313

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

Jeffrey A. Allen,[1] Erika Schirinzi,[2] Gabriele Siciliano,[2] Yessar M. Hussain,[3] Gwendl Le Masson,[4] Niraja Suresh,[5,*] Channa Hewamadduma,[6,7] Jie Lin,[8] Marta Lipowska,[9,10] Giuseppe Lauria,[11,12] Mihaela A. Simu,[13] Ting Chang,[14] Satoshi Kuwabara,[15] Jeffrey T. Guptill,[16,17] Tina Dysgaard,[18] Christian Eggers,[19] Frank Leypoldt[20]

[1]University of Minnesota, Minneapolis, MN, USA; [2]University of Pisa, Pisa, Italy; [3]Austin Neuromuscular Center, Austin, TX, USA; [4]AOC National Reference Center for Neuromuscular Disorders, ALS Center, University Hospital of Bordeaux (CHU Bordeaux), Bordeaux, France; [5]University of South Florida, Tampa, FL, USA; [6]Sheffield Institute for Translational Neurosciences (SITRAN), University of Sheffield, Sheffield, UK; [7]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [8]Huashan Hospital, Fudan University, Shanghai, China; [9]Medical University of Warsaw, Warsaw, Poland; [10]European Reference Network On Rare Neuromuscular Diseases (ERN EURO-NMD), Paris, France; [11]IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy; [12]University of Milan, Milan, Italy; [13a]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania; [14]Tangdu Hospital, The Fourth Military Medical University, Xi'an, China; [15]Chiba University, Chiba, Japan; [16]argenx, Ghent, Belgium; [17]Duke University, Durham, NC, USA; [18]University of Copenhagen, Copenhagen, Denmark; [19]Kepler University Hospital, Johannes Kepler University, Linz, Austria; [20]Institute of Clinical Chemistry, Christian-Albrecht University of Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany *At the time of the trials

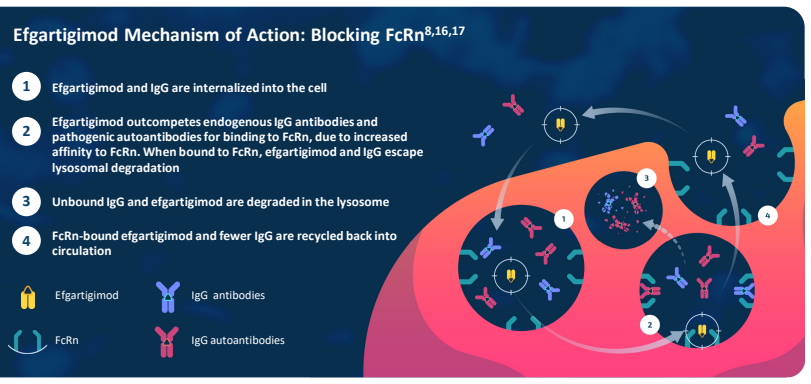
BACKGROUND | METHODS

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[1,2]
- Evidence supports a role for pathogenic IgGs in the development of CIDP, although in most patients a specific antibody is currently not detectable[3–6]
- FcRn recycles IgG, extending its half -life, and maintaining serum concentrations of both IgG and pathogenic IgG autoantibodies[7]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity for FcRn[8]
- 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
- 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]

Efgartigimod Mechanism of Action: Blocking FcRn[8,16,17]

1. Efgartigimod and IgG are internalized into the cell
2. Efgartigimod outcompetes endogenous IgG antibodies and pathogenic autoantibodies for binding to FcRn, due to increased affinity to FcRn. When bound to FcRn, efgartigimod and IgG escape lysosomal degradation
3. Unbound IgG and efgartigimod are degraded in the lysosome
4. FcRn-bound efgartigimod and fewer IgG are recycled back into circulation

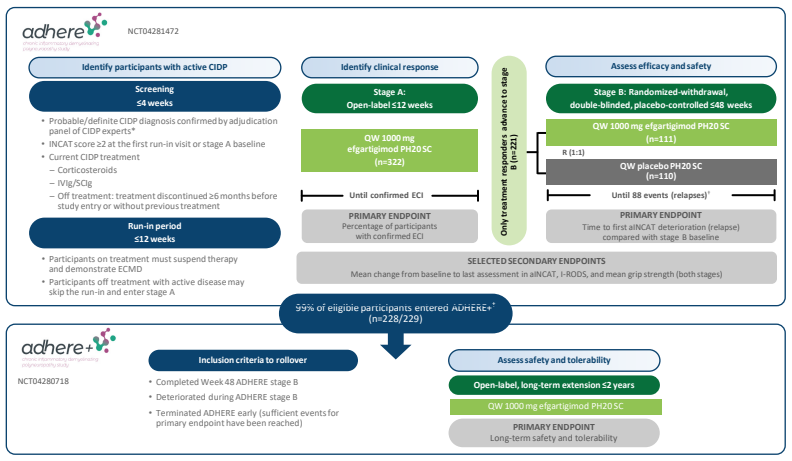


OBJECTIVE

To evaluate the safety and efficacy of efgartigimod PH20 SC in the ADHERE and ADHERE+ (data cut-off: June 15, 2023) trials in adult participants with CIDP

- The multi-stage, double-blinded, placebo-controlled, randomized-withdrawal ADHERE trial, and ongoing OLE ADHERE+ trial assessed the efficacy and safety of efgartigimod PH20 SC in CIDP (**Figure 1**)

FIGURE 1 Trial Designs of ADHERE and ADHERE+



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

Baseline characteristics were balanced between treatment arms and trials

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

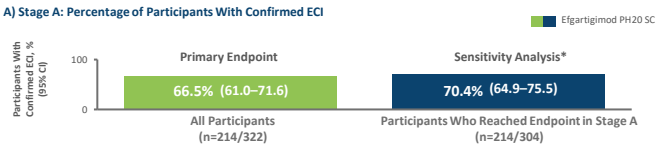
RESULTS

Efgartigimod PH20 SC Demonstrated Clinical Benefits

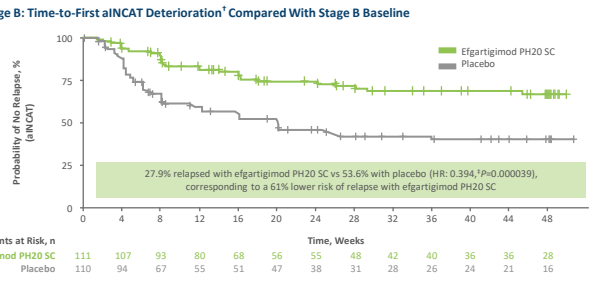
- The primary endpoints in both stages A and B were met (**Figure 2**); across all prior CIDP medication subgroups, most participants responded to efgartigimod PH20 SC and reduced risk of relapse was observed

FIGURE 2 ADHERE Trial Primary Endpoints

A) Stage A: Percentage of Participants With Confirmed ECI



B) Stage B: Time-to-First aINCAT Deterioration† Compared With Stage B Baseline



*Prespecified sensitivity analysis excluded participants ongoing in stage A at the time of trial completion and without full opportunity to achieve a response. †Defined as the number of days from first dose in stage B to the first occurrence of aINCAT deterioration compared with stage B baseline. ‡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 improvement on aINCAT score during stage A.

ADHERE Key Secondary Efficacy Endpoints Supported the Primary Endpoint

- Clinical improvements across aINCAT, I-RODS, and grip strength were observed in stage A and maintained with efgartigimod PH20 in stage B, but partially lost with placebo (**Table 1**)

TABLE 1 ADHERE Trial Key Secondary Efficacy Endpoints

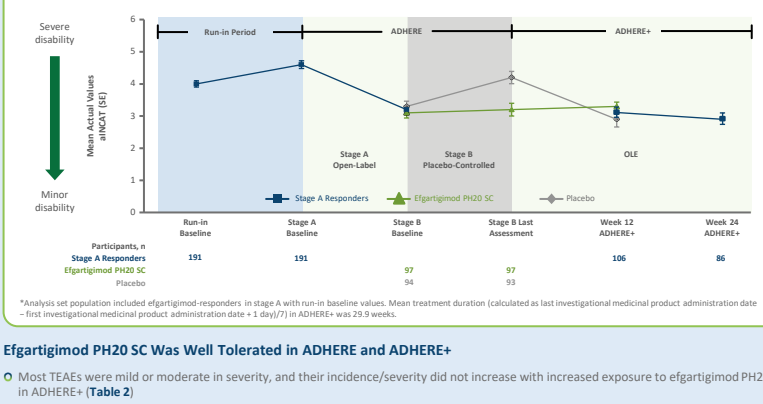
	ADHERE		
	Open-Label Stage A	Double-Blinded Stage B	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (N=111)	Placebo (N=110)
Change from baseline to last assessment,* mean (SD)			
aINCAT score†	–0.9 (1.71)	0.1 (1.08)	0.9 (1.98)
I-RODS score‡	7.7 (15.48)	0.8 (12.33)	–7.0 (19.10)
Grip strength (dominant hand), kPa	12.3 (18.68)	2.1 (13.29)	–8.2 (20.69)
Grip strength (non-dominant hand), kPa	11.2 (21.12)	2.0 (17.33)	–6.9 (21.30)
I-RODS decrease of ≥4 points, n (%)	–	40 (36.0)	57 (51.8)
HR (95% CI) [Nominal *P* value]	–	0.537 (0.354–0.814) [0.0034]	
I-RODS increase of ≥4 points, n (%)	–	50 (45.0)	40 (36.4)
HR (95% CI) [Nominal *P* value]	–	1.441 (0.814–2.567) [0.2294]	

*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.

Improvements in Functional Ability With Efgartigimod PH20 SC From Stage A Baseline to Stage B Baseline Were Maintained Through ADHERE and Week 24 of ADHERE+ (at Data Cut-Off)

- During stage B, mean aINCAT scores deteriorated in placebo -treated participants, whereas efgartigimod-treated participants maintained improvements seen in stage A (**Figure 3**)
- Based on a *post hoc* analysis, mean aINCAT scores from ADHERE run-in baseline to ADHERE+ Week 24 decreased by 1.1 points (considered a CMI)[18] in stage A responders

FIGURE 3 Longitudinal Mean aINCAT Scores in ADHERE and ADHERE+*



*Analysis set population included efgartigimod-responders in stage A with run-in baseline values. Mean treatment duration (calculated as last investigational medicinal product administration date – first investigational medicinal product administration date + 1 day)/7) in ADHERE+ was 29.9 weeks.

Efgartigimod PH20 SC Was Well Tolerated in ADHERE and ADHERE+

- Most TEAEs were mild or moderate in severity, and their incidence/severity did not increase with increased exposure to efgartigimod PH20 SC in ADHERE+ (**Table 2**)

TABLE 2 Overview of Safety

	ADHERE			ADHERE+
	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 (N=110; PYFU=42.1)	Efgartigimod PH20 SC (N=228; PYFU=137.4)
Any TEAE	63.4 [13.4]	64.0 [3.5]	56.4 [5.1]	57.5 [3.5]
Any SAE	6.5 [0.5]	5.4 [0.1]	5.5 [0.2]	9.2 [0.3]
Any injection site reactions	19.3 [2.6]	14.4 [0.4]	6.4 [0.2]	9.6 [0.3]
Discontinued due to AEs†	6.8 [0.5]	2.7 [0.05]	0.9 [0.02]	3.9 [0.09]
Deaths‡	0.6 [0.04]	0	0.9 [0.02]	0.4 [0.007]
Most common TEAEs (≥5% of participants in any group)				
Injection site erythema	10.2 [1.13]	5.4 [0.11]	0	3.1 [0.1]
CIDP§	5.3 [0.41]	0.9 [0.02]	0.9 [0.02]	2.2 [0.06]
Headache	5.0 [0.6]	3.6 [0.11]	1.8 [0.05]	3.5 [0.09]
Upper respiratory tract infection	3.4 [0.26]	1.8 [0.05]	10.0 [0.26]	6.1 [0.12]
COVID-19	2.2 [0.17]	17.1 [0.35]	12.7 [0.33]	13.6 [0.23]
Injection site bruising	1.2 [0.11]	5.4 [0.11]	0.9 [0.02]	2.6 [0.05]

*Event rate was calculated as the number of events divided by the total PYFU. †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. ‡Two deaths (cardiac arrest and CIDP deterioration) in stage A were considered not related to efgartigimod PH20 SC; 1 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.

KEY TAKEAWAYS

- Participants treated with efgartigimod PH20 SC demonstrated clinical benefits, including reduced risk of relapse and sustained improvements across functional ability assessments versus placebo
- 99% of eligible participants rolled over from ADHERE to ADHERE+ (at the time of data cut-off)
- Weekly efgartigimod PH20 SC was well tolerated, with a safety profile that was:
  - Similar between ADHERE and ADHERE+
  - Consistent with that of efgartigimod in clinical trials in other autoimmune diseases[9,12,13,19]
- 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 55TH CONGRESS OF THE ITALIAN SOCIETY OF NEUROLOGY (SIN); OCTOBER 24–28, 2025; PADUA, ITALY

ABBREVIATIONS

AE, adverse event; **aINCAT**, adjusted Inflammatory Neuropathy Cause and Treatment; **CIDP**, chronic inflammatory demyelinating polyneuropathy; **CMI**, clinically meaningful improvement; **COVID-19**, coronavirus disease 2019; **ECI**, evidence of clinical improvement; **ECMD**, evidence of clinically meaningful deterioration; **FcRn**, neonatal Fc receptor; **HR**, hazard ratio; **Ig**, immunoglobulin; **I-RODS**, Inflammatory Rasch-Built Overall Disability Scale; **IVIg**, intravenous immunoglobulin; **OLE**, open-label extension; **PH20**, recombinant human hyaluronidase PH20; **PYFU**, participant-years of follow-up; **QW**, once weekly; **R**, randomization; **s**, second; **SAE**, serious adverse event; **SC**, subcutaneous; **SCIg**, subcutaneous immunoglobulin; **SE**, standard error; **TEAE**, treatment-emergent adverse event.

DISCLOSURES AND ACKNOWLEDGMENTS

JAA: Akcea Therapeutics, Alexion, Alnylam, Annexon Biosciences, argenx, CSL Behring, Grifols, Immunovant, ImmuPharma, Johnson & Johnson, Pfizer, and Takeda Pharmaceuticals; **YMH, GLM, JL, M-AS, TC, and TD:** No financial disclosures; **ES:** Alexion, Alnylam, argenx, CSL-Behring, Kedrion Biopharma, Sanofi, Takeda Pharmaceuticals; **GS:** Alexion, Alnylam, Amicus, argenx, Biogen, CSL-Behring, Grifols, Kedrion Biopharma, Lupin, Roche, Sanofi, Sarepta, Takeda Pharmaceuticals; **NS:** Alnylam, Takeda Pharmaceuticals; **CH:** argenx, Biogen, Lupin, Roche, UCB; **ML:** argenx, CSL Behring, Kedrion Biopharma, Medison Pharma/Alnylam, Pfizer, Sanofi, Sobi, Takeda Pharmaceuticals; **GL:** Biogen, Chromocell, CSL Behring, Home Biosciences, Janssen, Lilly, Sangamo Therapeutics, Vertex Pharmaceuticals, Zambon; **SK:** Alexion, argenx, CSL Behring, Takeda Pharmaceuticals; **JTG:** Employee of argenx (may hold stock or stock options); **CE:** argenx, Biogen, GlaxoSmithKline, UCB; **FL:** Alexion, Bayer, Biogen, Fresenius Kabi, Grifols, Merck, Novartis, Roche, Teva Pharmaceuticals.

These trials were sponsored by argenx. Medical writing support was provided by Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, and was funded by argenx. The authors gratefully acknowledge the trial participants and investigators involved. Previously presented at the 19th World Congress on Controversies in Neurology (CONy) 2025, March 20–25, 2025, Prague, Czech Republic.

REFERENCES

1. Cox ZC, Gwathmey KG. *Clin Geriatr Med.* 2021;37:327–45. **2.** Van den Bergh PYK, et al. *Eur J Neurol.* 2021;28:3556–83. **3.** Querol L, et al. *Sci Rep.* 2017;7:14411. **4.** Mathey EK, et al. *J Neurol Neurosurg Psychiatry.* 2015;86:973–85. **5.** Yan WX, et al. *Ann Neurol.* 2000;47:765–75. **6.** Manso C, et al. *J Clin Invest.* 2019;129:2222–36. **7.** Sesarman A, et al. *Cell Mol Life Sci.* 2010; 67:2533–50. **8.** Ulrichts P, et al. *J Clin Invest.* 2018;128:4372–86. **9.** Howard JF Jr, et al. *Lancet Neurol.* 2021;20:526–36. **10.** Vaccaro C, et al. *Nat Biotech.* 2005;23:1283–8. **11.** Nixon AE, et al. *Front Immunol.* 2015;6:176. **12.** Broome CM, et al. *Lancet.* 2023;402:1648–59. **13.** Goebeler M, et al. *Br J Dermatol.* 2022;186:429–39. **14.** Locke KW, et al. *Drug Deliv.* 2019; 26:98–106. **15.** VYVGART HYTRULO. Prescribing information. argenx; 2025. https://www.argenx.com/product/vyvgart-hytrulo-prescribing-information.pdf. Accessed September 12, 2025. **16.** Roopenian DC, Akilesh S. *Nat Rev Immunol.* 2007;7:715–25. **17.** Ward ES, Ober RJ. *Trends Pharmacol Sci.* 2018;39:892–904. **18.** Breiner A, et al. *Muscle Nerve.* 2014;50:40–6. **19.** Howard JF Jr, et al. *Front Neurol.* 2024;14:1284444.