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ADHERE+ Trial Interim Analysis: Long-Term Safety and Efficacy of Efgartigimod in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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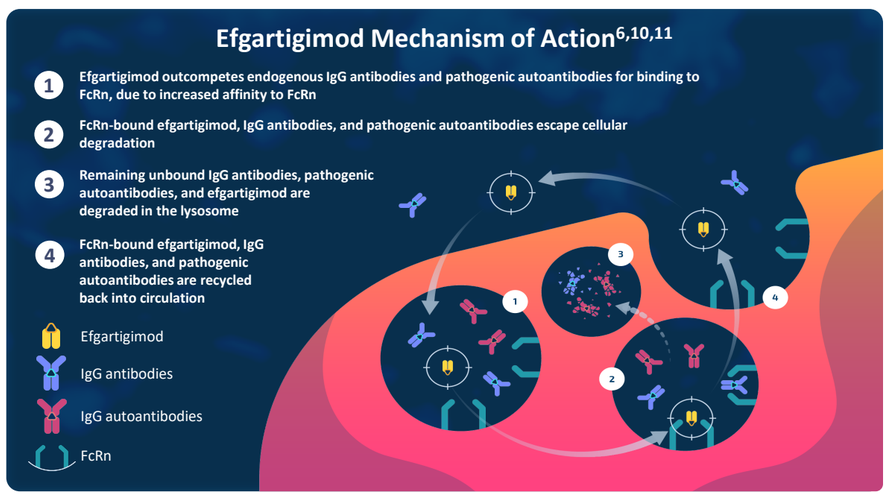
BACKGROUND

Efgartigimod Blocks FcRn and Reduces IgG Levels

- CIDP is a severe autoimmune peripheral neuropathy characterized by progressive or relapsing muscle weakness and sensory disturbance and is associated with a high treatment burden[1–5]
- Efgartigimod is an IgG1 antibody Fc fragment engineered for increased affinity for FcRn compared with endogenous IgG, and is uniquely composed of the only part of the IgG antibody that normally binds FcRn[6–8]
- Efgartigimod selectively reduces IgG by blocking FcRn-mediated IgG recycling without impacting antibody production, reducing albumin levels, or affecting other parts of the immune system[6–9]



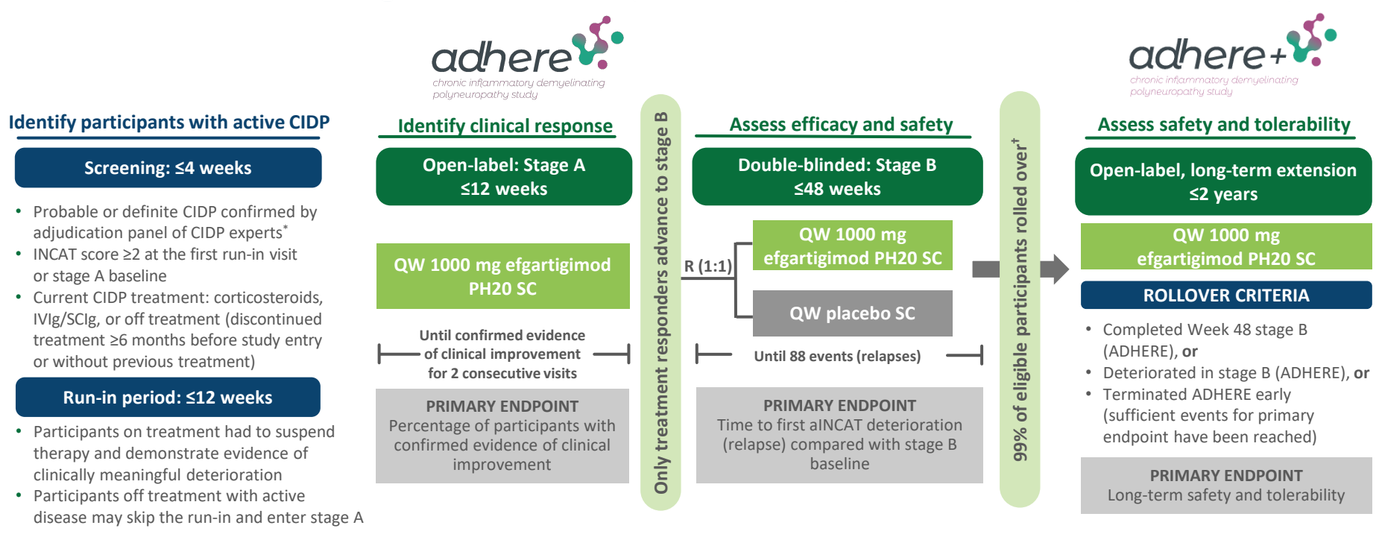
- In the ADHERE trial, efgartigimod PH20 SC reduced the risk of relapse and led to clinically meaningful improvements in functional ability, daily activity, or grip strength versus placebo, and was well tolerated in participants with CIDP[12]

OBJECTIVE

- To report safety and efficacy from an interim analysis (data cutoff: February 16, 2024) of the open-label extension ADHERE+ trial

METHODS

FIGURE 2 Trial Designs of ADHERE[12] (NCT04281472) and ADHERE+ (NCT04280718)



*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. †n=228/229. 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 open-label extension period, as 1 participant discontinued before receiving the first dose of efgartigimod PH20 SC.

Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid (30–90s single injection) SC administration[13,14]

RESULTS

Baseline Characteristics

- Baseline characteristics were similar between stages and treatment groups in ADHERE and in ADHERE+ (**Table 1**)

TABLE 1 Baseline Characteristics in ADHERE and ADHERE+

	ADHERE[12]			ADHERE+ Open-Label Extension
	Open-Label Stage A	Double-Blinded Stage B		
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (n=111)	Placebo SC (n=110)	Efgartigimod PH20 SC (N=228)
Scores shown were assessed at screening in ADHERE and baseline in ADHERE+				
Age, years, mean (SD)	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)	53.2 (14.1)
Sex, male, n (%)	208 (64.6)	73 (65.8)	69 (62.7)	142 (62.3)
Time since diagnosis, years, mean (SD)	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 (within 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)
Scores shown were assessed at beginning of each stage for ADHERE and at ADHERE stage A baseline for ADHERE+				
INCAT 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), kPa, mean (SD)‡	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)	39.0 (23.6)

*Unstable active disease was defined as abnormal examination with progressive or relapsing course.[15] †Lower scores represent improvement on INCAT, while higher scores represent improvement for I-RODS. ‡Grip strength scores in nondominant hand were similar.

Efgartigimod PH20 SC Was Well Tolerated in ADHERE and ADHERE+

- Efgartigimod was well tolerated in ADHERE and ADHERE+ (**Table 2**); most TEAEs were mild or moderate in severity
- The incidence of infections with efgartigimod PH20 SC treatment was low regardless of IgG level (**Figure 3**), and infections were mild to moderate in severity
  - Most common infections were COVID-19, nasopharyngitis, urinary tract infection, and upper respiratory infection (**Table 2**)
- ISRs in ADHERE+ were mild and usually occurred within 24 hours of injection
  - 29/228 (12.7%) participants experienced ISRs and 1/228 (0.4%) experienced moderate ISRs; no severe ISRs were reported

TABLE 2 Safety and Tolerability in ADHERE and ADHERE+

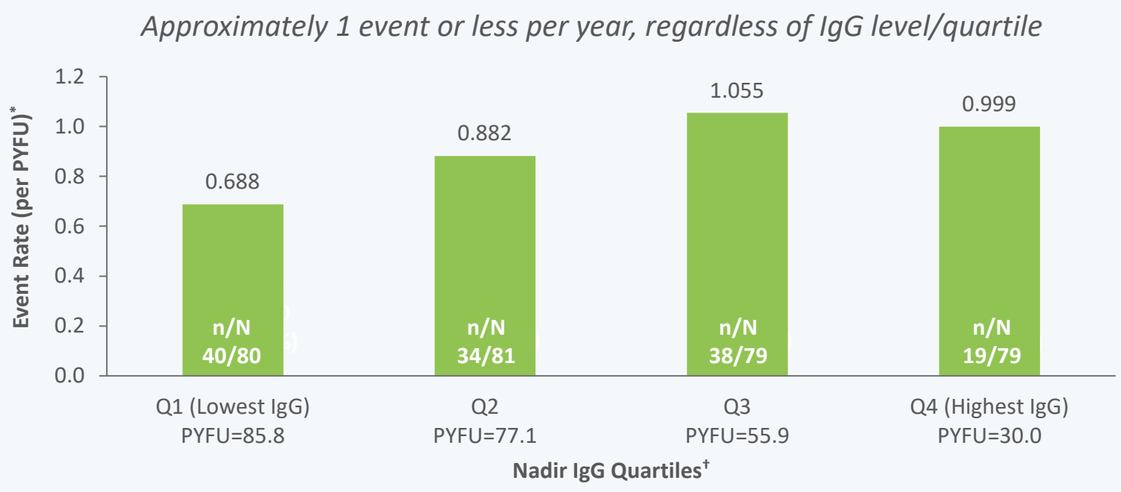
	ADHERE[12]			ADHERE+ Open-Label Extension*
	Open-Label Stage A	Double-Blinded Stage B		
n (%) [event rate,†]	Efgartigimod PH20 SC (N=322; PYFU=46.9)	Efgartigimod PH20 SC (n=111; PYFU=56.7)	Placebo SC (n=110; PYFU=42.1)	Efgartigimod PH20 SC (N=228; PYFU=263.0)
Any TEAE	204 (63.4) [13.43]	71 (64.0) [3.48]	62 (56.4) [5.11]	171 (75.0) [3.10]
Any SAE	21 (6.5) [0.51]	6 (5.4) [0.14]	6 (5.5) [0.19]	35 (15.4) [0.25]
Any Grade ≥3 TEAE	25 (7.8) [0.62]	7 (6.3) [0.14]	7 (6.4) [0.21]	41 (18.0) [0.31]
Any ISRs	62 (19.3) [2.64]	16 (14.4) [0.39]	7 (6.4) [0.21]	29 (12.7) [0.27]
Discontinued due to TEAEs	22 (6.8) [0.47]	3 (2.7) [0.05]	1 (0.9) [0.02]	18 (7.9) [0.14]‡
Deaths§	2 (0.6) [0.04]	0	1 (0.9) [0.02]	2 (0.9) [0.008]
Most common TEAEs (≥5% of participants in the total group in ADHERE+)				
Headache	16 (5.0) [0.60]	4 (3.6) [0.11]	2 (1.8) [0.05]	14 (6.1) [0.09]
Upper respiratory tract infection	11 (3.4) [0.26]	2 (1.8) [0.05]	11 (10.0) [0.26]	24 (10.5) [0.15]
COVID-19	7 (2.2) [0.17]	19 (17.1) [0.35]	14 (12.7) [0.33]	37 (16.2) [0.14]
Urinary tract infection	5 (1.6) [0.13]	2 (1.8) [0.04]	2 (1.8) [0.05]	12 (5.3) [0.06]
Nasopharyngitis	5 (1.6) [0.11]	5 (4.5) [0.09]	3 (2.7) [0.07]	16 (7.0) [0.08]

*Mean (SD) study duration was 60.61 (32.87) weeks. Study duration was calculated as (date of last contact – earliest date of informed consent form or date of rollover + 1 day) / 7. †Event rates were calculated as the number of events divided by the PYFU. ‡TEAEs leading to efgartigimod PH20 SC discontinuation in ≥2 patients were: CIDP (n=5) and breast cancer (n=2). §Two deaths (cardiac arrest and deterioration of CIDP) in ADHERE stage A were considered unlikely related to efgartigimod PH20 SC by the investigator; 1 death (pneumonia) in the placebo SC arm of ADHERE stage B was considered treatment related by the investigator; in ADHERE+, 1 participant had a fatal SAE of CIDP deterioration (considered to be related to efgartigimod PH20 SC by the investigator due to postexposure onset but considered not related to treatment according to the sponsor because of the long treatment duration of >1 year with resulting clinical improvements and plausible alternative explanations. An independent DSMB reviewed the case and concluded that overall, the safety data did not reveal any concern), and 1 participant had a fatal SAE of cardiac arrest (considered not related to efgartigimod PH20 SC or study procedures by the investigator and sponsor).

Improvements From ADHERE Run-In Baseline to ADHERE+ Week 36 Were Observed With Efgartigimod PH20 SC Across Clinical Efficacy Endpoints

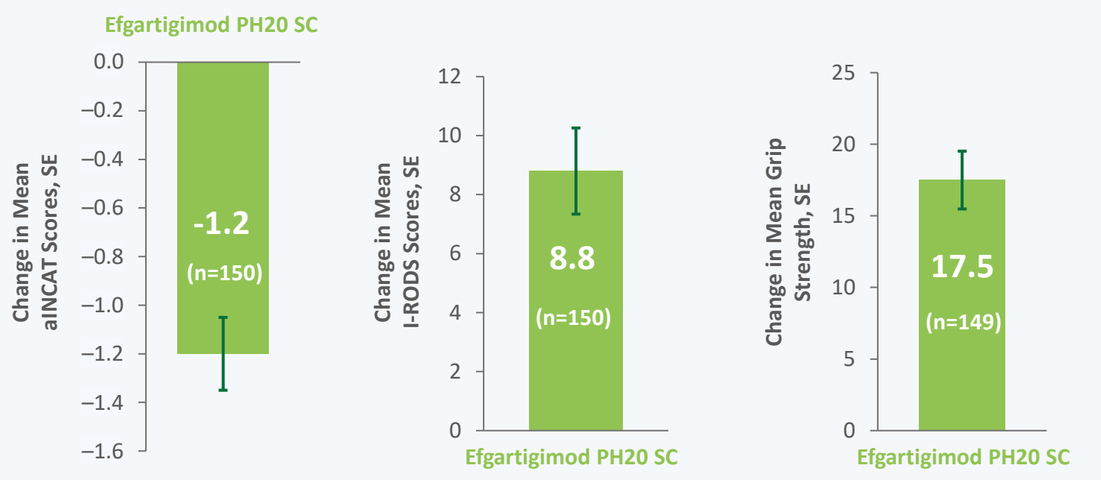
- Based on a *post hoc* analysis, minimal clinically important differences in aINCAT, I-RODS, and grip strength from ADHERE run-in to ADHERE+ Week 36 were observed (**Figure 4**)

FIGURE 3 Event Rate for All Infections per PYFU With Efgartigimod PH20 SC by Lowest Recorded IgG Level Split Into Quartiles in ADHERE and ADHERE+



*Event rates were calculated as the number of events divided by the PYFU. †Concentrations of IgG were 1.220–2.380 g/L (first quartile), 2.381–3.240 g/L (second quartile), 3.241–4.500 g/L (third quartile), and 4.501–19.550 (fourth quartile). ADHERE+ data cut-off: June 15, 2023.
n=number of participants with event; N=total number of participants in each subgroup.

FIGURE 4 *Post Hoc* Analysis:* Change in Different Efficacy Parameters From ADHERE Run-In Baseline to ADHERE+ Week 36



*Analysis set population included efgartigimod responders in stage A with run-in baseline values and ongoing on ADHERE+ at the time of data cutoff (N=221).

KEY TAKEAWAYS

Interim results from ADHERE+ indicate long-term safety and clinical efficacy of efgartigimod PH20 SC in participants with CIDP

Efgartigimod PH20 remained well tolerated in ADHERE+:
- **Similar safety profile as ADHERE with no increased rate or severity of TEAEs with longer exposure**
- **Low incidence of infections regardless of IgG level**
- **ISRs were mostly mild and usually occurred within 24 hours of injection**

Meaningful clinical improvements in aINCAT, I-RODS, and grip strength (dominant hand) were observed with efgartigimod PH20 from ADHERE run-in baseline to ADHERE+ Week 36

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ABBREVIATIONS

aINCAT, adjusted INCAT; CDAS, chronic inflammatory demyelinating polyradiculoneuropathy disease activity status; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; COVID-19, coronavirus disease 2019; DSMB, data and safety monitoring board; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; ISR, injection site reaction; IVIg, intravenous immunoglobulin; PYFU, participants years of follow-up; Q, quartile; R, randomization; rHuPH20, recombinant human hyaluronidase PH20; 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.

DISCLOSURES AND ACKNOWLEDGMENTS

JAA: Akcea, Alexion, Alnylam, Annexon argenx, CSL Behring, Grifols, Immunovant, ImmuPharma, Johnson & Johnson, Pfizer, Takeda; **JL:** Nothing to declare; **MS:** argenx, Bayer, Biogen, Biotest, CSL Behring, Genzyme, Grifols, Immunovant, Kedrion, Merck, Novartis, Octapharma, PPTA, Roche, Sanofi-Aventis, TEVA, UCB; **TG, GI, ADR and BVH:** employees of argenx; **SK:** Alexion, argenx, CSL Behring, Takeda; **GL:** Biogen, Chromocell, CSL Behring, Home Biosciences, Janssen, Lilly, Sangamo, Vertex, Zambon; **LQ:** Alnylam, Annexon, argenx, Avilar, Biogen, CIBERER, Fundació La Marató, CSL Behring, Dianthus, 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; **NS:** Alnylam, Takeda; **CK:** Alexion, Alpine, Alnylam, Annexon, argenx, AstraZeneca, Biogen, Corino, CSL Behring, Genentech, Ionis, Neuroderm, Novo Nordisk, Pfizer, Sanofi, UCB, Takeda, Zai Lab; **TS:** Alexion, Alnylam, argenx, Bayer Vital, Biogen, Bristol Myers Squibb, Celgene, Centogene, CSL Behring, Euroimmun, Grifols, Hexal, Horizon, Janssen-Cilag, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Siemens, Swedish Orphan Biovitrum, Teva, Viatris; **SR:** Annexon, argenx, the Beijing Association of Holistic and Integrated Medicine, British Medical Association, CSL Behring, Dianthus, Excemed, Fresenius, GBS/CIDP Foundation International, Guillain-Barré syndrome and Related Inflammatory Neuropathies (GAIN) charity, Hansa Biopharma, the Irish Institute of Clinical Neuroscience, Medical Research Council (UK), National Institute of Health Research (NIHR), the Pathological Society of Great Britain Ireland, Peripheral Nerve Society, Takeda, UCB, the University of Oxford's John Fell Fund, Wellcome Trust; **AE-L:** Alnylam, argenx, CSL Behring, Grifols, LFB, Pfizer, Sanofi; **CH:** argenx, Biogen, Lupin, Roche, UCB; **RY:** Alnylam Japan, CSL Behring, FP Pharm, Japan Tobacco, Kyowa Kirin, Ono Pharmaceutical, Takeda; **PAvD:** Annexon, argenx, Grifols, Hansa Biopharma, Octapharma, Prinses Beatrix Spierfonds, Roche, Sanofi, Sanquin, Takeda; **RAL:** Alexion, Annexon Biosciences, argenx, Avilar Therapeutics, BioCryst, Boehringer Ingelheim, CSL Behring, Dianthus Therapeutics, Grifols, GBS/CIDP Foundation International, Immunovant, Intellia, Johnson & Johnson, Medscape, MGFA, Novartis, Nervosave, Nuvig, Sanofi, Seismic, Takeda, TGTX, UptoDate.
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