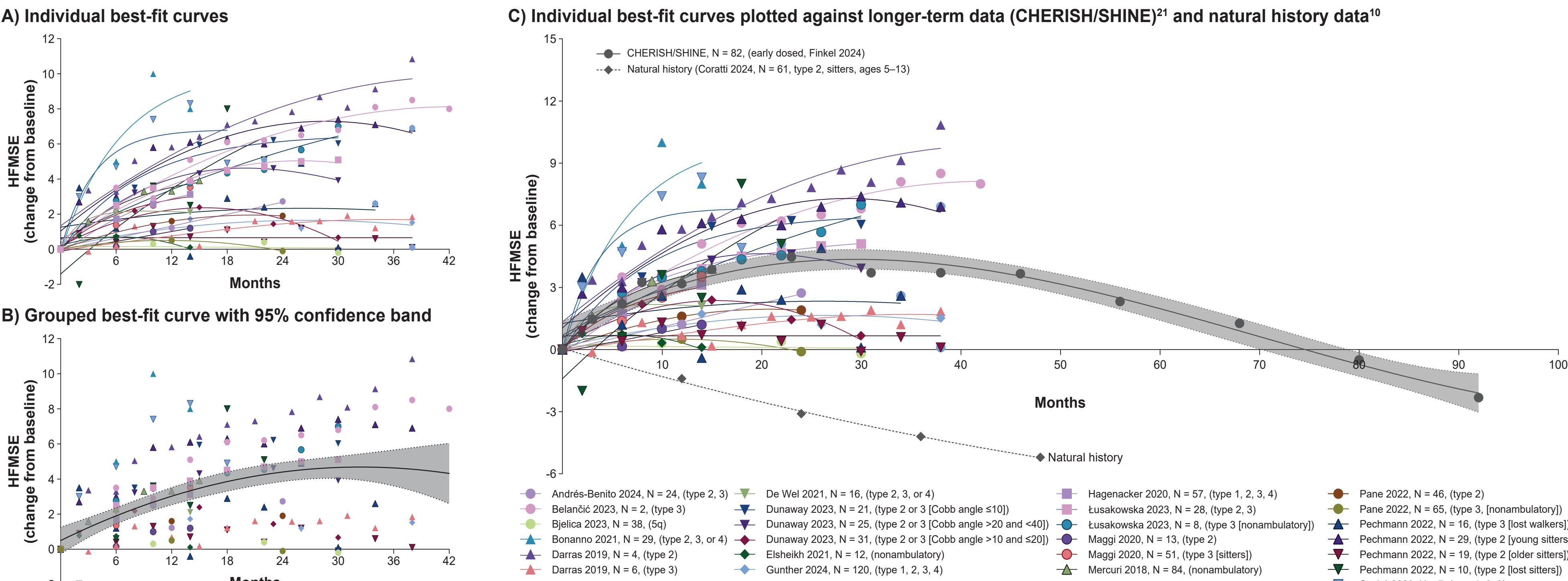
Disclosures

JMK has participated as the site principal investigator for clinical trials sponsored by Biogen, Flaxogen, Genentech, Novartis, Roche, and Scholar Rock, Inc., and has served as a consultant for Astellas as a member of an independent data monitoring committee. RLJ has participated as the site clinical evaluator for clinical trials sponsored by Biogen, Flaxogen, Genentech, Novartis, Roche, and Scholar Rock, Inc. JS is an employee of Value Matters, LLC, and was contracted by Scholar Rock, Inc., to perform the analysis. CC, RF, and TB are employees and stockholders of Scholar Rock, Inc.

HFMSE

- In total, 16 studies<sup>6-22</sup> reported a mean change from baseline at ≥2 time points with ≥1 assessment beyond 12 months
- Gain in HFMSE scores varied between studies, and the greatest change from baseline in HFMSE score for any single study was 10.8 points occurring at 38 months post-treatment initiation (**Figure 2A**)
- The maximum score on the HFMSE scale is 66 total points. However, across all studies, the average maximum total HFMSE score was 31.7 points
- Trajectories were largely consistent with a gain in HFMSE score occurring within the first 2 years following nusinersen initiation, after which the rate of improvement attenuated (**Figure 2A** and **2B**)
  - Comparison of the HFMSE scores from the CHERISH/SHINE extension study, with the best-fit curves of the other clinical trials and real-world studies, illustrated a consistent trajectory of change in HFMSE score following nusinersen treatment initiation (**Figure 2C**). CHERISH/SHINE was the only published study with longitudinal data beyond 42 months at the completion of this SLR
    - The CHERISH/SHINE study suggests there is a progressive decline in HFMSE scores after 42 months that continues to 92 months, though the rate of decline is still lower than would be expected in untreated individuals as reported by Coratti G, et al. 2024<sup>10</sup> (**Figure 2C**)

Figure 2. Improvement in HFMSE scores with nusinersen treatment primarily occurred within the first 2 years following treatment initiation

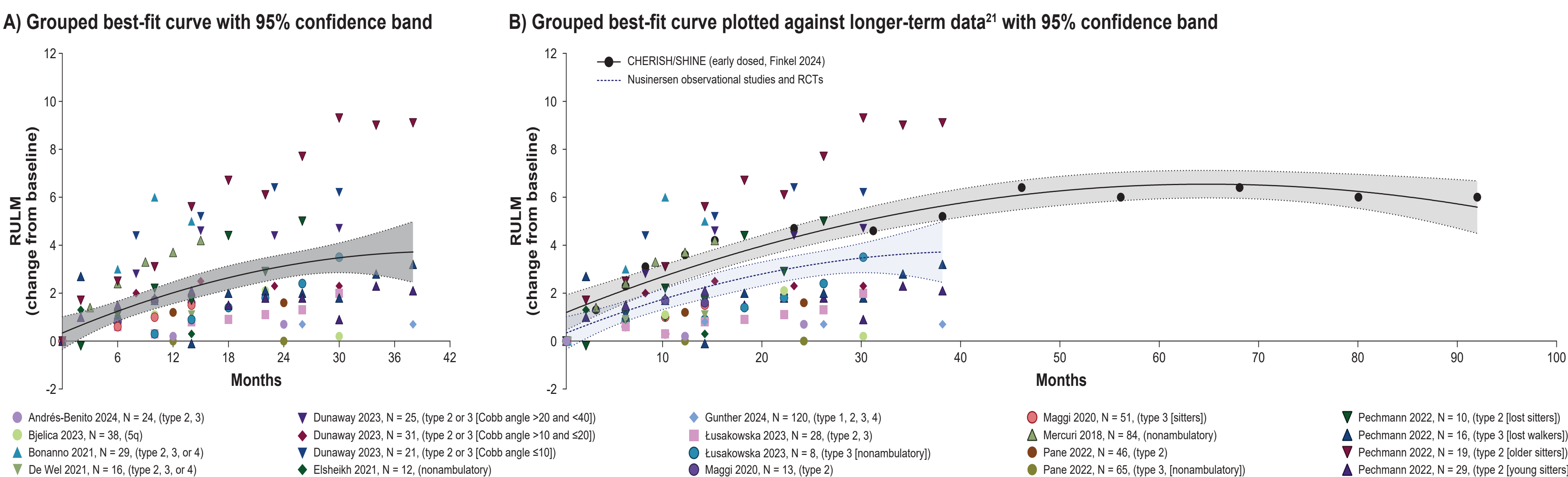


In panel A, the individual curves are best curve fits using polynomial (second and third order, centered and noncentered), exponential, or log normal. In panel B, the nonlinear curve fit is a second-order polynomial (quadratic) with 95% confidence bands. In panel C, the individual curves are best curve fits using polynomial (second and third order, centered and noncentered), exponential, or log normal. Longer-term data from Finkel et al<sup>21</sup> were plotted using a third-order polynomial (cubic) with 95% confidence band, and natural history data from Coratti et al<sup>10</sup> were plotted using a second-order polynomial (quadratic). HFMSE, Hammersmith Functional Motor Scale Expanded.

RULM

- In total, 12 studies<sup>6,8,9,12-14,16,17,19,20,23,24</sup> reported a mean change from baseline in RULM scores at ≥2 time points with ≥1 assessment beyond 12 months
- Gain in RULM scores varied between studies, and the greatest change from baseline in RULM score for any single study was 9.3 points at 30 months post-treatment initiation (**Figure 3**)
- The maximum score on the RULM scale is 37 total points. However, across all studies, the average maximum total RULM score was 22.7 points
- RULM scores demonstrated a rapid initial improvement in motor function that occurred in the first 2 to 3 years following treatment initiation, followed by a plateau with limited or no further gain (**Figure 3**)

Figure 3. Improvement in RULM scores with nusinersen treatment primarily occurred within the first 2 to 3 years following treatment initiation



In panel A and B, the nonlinear curve fits are a second-order polynomial (quadratic) with 95% confidence bands. RCT, randomized controlled trial; RULM, Revised Upper Limb Module.

Conclusions

- Clinical trials and real-world studies for nusinersen demonstrate the effectiveness of SMN-targeted treatment in improving motor function relative to the natural history of untreated individuals with SMA
- Longer-term clinical trial data suggest there is a plateau in gains for motor function as assessed by HFMSE and RULM scores approximately 2 years following treatment initiation
- While nusinersen is essential for preserving motor neurons, there remains significant residual disability and unmet need, as indicated by the degree of motor function attained as well as the progressive decline that was observed in HFMSE scores after 42 months of nusinersen treatment
- Longer-term follow-up assessing motor function in the real-world setting is required to further characterize the trajectory of motor function in patients receiving SMN-targeted treatments
- These data highlight the need for additional treatment approaches that can further improve motor function and prevent long-term decline