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

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BACKGROUND

Efgartigimod Blocks Neonatal Fc Receptor (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[8–11]:
  - 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

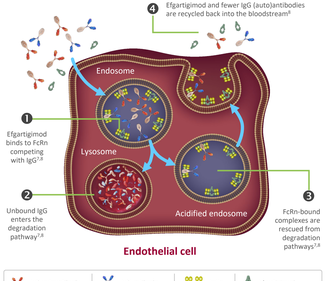


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

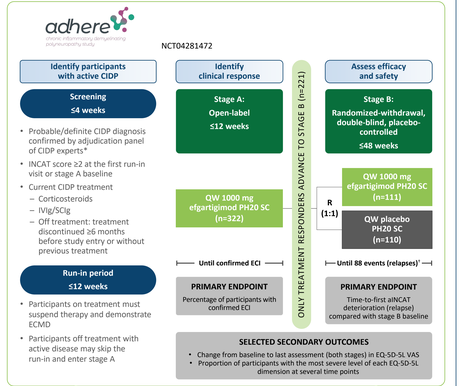
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90 s single injection) SC administration[12,13]
- The multi-stage, double-blind, placebo-controlled, randomized-withdrawal ADHERE trial and the ongoing OLE ADHERE+ 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 three 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 one participant discontinued before receiving the first dose of efgartigimod PH20 SC.

Baseline characteristics were balanced between treatment arms and trials

Definitions

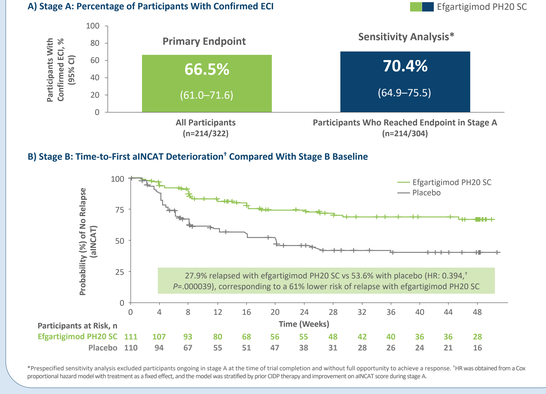
- **Evidence of clinically meaningful deterioration (ECMD)**: aINCAT increase of ≥1 points, an I-RODS decrease of ≥4 points (centile metric), or a grip strength decrease of ≥8 kPa
- **Evidence of clinical improvement (ECI)**: clinical improvement on the parameters that the participant worsened in during 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 risk reduction was observed

FIGURE 3 ADHERE Trial Primary Endpoints

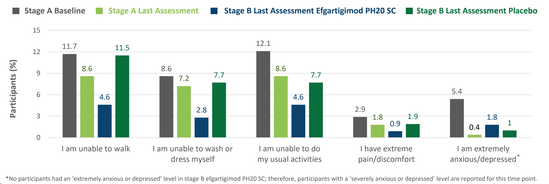


*Prespecified sensitivity analysis excluded participants ongoing in stage A at the time of trial completion and without full opportunity to achieve a response. †HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and improvement on aINCAT score during stage A.

Improvements in QoL Were Seen With Efgartigimod PH20 SC

- Improvements in the proportion of participants experiencing the most severe level of each EQ-5D-5L dimension were observed with efgartigimod PH20 SC from stage A baseline to last assessment. During stage B, improvements were maintained in efgartigimod-treated participants but lost with placebo (**Figure 4**)
- Mean changes (SE) from their corresponding baselines in the EQ-5D-5L VAS were 10.7 (1.34), 0.5 (1.77), and –10.2 (2.47) at last assessment in stages A (efgartigimod PH20 SC) and B (efgartigimod PH20 SC and placebo), respectively

FIGURE 4 EQ-5D-5L: Tabulation of Most Severe Level of Each Dimension

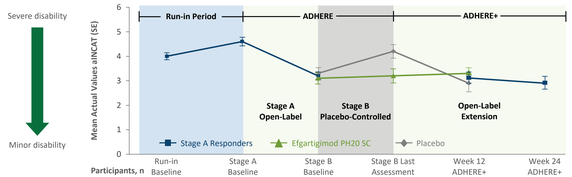


*No participants had an 'extremely anxious or depressed' level in stage B efgartigimod PH20 SC; therefore, participants with a 'severely anxious or depressed' level are reported for this time point.

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 clinically meaningful improvement)[14] 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 With a Favorable Safety Profile

- 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 1**)

TABLE 1 Overview of Safety

	ADHERE			ADHERE+
	Open-Label Stage A	Double-Blinded Stage B		
% [event rate*]	Efgartigimod PH20 SC (N=322; PYFU=46.3)	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	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 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. §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 in QoL and functional ability 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[9,15–17]

A single, rapid (30–90 s) injection of weekly efgartigimod PH20 SC was recently approved in the US for adults with CIDP,[13] representing a new therapeutic option that may reduce CIDP treatment burden and improve QoL

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ABBREVIATIONS

AE, adverse event; **aINCAT**, adjusted Inflammatory Neuropathy Cause and Treatment; **CI**, confidence interval; **CIDP**, chronic inflammatory demyelinating polyneuropathy; **COVID-19**, coronavirus disease 2019; **ECI**, evidence of clinical improvement; **ECMD**, evidence of clinically meaningful deterioration; **EQ-5D-5L**, EuroQol 5-dimensions 5-levels; **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; **QoL**, quality of life; **QW**, once weekly; **R**, randomization; **SAE**, serious adverse event; **SC**, subcutaneous; **SCIg**, subcutaneous immunoglobulin; **SD**, standard deviation; **SE**, standard error; **TEAE**, treatment-emergent adverse event; **VAS**, Visual Analog Scale.

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