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Efficacy and Safety of Subcutaneous Efgartigimod PH20 in Chronic Inflammatory Demyelinating Polyneuropathy: ADHERE Trial Subgroup Analysis

Jeffrey A. Allen,[1] Richard A. Lewis,[2] Luis Querol,[3,4] Yessar Hussain,[5] Kelly Gwathmey,[6] Niraja Suresh,[7]* Jeffrey T. Guptill,[8,9] Erik Hofman,[8] Benjamin Van Hoorick,[8] Trevor Mole,[8] Satoshi Kuwabara,[10] Ivana Basta,[11] Pieter A. van Doorn[12]

[1]Department of Neurology, University of Minnesota, Minneapolis, MN, USA; [2]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Department of Neurology, Neuromuscular Diseases Unit, Hospital de La Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Madrid, Spain; [5]Austin Neuromuscular Center, Austin, TX, USA; [6]Department of Neurology, Virginia Commonwealth University, Richmond, VA, USA; [7]Department of Neurology, University of South Florida, Tampa, FL, USA; [8]argenx, Ghent, Belgium; [9]School of Medicine, Duke University, Durham, NC, USA; [10]Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan; [11]Neurology Clinic, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [12]Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands. *At the time of the trial.

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BACKGROUND

Efgartigimod Blocks FcRn and Reduces IgG Levels

- CIDP is an immune, inflammatory, demyelinating neuropathy resulting in distal/proximal weakness and/or sensory deficits, with a high treatment burden[1,2]
- Evidence supports a role for pathogenic IgG in the development of CIDP, although there is currently not a known pathogenic autoantibody identified in most patients[3–6]
- FcRn recycles IgG, extending its half-life, and maintaining serum concentrations of both IgG and the pathogenic IgG autoantibodies[7]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity for FcRn[8,9] (**Figure 1**)
- Efgartigimod was designed to outcompete endogenous IgG at FcRn, including pathogenic IgG, preventing recycling and promoting lysosomal degradation of IgG, without impacting its production, leading to[8–13]:
  - Targeted reduction of all IgG subtypes
  - No impact on other immunoglobulins (IgA or IgM)
  - No reduction in albumin or increase in cholesterol levels

FIGURE 1 Efgartigimod Mechanism of Action

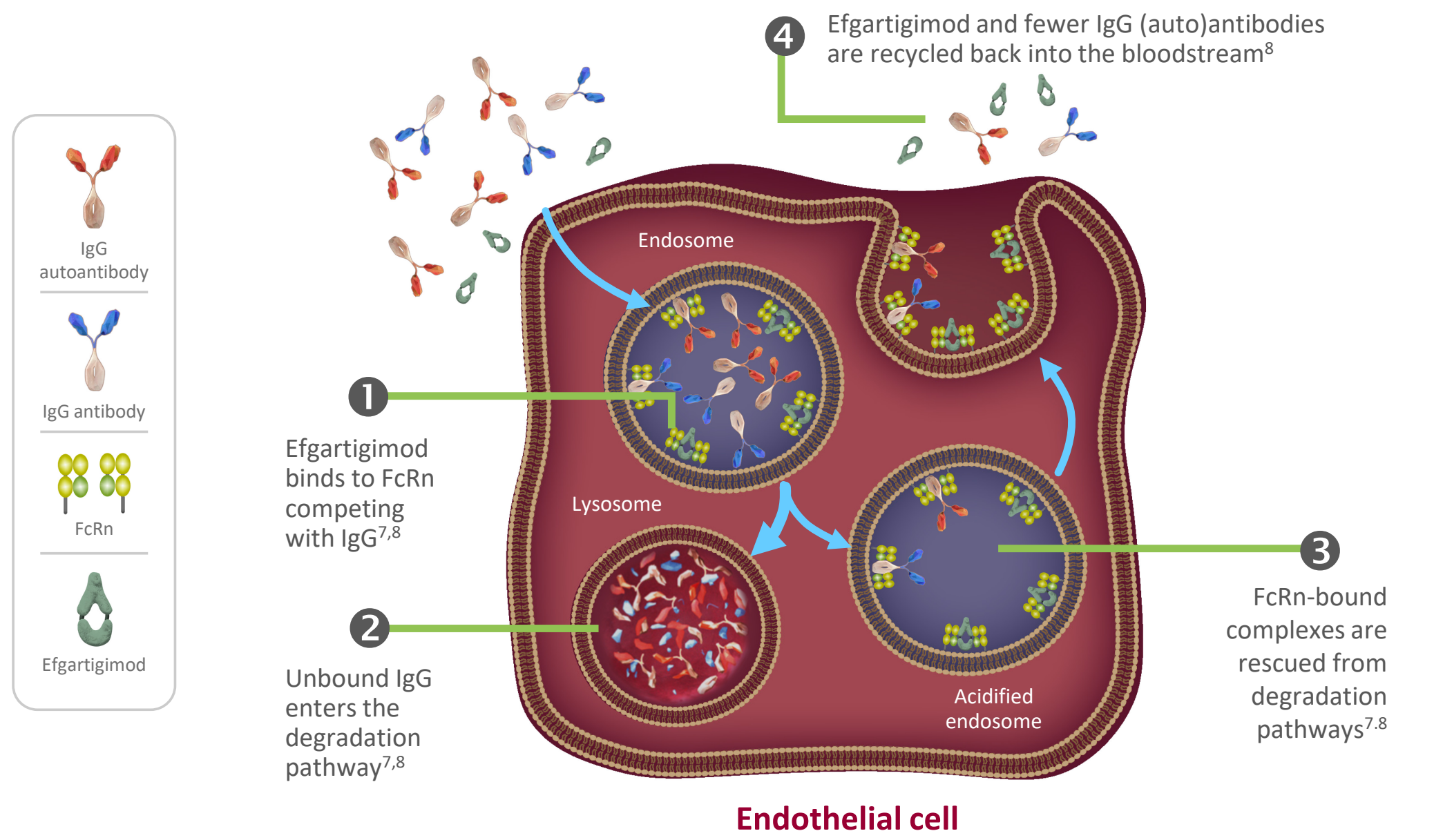


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

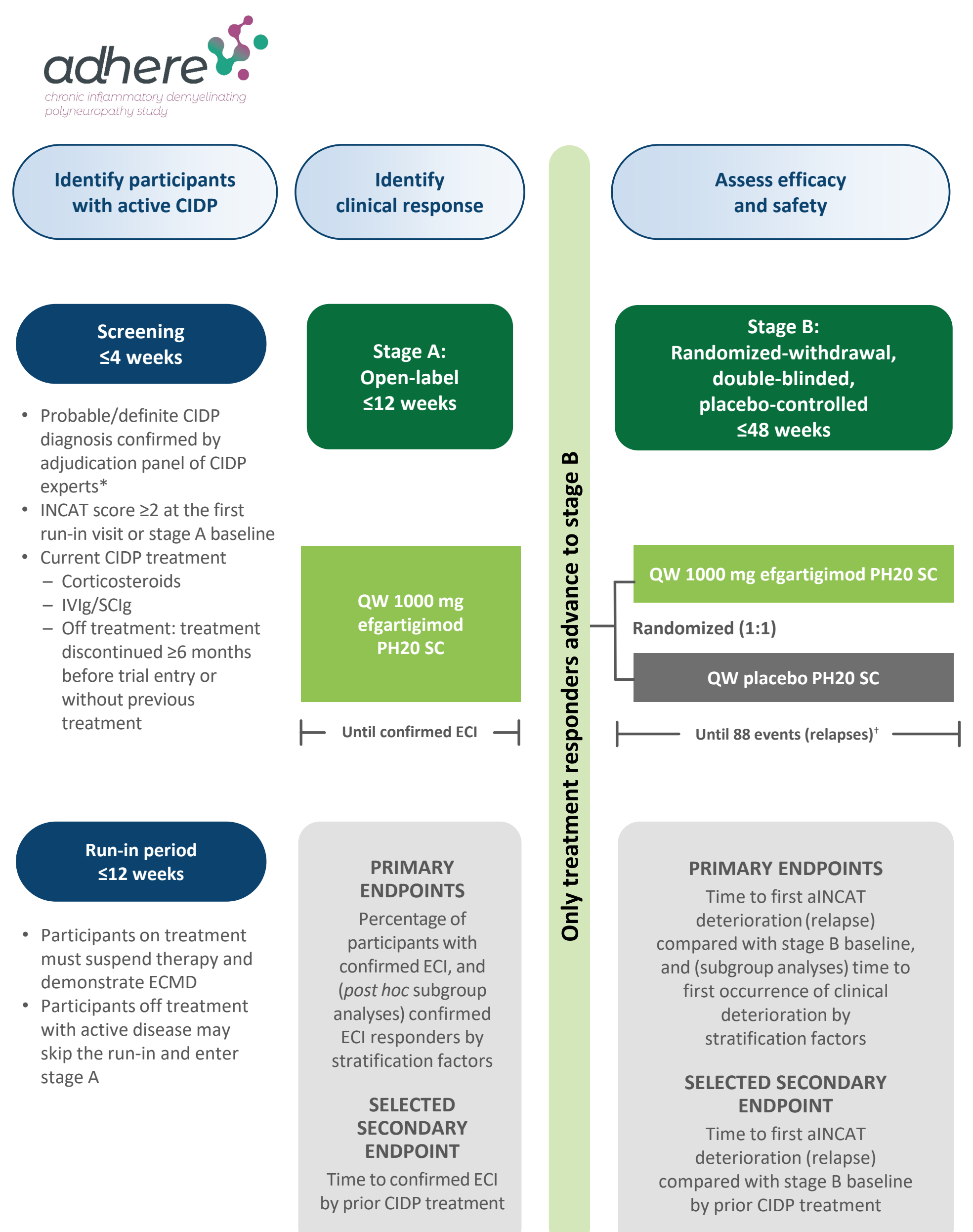
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90s single injection) SC administration[14,15]
- The multi-stage, double-blinded, placebo-controlled, randomized-withdrawal ADHERE trial assessed the efficacy and safety of efgartigimod PH20 SC in CIDP (**Figure 2**)

OBJECTIVE

- To assess the efficacy of weekly efgartigimod PH20 SC 1000 mg by participant subgroups

METHODS

FIGURE 2 Trial Design of ADHERE (NCT04281472)



- Probable/definite CIDP diagnosis confirmed by adjudication panel of CIDP experts*
- INCAT score ≥2 at the first run-in visit or stage A baseline
- Current CIDP treatment
  - Corticosteroids
  - IVIg/SCIg
  - Off treatment: treatment discontinued ≥6 months before trial entry or without previous treatment

- Participants on treatment must suspend therapy and demonstrate ECMD
- Participants off treatment with active disease may skip the run-in and enter stage A

PRIMARY ENDPOINTS (Stage A)
Percentage of participants with confirmed ECI, and (*post hoc* subgroup analyses) confirmed ECI responders by stratification factors

SELECTED SECONDARY ENDPOINT
Time to confirmed ECI by prior CIDP treatment

PRIMARY ENDPOINTS (Stage B)
Time to first aINCAT deterioration (relapse) compared with stage B baseline, and (subgroup analyses) time to first occurrence of clinical deterioration by stratification factors

SELECTED SECONDARY ENDPOINT
Time to first aINCAT deterioration (relapse) compared with stage B baseline by prior CIDP treatment

*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 achieved in stage B; this is the time point when the ADHERE trial terminated.

Definitions

- **Evidence of clinically meaningful deterioration (ECMD)**: aINCAT score increase of ≥1 points, an I-RODS score 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 score and/or ≥8-kPa increase in mean grip strength) or clinical improvement (≥1-point decrease) in INCAT score; 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 score confirmed at a consecutive visit after the first 1-point increase in aINCAT score, or ≥2-point increase observed at a single visit

RESULTS

Efgartigimod PH20 SC Demonstrated Clinical Benefits and Was Well Tolerated

- Baseline characteristics were similar between stages A and B and well balanced between treatment groups (**Table 1**)
- Primary endpoint data have previously been reported[16]
- Across all prior CIDP medication subgroups, the majority of participants responded to treatment with efgartigimod PH20 SC (**Figure 3A**); efgartigimod PH20 SC significantly reduced the risk of aINCAT deterioration versus placebo, with prior IVIg/SCIg and corticosteroids subgroups showing the greatest clinical benefit (**Figure 3B**)
- The effect of efgartigimod PH20 SC was consistent across the population, and no signals for differences in response across subgroups were identified (**Figures 4A and B**)
- No new safety signals were identified with efgartigimod PH20 SC (**Table 2**); most TEAEs were mild or moderate in severity

TABLE 1 Demographics and Baseline Disease Characteristics

	Open-Label Stage A	Double-Blinded Stage B	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (n=111)	Placebo (n=110)
Age, mean (SD), years	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)
Sex, male, n (%)	208 (64.6)	73 (65.8)	69 (62.7)
Race, n (%)*			
Asian	89 (27.6)	33 (29.7)	34 (30.9)
Black or African American	4 (1.2)	1 (0.9)	1 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0
White	211 (65.5)	73 (65.8)	71 (64.5)
Other	6 (1.9)	2 (1.8)	1 (0.9)
Time since diagnosis, mean (SD), years	4.9 (6.1)	3.7 (4.4)	3.8 (4.7)
Typical CIDP diagnosis, n (%)	268 (83.2)	97 (87.4)	95 (86.4)
Unstable active disease (CDAS: 5), n (%)	197 (61.2)	74 (66.7)	76 (69.1)
Prior treatment (in past 6 months), n (%)			
Corticosteroids	63 (19.6)	24 (21.6)	23 (20.9)
Immunoglobulins (IVIg, SCIg)	165 (51.2)	48 (43.2)	48 (43.6)
Off treatment	94 (29.2)	39 (35.1)	39 (35.5)
aINCAT score, mean (SD)†,‡	4.6 (1.7)	3.1 (1.5)	3.3 (1.6)
I-RODS score, mean (SD)†,§	40.1 (14.7)	53.6 (17.9)	51.2 (15.4)
Grip strength (dominant hand), mean (SD), kPa†,‖	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)

*A total of 11 participants in stage A and 5 in stage B (2 in the efgartigimod PH20 SC group and 3 in the placebo group) did not report race. †Clinical assessments were performed at the beginning of each stage. ‡Lower aINCAT scores represent improvement. §Raw sum scores of the 24-item I-RODS score (0–48) were converted to a centile metric score (0–100), with higher scores representing improvement. ‖Nondominant hand scores were similar.

TABLE 2 Overview of Safety

	Open-Label Stage A	Double-Blinded Stage B	
% (event rate*)	Efgartigimod PH20 SC (N=322; PYFU=46.9)	Efgartigimod PH20 SC (n=111; PYFU=56.7)	Placebo SC (n=110; PYFU=42.1)
Any TEAE†	63.4 (13.4)	64.0 (3.5)	56.4 (5.1)
Any SAE	6.5 (0.5)	5.4 (0.1)	5.5 (0.2)
Any injection site reactions	19.3 (2.6)	14.4 (0.4)	6.4 (0.2)
Discontinued due to AEs‡	6.8 (0.5)	2.7 (0.05)	0.9 (0.02)
Deaths§	0.6 (0.04)	0	0.9 (0.02)
Most common TEAEs (≥5% of participants in any group)			
Injection site erythema	10.2 (1.13)	5.4 (0.11)	0
CIDP‖	5.3 (0.41)	0.9 (0.02)	0.9 (0.02)
Headache	5.0 (0.6)	3.6 (0.11)	1.8 (0.05)
Upper respiratory tract infection	3.4 (0.26)	1.8 (0.05)	10.0 (0.26)
COVID-19	2.2 (0.17)	17.1 (0.35)	12.7 (0.33)
Injection site bruising	1.2 (0.11)	5.4 (0.11)	0.9 (0.02)

*Event rate was calculated as the number of events divided by the total PYFU. †There were no reports of anaphylaxis. ‡TEAEs grouped under 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 SC. §Two deaths (cardiac arrest and deterioration of CIDP) in stage A were considered unlikely related to efgartigimod PH20 SC by the investigator; one death (pneumonia) in the placebo arm of stage B was considered possibly treatment related by the investigator. ‖CIDP signs/symptoms recorded as TEAEs (regardless of causality) if there was CIDP worsening/deterioration.

FIGURE 3 (A) Time to Confirmed ECI in Stage A and (B) Time to First aINCAT Deterioration in Stage B Compared With Stage B Baseline by Prior CIDP Treatment

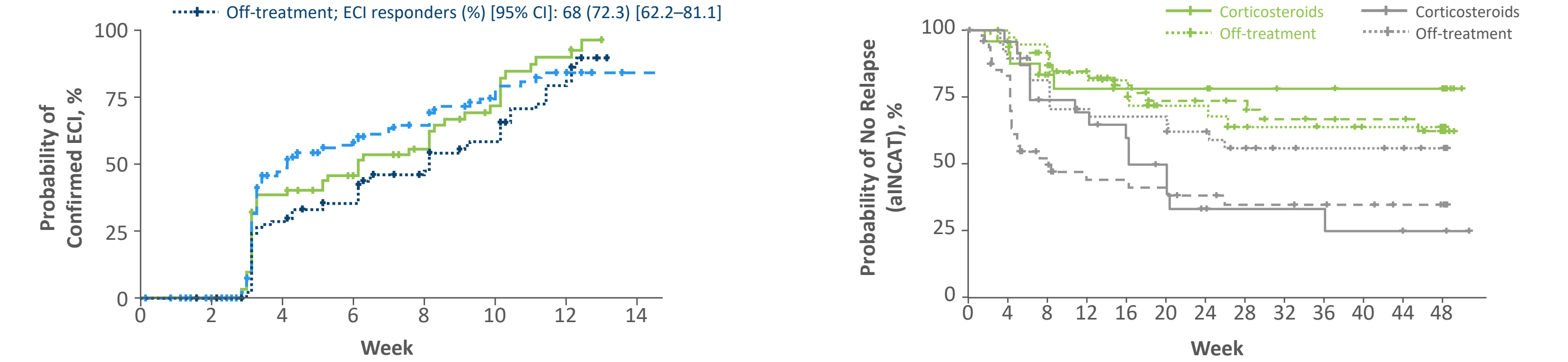
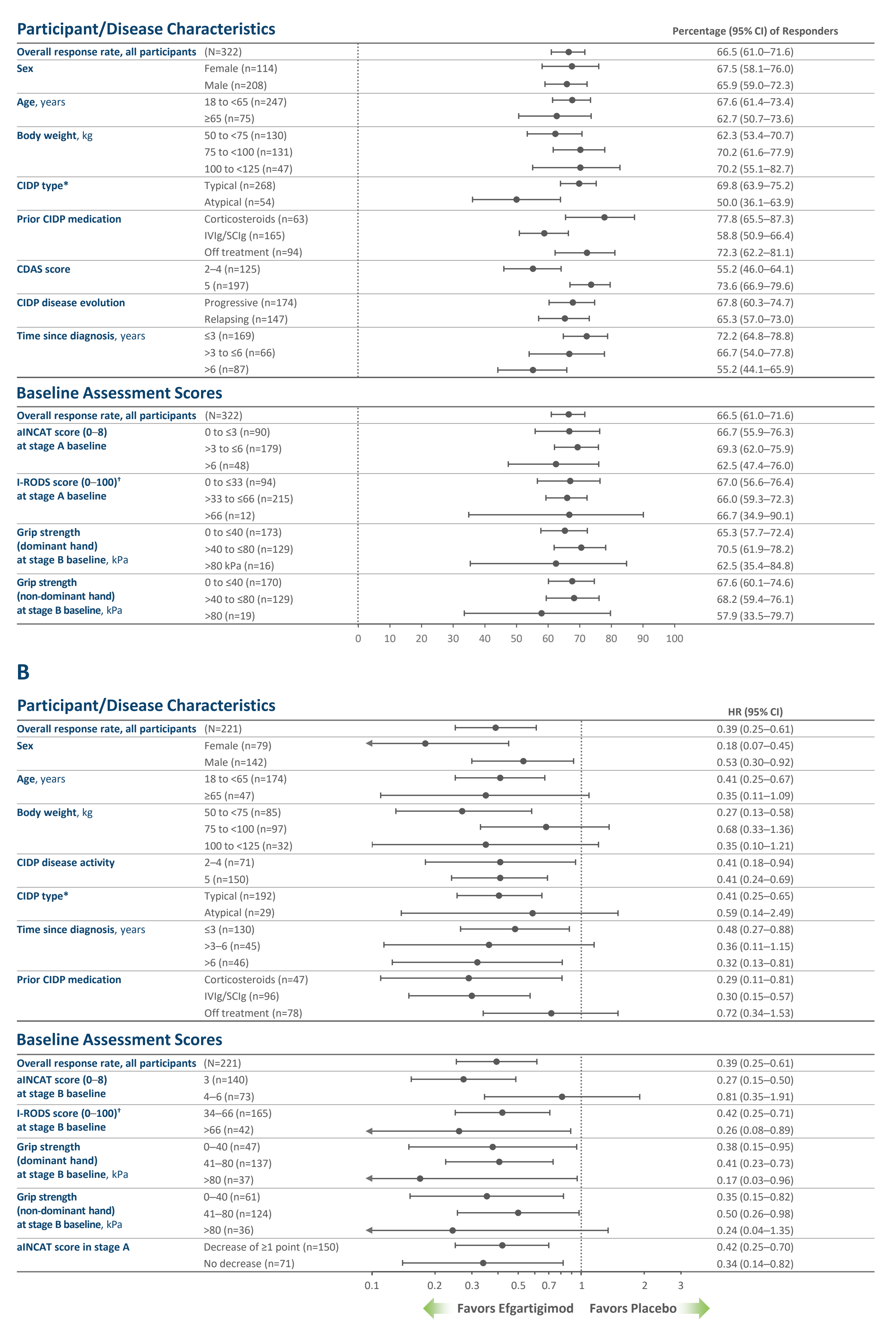


FIGURE 4 Forest Plots of (A) Confirmed ECI Responders (Stage A) and (B) Time to First Occurrence of Clinical Deterioration (Stage B) in the Overall Population and by Subgroups



*Typical and atypical CIDP were defined according to 2010 criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (Van den Bergh PYK, et al. *Eur J Neurol.* 2010). †Raw sum scores of the 24-item I-RODS score (0–48) were converted to a centile metric score (0–100).

KEY TAKEAWAYS

Across a range of subgroups, including prior CIDP treatment, the majority of participants treated with efgartigimod PH20 SC responded and experienced a reduced risk of relapse versus placebo

Clinical benefit regarding confirmed ECI responders in both stages A and B, and time to first occurrence of clinical deterioration in stage B with efgartigimod PH20 SC, was demonstrated across most baseline characteristics and assessment scores

Weekly efgartigimod PH20 SC was well tolerated, with a safety profile that was consistent with that of efgartigimod in clinical trials in other autoimmune diseases[9,12,13,17]

A single, rapid (30–90s) injection of weekly efgartigimod PH20 SC was recently approved in the US for adults with CIDP,[15] representing a new therapeutic option that may reduce CIDP treatment burden

Presented at the 2024 American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Annual Meeting; October 15–18, 2024; Savannah, GA, USA

ABBREVIATIONS

AE, adverse event; aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CDAS, CIDP disease activity status; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; HR, hazard ratio; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory-Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; rHuPH20, recombinant human hyaluronidase PH20; PYFU, participant-years of follow-up; QW, once weekly; SAE, serious adverse event; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; TEAE, treatment-emergent adverse event.

DISCLOSURES AND ACKNOWLEDGMENTS

JAA: Akcea Therapeutics, Alexion, Alnylam, Annexon Biosciences, argenx, CSL Behring, Grifols, Immunovant, Immupharma, Johnson & Johnson, Pfizer, Takeda; **RAL:** Akcea Therapeutics, Alexion, Alnylam, Annexon Biosciences, argenx, Boehringer Ingelheim, CSL Behring, GBS/CIDP Foundation International, Grifols, Johnson & Johnson, Medscape, MGFA, Novartis, Peripheral Nerve Society, Pfizer, Roche, Sanofi, Takeda; **LQ:** Alnylam, Annexon Biosciences, argenx, Avilar Therapeutics, Biogen, CIBERER, CSL Behring, Dianthus, 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; **YH:** nothing to declare; **KG**: Alexion, argenx, UCB, Xeris Pharmaceuticals; **NS**: Alnylam, Takeda; **JTG, EH, BVH, TM:** employees of argenx; **SK**: Alexion, argenx, CSL Behring, Takeda; **IB**: Actavis, Dinathus, Mylan, Pfizer, Salveo; **PAvD**: Annexon Biosciences, argenx, Grifols, Hansa Biopharma, Octapharma, Prinses Beatrix Spierfonds, Roche, Sanofi, Sanquin, Takeda.

This trial was 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.

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