Subcutaneous Efgartigimod PH20 in Chronic Inflammatory Demyelinating Polyneuropathy: Key Secondary Outcomes From the ADHERE Trial

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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 IgG 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

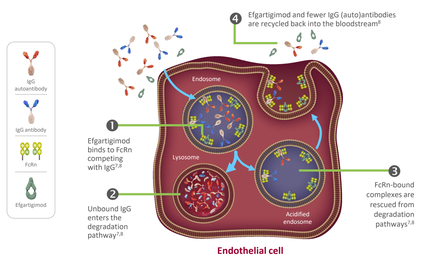


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

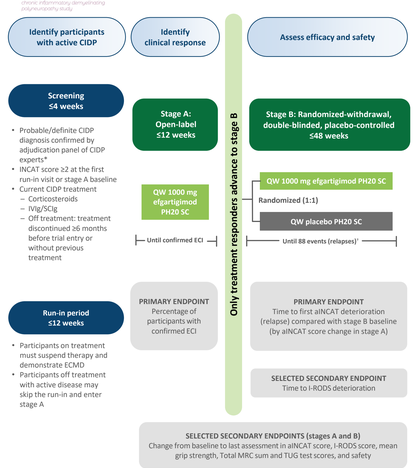
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90s single injection) SC administration[14,15]
- The multi-stage, double-blinded, placebo-controlled, randomized-withdrawal ADHERE trial assessed the efficacy and safety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

OBJECTIVE

- To report new analyses related to selected secondary endpoints of the ADHERE trial that were considered clinically relevant by argenx

METHODS

FIGURE 2 Trial Design of ADHERE (NCT04281472)



*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 form. †Stage B primary endpoint was assessed once 88 total relapses or events were achieved in stage B; this is the time point when the ADHERE trial terminated.

The ADHERE study protocol did not specify any key secondary endpoints; in this poster, key secondary endpoints are selected post-hoc analyses that were considered clinically relevant by argenx.

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**: ≥1-point increase in aINCAT score compared with stage B baseline, which was confirmed at a consecutive visit after the first 1-point increase in aINCAT score, or ≥2-point increase observed at a single visit

RESULTS

The ADHERE Trial Enrolled a Sample Representative of the General CIDP Population

- Baseline characteristics were similar between stages A and B and well balanced between treatment groups (**Table 1**)

TABLE 1 Demographics and Baseline Disease Characteristics

	Open-Label Stage A	Double-Blinded Stage B	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (n=111)	Placebo (n=110)
Age, mean (SD), years	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)
Sex, male, n (%)	208 (64.6)	73 (65.8)	69 (62.7)
Race, n (%)*			
Asian	89 (27.6)	33 (29.7)	34 (30.9)
Black or African American	4 (1.2)	1 (0.9)	1 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0
White	211 (65.5)	73 (65.8)	71 (64.5)
Other	6 (1.9)	2 (1.8)	1 (0.9)
Time since diagnosis, mean (SD), years	4.9 (6.1)	3.7 (4.4)	3.8 (4.7)
Typical CIDP diagnosis, n (%)	268 (83.2)	97 (87.4)	95 (86.4)
Unstable active disease (CDAS: 5), n (%)	197 (61.2)	74 (66.7)	76 (69.1)
Prior treatment (in past 6 months), n (%)			
Corticosteroids	63 (19.6)	24 (21.6)	23 (20.9)
Immunoglobulins (IVIg, SCIg)	165 (51.2)	48 (43.2)	48 (43.6)
Off treatment	94 (29.2)	39 (35.1)	39 (35.5)
aINCAT score, mean (SD)†,‡	4.6 (1.7)	3.1 (1.5)	3.3 (1.6)
I-RODS score, mean (SD)†,§	40.1 (14.7)	53.6 (17.9)	51.2 (15.4)
Grip strength (dominant hand), mean (SD), kPa†,‖	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)

*A total of 11 participants in stage A and 5 in stage B (2 in the efgartigimod PH20 SC group and 3 in the placebo group) did not report race. †Clinical assessments were performed at the beginning of each stage. ‡Lower aINCAT scores represent improvement. §Raw sum scores of the 24-item I-RODS score (0–48) were converted to a centile metric score ranging from 0–100, with higher scores representing improvement. ‖Nondominant hand scores were similar.

Efgartigimod PH20 SC Demonstrated Clinical Benefits Across Secondary Endpoints

- Primary endpoints in ADHERE were met; efficacy and safety data have previously been reported[16]
- In stage A, clinically meaningful improvements were observed across aINCAT, I-RODS, grip strength, Total MRC sum, and TUG test scores (**Table 2**), supportive of the primary endpoint

TABLE 2 Changes in Selected Clinical Efficacy Endpoints in Stage A

	Efgartigimod PH20 SC (N=322)		
Change from baseline to last assessment,* mean (SD)	Overall	ECI Responders	ECI Nonresponders
aINCAT score†	–0.9 (1.7)	–1.4 (1.5)	0.2 (1.5)
I-RODS score†	7.7 (15.5)	12.0 (14.6)	–0.7 (13.6)
Grip strength (dominant hand), kPa†	12.3 (18.7)	17.9 (17.0)	0.8 (16.7)
Grip strength (nondominant hand), kPa†	11.2 (21.1)	17.2 (19.3)	–1.3 (19.2)
Total MRC sum score	3.8 (7.2)	5.9 (6.1)	–0.5 (7.5)
TUG test score, s	–4.3 (14.0)	–6.1 (11.5)	–0.4 (17.9)

*Stage A baseline was defined as the last available value before the first administration of the investigational medicinal product in stage A, and stage A last assessment was defined as the last non-missing, postbaseline value in stage A. †A decrease of ≥1 points in aINCAT,[17] an increase of ≥4 points in I-RODS,[18] and ≥8 kPa in grip strength[19] were considered minimal clinically important differences.[2]

Efgartigimod PH20 SC Treatment Maintained the Clinical Benefits Observed in Stage A

- Improvements in motor function, muscle strength, and disease-related disability outcomes observed in stage A were maintained with efgartigimod PH20 SC through stage B, but partially lost with placebo (**Tables 2 and 3**)
- In stage B, a numerically higher percentage of participants experienced improvements in I-RODS in the efgartigimod PH20 SC group compared with the placebo group (**Table 3**)

TABLE 3 Summary of Selected Clinical Efficacy Endpoints in Stage B

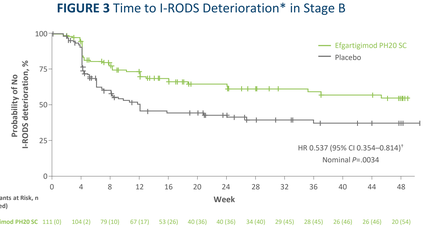
	Efgartigimod PH20 SC (n=111)	Placebo (n=110)
I-RODS deterioration of ≥4 points, n (%)	40 (36.0)	57 (51.8)
HR (95% CI) [Nominal *P* value]*	0.537 (0.354–0.814) [0.0034]	
I-RODS improvement of ≥4 points, n (%)	50 (45.0)	40 (36.4)
Odds ratio (95% CI) [Nominal *P* value]†	1.441 (0.814–2.567) [0.2294]	
Change from baseline to last assessment,‡ mean (SD)		
aINCAT score§	0.1 (1.1)	0.9 (2.0)
I-RODS score§	0.8 (12.3)	–7.0 (19.1)
Grip strength (dominant hand), kPa§	2.1 (13.3)	–8.2 (20.7)
Grip strength (nondominant hand), kPa§	2.0 (17.3)	–6.9 (21.3)
Total MRC sum score	–0.3 (4.5)	–3.0 (9.0)
TUG test score, s	0.8 (3.7)	1.9 (6.1)

*The HR was obtained from a Cox proportional hazards model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during stage A. †The odds ratio was obtained from an exact logistic regression model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during stage A. ‡Stage B baseline was defined as the last available value before the first administration of the investigational medicinal product in stage B, and the last assessment in stage B was defined as the last non-missing post-baseline value. §A decrease of ≥1 points in aINCAT,[17] an increase of ≥4 points in I-RODS,[18] and ≥8 kPa in grip strength[19] were considered minimal clinically important differences.[2]

Efgartigimod PH20 SC Reduced the Risk of I-RODS Deterioration

- The rate of CIDP disease progression, as measured by I-RODS, in stage B was lower in the efgartigimod PH20 SC group than in the placebo group (**Figure 3**)

FIGURE 3 Time to I-RODS Deterioration* in Stage B



*Defined as time from first dose in stage B to the first ≥4-point decrease in I-RODS score compared with stage B baseline. †The HR was obtained from a Cox proportional hazards model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during stage A.

KEY TAKEAWAYS

- **Clinical benefit was observed across several selected secondary endpoints, supportive of the primary endpoint**
- **Improvements observed in stage A were maintained with efgartigimod PH20 SC in stage B, but (partially) lost with placebo**
- **Efgartigimod PH20 SC was observed to reduce the risk of I-RODS deterioration compared with placebo**
- **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 2024 American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Annual Meeting; October 15–18, 2024; Savannah, GA, USA

ABBREVIATIONS

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CDAS, CIDP disease activity status; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; 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; MRC, Medical Research Council; QW, once weekly; rHuPH20, recombinant human hyaluronidase PH20; s, second; SC, subcutaneous; SCIg, subcutaneous immunoglobulin; SD, standard deviation; TUG, Timed Up and Go.

DISCLOSURES AND ACKNOWLEDGMENTS

RAL: Akcea Therapeutics, Alexion, Alnylam, Annexon Biosciences, argenx, Boehringer Ingelheim, CSL Behring, GBS/CIDP Foundation International, Grifols, Johnson & Johnson, Medscape, MGFA, Novartis, Peripheral Nerve Society, Pfizer, Roche, Sanofi, Takeda; **NS**: Alnylam, Takeda; **JAA**: Akcea Therapeutics, Alexion, Alnylam, Annexon Biosciences, argenx, CSL Behring, Grifols, Immunovant, ImmuPharma, Johnson & Johnson, Pfizer, Takeda; **LQ**: Alnylam, Annexon Biosciences, argenx, Avilar Therapeutics, Biogen, CIBERER, CSL Behring, Dianthus, Fundació La Marató, GBS/CIDP Foundation International, Grifols, Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), Janssen, LFB, Lundbeck, Merck, Novartis, Octapharma, Roche, Sanofi, UCB; **YH**: Nothing to declare; **KG**: Alexion, argenx, UCB, Xeris Pharmaceuticals; **JTG, GI, BVH, TM**: Employees of argenx; **SK**: Alexion, argenx, CSL Behring, Takeda; **IB**: Actavis, Dinathus, Mylan, Pfizer, Salveo; **PAvD**: Annexon Biosciences, argenx, Grifols, Hansa Biopharma, Octapharma, Prinses Beatrix Spierfonds, Roche, Sanofi, Sanquin, Takeda.

This trial was sponsored by argenx. Medical writing support was provided by Envision Pharma Group, funded by argenx. The authors gratefully acknowledge the trial participants and investigators involved.

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