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Efficacy, Safety, and Tolerability of Subcutaneous Efgartigimod PH20 in Patients With Chronic Inflammatory Demyelinating Polyneuropathy: Results From the ADHERE Trial

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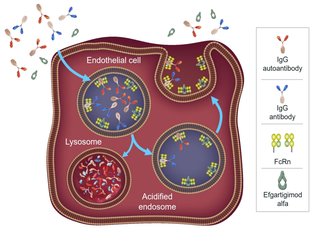
BACKGROUND

Efgartigimod Mechanism of Action: Blocking FcRn

- The neonatal Fc receptor (FcRn) recycles immunoglobulin G (IgG), extending its half-life and serum concentration[1]
- Efgartigimod (EFG) is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity for FcRn[2]
- EFG was designed to outcompete endogenous IgG, preventing recycling, and promoting lysosomal degradation of IgG, without impacting its production[2–5]
  - Targeted reduction of all IgG subtypes
  - No impact on IgA, IgD, IgE, and IgM
  - No reduction in albumin or increase in cholesterol levels
- Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20 (rHuPH20), which allows for rapid SC administration of larger volumes[6,7]



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Chronic Inflammatory Demyelinating Polyneuropathy: A Rare, Immune-Mediated Neuropathy[8–10]

- Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare and debilitating immune-mediated neuropathy that causes muscle weakness and sensory disturbance, leading to disability, pain, and fatigue
- Increasing evidence suggests that IgG autoantibodies play a key role in CIDP, including the effectiveness of plasma exchange, and immunoadsorption in treating patients with CIDP, the presence of IgG antibodies directed against components of myelinated nerves, and the passive transfer of disease by sera or IgG of patients with CIDP in experimental animal models
- There is an unmet need for a first-line treatment with long-term efficacy that maintains or improves quality of life, has an early onset of action, is well tolerated, is not dependent on plasma donation, and has greater convenience

CIDP Confirmation Committee Adjudication Process

- In the ADHERE trial, an 8-member independent CIDP Confirmation Committee (CCC) was established to confirm an accurate diagnosis for enrollment
- The CCC comprises neurologists with extensive clinical and research experience in CIDP
- De-identified patient data were reviewed via an electronic adjudication system following screening
- Eligibility was confirmed when 2 experts independently confirmed a patient had definite/probable CIDP
- If discordance existed (ie, definite/probable vs possible/non-CIDP or typical vs atypical CIDP), the CCC Chair provided the final determination

KEY TAKEAWAYS

- The ADHERE trial of efgartigimod PH20 SC recruited adults with a confirmed diagnosis of CIDP and active disease
- Clinical benefit was demonstrated across multiple CIDP efficacy measures regardless of prior CIDP treatment
- In Stage A, 66% of participants demonstrated evidence of clinical improvement and a rapid onset of effect with efgartigimod PH20, supporting the vital role of IgG autoantibodies in CIDP
- ADHERE is the largest randomized, controlled trial of any CIDP treatment to date, with up to 60 weeks of exposure, and 99.1% (226/228) of eligible participants entered the open-label extension
- Efgartigimod PH20 SC reduced the risk of relapse versus placebo based on time to first adjusted INCAT deterioration (hazard ratio=0.39; *P*=0.000039)
- Efgartigimod PH20 was well tolerated and demonstrated a consistent safety profile with prior clinical trials in other autoimmune indications

METHODS

ADHERE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

adhere — chronic inflammatory demyelinating polyneuropathy study

Identify patients with active CIDP

Screening
≤4 weeks
CIDP diagnosis confirmed by external expert committee

Run-in period
≤12 weeks
Patients need to demonstrate disease worsening (based on INCAT, I-RODS, grip strength) after current treatment discontinued

Evaluate clinical improvement

Stage A: Open-label
Stage A
≤12 weeks
Efgartigimod PH20 SC weekly

Stage A: Primary Endpoint
Percentage confirmed evidence of clinical improvement

Only treatment responders advance to Stage B

Assess efficacy and safety

Stage B: Randomized-withdrawal, double-blind, placebo-controlled
Stage B
≤48 weeks
Placebo PH20 SC weekly
Efgartigimod PH20 SC weekly

Stage B: Primary Endpoint
Time to first adjusted INCAT deterioration compared to Stage B baseline

INCLUSION CRITERIA

Male or female
≥18 years
Probable or definite CIDP*

- CIDP Disease Activity Status (CDAS) score ≥2 at screening
- INCAT score ≥2 at the first run-in visit or Stage A baseline
- Currently treated with corticosteroids and/or IVIg or SCIg: a) discontinued at first run-in visit; b) no prior treatment (treatment-naïve), or no use of corticosteroids and/or IVIg or SCIg in the last 6 months before screening

*According to criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS, 2010),[9] progressing or relapsing forms.

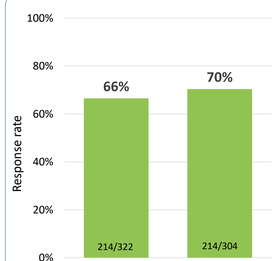
RESULTS

Baseline Characteristics

	Stage A	Stage B*	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (N=111)	Placebo PH20 SC (N=110)
Age, mean (SD), years	54.0 (13.9)	54.5 (13.2)	51.3 (14.5)
Sex, female, n (%)	114 (35.4)	38 (34.2)	41 (37.3)
Time since diagnosis, mean (SD), years	4.9 (6.1)	3.7 (4.4)	3.8 (4.7)
Atypical CIDP diagnosis, n (%)	54 (16.8)	14 (12.6)	15 (13.6)
Adjusted INCAT score, mean (SD)†	4.6 (1.67)	3.1 (1.5)	3.3 (1.6)
I-RODS, mean (SD)†	40.1 (14.7)	53.6 (17.9)	51.2 (15.4)
Grip strength (in dominant hand),‡ mean (SD), kPa	38.5 (24.2)	54.9 (23.6)	58.0 (25.1)
Prior treatment within the 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)
Treatment-naïve‖	94 (29.2)	39 (35.1)	39 (35.5)
CDAS score, n (%)			
Stable active disease (CDAS=2–4)	125 (38.8)	37 (33.3)	34 (30.9)
Unstable active disease (CDAS=5)	197 (61.2)	74 (66.7)	76 (69.1)

*Most baseline characteristics in Stage B refer to Stage A baseline, except for INCAT, I-RODS, Grip strength. †Lower scores represent improvement on adjusted INCAT while higher scores represent improvement for I-RODS. ‡Non-dominant scores are similar. §Stage B baseline levels are based on randomized stratification factors. ‖Not treated for CIDP before entering the study, or not treated with corticosteroids, IVIg, or SCIg for ≥6 months prior to screening.

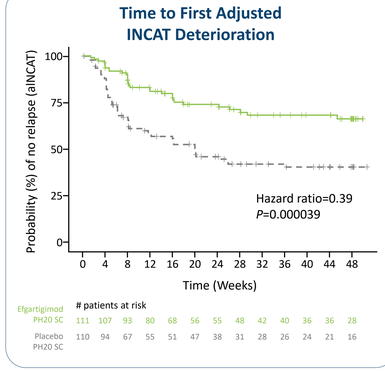
Stage A Response Rates



†Prespecified sensitivity analysis excluding participants who are ongoing at the time of 1802 study completion, after 88th event had occurred.

- Response rates suggest IgG autoantibodies play a significant role in the underlying biology of CIDP in the majority of CIDP patients
- Majority of patients were responders in all prior CIDP medication subgroups with efficacy on INCAT, I-RODS, and grip strength

Stage B Efficacy



- **Primary endpoint met**, demonstrating a **61% lower risk of relapse** based on time to first adjusted INCAT deterioration with efgartigimod PH20 compared with placebo PH20
- Clinical benefit also observed on I-RODs and mean grip strength, and in all prior CIDP medication groups

Secondary Endpoints

	Stage A	Stage B	
	Efgartigimod PH20 SC (N=322)	Efgartigimod PH20 SC (N=111)	Placebo PH20 SC (N=110)
I-RODS deterioration of at least 4 points, n (%)	-	40 (36.0)	57 (51.8)
Hazard ratio (95% CI)	-	0.54 (0.35–0.81)	
Nominal *P* value	-	0.0034	
I-RODS improvement of at least 4 points, n (%)	-	50 (45.0)	40 (36.4)
Odds ratio (95% CI)	-	1.44 (0.81–2.57)	
Nominal *P* value	-	0.2294	
Mean (SD) change from baseline to last assessment*			
Adjusted INCAT score	–0.9 (1.7)	0.1 (1.1)	0.9 (2.0)
I-RODS score	7.7 (15.5)	0.8 (12.3)	–7.0 (19.1)
Mean grip strength (dominant hand), kPa	12.3 (18.7)	2.1 (13.3)	–8.2 (20.7)
Mean grip strength (non-dominant hand), kPa	11.2 (21.1)	2.0 (17.3)	–6.9 (21.3)

*For Stage A, this was the change from Stage A baseline to Stage A last assessment, and for Stage B, this was the change from Stage B baseline to Stage B last assessment.

Efgartigimod PH20 patients had a mean improvement of 7.7 points on I-RODS and 12.3 kPa on mean grip strength in Stage A, which was maintained in Stage B, but (partially) lost in patients receiving placebo PH20

Safety

	Stage A	Stage B	
n (%)	Efgartigimod PH20 SC (N=322) PYFU=46.9	Efgartigimod PH20 SC (N=111) PYFU=56.7	Placebo PH20 SC (N=110) PYFU=42.1
Any TEAE	204 (63.4)	71 (64.0)	62 (56.4)
Any treatment-related TEAE*	101 (31.4)	27 (24.3)	22 (20.0)
Any SAE	21 (6.5)	6 (5.4)	6 (5.5)
Treatment-related SAE*	4 (1.2)	0 (0.0)	4 (3.6)
Injection site reaction	62 (19.3)	16 (14.4)	7 (6.4)
Headache	16 (5.0)	4 (3.6)	2 (1.8)
Infections	44 (13.7)	35 (31.5)	37 (33.6)
COVID-19	7 (2.2)	19 (17.1)	14 (12.7)
Discontinued due to TEAEs	22 (6.8)	3 (2.7)	1 (0.9)
Malignancies†	1 (0.3)	2 (1.8)	0 (0.0)
Death‡	2 (0.6)	0 (0.0)	1 (0.9)

*Deemed treatment-related by the investigator. †Reported malignancies (prostate cancer, localized squamous cell carcinoma, and transitional cell carcinoma) not unexpected for age, gender, and duration of study; only malignant neoplasms were included. ‡Fatal outcomes included two in Stage A considered not related (cardiac arrest following COVID-19) and unlikely related to treatment (CIDP worsening) and one in Stage B considered possibly related (pneumonia) but after unblinding was a placebo patient.

- Most AEs were mild or moderate in severity
- No new safety signals were identified with up to 60 weeks of treatment
- No increased infection rate with increased exposure

EFG is approved for the treatment of generalized myasthenia gravis (gMG) in adult patients positive for anti-acetylcholine receptor (AChR) antibodies in the US and Europe, and in Japan for patients regardless of antibody status

ABBREVIATIONS
AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; Ig, immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory-Rasch-built Overall Disability Scale; IV, intravenous; PH20, recombinant human hyaluronidase for subcutaneous injection; PYFU, person-years of follow-up; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation; TEAE, treatment-emergent adverse event.

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SCAN ME

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