Efficacy and Safety of Efgartigimod PH20 in Chronic Inflammatory Demyelinating Polyneuropathy: Results of ADHERE/ADHERE+

EPR-269

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

[1]Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; [2]Minneapolis, MN, USA; [3]Belgrade, Serbia; [4]Copenhagen, Denmark; [5]Linz, Austria; [6]Durham, NC, USA; [7]argenx, Ghent, Belgium; [8]Richmond, VA, USA; [9]Sheffield, UK; [10]Austin, TX, USA; [11]Chiba, Japan; [12]Bordeaux, France; [13]Kiel, Germany; [14]Shanghai, China; [15]Warsaw, Poland; [16]Paris, France; [17]Milan, Italy; [18]Barcelona, Spain; [19]Madrid, Spain; [20]Timisoara, Romania; [21]Xi'an, China; [22]Fukuoka, Japan; [23]Los Angeles, CA, USA.
*At the time of the study.

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Pieter A. van Doorn	Annexon Biosciences, argenx, Grifols, Hansa Biopharma, Immunic Therapeutics, Octapharma, Prinses Beatrix Spierfonds, Roche, Sanofi, Sanquin
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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
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Murray Lowe **Anissa Tse**	Employees of argenx at the time of the study
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Jeffrey T. Guptill **Erik Hofman** **Peter Ulrichts** **Benjamin Van Hoorick**	Employees of argenx
Tina Dysgaard **Yessar M. Hussain** **Gwendal Le Masson** **Jie Lin** **Mihaela-Adriana Simu** **Ting Chang** **Ryo Yamasaki**	Nothing to declare

Efgartigimod alfa with recombinant human hyaluronidase is not approved by the European Medicines Agency for the treatment of patients with CIDP as efficacy and safety have not been established

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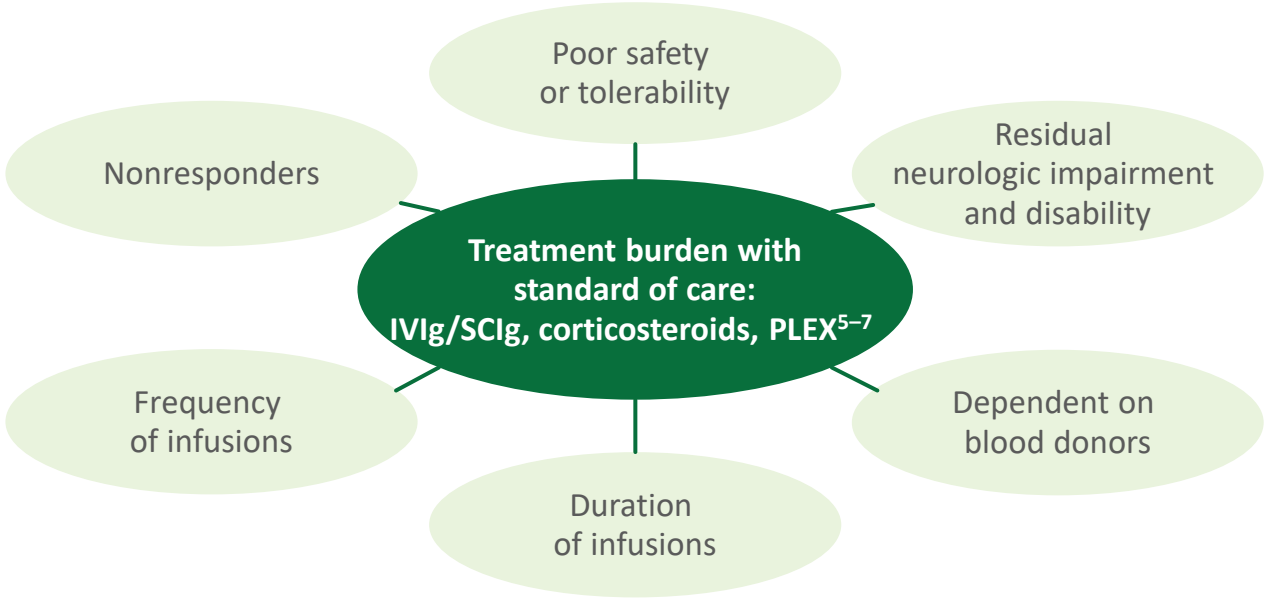
CIDP is a Severe and Progressing Immune-Mediated Polyneuropathy[1–3]

- 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 IgGs** in the pathogenesis of CIDP, although in most patients a specific antibody is currently not detectable[1,8–10]
- **Efgartigimod** is a human IgG1 Fc fragment that outcompetes endogenous IgG, preventing recycling and promoting lysosomal degradation of IgG, leading to lower IgG levels **without impacting IgG production**[11–16]
- **Efgartigimod PH20 SC** is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for a **rapid (30–90s) single SC injection**[17,18]

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

The ADHERE study was designed to investigate the efficacy, safety, and tolerability of efgartigimod PH20 SC in adult patients with CIDP

CIDP, chronic inflammatory demyelinating polyneuropathy; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; PLEX, plasma exchange; s, second; SC, subcutaneous; SCIg, subcutaneous immunoglobulin.

1. Querol L, et al. *Sci Rep*. 2017. **2.** Broers MC, et al. *Neuroepidemiology*. 2019. **3**. Nobile-Orazio E. *J Peripher Nerv Syst*. 2014. **4.** Van den Bergh PYK, et al. *Eur J Neurol*. 2021. **5.** Brun S, et al. *Immuno*. 2022. **6**. Bus SRM, et al. *J Neurol*. 2022. **7**. Gorson KC. *Ther Adv Neurol Disord*. 2012. **8.** Mathey EK, et al. *J Neurol Neurosurg Psychiatry*. 2015. **9.** Yan WX, et al. *Ann Neurol*. 2000. **10**. Manso C, et al. *J Clin Invest*. 2019. **11.** Ulrichts P, et al. *J Clin Invest*. 2018. **12.** Vaccaro C, et al. *Nat Biotech*. 2005. **13**. Howard JF Jr, et al. *Lancet Neurol*. 2021. **14**. Goebeler M, et al. *Br J Dermatol*. 2022. **15.** Broome CM, et al. *Lancet*. 2023. **16.** Howard JF Jr, et al. *Front Neurol*. 2024. **17**. Locke KW, et al. *Drug Deliv*. 2019. **18.** VYVGART HYTRULO. Prescribing information. argenx; 2024. https://www.argenx.com/product/vyvgart-hytrulo-prescribing-information.pdf. Accessed June 21, 2024.

Efgartigimod in CIDP: Study Designs of ADHERE and ADHERE+

99% Rollover

ADHERE

IDENTIFY PARTICIPANTS WITH ACTIVE DISEASE

SCREENING ≤4 weeks

- Probable or definite CIDP confirmed by adjudication panel of CIDP experts[1]

RUN-IN PERIOD ≤12 weeks

- Participants on treatment must suspend therapy (Ig or corticosteroids) and demonstrate evidence of clinically meaningful deterioration*
- Participants off treatment with active disease may skip the run-in and enter stage A

TREATMENT PERIOD

OPEN-LABEL: STAGE A ≤12 weeks

DOUBLE-BLINDED: STAGE B ≤48 weeks

QW 1000 mg efgartigimod PH20 SC → **Responders**

- **QW 1000 mg efgartigimod PH20 SC**
- **R (1:1)**
- **QW placebo PH20 SC**

Until confirmed evidence of clinical improvement† for 2 consecutive visits

PRIMARY ENDPOINT
Percentage of participants with confirmed evidence of clinical improvement

Until 88 events (relapses)‡

PRIMARY ENDPOINT
Time to first aINCAT deterioration§ (relapse) compared with stage B baseline

ADHERE+

OPEN-LABEL EXTENSION

OLE TREATMENT ≤2 years

QW 1000 mg efgartigimod PH20 SC

ROLLOVER CRITERIA

- Completed Week 48 stage B (ADHERE)
- Deteriorated in stage B (ADHERE)
- Terminated ADHERE early (sufficient primary endpoint events)

PRIMARY ENDPOINT
Long-term safety and tolerability

Baseline characteristics were similar between stages A and B and well-balanced between treatment groups in ADHERE

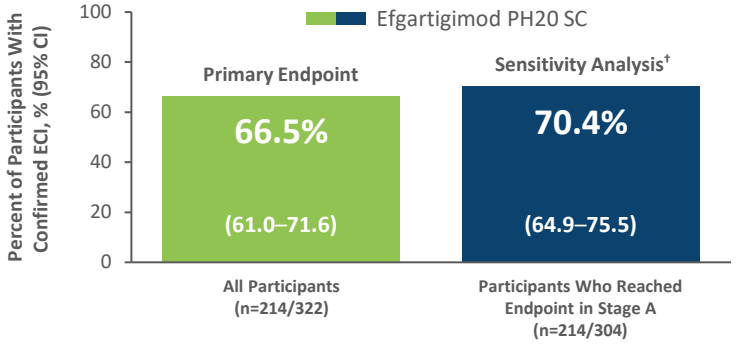
aINCAT, adjusted INCAT; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; HR, hazard ratio; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; OLE, open-label extension; PH20, recombinant human hyaluronidase PH20; QW, once weekly; R, randomisation; SC, subcutaneous.

*ECMD was defined as an aINCAT increase of ≥1 points, an I-RODS decrease of ≥4 points (centile metric), or a grip strength decrease of ≥8 kPa. †ECI was defined as a 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 four injections and two consecutive visits. ‡The primary endpoint was assessed once 88 total relapses or events were achieved in stage B and was based on the HR for the time to first aINCAT deterioration (ie, relapse). §aINCAT deterioration was defined as a ≥1-point increase in aINCAT compared with stage B baseline, which was confirmed at a consecutive visit after the first 1-point increase in aINCAT or not confirmed for participants with ≥2-point increase in aINCAT compared with stage B baseline.

1. Van den Bergh PYK, et al. *Eur J Neurol.* 2010.

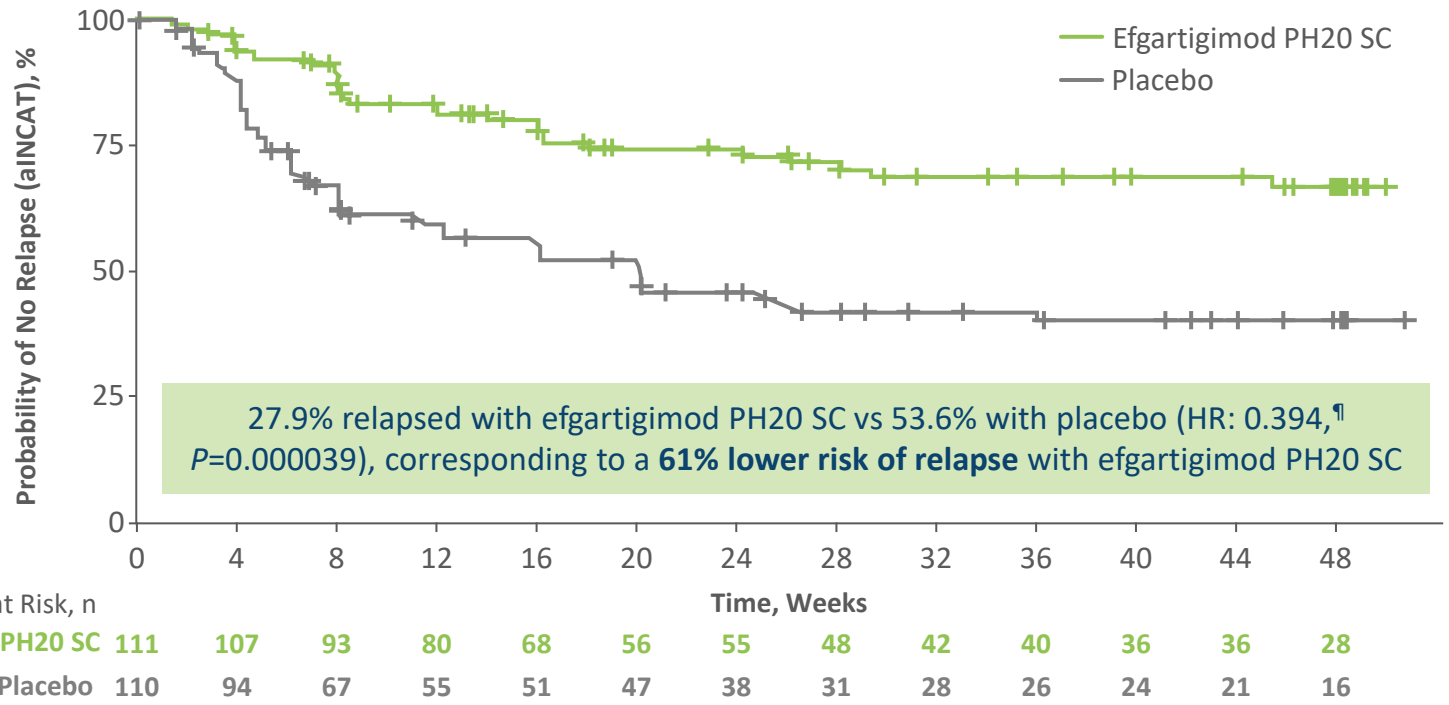
Confirmed Evidence of Clinical Improvement With Efgartigimod in 66.5% of Participants (Stage A) and 61% Reduced Relapse Risk Compared With Placebo (Stage B)

Stage A Primary Endpoint:
Percent of Participants With Confirmed ECI*



Stage A Secondary Endpoint:
Time to First Clinical Improvement‡ Compared With Stage A Baseline

Stage B Primary Endpoint:
Time to First aINCAT Deterioration‖ Compared With Stage B Baseline

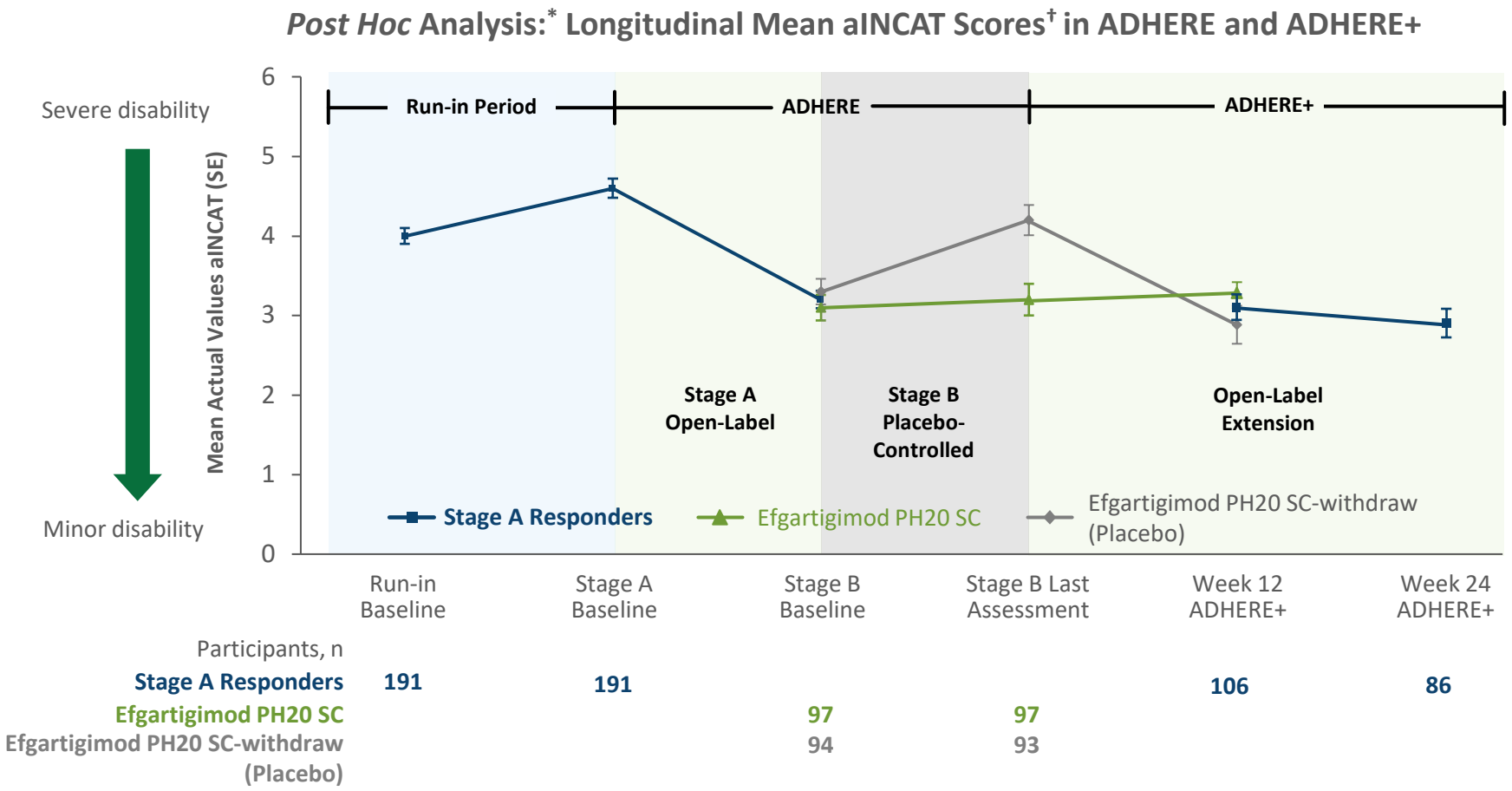


Participants at Risk, n													
Efgartigimod PH20 SC	111	107	93	80	68	56	55	48	42	40	36	36	28
Placebo	110	94	67	55	51	47	38	31	28	26	24	21	16

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; HR, hazard ratio; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

*ECI was defined as a 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 four injections and two consecutive visits. †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. ‡First improvement was defined as an improvement on any of the following efficacy parameters at 2 consecutive visits: decrease ≥1 points in aINCAT, increase ≥4 points in I-RODS, or increase ≥8 kPa in grip strength in at least one hand, versus stage A baseline, regardless of the participant's run-in ECMD deterioration. §Participants were assessed around day 7±2 days, so within 9 days after receiving the first dose. ‖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. ¶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.

Improvements in Functional Ability with Efgartigimod From Stage A Baseline Were Maintained Through ADHERE and up to Week 24 of ADHERE+



Post Hoc Analysis‡

- During randomized-withdrawal in stage B, **mean aINCAT scores deteriorated in participants receiving placebo,** whereas **active efgartigimod participants maintained the improvements** seen in stage A
- **Mean aINCAT scores** from run-in baseline of ADHERE to Week 24 of ADHERE+ **decreased** by **1.1 points (considered a clinically meaningful improvement)**[1] in stage A responders

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

*Analysis set population included efgartigimod-responders in stage A with run-in baseline values. Mean treatment duration was 29.9 weeks. †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. 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. Higher aINCAT score indicates worsening of functional ability. ‡Analysis set population included efgartigimod-responders in stage A who completed week 24 of ADHERE+ at the time of the Interim Analysis I of the ADHERE+ data cut-off (June 15, 2023).

1. Breiner A, et al. *Muscle Nerve*. 2014.

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

	ADHERE			ADHERE+
	Open-Label Stage A	Double-Blinded Stage B		
n (%) [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)	Efgartigimod PH20 SC (N=228; PYFU=137.4)
Any TEAE	204 (63.4) [13.4]	**71 (64.0) [3.5]**	**62 (56.4) [5.1]**	131 (57.5) [3.5]
Any SAE	21 (6.5) [0.5]	6 (5.4) [0.1]	6 (5.5) [0.2]	21 (9.2) [0.3]
Any injection site reactions	62 (19.3) [2.6]	**16 (14.4) [0.4]**	**7 (6.4) [0.2]**	22 (9.6) [0.3]
Discontinued due to TEAEs†	22 (6.8) [0.5]	**3 (2.7) [0.05]**	**1 (0.9) [0.02]**	9 (3.9) [0.09]
Deaths‡	2 (0.6) [0.04]	0	1 (0.9) [0.02]	1 (0.4) [0.007]
Most common TEAEs (≥5% of participants in any group)				
Injection site erythema	33 (10.2) [1.13]	**6 (5.4) [0.11]**	**0**	7 (3.1) [0.1]
CIDP§	17 (5.3) [0.41]	1 (0.9) [0.02]	1 (0.9) [0.02]	5 (2.2) [0.06]
Headache	16 (5.0) [0.6]	**4 (3.6) [0.11]**	**2 (1.8) [0.05]**	8 (3.5) [0.09]
Upper respiratory tract infection	11 (3.4) [0.26]	**2 (1.8) [0.05]**	**11 (10.0) [0.26]**	14 (6.1) [0.12]
COVID-19	7 (2.2) [0.17]	19 (17.1) [0.35]	14 (12.7) [0.33]	31 (13.6) [0.23]
Injection site bruising	4 (1.2) [0.11]	**6 (5.4) [0.11]**	**1 (0.9) [0.02]**	6 (2.6) [0.05]

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.

*Event rates were calculated as the number of events divided by the PYFU. †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 ADHERE stage A; COVID-19 pneumonia (n=1), prostate cancer (n=1), and transitional cell carcinoma (n=1) in ADHERE stage B efgartigimod PH20 SC; pneumonia (n=1) in ADHERE stage B placebo SC; 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. ‡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; one death (CIDP deterioration) in ADHERE+ was considered related to efgartigimod PH20 SC by the investigator. §Signs or symptoms of CIDP were recorded as TEAEs (regardless of causality) if there was worsening or deterioration of CIDP observed.

ADHERE+ data cut-off: June 15, 2023.

Conclusions

Participants treated with efgartigimod PH20 SC demonstrated clinical benefits:

- 66.5% showed confirmed evidence of clinical improvement (ADHERE stage A)
- Evidence of rapid clinical improvement in efficacy parameters by day 9 in 25% of participants (ADHERE stage A)
- 61% reduced risk of relapse compared with placebo (ADHERE stage B)
- Improvements in functional ability from stage A baseline through ADHERE, maintained up to Week 24 of ADHERE+

99% of eligible participants rolled over from ADHERE to open-label extension ADHERE+

Weekly efgartigimod PH20 SC was well tolerated:

- The safety profile of efgartigimod was similar between ADHERE and ADHERE+, with no increased rate of TEAEs with increased exposure
- The safety profile of efgartigimod was consistent 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; TEAE, treatment-emergent adverse event.

1. Howard JF Jr, et al. *Lancet Neurol*. 2021. **2.** Goebeler M, et al. *Br J Dermatol.* 2022. **3.** Broome CM, et al. *Lancet*. 2023. **4.** Howard JF Jr, et al. *Front Neurol.* 2024.