

Magnitude of Response With Subcutaneous Efgartigimod PH20 in Chronic Inflammatory Demyelinating Polyneuropathy: ADHERE/ADHERE+ Trials



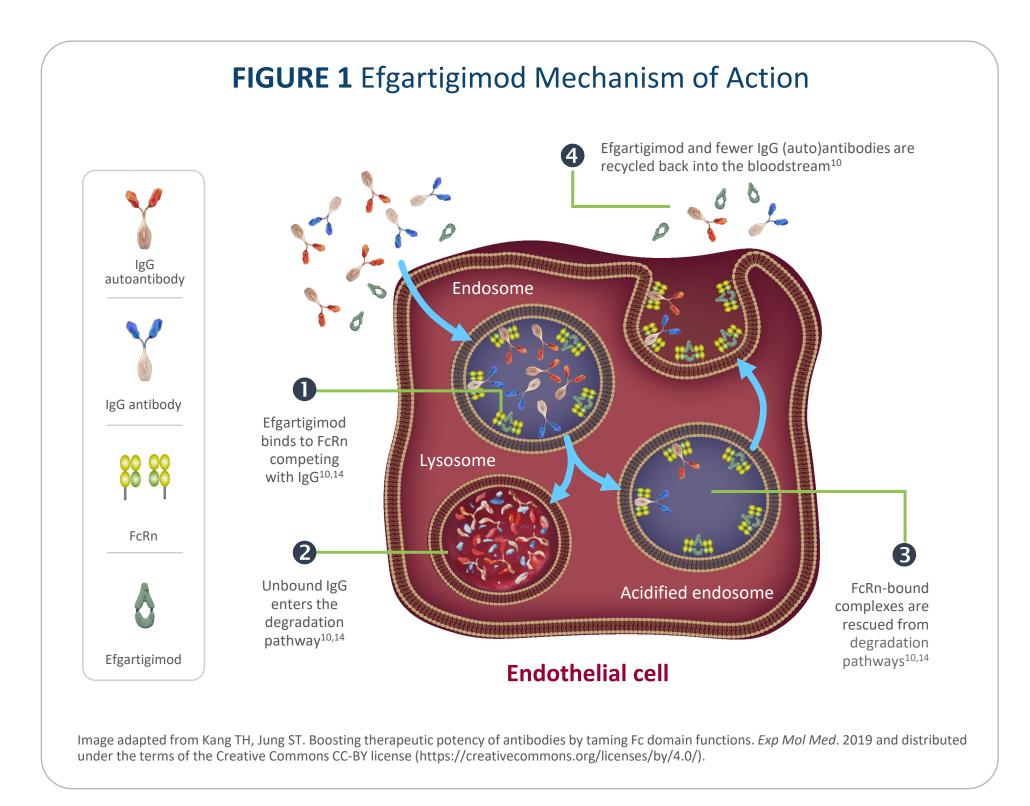
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BACKGROUND

Efgartigimod Blocks FcRn and Reduces IgG Levels

- CIDP is an autoimmune, inflammatory, demyelinating neuropathy resulting in distal/proximal weakness and/or sensory deficits, with a high treatment burden^{1–4}
- Evidence supports a role for pathogenic IgG antibodies in the pathophysiology of CIDP, although in most patients, a specific antibody is currently not detectable^{5–8}
- FcRn recycles IgG antibodies, saving them from lysosomal degradation resulting in IgG antibodies having the longest half-life and being the most abundant of all Ig⁹⁻¹¹
- Efgartigimod is an IgG1 antibody Fc fragment engineered for increased affinity for FcRn compared to endogenous IgG, and is uniquely composed of the only part of the IgG antibody that normally binds FcR^{10,12}
- Efgartigimod selectively reduces IgG by blocking FcRn-mediated IgG recycling without impacting antibody production, reducing albumin levels, or affecting other parts of the immune system^{10–13} (**Figure 1**)



Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for low volume (~5 mL) and rapid (30–90s single injection) SC administration^{15,16}

METHODS

• The multi-stage, double-blinded, placebo-controlled, randomized-withdrawal ADHERE trial, and ongoing OLE ADHERE+ trial (data cut-off: June 15, 2023) assessed the efficacy and safety of efgartigimod PH20 SC in adults with CIDP (Figure 2)

FIGURE 2 Trial Designs of ADHERE and ADHERE+ Baseline characteristics were balanced between treatment arms and trials adhere **Identify participants** Assess efficacy and safety with active CIDP clinical respons Stage A: Open-label Screening ≤4 weeks by adjudication panel of CIDP experts* • INCAT score ≥2 at the first run-in visit or QW 1000 mg stage A baseline efgartigimod PH20 SC Current CIDP treatment (n=322) QW placebo PH20 SC - Corticosteroids – IVIg/SCIg Off treatment: treatment discontinued Until confirmed ECI ≥6 months before study entry or without previous treatment PRIMARY ENDPOINT PRIMARY ENDPOINT Time to first aINCAT deterioration (relapse) Percentage of participants with confirmed ECI compared with stage B baseline Run-in period ≤12 weeks SELECTED SECONDARY ENDPOINT Improvement in efficacy parameters at Participants on treatment must suspend stage B best assessment from run-in baseline therapy and demonstrate ECMD (post hoc analysis) Participants off treatment with active disease may skip the run-in and enter **SELECTED SECONDARY ENDPOINTS** Mean change from baseline to last assessment in aINCAT score, I-RODS score, mean grip strength, EQ-5D-5L, Total MRC sum and TUG test scores, and safety (both stages) 99% of eligible participants entered ADHERE+‡ (n=228/229) adhere+ Assess safety and tolerability Open-label, long-term extension Inclusion criteria to rollover QW 1000 mg efgartigimod PH20 SC Completed Week 48 ADHERE stage B, OR Deteriorated during ADHERE stage B, OR PRIMARY ENDPOINT Terminated ADHERE early (sufficient events for primary endpoint Long-term safety and tolerability

*According to 2010 criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (Van den Bergh PYK, et al. Eur J Neurol. 2010), progressing or relapsing forms.

†Stage B primary endpoint was assessed once 88 total relapses or events were reached in stage B; this is the time point when the ADHERE trial terminated. ‡229 participants enrolled in ADHERE+,

including 3 participants who inadvertently rolled over without meeting per-protocol inclusion criteria. The safety population for ADHERE+ included 228 participants who received ≥1 dose of

Definitions

- Evidence of clinically meaningful deterioration (ECMD): aINCAT increase of ≥1 points, an I-RODS decrease of ≥4 points (centile metric), or a grip strength decrease of ≥8 kPa
- Evidence of clinical improvement
 (ECI): clinical improvement on the
 parameters that the participant
 worsened in during run-in (≥4-point
 increase in I-RODS and/or ≥8 kPa
 increase in mean grip strength) or
 clinical improvement (≥1-point
 decrease) in INCAT; ECI was
 confirmed after these criteria were
 met after 4 injections and 2
 consecutive visits
- Adjusted Inflammatory Neuropathy
 Cause and Treatment (aINCAT)
 deterioration: compared with stage
 B baseline, ≥1-point increase in
 aINCAT confirmed at a consecutive
 visit after the first 1-point increase in
 aINCAT, or ≥2-point increase in
 aINCAT observed at a single visit

Primary endpoints in ADHERE were met; efficacy and safety data have previously

with efgartigimod PH20 in stage B, but partially lost with placebo (**Table 1**)

Efgartigimod PH20 SC Demonstrated Clinical Benefits

been reported¹⁷
 Clinical improvements across aINCAT score, I-RODS score, mean grip strength, EQ-5D-5L,
 Total MRC sum score, and TUG test scores were observed in stage A and maintained

TABLE 1 ADHERE Trial Selected Secondary Efficacy Endpoints

		ADHERE		
	Open-Label Stage A	Double-Blinded Stage B		
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (n=111)	Placebo (n=110)	
-RODS decrease of ≥4 points, n (%)	-	40 (36.0)	57 (51.8)	
HR (95% CI) [Nominal <i>P</i> value]		0.537 (0.354–0.814) [0.0034]		
-RODS increase of ≥4 points, n (%)	-	50 (45.0)	40 (36.4)	
Odds ratio (95% CI) [Nominal P value]		1.441 (0.814–2.567) [0.2294]		
change from respective baseline to last assess	ment,* mean (SE)			
change from respective baseline to last assess	ment,* mean (SE) -0.9 (0.10)	0.1 (0.10)	0.9 (0.19)	
<u> </u>		0.1 (0.10) 0.8 (1.17)	0.9 (0.19) -7.0 (1.84)	
aINCAT score [†]	-0.9 (0.10)			
aINCAT score [†] I-RODS score [‡]	-0.9 (0.10) 7.7 (0.87)	0.8 (1.17)	-7.0 (1.84)	
aINCAT score [†] I-RODS score [‡] Grip strength (dominant hand), kPa	-0.9 (0.10) 7.7 (0.87) 12.3 (1.05)	0.8 (1.17) 2.1 (1.26)	-7.0 (1.84) -8.2 (1.98)	

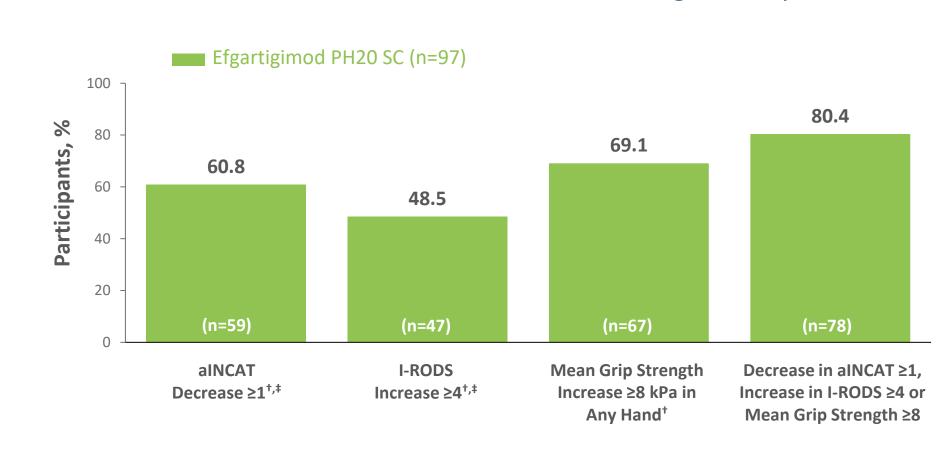
*For stage A, this was the change from stage A baseline to stage A last assessment, and for stage B, this was the change from stage B baseline to stage B last assessment.

†Higher aINCAT score indicates worsening of disease. ‡Lower I-RODS score indicates worsening of disease. §Lower EQ-5D-5L VAS values indicate worse quality of life.

|Lower Total MRC sum score indicates greater muscle weakness.

- In ADHERE, 60.8%, 48.5%, and 69.1% of participants treated with efgartigimod PH20 SC experienced, respectively, a decrease of ≥1 points in aINCAT score, ¹⁸ an increase of ≥4 points in I-RODS score ¹⁹ and ≥8 kPa in grip strength, ²⁰ all considered clinically meaningful improvements ²¹ (**Figures 3 and 4**)
 - 80.4% of participants experienced clinically meaningful improvements in at least one of these assessments (**Figure 3**)

FIGURE 3 Post Hoc Analysis*: Improvement in Efficacy Parameters at Stage B Best Assessment From Run-In Baseline in Stage A Responders



*Analysis set population included efgartigimod-responders in stage A with run-in baseline values. †Mean run-in baseline in aINCAT was 4.0, 48.2 in I-RODS, and 42.6 kPa in grip strength. ‡Some participants could not improve beyond a certain level due to their baseline aINCAT and I-RODS score (ie, participants with an aINCAT baseline score of 2 or 3 could not reach improvements of 3 or 4, respectively).

Efgartigimod PH20 SC Was Well Tolerated in ADHERE and ADHERE+

• The incidence of TEAEs did not increase with increased exposure to efgartigimod PH20 SC in ADHERE+ (**Table 2**); most TEAEs were mild or moderate in severity

RESULTS

FIGURE 4 *Post Hoc* Analyses*: Cumulative Frequencies of Stage B Best Assessment From Run-In Baseline in Stage A Responders in Different Efficacy Parameters in ADHERE

efgartigimod PH20 SC in the OLE, as 1 participant discontinued before receiving the first dose of efgartigimod PH20 SC.

*Analysis set population included efgartigimod-responders in stage A with run-in baseline values. †The INCAT disability score¹⁷ is a 10-point scale that assesses activity limitations of arms and legs; both are scored separately from 0–5, with 0 representing no functional impairment and 5 representing inability to make any purposeful movement. ‡Changes in the function of the upper limbs from 0 (normal) to 1 (minor symptoms) or vice versa were not recorded as deterioration or improvement, because these changes were not considered clinically significant. §Some participants could not improve beyond a certain level due to their baseline score (ie, participants with a score of 2 or 3

Functional Ability: aINCAT^{17,†,‡}

Daily Ability: Centile Metric I-RODS^{18,||}
Mean (min, max) I-RODS run-in baseline score:
48.2 (14, 100)

The I-RODS¹⁸ is a patient-reported disability score,

could not reach improvements of 3 or 4, respectively).

a 24-item scale with each item representing a common daily activity that ranges from very difficult to do to very easy to do; scores range from 0–48 and are converted to a centile metric score ranging from 0–100. ¶Some participants could not improve beyond a certain level due to their baseline score.

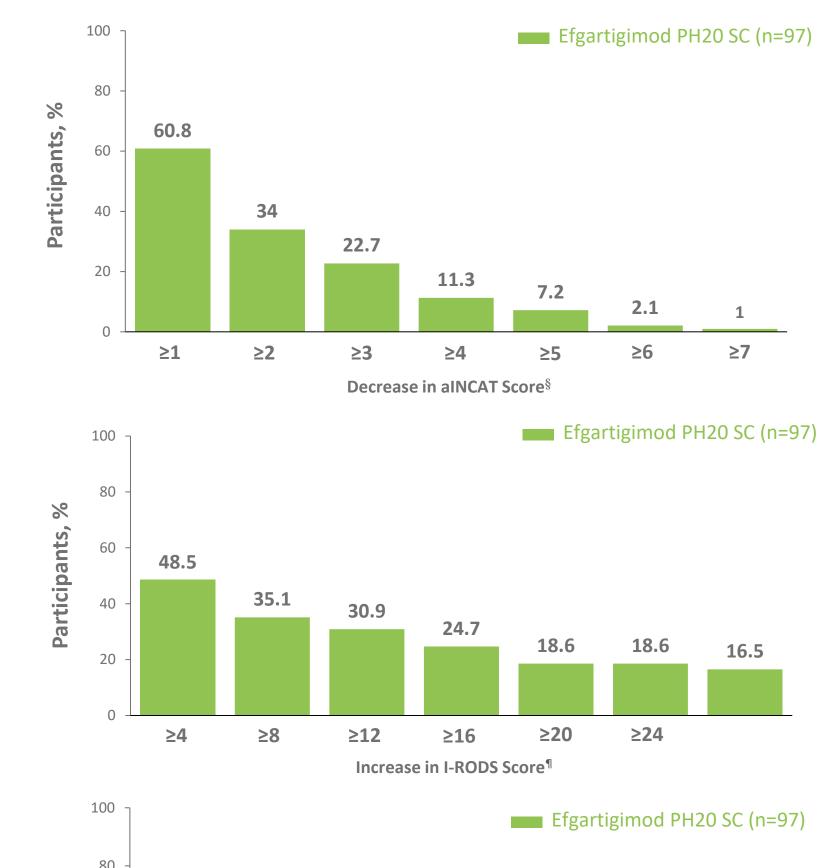
Mean (min, max) grip strength (dominant hand)
run-in baseline score: 44.4 kPa (0, 97)

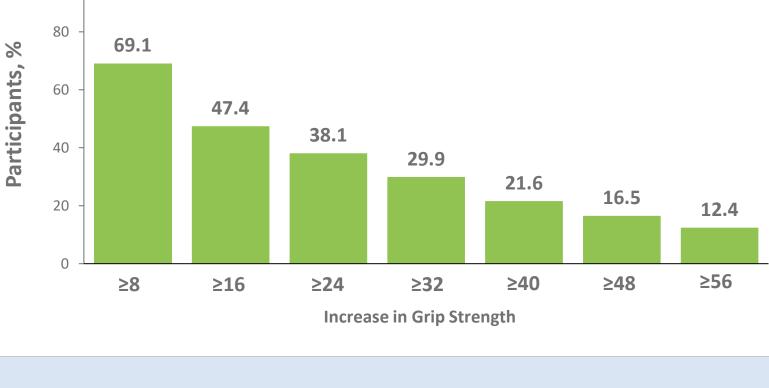
Mean (min, max) grip strength (non-dominant hand)
run-in baseline score: 42.6 kPa (0, 90)

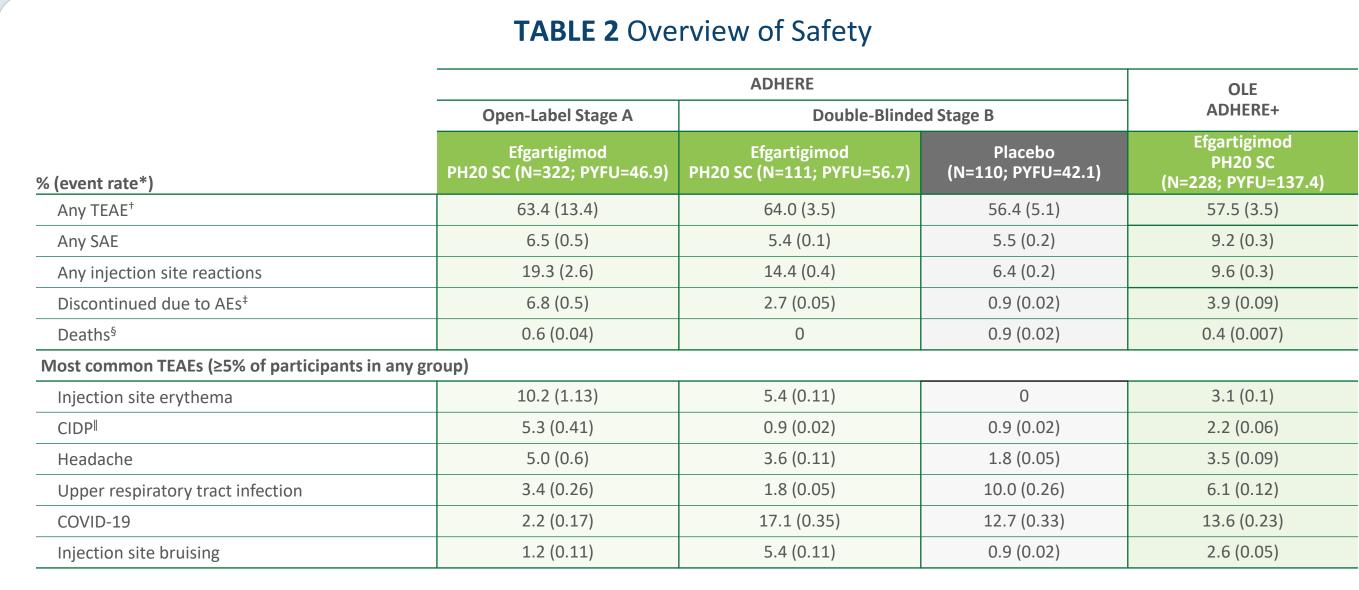
**Participants performed three assessments with a handheld

Mean Grip Strength: Either Dominant or Non-Dominant Hand (kPa)**

Martin-Vigorimeter for each hand in an arbitrary order (with an approximately 30 second rest period between each assessment) at approximately the same time during the day.







*Event rate was calculated as the number of events divided by the total PYFU. †There were no reports of anaphylaxis. ‡TEAEs (Preferred Terms) leading to efgartigimod PH20 SC discontinuation were: cardiac arrest (n=1), injection site rash (n=1), COVID-19 (n=1), COVID-19 pneumonia (n=1), muscular weakness (n=1), CIDP (n=15), quadriparesis (n=1), and pruritus (n=1) in stage A; COVID-19 pneumonia (n=1), prostate cancer (n=1), and transitional cell carcinoma (n=1) in stage B efgartigimod PH20 SC; pneumonia (n=1) in stage B placebo; lymphadenitis (n=1), eye movement disorder (n=1), asthenia (n=1), hepatic function abnormal (n=1), COVID-19 (n=1), CIDP (n=4), and cranial nerve disorder (n=1) in ADHERE+ efgartigimod PH20 SC; one death (pneumonia) in the placebo arm of stage B was considered treatment related; 1 death (CIDP deterioration) in ADHERE+ was considered related to efgartigimod PH20 SC. ||CIDP signs/symptoms recorded as TEAEs (regardless of causality) if there was CIDP worsening/deterioration.

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KEY TAKEAWAYS



Participants treated with efgartigimod PH20 SC demonstrated clinical benefits in ADHERE

- Clinical improvements across different selected secondary efficacy endpoints supported the primary endpoint
- Approximately half of the participants experienced clinically meaningful improvements across different efficacy parameters



Weekly efgartigimod PH20 SC was well tolerated, with a safety profile that was:

- Similar between ADHERE and ADHERE+, with no increase in TEAE rates with increased exposure
- Consistent with that of efgartigimod in clinical trials in other autoimmune diseases^{12,22–24}



A single, rapid (30–90s) injection of weekly efgartigimod PH20 SC was recently approved in the US for adults with CIDP, 17 representing a new therapeutic option that may reduce CIDP treatment burden

Presented at the 2025 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference; March 16–19, 2025; Dallas, TX, USA

ABBREVIATIONS

AE, adverse event; aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; EQ-5D-5L, EuroQol-5 Dimension-5 Levels; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; HR, hazard ratio; Ig, immunoglobulin; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; IVIg, intravenous immunoglobulin; max, maximum; min, minimum; MRC, Medical Research Council; OLE, open-label extension; PH20, recombinant human hyaluronidase PH20; PYFU, participant-years of follow-up; QW, once weekly; R, randomization; SAE, serious adverse event; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; TUG, Timed Up and Go; VAS, visual analog scale.

DISCLOSURES AND ACKNOWLEDGMENTS

JAA: Akcea Therapeutics, Alexion, Alnylam Pharmaceuticals, Annexon Biosciences, argenx, CSL Behring, Grifols, Immunovant, ImmuPharma, Johnson & Johnson, Pfizer, Takeda; RAL: Alexion, Annexon Biosciences, argenx, Avilar Therapeutics, BioCryst, Boehringer Ingelheim, CSL Behring, Dianthus Therapeutics, GBS/CIDP Foundation International, Grifols, Immunovant, Intellia Therapeutics, Johnson & Johnson, Medscape, MGFA, Nervosave Therapeutics, Novartis, Nuvig Therapeutics, Peripheral Nerve Society, Sanofi, Seismic Therapeutic, Takeda, TGTX, UpToDate; LQ: Alnylam Pharmaceuticals, Annexon Biosciences, argenx, Avilar Therapeutics, Biogen, CIBERER, CSL Behring, Dianthus Therapeutics, Fundació La Marató, GBS/CIDP Foundation International, Grifols, Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), Janssen, LFB, Lundbeck, Merck, Novartis, Octapharma, Roche, Sanofi, UCB; CE: argenx, Biogen, GlaxoSmithKline, UCB; SK: Alexion, argenx, CSL Behring, Takeda; YMH: Nothing to declare; KGG: Alexion, argenx, UCB, Xeris Pharmaceuticals; JTG, GI, BVH, ADR: Employees of argenx; IB: Actavis, Dianthus Therapeutics, Mylan, Pfizer, Salveo Pharma; PAvD: Annexon Biosciences, argenx, Grifols, Hansa Biopharma, Octapharma, Prinses Beatrix Spierfonds, Roche, Sanofi, Sanquin, Takeda.

These trials were sponsored by argenx. Medical writing support was provided by Envision Pharma Group, funded by argenx. The authors gratefully acknowledge the trial participants and investigators involved Previously presented at the 18th International Congress on Neuromuscular Diseases (ICNMD), Perth, Australia, October 25–29, 2024.

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