Efficacy, Safety, and Tolerability of Subcutaneous Efgartigimod in Chronic Inflammatory Demyelinating Polyneuropathy: Results From the ADHERE Trial

Zaeem Siddiqi,[1] Jeffrey A. Allen,[2] Ivana Basta,[3] Christian Eggers,[4] Jeffrey T. Guptill,[5,6] Kelly G. Gwathmey,[7] Channa Hewamadduma,[8,9] Erik Hofman,[5] Yessar M. Hussain,[10] Satoshi Kuwabara,[11] Frank Leypoldt,[12] Jie Lin,[13] Marta Lipowska,[14,15] Murray Lowe,[5*] Giuseppe Lauria,[16,17] Luis Querol,[18,19] Niraja Suresh,[20*] Ting Chang,[21] Anissa Tse,[5*] Peter Ulrichts,[5] Pieter A. van Doorn,[22] Benjamin Van Hoorick,[5] Ryo Yamasaki,[23] Richard A. Lewis,[24] in collaboration with the ADHERE Study Group

[1]Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada; [2]Department of Neurology, University of Minnesota, Minneapolis, MN, USA; [3]Neurology Clinic, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [4]Department of Neurology, Kepler University Hospital, Linz, Austria; [5]argenx, Ghent, Belgium; [6]School of Medicine, Duke University, Durham, NC, USA; [7]Neuromuscular Division, Department of Neurology, Virginia Commonwealth University, Richmond, VA, USA; [8]Academic Neurology Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [9]Sheffield Institute for Translational Neuroscience (SITRAN), University of Sheffield, Sheffield, UK; [10]Austin Neuromuscular Center, Austin, TX, USA; [11]Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan; [12]Department of Neurology, and Neuroimmunology, Institute of Clinical Chemistry, Christian-Albrecht University of Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany; [13]Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China; [14]Department of Neurology, Medical University of Warsaw, Warsaw, Poland; [15]European Reference Network On Rare Neuromuscular Diseases (ERN EURO-NMD), Paris, France; [16]IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [17]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; [18]Department of Neurology, Neuromuscular Diseases Unit, Hospital de La Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; [19]Centro Para La Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Madrid, Spain; [20]Department of Neurology, University of South Florida, Tampa, FL, USA; [21]Department of Neurology, Tangdu Hospital, The Fourth Military Medical University, Xi'an, China; [22]Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; [23]Department of Neurology, Kyushu University Hospital, and Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [24]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, USA. *Institutions shown were at the time of the study

Presented at the 2024 Canadian Neurological Sciences Federation's (CNSF) Congress; May 20–26, 2024; Toronto, Canada

Disclosures and Acknowledgements

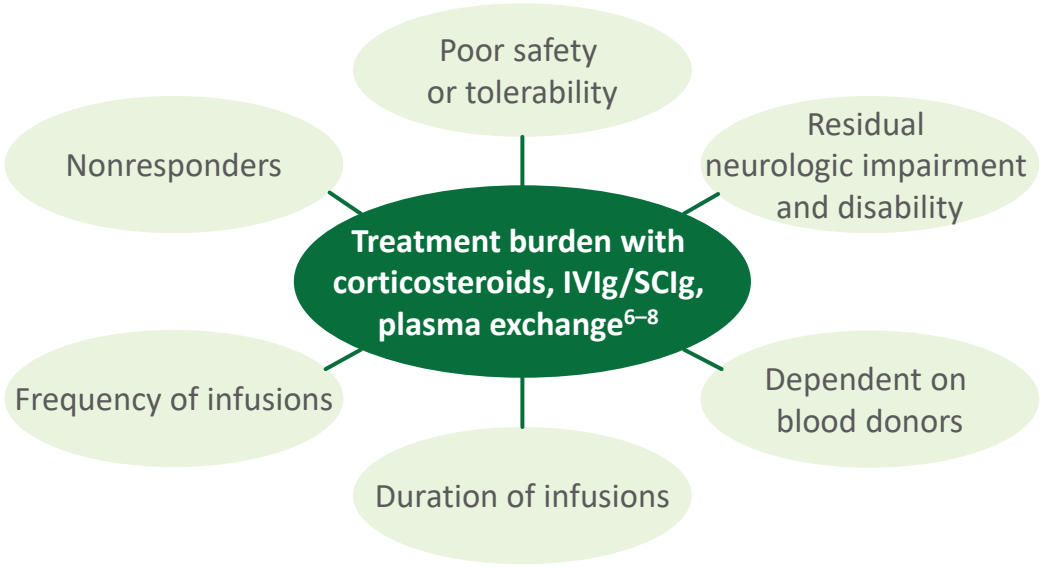
Jeffrey A. Allen	Akcea Therapeutics, Alexion, Alnylam, Annexon Biosciences, argenx, CSL Behring, Grifols, Immunovant, ImmuPharma, Johnson & Johnson, Pfizer, Takeda
Ivana Basta	Actavis, Dianthus Therapeutics, Mylan, Pfizer, Salveo Pharma
Christian Eggers	argenx, Biogen, GlaxoSmithKline, UCB
Kelly G. Gwathmey	Alexion, argenx, UCB, Xeris Pharmaceuticals
Channa Hewamadduma	argenx, Biogen, Lupin, Roche, UCB
Satoshi Kuwabara	CSL Behring, Takeda
Frank Leypoldt	Alexion, Bayer, Biogen, Fresenius Kabi, Grifols, Merck, Novartis, Roche, Teva Pharmaceuticals
Marta Lipowska	argenx, CSL Behring, Kedrion, Medison Pharma/Alnylam, Pfizer, Sanofi, Sobi, Takeda
Murray Lowe **Anissa Tse**	Employees of argenx at the time of the study
Giuseppe Lauria	Biogen, Chromocell, CSL Behring, Home Biosciences, Janssen, Lilly, Sangamo Therapeutics, Vertex Pharmaceuticals, Zambon
Luis Querol	Annexon Biosciences, Alnylam, 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 Genzyme, UCB
Niraja Suresh	Alnylam, Takeda
Pieter A. van Doorn	Annexon Biosciences, argenx, Grifols, Hansa Biopharma, Immunic Therapeutics, Octapharma, Prinses Beatrix Spierfonds, Roche, Sanofi, Sanquin
Richard A. Lewis	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
Jeffrey T. Guptill **Erik Hofman** **Peter Ulrichts** **Benjamin Van Hoorick**	Employees of argenx
Zaeem Siddiqi **Yessar M. Hussain** **Jie Lin** **Ting Chang** **Ryo Yamasaki**	Nothing to declare

Efgartigimod is an investigational drug. Efgartigimod has not been approved as safe or effective by the FDA or Health Canada for use in CIDP

This study was funded by **argenx** and **Zai Lab**. Medical writing support was provided by Envision Pharma Group and funded by **argenx**

CIDP is a Severe and Debilitating Immune-Mediated Polyneuropathy[1–4]

- CIDP is an **autoimmune, inflammatory, demyelinating neuropathy** resulting in distal/proximal weakness and/or sensory deficits, with a high treatment burden[1,5]



- Evidence supports **a role for pathogenic IgGs** in the pathogenesis of CIDP, although in most patients a specific antibody is not detectable[2,9–11]
- **Efgartigimod** is a human IgG1 Fc fragment that outcompetes endogenous IgG, preventing recycling, and promoting lysosomal degradation of IgG, **without impacting IgG production**[12–17]
- **Efgartigimod PH20 SC** is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for **rapid (30–90s single injection)** SC administration of larger volumes[18,19]

Efgartigimod has been shown to **reduce IgG antibody levels** in healthy volunteers and patients with other autoimmune diseases[12,14–17]

CIDP, chronic inflammatory demyelinating polyneuropathy; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; PH20, recombinant human hyaluronidase PH20; s, second; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

1. Cox ZC, Gwathmey KG. *Clin Geriatr Med*. 2021;37(2):327–45. **2.** Querol L, et al. *Sci Rep.* 2017;7(1):14411. **3.** Broers MC, et al. *Neuroepidemiology*. 2019;52(3–4):161–72. **4**. Nobile-Orazio. *J Peripher Nerv Syst*. 2014;19(1):2–13. **5.** Van den Bergh PYK, et al. *Eur J Neurol*. 2010;17(3):356–63. **6.** Brun, et al. *Immuno.* 2022;2(1):118–31. **7**. Bus SRM, et al. *J Neurol*. 2022;269(2):945–55. **8**. Gorson KC. *Ther Adv Neurol Disord*. 2012;5(6)359–73. **9.** Mathey EK, et al. *J Neurol Neurosurg Psychiatry*. 2015;86(9):97–85. **10.** Yan WX, et al. *Ann Neurol.* 2000;47(6):765–75. **11.** Manso C, et al. *J Clin Invest.* 2019;124(6):2222–36. **12.** Ulrichts P, et al. *J Clin Invest*. 2018;128(10):4372–86. **13.** Vaccaro C, et al. *Nat Biotech*. 2005;23(10):1283–8. **14**. Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526–36. **15**. Goebeler M, et al. *Br J Dermatol*. 2022;186(3):429–39. **16.** Broome CM, et al. *Lancet*. 2023;402(10413):1648–59. **17.** Howard JF Jr, et al. *Front Neurol*. 2024;17;14:1284444. **18**. Locke KW, et al. *Drug Deliv*. 2019;26(1):98–106. **19.** VYVGART HYTRULO. Prescribing information. argenx; 2023. https://www.argenx.com/product/vyvgart-hytrulo-prescribing-information.pdf. Accessed May 20, 2024.

ADHERE (NCT04281472): A Multicenter, Multi-Stage, Randomized-Withdrawal, Double-Blinded, Placebo-Controlled Trial of Efgartigimod in CIDP

IDENTIFY PATIENTS WITH ACTIVE DISEASE

SCREENING

- Diagnosis of probable or definite CIDP confirmed by adjudication panel of CIDP experts[1]
- Current CIDP treatment:
  - Corticosteroids
  - IVIg/SCIg
  - Off treatment: treatment discontinued ≥6 months before study entry or without previous treatment

RUN-IN PERIOD

≤12 weeks

- Participants on treatment must suspend therapy and demonstrate evidence of clinically meaningful deterioration[a]
- Patients off treatment with active disease may skip the run-in and enter stage A

TREATMENT PERIOD

OPEN-LABEL STAGE A

1000 mg (5.56 mL) efgartigimod PH20 SC weekly

Responders

≤12 weeks

Until evidence of clinical improvement[b] for 2 consecutive visits

PRIMARY ENDPOINT
Percentage of participants with evidence of clinical improvement

DOUBLE-BLINDED STAGE B

1000 mg (5.56 mL) efgartigimod PH20 SC weekly

Placebo PH20 SC weekly

≤48 weeks

Until 88 events (relapses)[c]

PRIMARY ENDPOINT
Time to first aINCAT deterioration[d] (relapse) compared with stage B baseline

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

[a]ECMD was defined as an aINCAT increase of ≥1 points, an I-RODS decrease of ≥4 points, or a grip strength decrease of ≥8 kPa. [b]ECI was defined as an improvement (≥1-point decrease) in aINCAT score compared with stage A baseline score. For non–off-treatment participants who had no change in aINCAT score and deteriorated on I-RODS and/or grip strength during the run-in period, ECI was defined as an increase of ≥4 points in I-RODS and/or an increase of ≥8 kPa in grip strength during stage A, or improvement in aINCAT. [c]The primary endpoint was assessed once 88 total relapses or events were achieved in stage B and was based on the hazard ratio for the time to first aINCAT deterioration (ie, relapse). [d]aINCAT deterioration was defined as an increase of ≥1 points in aINCAT score compared with stage B baseline.

1. Van den Bergh PYK, et al. *Eur J Neurol.* 2010;17(3):356–63.

Baseline Characteristics Were Similar Between Stages A and B and Well Balanced Between Treatment Groups

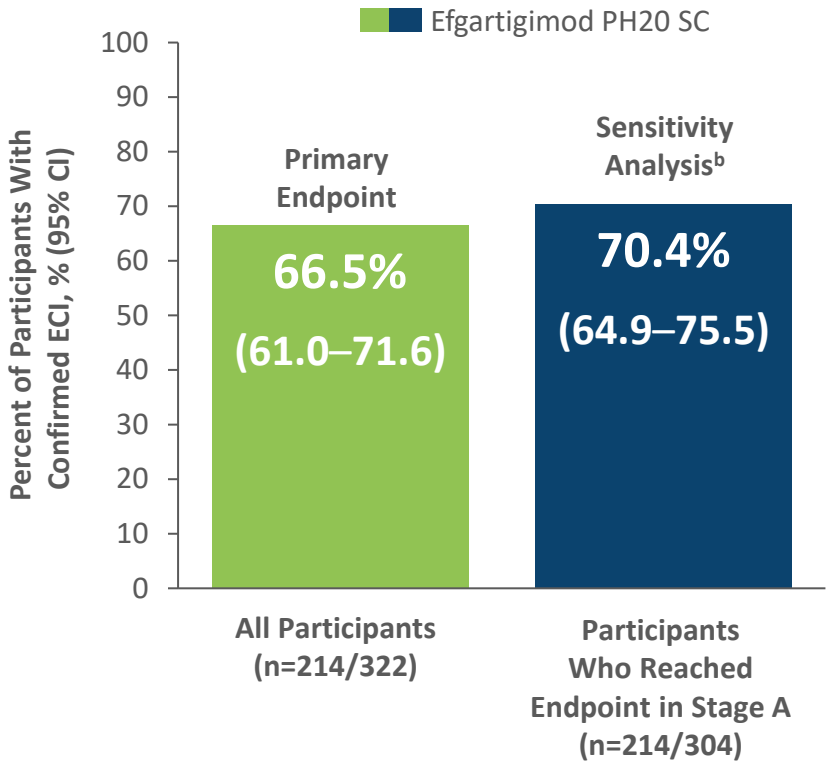
	Open-Label Stage A	Double-Blinded Stage B	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (N=111)	Placebo (N=110)
Age, y, mean (SD)	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)
Sex, male, n (%)	208 (64.6)	73 (65.8)	69 (62.7)
Time since diagnosis, y, mean (SD)	4.9 (6.1)	3.7 (4.4)	3.8 (4.7)
Typical CIDP diagnosis, 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 (within 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[a]	94 (29.2)	39 (35.1)	39 (35.5)
aINCAT score, mean (SD)[b,c]	4.6 (1.7)	3.1 (1.5)	3.3 (1.6)
I-RODS score, mean (SD)[b,c]	40.1 (14.7)	53.6 (17.9)	51.2 (15.4)
Grip strength (dominant hand), kPa, mean (SD)[b,d]	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CDAS, CIDP disease activity status; CIDP, chronic inflammatory demyelinating polyneuropathy; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; kPa, kilopascal; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; y, year.

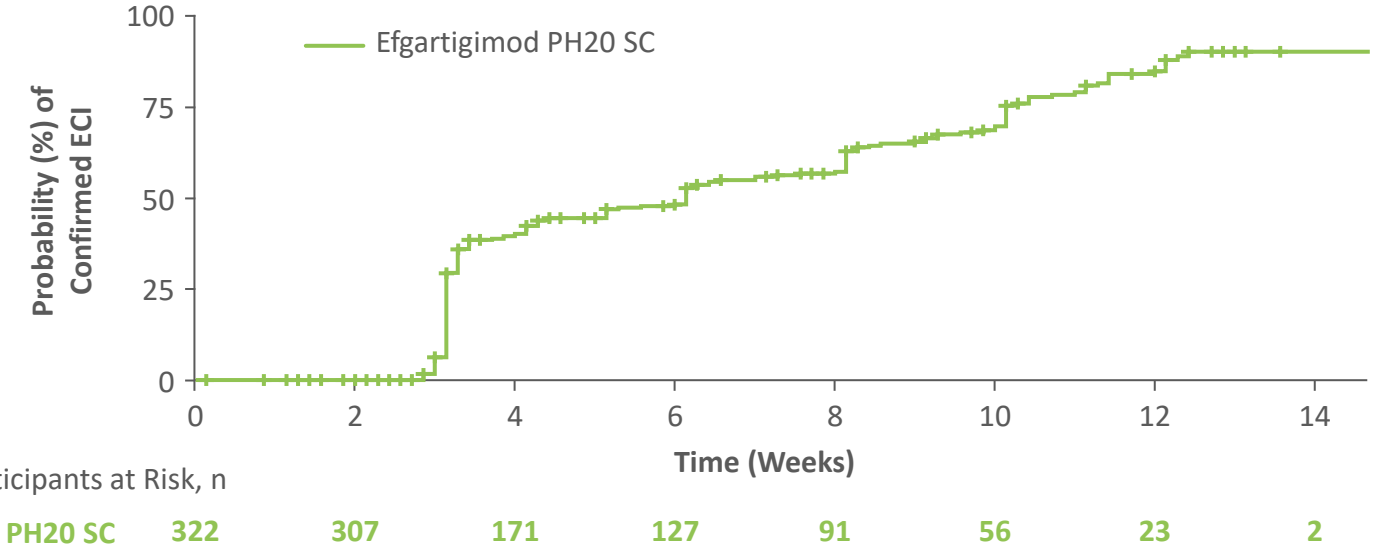
[a]Off treatment was defined as participants who had discontinued treatment ≥6 months before study entry or without previous treatment. [b]Clinical assessments were performed at the beginning of each stage. [c]Lower scores represent improvement on aINCAT, while higher scores represent improvement for I-RODS. [d]Nondominant scores were similar.

Efgartigimod Was Clinically Effective: 66.5% of Participants Demonstrated Evidence of Confirmed Clinical Improvement in Stage A

Open-Label Stage A: Percent of Participants With Confirmed ECI[a]



Open-Label Stage A: Secondary Endpoint Time to Initial Confirmed ECI[a]



Participants at Risk, n								
EFG PH20 SC	322	307	171	127	91	56	23	2

Rapid onset of clinically meaningful improvement with efgartigimod: 39.8% (128/322) of participants demonstrated ECI by Week 4

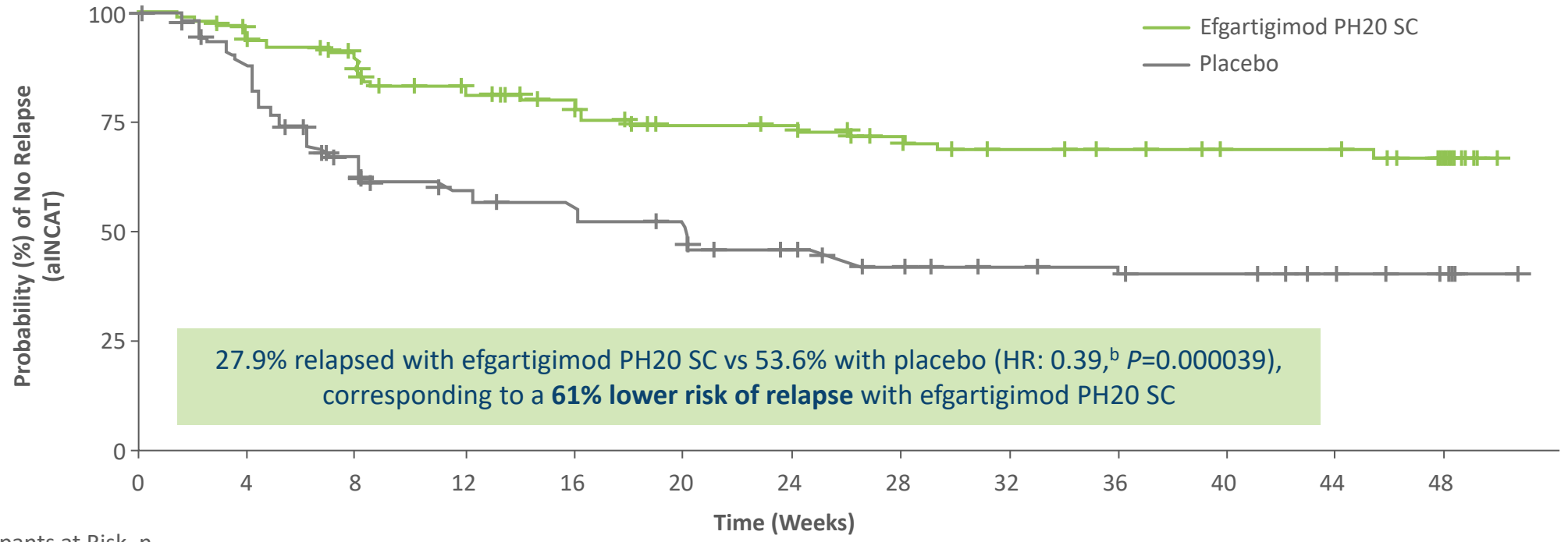
Week 4 was the earliest time point at which the ECI criteria could have been met

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; I-RODS, Inflammatory Rasch-built Overall Disability Scale; kPa, kilopascal; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

[a]ECI was defined as an improvement (≥1-point decrease) in aINCAT score compared with stage A baseline score. For non–off-treatment participants who had no change in aINCAT score and deteriorated on I-RODS and/or grip strength during the run-in period, ECI was defined as an increase of ≥4 points in I-RODS and/or an increase of ≥8 kPa in grip strength during stage A or improvement in aINCAT. [b]Prespecified sensitivity analysis excluded participants who were ongoing in stage A at the time of study completion (after the 88th event had occurred) and did not have the full opportunity to achieve a response.

Efgartigimod Significantly Reduced the Risk of Relapse by 61% Compared With Placebo in Stage B

Double-Blinded Stage B: Primary Endpoint
Time to First aINCAT Deterioration[a] Compared With Stage B Baseline



Participants at Risk, n

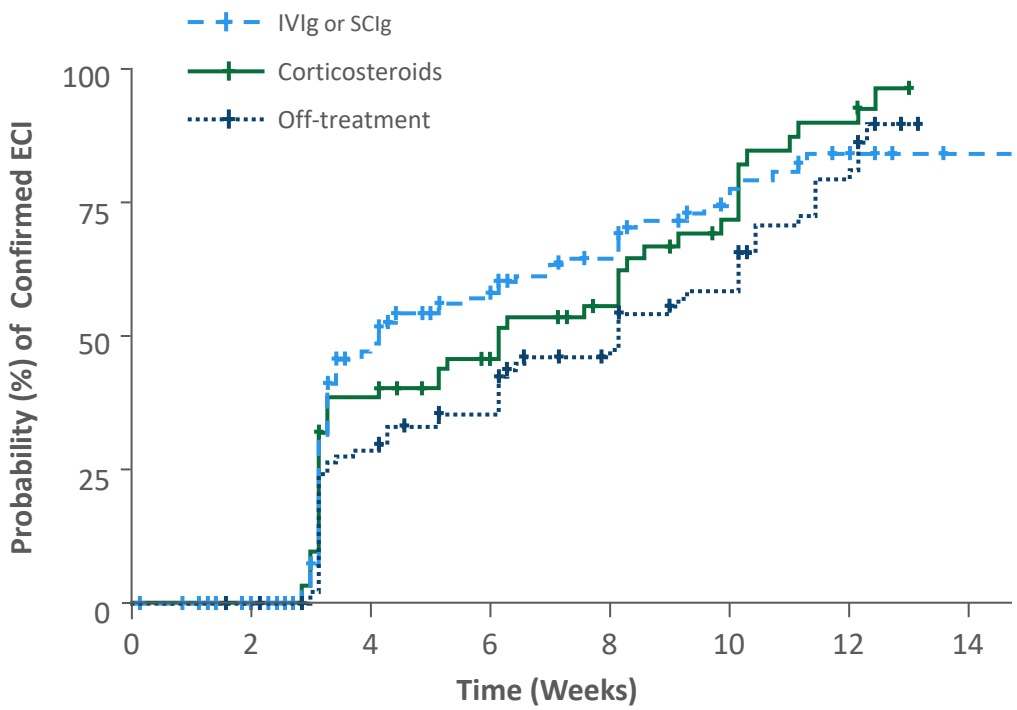
EFG PH20 SC	111	107	93	80	68	56	55	48	42	40	36	36	28
Placebo	110	94	67	55	51	47	38	31	28	26	24	21	16

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, chronic inflammatory demyelinating polyneuropathy; HR, hazard ratio; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

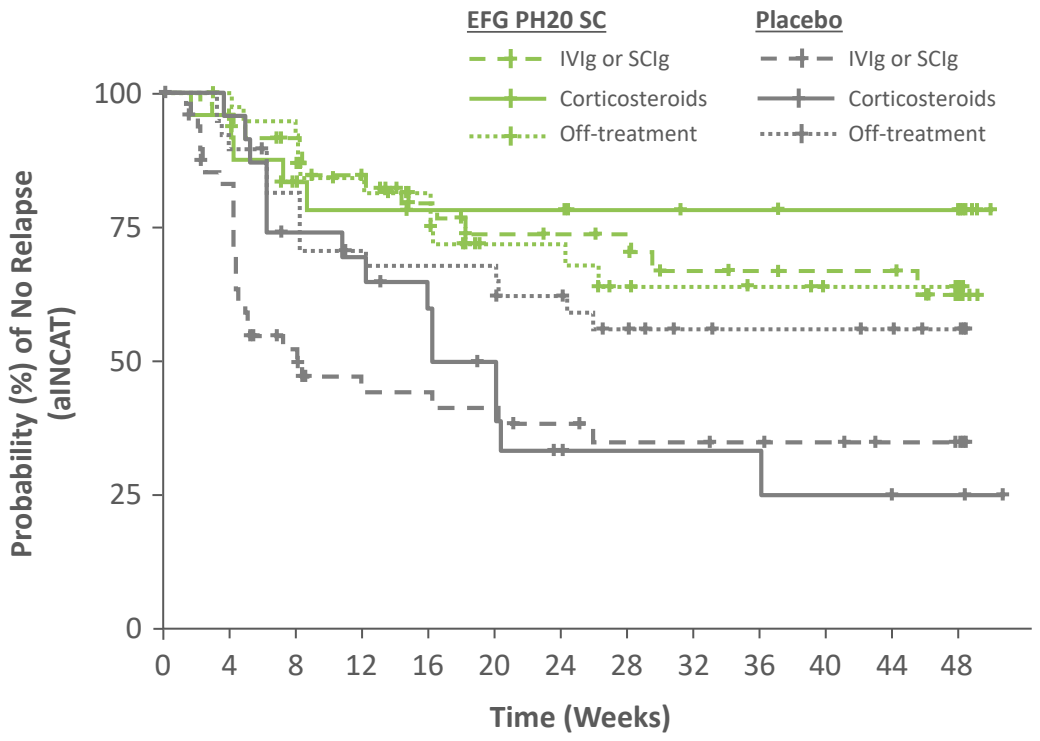
[a]The time to first aINCAT deterioration was defined as the number of days from first dose in stage B to the first occurrence of an increase of ≥1 points on the aINCAT score compared with stage B baseline. [b]The HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during stage A.

Clinical Benefit Was Demonstrated Across Multiple Efficacy Measures, Regardless of Prior CIDP Treatment

Open-Label Stage A: Secondary Endpoint
Time to Initial Confirmed ECI by Prior Treatment[a]



Double-Blinded Stage B: Primary Endpoint
Time to First aINCAT Deterioration[b] Compared With Stage B Baseline by Prior Treatment

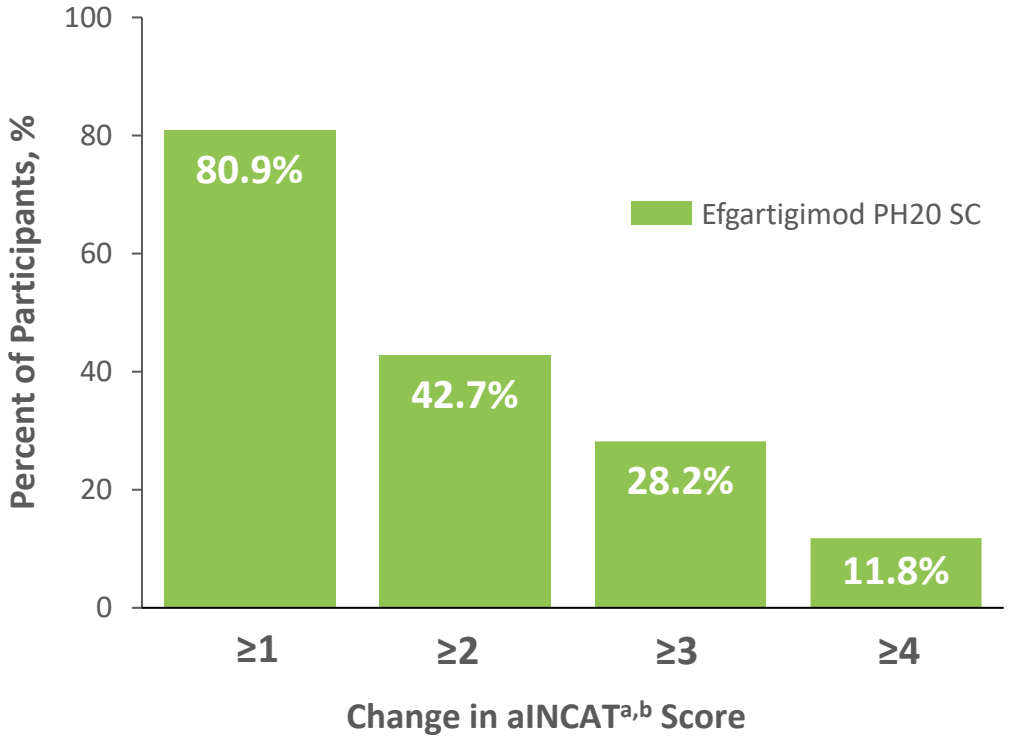


aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; EFG, efgartigimod; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

[a]ECI was defined as an improvement (≥1-point decrease) in aINCAT score compared with stage A baseline score. For non–off-treatment participants who had no change in aINCAT score and deteriorated on I-RODS and/or grip strength during the run-in period, ECI was defined as an increase of ≥4 points in I-RODS and/or an increase of ≥8 kPa in grip strength during stage A or improvement in aINCAT. [b]The time to first aINCAT deterioration was defined as the number of days from first dose in stage B to the first occurrence of an increase of ≥1 points on the aINCAT score compared with stage B baseline.

Efgartigimod-Treated Participants Experienced Deep and Clinically Meaningful Improvements in Functional Ability

Functional Ability (aINCAT):
Cumulative Frequency of Stage B Best Improvement From Stage A Baseline (n=110)



INCAT Disability Scale: Arm Disability[1c]

0= No upper limb problems; 1= Symptoms in one/both arms without impacting the ability to perform certain functions[d]; 2= Symptoms in one/both arms affecting but not preventing the ability to perform functions; 3= Symptoms in one/both arms preventing the performance of 1-2 functions; 4= Symptoms in one/both arms preventing the performance of ≥3 functions; 5= Inability to use either arm for any purposeful movement

INCAT Disability Scale: Leg Disability[1c]

0= Walking not affected; 1= Walking affected, but walks independently outdoors; 2= Usually uses unilateral support to walk outdoors; 3= Usually uses bilateral support to walk outdoors; 4= Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help; 5= Restricted to wheelchair, unable to stand and walk a few steps with help

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

[a]Mean stage A baseline aINCAT score was 4.5. Some participants could not improve beyond a certain level due to their baseline aINCAT score, ie, participants with an aINCAT baseline score of 2 or 3 could not reach improvements of 3 or 4, respectively.
[b]For the aINCAT score, 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.
[c]The INCAT disability score[1] 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.
[d]Functions include: doing all zips and buttons, washing or brushing hair, using a knife and fork together, and handling small coins.

1. Breiner A, et al. *Muscle Nerve*. 2014;50(2):164–9.

Efgartigimod Was Well Tolerated and Most TEAEs Were Mild or Moderate in Severity

	Open-Label Stage A	Double-Blinded Stage B	
n (%)	Efgartigimod PH20 SC (N=322; PYFU=46.9)	Efgartigimod PH20 SC (N=111; PYFU=56.7)	Placebo (N=110; PYFU=42.1)
Participant with event			
Any TEAE	204 (63.4)	71 (64.0)	62 (56.4)
Any SAE	21 (6.5)	6 (5.4)	6 (5.5)
Injection site reactions	62 (19.3)	16 (14.4)	7 (6.4)
Discontinued due to AEs[a]	22 (6.8)	3 (2.7)	1 (0.9)
Deaths[b]	2 (0.6)	0 (0)	1 (0.9)
Most common TEAEs (≥5% of participants in any group)			
Injection site erythema	33 (10.2)	6 (5.4)	0 (0)
CIDP	17 (5.3)	1 (0.9)	1 (0.9)
Headache	16 (5.0)	4 (3.6)	2 (1.8)
Upper respiratory tract infection	11 (3.4)	2 (1.8)	11 (10.0)
COVID-19	7 (2.2)	19 (17.1)	14 (12.7)
Injection site bruising	4 (1.2)	6 (5.4)	1 (0.9)

AE, adverse event; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; PH20, recombinant human hyaluronidase PH20; PYFU, participants years of follow-up; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

[a]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; and Pneumonia (n=1) in stage B placebo SC. [b]Two deaths (cardiac arrest and deterioration of CIDP) in stage A were considered not related to efgartigimod PH20 SC by the investigator; one death (pneumonia) in the placebo arm of stage B was considered treatment related by the investigator.

Conclusions

ADHERE, the largest randomized, controlled trial of any CIDP treatment to date, supports a key role for IgG autoantibodies in CIDP pathology

Regardless of prior CIDP therapy, participants treated with efgartigimod PH20 SC demonstrated clinical benefits:

- Evidence of rapid clinical improvement (stage A)
- Maintained clinical response to treatment (stage B)
- 61% reduced risk of relapse compared with placebo (stage B)

Weekly efgartigimod PH20 SC was well tolerated and demonstrated a consistent safety profile with prior clinical trials in other autoimmune diseases[1–4]

A single, rapid (30–90s) injection of weekly efgartigimod PH20 SC may provide a new therapeutic option to reduce treatment burden in patients with CIDP

CIDP, chronic inflammatory demyelinating polyneuropathy; IgG, immunoglobulin G; PH20, recombinant human hyaluronidase PH20; s, second; SC, subcutaneous.

1. Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526–36. **2.** Goebeler M, et al. *Br J Dermatol.* 2022;186(3):429–39. **3.** Broome CM, et al. *Lancet*. 2023;402:1648–59. **4.** Howard JF Jr, et al. *Front Neurol.* 2024;17;14:1284444.