

Mexiletine Paediatric Investigation Plan, PIP4 Study: Efficacy findings in children with myotonia

Christine Barnérias¹; Arnaud Isapof²; Jean-Yves Hogrel³; Nikki Adetoro⁴; Alla Zozulya-Weidenfeller⁵

1. Hôpital Necker-Enfants Malades, Paris, France; 2. CHU Paris Est - Hôpital d'Enfants Armand-Trousseau, Paris, France; 3. Institute of Myology, Paris, France; 4. Lupin Pharmaceuticals, Baltimore, USA; 5. Lupin Neurosciences, Zug, Switzerland

Introduction

- Many patients with non-dystrophic myotonia (NDM) or myotonic dystrophy (DM) begin to experience myotonia symptoms during childhood.^{3,4}
- Myotonia can adversely impact physical, educational and social development, and is associated with negative burden, both on patients and caregivers.⁵
- Mexiletine is approved within the European Union and the United Kingdom for treating myotonia in adults with NDM.^{1,2}
- Given that no myotonia treatments are licensed for paediatric use, there is particular interest in examining the efficacy and safety of mexiletine in children and adolescents with NDM or DM.
- The Paediatric Investigation Plan (PIP) explores the safety, efficacy, and pharmacokinetics (PK) of mexiletine treatment in children and adolescents aged 0 – <18 years, with myotonic disorders.
- This poster examines the efficacy findings from PIP4 in children aged 6–<18 years; safety findings are reported separately; findings in younger children will be reported in future.⁶

Methods

- PIP4 (EudraCT2019-003757-28) was a 12-week (56 days) open-label exploration of mexiletine in sequential cohorts of patients with NDM or DM:
 - Cohort 1:** patients aged 12 – <18 years;
 - Cohort 2:** patients aged 6 – <12 years.
- Cohort 2 was only enrolled when the Data Safety Monitoring Board assessed there were no safety concerns and the dose for the younger age group had been confirmed by PK modelling.
- The study included 4 weeks' screening; 4 weeks' mexiletine titration (62, 83 or 167mg once-daily* titrated to maximum 3-times-daily), and 4 weeks' maintenance treatment at best-tolerated dose:
 - During titration, the mexiletine dose was increased every 14 days based on tolerability.
- Efficacy endpoints (baseline to end of study):
 - Relaxation time measured by handgrip dynamometer;
 - Patient-reported visual-analogue scale (VAS) 0–100 scores (stiffness, pain, weakness/fatigue);
 - Myotonia Behavioural Scale (MBS) scores;
 - Pediatric Quality of Life Inventory™ (PedsQL) findings;
 - Clinical Global Impression (CGI) scores.
- Summary statistics are provided for all collected parameters:
 - Statistical analyses were undertaken with Student-Newman-Keuls or Wilcoxon tests as appropriate;
 - Significance set at P < 0.05.
- PIP4 received appropriate Institutional Review Board/Independent Ethics Committee approval and was conducted in compliance with International Council on Harmonization Guidelines and Good Clinical Practice.
- Informed consent was obtained from study participants (or their legal representatives).

*Mexiletine hydrochloride 75 mg capsules containing 62 mg mexiletine, 100 mg capsules containing 83 mg mexiletine, or 200 mg capsules containing 167 mg mexiletine.

Results

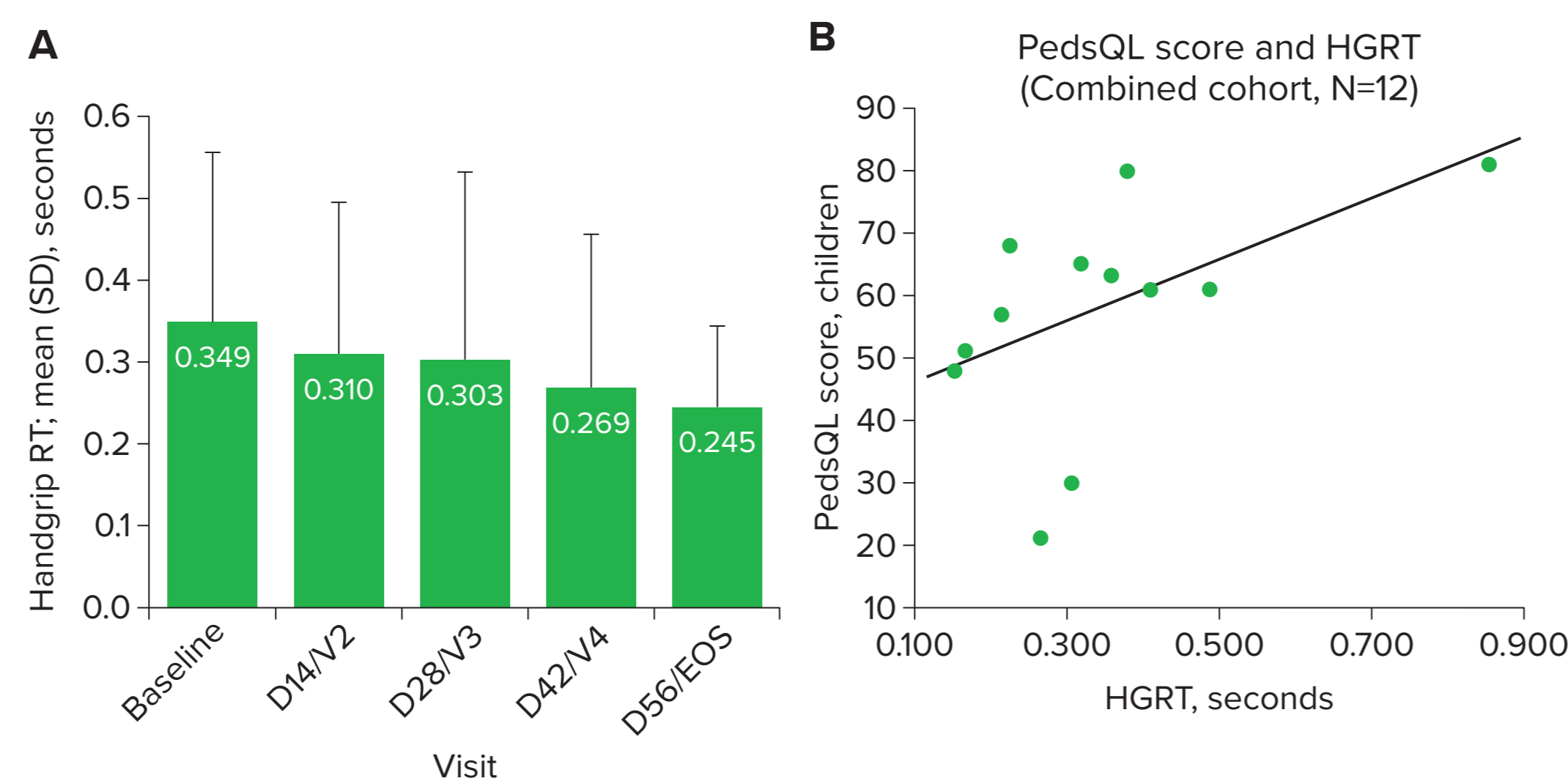
Patient demographics:

- Cohort 1 (N=7): Mean age 13 years; male, n=3; female, n=4; DM type 1 (DM1), n=2; Becker NDM, n=3; Thomsen NDM, n=2.
- Cohort 2 (N=5): Mean age 8 years; male, n=2, female n=3; paramyotonia congenita, n=2; Becker NDM, n=1; Thomsen NDM, n=2.

Handgrip relaxation time

- Mexiletine treatment improved mean relaxation time (all cohorts, **Figure 1**).

Figure 1. (A) Mexiletine treatment improved handgrip relaxation time (RT), as measured by dynamometer, over time; n= 10. A positive correlation between HGRT and PedsQL score was observed at baseline across the cohort (N=12)

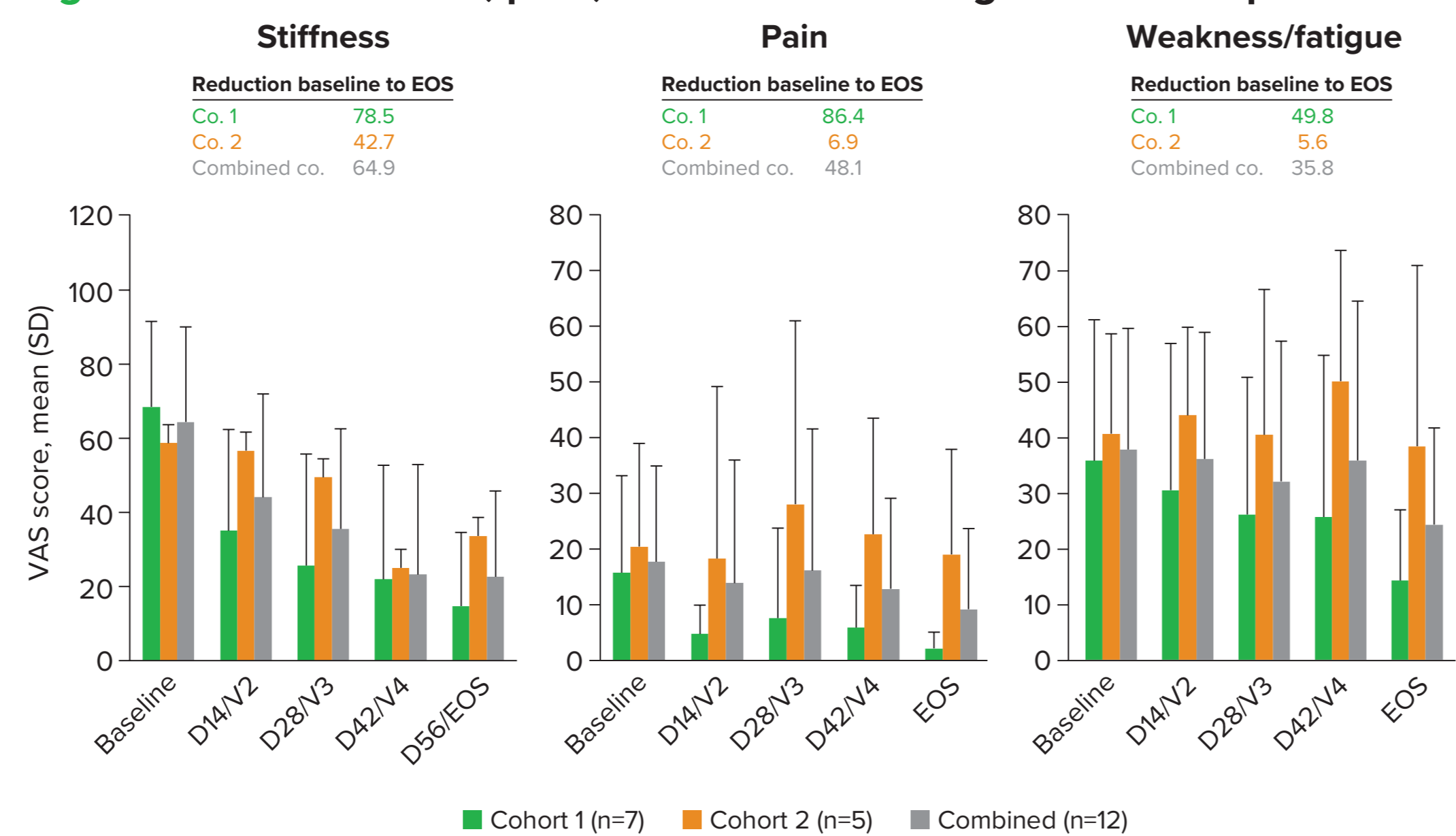


D, day; EOS, end of study; RT, relaxation time; SD, standard deviation; V, visit.

Visual-Analog Scale scores

- Across the cohorts, patients' scores for stiffness, pain, and weakness/fatigue consistently showed improvements following mexiletine treatment (**Figure 2**).

Figure 2. VAS* stiffness, pain, and weakness/fatigue scores improved

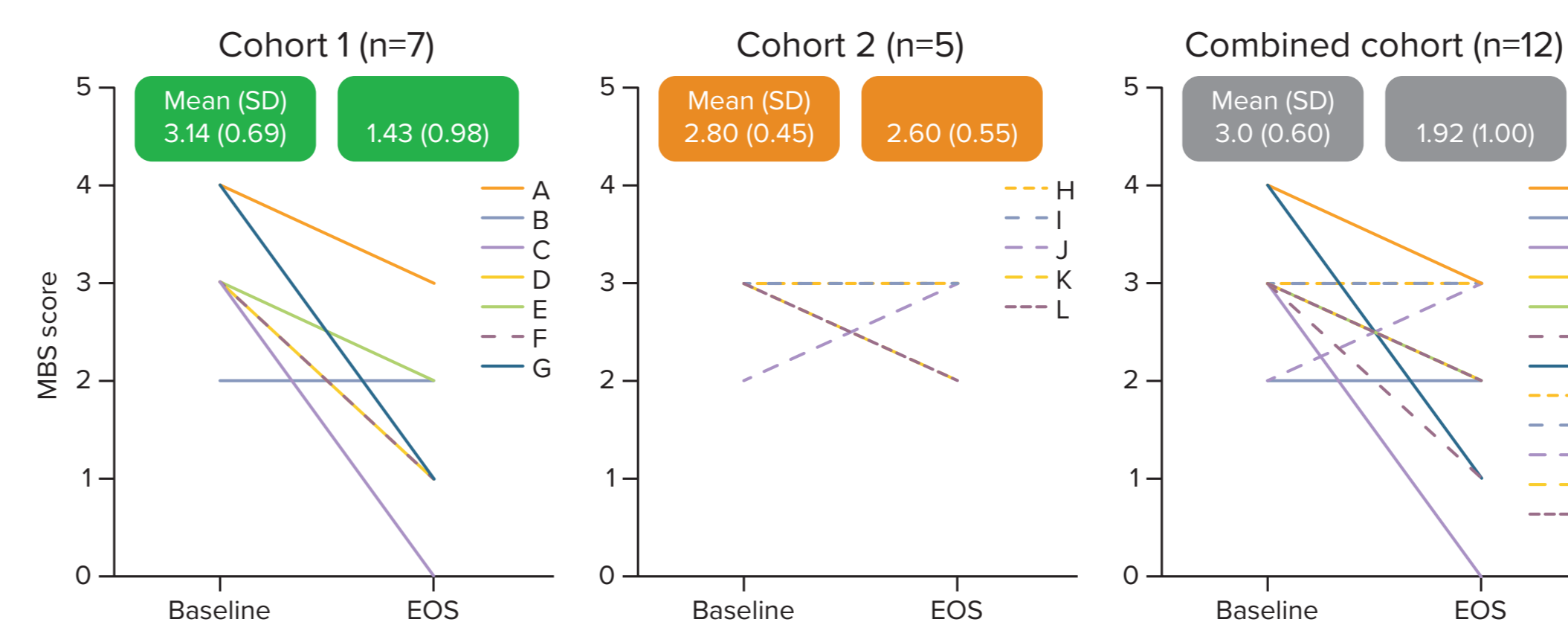


VAS score: 0-100, 0=no issue with the symptom, 100=symptom as bad as it could be. Lower scores indicate lower symptom burden. *n=2 patients had Facial Affective Scale (0-10 scale) rather than VAS scores, these were converted by multiplying by 10. D, day; Co., cohort; EOS, end-of-study; SD, standard deviation; V, visit.

MBS scores

- MBS scores improved (n=8; 67%), were stable (n=3; 25%) or worsened (n=1; 8%).
- Overall, MBS scores improved with treatment (**Figure 3**).

Figure 3. MBS scores improved, with the majority of children experiencing less stiffness after receiving mexiletine for myotonia

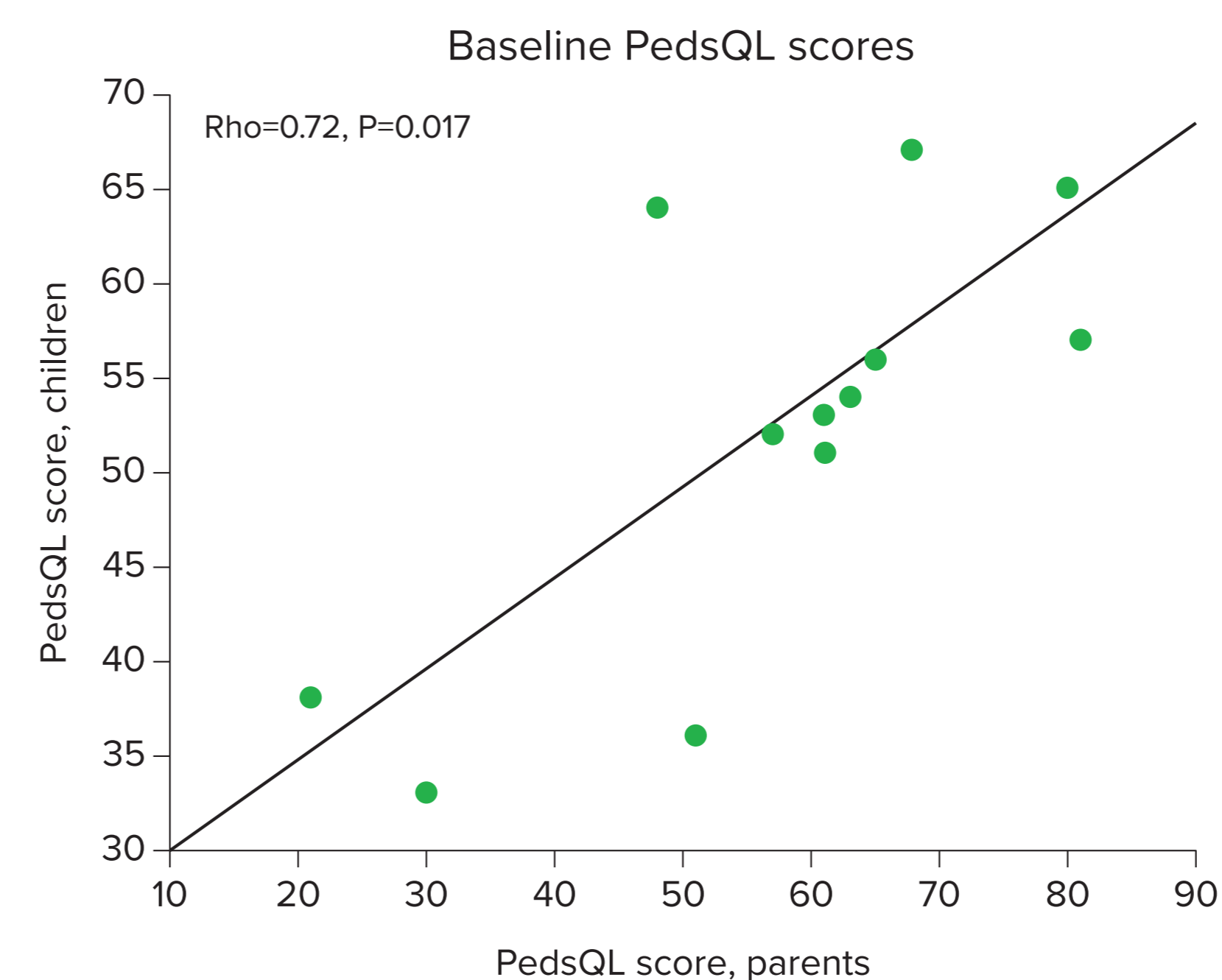


MBS scoring: 0=No stiffness, 1=Some stiffness exists, which can be ignored, 2=Some stiffness exists, which can be ignored at times, but doesn't impair daily activities, 3=Stiffness exists, which demands a higher level of mental awareness when performing some duties and activities, 4=Severe stiffness exists, which impairs every duty and activity, 5=Incapacitating stiffness exists, which demands constant moving not to be totally locked up, with regard to movement. EOS, end of study; MBS, myotonia behaviour score; SD, standard deviation. Letters indicate individual participants.

PedsQL scores

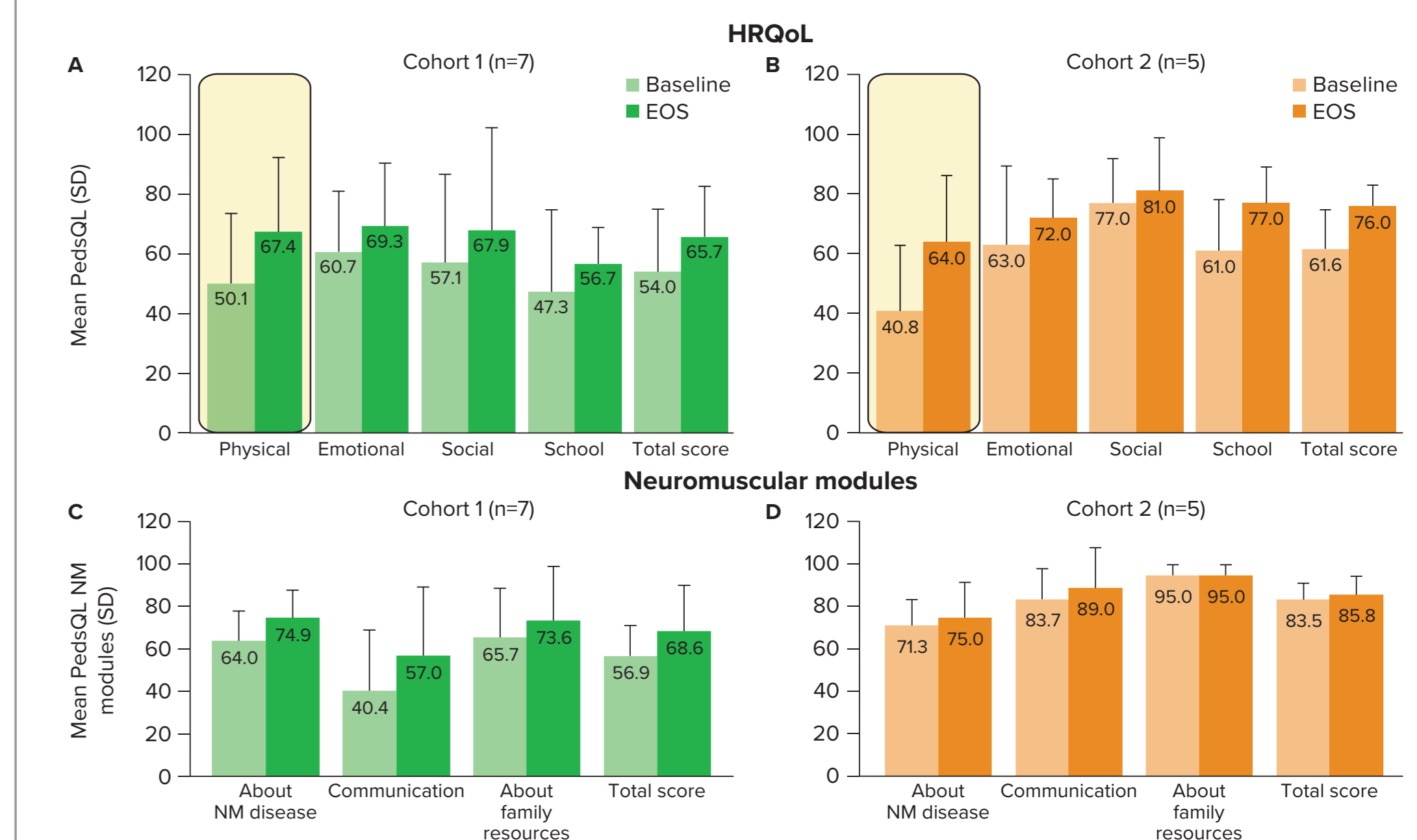
- There was a clear correlation between parents' and children's baseline PedsQL scores (**Figure 4**):
 - Parental-reported PedsQL and neuromuscular scores were generally consistent with patient-reported scores (data not shown).

Figure 4. There was a clear correlation between parents' and children's baseline PedsQL scores



- Improvements were observed for patient-reported PedsQL (**Figure 5**), especially physical domain (most impacted at baseline) and among older children.
- PedsQL neuromuscular scores also improved, especially in Cohort 1.

Figure 5. Improvements were observed in patient-reported PedsQL scores, Health-related quality of life (A, B) and Neuromuscular Modules (C, D) especially for Physical domain (highlighted)



PedsQL score: 100=never, 75=almost never, 50=sometimes, 25=often, 0=almost always. Higher scores indicate better quality of life. Total Score - mean computed as sum of all items over number of items answered on all scales. EOS, end of study; HRQoL, health-related quality-of-life; NM, neuromuscular; PedsQL, Paediatric Quality of Life Inventory; SD, standard deviation.

Clinical Global Impression scores

- For CGI, mexiletine was rated very efficient (25%), good (66.7%), fair (8.3%) (all cohorts).
 - In Cohort 1, mexiletine was rated as very efficient (42.9%) or good (57.1%);
 - In Cohort 2, mexiletine was rated as good (80%) or fair (20%).

Conclusions

- PIP4 confirms that mexiletine is efficacious treatment for myotonia in children aged 6 – <18 years.
- Improvements were observed across most outcomes including handgrip relaxation time; VAS stiffness, pain and weakness/fatigue; MBS; PedsQL; and CGI.
- There were trends towards greater improvements in VAS scores, MBS, and PedsQL neuromuscular modules in the older versus the younger patient cohort.
- PIP4 participants all enrolled in the extension study, PIP7 (EudraCT: 2019-003758-97) and are being followed for ≥2 years.

References

- Namuscla (mexiletine) 167 mg hard capsules. EU Summary of Product Characteristics. Accessed at: https://www.ema.europa.eu/en/documents/product-information/namuscla-epar-product-information_en.pdf. Accessed on 07 May 2025.
- Namuscla (mexiletine) 167 mg hard capsules. UK Summary of Product Characteristics. <https://www.medicines.org.uk/emc/product/9838/smpc#ref>. Accessed on 07 May 2025.
- Stunnenberg CC, et al. Muscle Nerve 2020;62:430-444.
- Wahbi K, et al. Arch Cardiovasc Dis 2024;117:450-456.
- Díaz-Manera J, et al. EMJ 2021;6:37-46.
- Barnérias C, et al. EPNS 2025; Abstract A-25-13754; Poster EPO-466.

Acknowledgements

Professional medical writing and editorial assistance was provided by Mike Lappin PhD of Curve Medical Ltd, and Linda Edmondson of LEMC, funded by Lupin Neurosciences.

Disclosures/conflicts of interest

CB, AI, J-YH: consultancy fees from Lupin
NA, AZ-W: employee of Lupin

