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


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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[1,2]
- 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] (**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

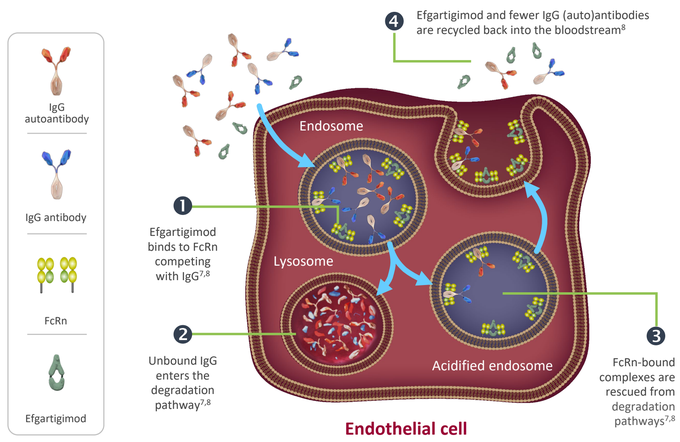



Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

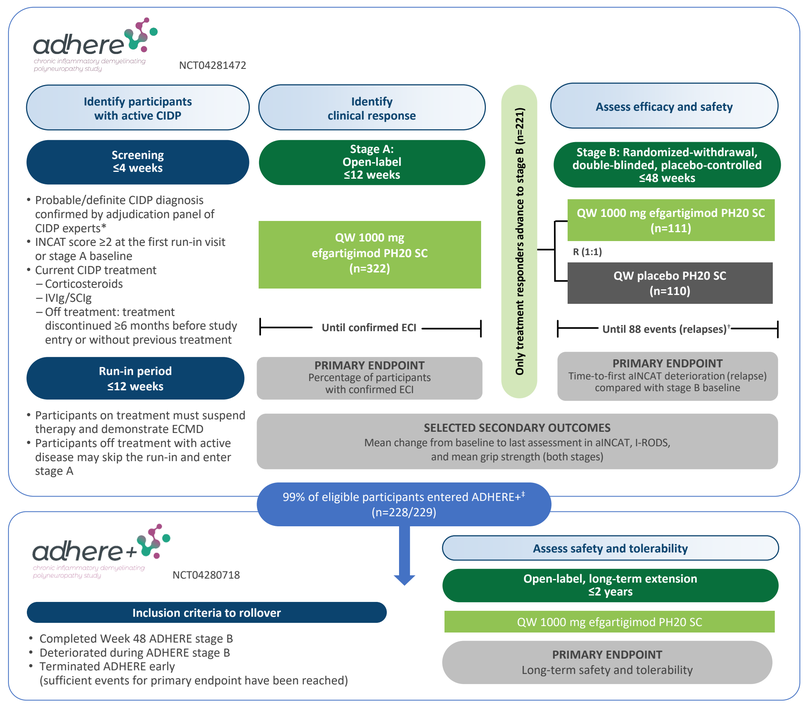
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90 s single injection) SC administration[14,15]
- The multi-stage, double-blinded, placebo-controlled, randomized-withdrawal ADHERE trial, and ongoing, OLE ADHERE+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

## 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

## METHODS

**FIGURE 2** 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

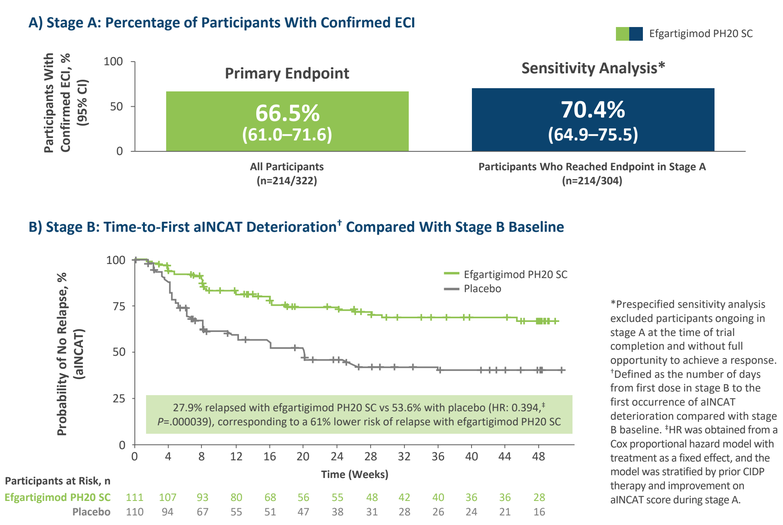
- **Evidence of clinically meaningful deterioration (ECMD)**: aINCAT increase of ≥1 points, an I-RODS decrease of ≥4 points (centile metric), or a grip strength decrease of ≥8 kPa
- **Evidence of clinical improvement (ECI)**: clinical improvement on the parameters that the participant worsened in during 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 3**); across all prior CIDP medication subgroups, most participants responded to efgartigimod PH20 SC and reduced risk of relapse was observed

**FIGURE 3** ADHERE Trial Primary Endpoints




*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

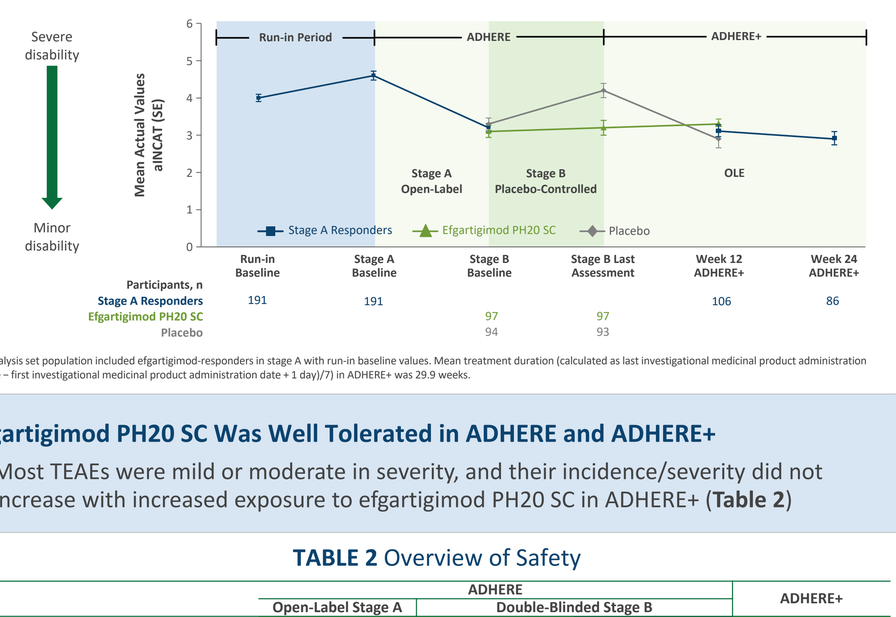
| | ADHERE | | |
|---|---|---|---|
| | Open-Label Stage A | Double-Blinded Stage B | |
| | Efgartigimod PH20 SC (N=322) | Efgartigimod PH20 SC (N=111) | Placebo (N=110) |
| **Mean (SD) change from baseline to last assessment*** | | | |
| aINCAT score† | –0.9 (1.71) | 0.1 (1.08) | 0.9 (1.98) |
| I-RODS score‡ | 7.7 (15.48) | 0.8 (12.33) | –7.0 (19.10) |
| Mean grip strength (dominant hand), kPa | 12.3 (18.68) | 2.1 (13.29) | –8.2 (20.69) |
| Mean 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 5**)
- Based on *post hoc* analyses, mean aINCAT scores from ADHERE run-in baseline to ADHERE+ Week 24 decreased by 1.1 points (considered a CMI)[16] in stage A responders

**FIGURE 5** 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; 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.

## 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[9,12,13,17]

**A single, rapid (30–90 s) 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**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### ABBREVIATIONS

**AE**, adverse event; **aINCAT**, adjusted Inflammatory Neuropathy Cause and Treatment; **CI**, confidence interval; **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; **Fc**, fragment crystallizable; **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**, participants years of follow-up; **QW**, once weekly; **R**, randomization; **s**, second; **SAE**, serious adverse event; **SC**, subcutaneous; **SCIg**, subcutaneous immunoglobulin; **SD**, standard deviation; **SE**, standard error; **TEAE**, treatment-emergent adverse event.


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