P-029

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

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SCAN ME

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]
- The 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, including pathogenic IgG, preventing recycling and promoting lysosomal degradation of IgG, without impacting its production[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

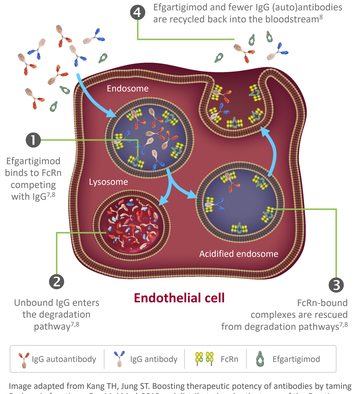


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

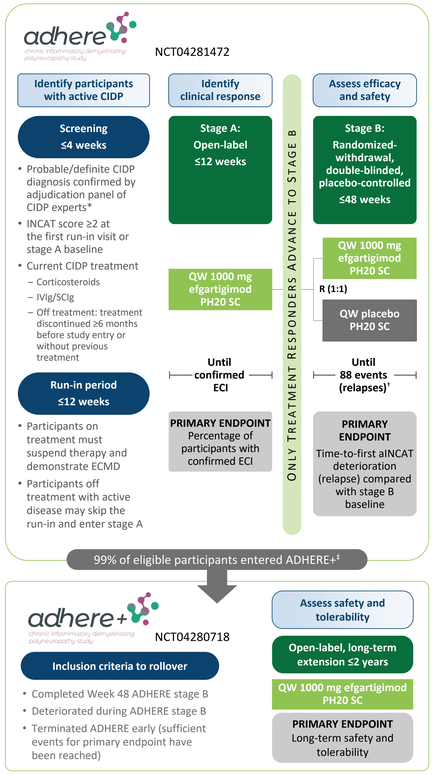
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90 s single injection) SC administration[14,15]
- The multi-stage, double-blind, placebo-controlled, randomized-withdrawal ADHERE trial, and ongoing, open-label extension 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 achieved in stage B; this is the time point at which 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.

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
- **aINCAT deterioration**: ≥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

RESULTS

TABLE 1 Demographics and Baseline Disease Characteristics

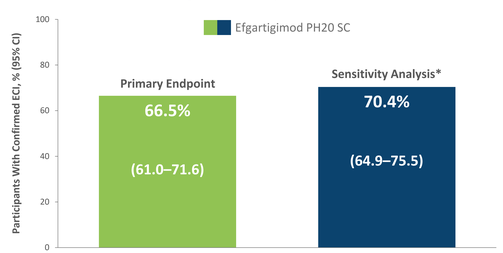
	ADHERE			ADHERE+
	Open-Label Stage A	Double-Blinded Stage B		
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (N=111)	Placebo (N=110)	Efgartigimod PH20 SC (N=228)
Age, mean (SD), years*	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)	53.2 (14.0)†
Male, n (%)*	208 (64.6)	73 (65.8)	69 (62.7)	142 (62.3)†
Time since diagnosis, mean (SD), years*	4.9 (6.1)	3.7 (4.4)	3.8 (4.7)	4.9 (5.6)†
Typical CIDP diagnosis, n (%)*	268 (83.2)	97 (87.4)	95 (86.4)	199 (87.3)†
Unstable active disease (CDAS: 5), n (%)*	197 (61.2)	74 (66.7)	76 (69.1)	151 (66.2)†
Prior treatment (in past 6 months), n (%)*				
Corticosteroids	63 (19.6)	26 (23.4)	24 (21.8)	51 (22.4)
Immunoglobulins (IVIg, SCIg)	165 (51.2)	49 (44.1)	47 (42.7)	104 (45.6)
Off treatment	94 (29.2)	36 (32.4)	39 (35.5)	73 (32.0)
aINCAT score, mean (SD)‡	4.6 (1.7)	3.1 (1.5)	3.3 (1.6)	4.5 (1.6)§
I-RODS score, mean (SD)‡	40.1 (14.7)	53.6 (17.9)	51.2 (15.4)	41.2 (15.4)§
Grip strength (dominant hand), mean (SD), kPa‡,‖	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)	39.0 (23.6)§

*Scores were assessed at screening in ADHERE. †Scores shown were assessed at baseline in ADHERE+. ‡Clinical assessments were performed at the beginning of each stage. §Scores were assessed at stage A baseline. ‖Non-dominant hand scores were similar.

Efgartigimod PH20 SC Demonstrated Clinical Benefits

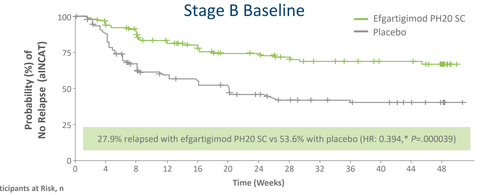
- 66.5% of participants showed confirmed ECI (stage A ADHERE; **Figure 3**); most participants responded to efgartigimod PH20 SC across all prior CIDP medication subgroups
- Efgartigimod PH20 SC significantly reduced the risk of relapse by 61% versus placebo (stage B ADHERE; **Figure 4**); risk reduction was also shown across all prior CIDP medication subgroups
- Improvements in functional ability with efgartigimod PH20 SC from stage A baseline were maintained through ADHERE and up to Week 24 of ADHERE+ (**Figure 5**)
  - During stage B, mean aINCAT scores deteriorated in placebo-treated participants, whereas efgartigimod-treated participants maintained improvements seen in stage A
  - Mean aINCAT scores from ADHERE run-in baseline to ADHERE+ Week 24 decreased by 1.1 points (considered a clinically meaningful improvement)[16] in stage A responders

FIGURE 3 Percentage of Participants With Confirmed ECI



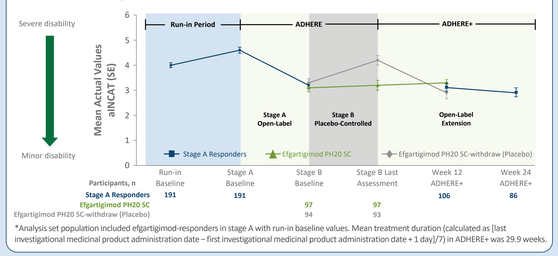
*Prespecified sensitivity analysis excluded participants ongoing in stage A at the time of trial completion and without full opportunity to achieve a response.

FIGURE 4 Time-to-First 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.

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 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 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; 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 versus placebo and sustained improvements in functional ability

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 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, 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; CDAS, CIDP disease activity status; CIDP, chronic inflammatory demyelinating polyneuropathy; COVID-19, coronavirus disease 2019; ECI, evidence of clinical improvement; ECMD, evidence of clinically meaningful deterioration; HR, hazard ratio; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; 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; SAE, serious adverse event; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; SE, serious adverse event; TEAE, treatment-emergent adverse event.

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