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

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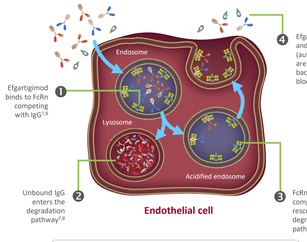
SCAN ME

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 there is currently not a known pathogenic autoantibody identified in most patients[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[8,9] (**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



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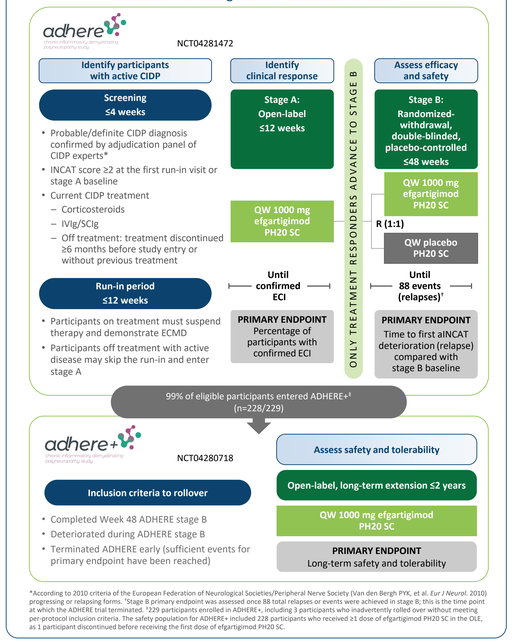
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90s single injection) SC administration[14,15]
- The multi-stage, double-blinded, placebo-controlled, randomized-withdrawal ADHERE trial, and ongoing, OLE ADHERE+ trial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

Definitions

- **Evidence of clinically meaningful deterioration (ECMD)**: aINCAT score increase of ≥1 points, I-RODS score decrease of ≥4 points (centile metric), or 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 score and/or ≥8 kPa increase in mean grip strength) or clinical improvement (≥1-point decrease) in INCAT score; 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 score confirmed at a consecutive visit after the first 1-point increase in aINCAT score, or ≥2-point increase observed at a single visit

RESULTS

TABLE 1 Demographics and Baseline Disease Characteristics

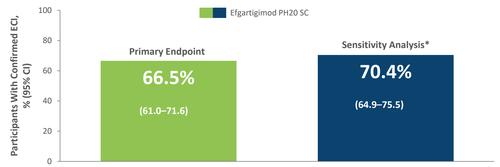
	ADHERE			ADHERE+
	Open-Label Stage A	Double-Blinded Stage B		
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (n=111)	Placebo (n=110)	Efgartigimod PH20 SC (N=228)
Age, mean (SD), years*	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)	53.2 (14.0)[†]
Sex, male, n (%)*	208 (64.6)	73 (65.8)	69 (62.7)	142 (62.3)[†]
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)	24 (21.6)	23 (20.9)	51 (22.4)
Immunoglobulins (IVIg, SCIg)	165 (51.2)	48 (43.2)	48 (43.6)	104 (45.6)
Off treatment	94 (29.2)	39 (35.1)	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

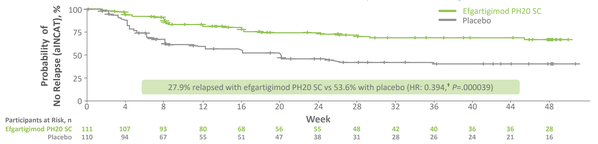
- 66.5% of participants showed confirmed ECI (stage A ADHERE; **Figure 3**); most participants responded to efgartigimod PH20 SC across all prior CIDP medication subgroups
- Efgartigimod PH20 SC significantly reduced the risk of relapse by 61% versus placebo (stage B ADHERE; **Figure 4**); reduced risk of relapse 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



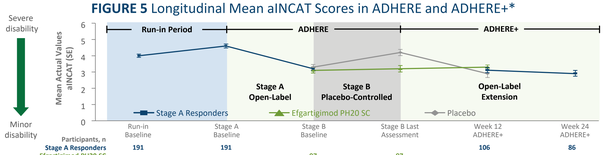
*Prespecified sensitivity analysis excluded participants ongoing in stage A at the time of trial completion and without full opportunity to achieve a response.

FIGURE 4 Time to First aINCAT Deterioration* Compared With Stage B Baseline



*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.

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+

- The incidence of TEAEs did not increase with increased exposure to efgartigimod PH20 SC in ADHERE+ (**Table 2**); most TEAEs were mild or moderate in severity

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. †There were no reports of anaphylaxis. ‡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 unlikely 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 possibly 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 that of efgartigimod in clinical trials in other autoimmune diseases[9,12,13,17]
- **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**

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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; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; HR, hazard ratio; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory-Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; OLE, open-label extension; rHuPH20, 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; SD, standard deviation; TEAE, treatment-emergent adverse event.

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