Safety Profile of Subcutaneous Efgartigimod PH20 From Clinical Trials in Immunoglobulin G-Mediated Autoimmune Diseases

EPR-253

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Efgartigimod PH20 SC is approved for the treatment of gMG in patients positive for AChR antibodies in the US, as an add-on to standard therapy in adult patients positive for AChR antibodies in the EU, in patients with or without AChR antibodies with insufficient response to steroids or nonsteroidal immunosuppressive therapies in Japan. Efgartigimod PH20 SC is also approved in adult patients with CIDP in the US

AChR, acetylcholine receptor; CIDP, chronic inflammatory demyelinating polyneuropathy; gMG, generalised myasthenia gravis; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

Efgartigimod Blocks FcRn to Reduce IgG Autoantibody Levels

IgG autoantibodies are implicated in multiple pathogenic actions in IgG-mediated autoimmune diseases such as gMG and CIDP[1–3]

- The neonatal Fc receptor, FcRn, recycles IgG, extending its half-life and serum concentration[1]
- **Efgartigimod is a human IgG1 Fc fragment,** a natural ligand of FcRn, engineered for increased affinity for FcRn[2]
- Efgartigimod was designed **to outcompete endogenous IgG, preventing recycling and promoting lysosomal degradation of IgG, without impacting its production**:[3–7]
  - Targeted reduction of all IgG subtypes
  - No impact on other immunoglobulins
  - No reduction in albumin levels or increase in cholesterol levels

Efgartigimod PH20 SC is a coformulation of efgartigimod and recombinant human hyaluronidase PH20, which allows for **rapid (30–90s single injection)** SC administration of larger volumes[8,9]

Safety of efgartigimod PH20 SC was assessed in patients with gMG and CIDP

Efgartigimod Mechanism of Action

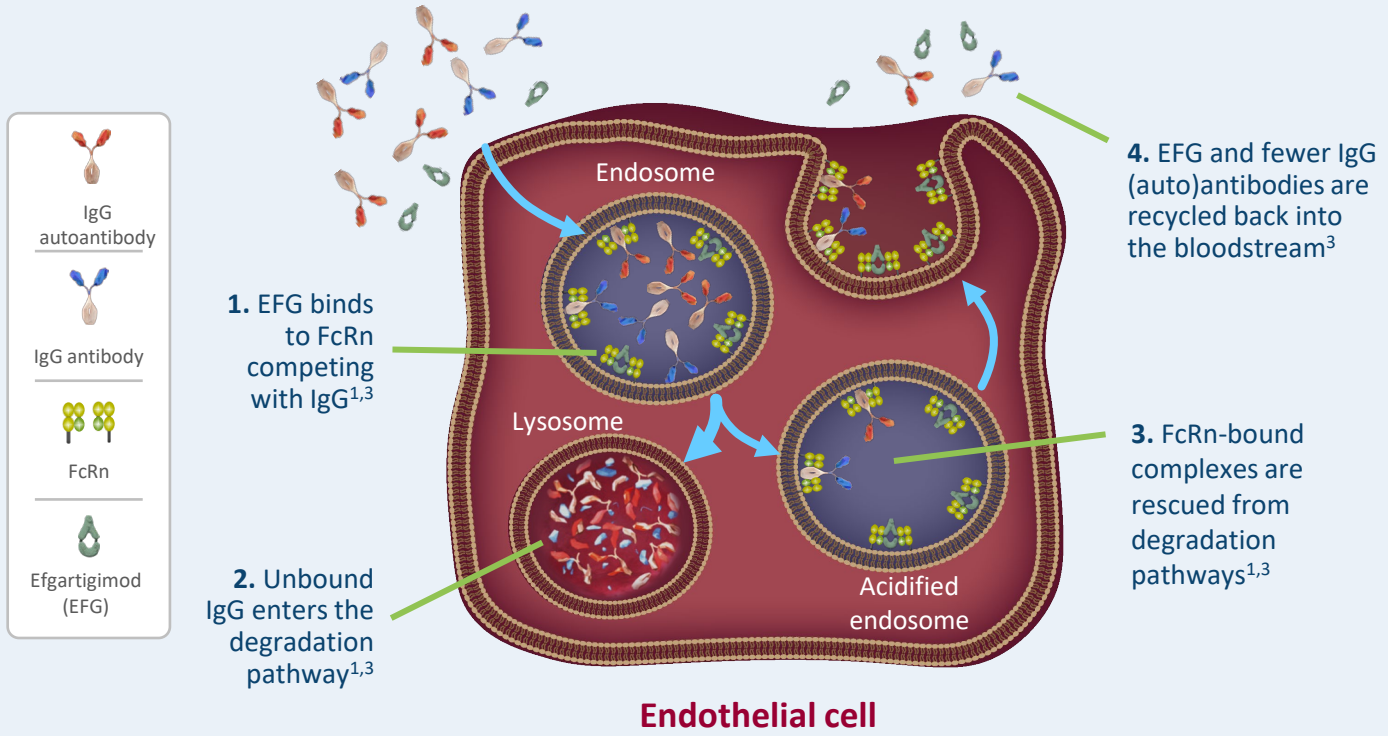

Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

CIDP, chronic inflammatory demyelinating polyneuropathy; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous.

1. Sesarman A, et al. *Cell Mol Life Sci.* 2010;67:2533–50. **2.** Querol L, et al. *Sci Rep*. 2017;7:14411. **3.** Ulrichts P, et al. *J Clin Invest.* 2018;128:4372–86. **4.** Vaccaro C, et al. *Nat Biotech.* 2005;23:1283–88. **5.** Howard JF Jr, et al. *Lancet Neurol.* 2021;20:526–36. **6.** Nixon AE, et al. *Front Immunol.* 2015;6:176. **7.** Ward ES, et al. *Front Immunol.* 2022;13:892534. **8.** Locke KW, et al. *Drug Deliv*. 2019;26:98–106. **9.** VYVGART HYTRULO. Prescribing information. argenx; 2024. https://www.argenx.com/product/vyvgart-hytrulo-prescribing-information.pdf. Accessed June 24, 2024.

Efgartigimod (EFG) was Investigated Across Registrational and Phase 3 Trials in IgG-Mediated Disorders

Participants treated with EFG IV across trials in IgG-mediated disorders showed a mean maximum reduction of 60.1–63.5% in total IgG levels[1–4]

In ADAPT-SC, efficacy of EFG PH20 SC was comparable to EFG IV, with a reduction in mean total IgG levels of 66.4%[5]

gMG

ADAPT-SC Phase 3[5]

adapt SC myasthenia gravis study — **10 weeks**

Cyclical dosing (4 once-weekly injections)
EFG PH20 SC* 1000 mg or EFG 10 mg/kg IV + stable dose of concurrent therapy

Participants:
- **EFG PH20 SC:** n=55
- **EFG IV:** n=55

Primary endpoint:
- **To demonstrate non-inferiority of EFG PH20 SC versus EFG IV** (reduction in total IgG from baseline at Day 29)

ADAPT-SC+ OLE[6]

adapt SC myasthenia gravis study — **≤3 years (ongoing)**

Participants (N=179) rolled over from:
- **ADAPT-SC:** n=102
- **ADAPT+:** n=77

Primary endpoint:
- **To evaluate the long-term safety and tolerability of EFG PH20 SC**

CIDP

ADHERE[7] registrational

adhere chronic inflammatory demyelinating polyneuropathy study — **≤60 weeks**

Weekly dosing of EFG PH20 SC* 1000 mg or placebo (ADHERE stage B only)

Participants:
Stage A – Open-label:
- **EFG PH20 SC:** N=322

Stage B – Double-blinded, placebo-controlled:
- **EFG PH20 SC:** n=111; **Placebo:** n=110

Primary endpoint:
- **Stage A:** Percentage of participants with ECI
- **Stage B:** Time to first aINCAT deterioration† (relapse) compared with stage B baseline

ADHERE+ OLE

adhere chronic inflammatory demyelinating polyneuropathy study — **≤2 years (ongoing)**

Participants:
- **EFG PH20 SC:** N=228

Participants with clinical deterioration in ADHERE stage B or those who completed ADHERE could enter ADHERE+ (up to 180 participants)

Primary endpoint:
- **To evaluate the long-term safety and tolerability of EFG PH20 SC**

aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; EFG, efgartigimod; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; IV, intravenous; OLE, open-label extension; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous. ADAPT-SC+ data cut-off: 01 December 2022; ADHERE+ data cut-off: 15 June 2023. *Coformulated with recombinant human hyaluronidase PH20. †aINCAT deterioration was defined as an increase of ≥1 points in aINCAT score compared with stage B baseline.

1. Howard JF Jr, et al. *Lancet Neurol.* 2021;20:526–36. **2.** Newland AC, et al. *Am J Hematol.* 2020;95:178–87. **3.** Goebeler M, et al. *Br J Dermatol.* 2022;186:429–39. **4.** Broome CM, et al. *Lancet.* 2023;402:1648–59. **5.** Lünemann JD, et al. 2023. Presented at the 26th Congress of the Medical-Scientific Advisory Board of the German Society for Muscle Diseases (DGM); Essen, Germany. **6.** Howard J, et al. *Neurology.* 2024;102 (17_suppl_1). **7.** Allen JA, et al. 2024. Presented at the 76th American Academy of Neurology (AAN) Annual Meeting; Denver, CO, USA.

Efgartigimod Was Well Tolerated and Demonstrated a Consistent Safety Profile in Participants With gMG and CIDP

In the current analysis, the safety of EFG PH20 SC was assessed in the ADAPT-SC and ongoing ADAPT-SC+ trial (data cut-off: 01 December 2022) and in the ADHERE and ongoing ADHERE+ trials (data cut-off: 15 June 2023)

Indication	**gMG**			**CIDP**			
Trial	**ADAPT-SC**		**ADAPT-SC+**	**ADHERE**			**ADHERE+**
Population	**EFG PH20 SC** (n=55; PYFU=10.73)	**EFG IV** (n=55; PYFU=10.53)	**EFG PH20 SC** (N=179; PYFU=193.4)	Stage A **EFG PH20 SC** (N=322; PYFU=46.9)	Stage B **EFG PH20 SC** (n=111; PYFU=56.7)	Stage B **Placebo SC** (n=110; PYFU=42.1)	**EFG PH20 SC** (N=228; PYFU=137.4)
	% [ER*]	**%** [ER*]	**%** [ER*]	**%** [ER*]	**%** [ER*]	**%** [ER*]	**%** [ER*]
Any TEAE	**67.3** [12.4]	**50.9** [7.6]	**84.9** [9.0]	**63.4** [13.4]	**64.0** [3.5]	**56.4** [5.1]	**57.5** [3.5]
Any SAE	**14.5** [0.9]	**7.3** [0.5]	**18.4** [0.3]	**6.5** [0.5]	**5.4** [0.1]	**5.5** [0.2]	**9.2** [0.3]
Any severe TEAE (or grade ≥3)	**16.4** [1.0]	**7.3** [0.5]	**20.1** [0.4]	**7.8** [0.6]	**6.3** [0.1]	**6.4** [0.2]	**11.0** [0.3]
Any treatment-related TEAE	**43.6** [4.9]	**21.8** [2.2]	**53.6** [4.1]	**31.4** [5.5]	**24.3** [1.1]	**20.0** [1.5]	**23.7** [0.9]
Discontinued due to TEAEs†	**3.6** [0.2]	**0**	**2.2** [0.03]	**6.8** [0.5]	**2.7** [0.05]	**0.9** [0.02]	**3.9** [0.09]
Any TEAEs of ISRs‡	**38.2** [1.9]	**0**	**45.8** [3.2]	**19.3** [2.6]	**14.4** [0.4]	**6.4** [0.2]	**9.6** [0.3]
Any serious infection	**1.8** [0.1]	**0**	**2.2** [0.02]	**1.2** [0.09]	**0.9** [0.02]	**2.7** [0.1]	**2.2** [0.04]
Fatal TEAEs§	**0**	**0**	**2.2** [0.03]	**0.6** [0.04]	**0**	**0.9** [0.02]	**0.4** [0.01]

The rates of discontinuation due to TEAEs and serious infections were consistently low across trials of EFG PH20 SC in participants with gMG and CIDP

CIDP, chronic inflammatory demyelinating polyneuropathy; EFG, efgartigimod; ER, event rate; gMG, generalised myasthenia gravis; ISR, injection site reaction; IV, intravenous; PH20, recombinant human hyaluronidase PH20; PYFU, patient-year(s) of follow-up; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event. *Event rates were calculated as the number of events divided by the PYFU. †TEAEs grouped under Preferred Terms leading to EFG PH20 SC discontinuation were 'COVID-19' (n=1) and 'Myasthenia gravis' (n=1) in ADAPT-SC EFG PH20 SC; 'Cardiac arrest' (n=1), 'COVID-19' (n=1), 'Renal cancer metastatic' (n=1), 'Myasthenia gravis crisis' (n=1) and 'Respiratory failure' (n=1) in ADAPT-SC+; 'Cardiac arrest' (n=1), 'Injection site rash' (n=1), 'COVID-19' (n=1), 'COVID-19 pneumonia' (n=1), 'Muscular weakness' (n=1), 'Chronic inflammatory demyelinating polyradiculoneuropathy' (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 EFG PH20 SC; 'Pneumonia' (n=1) in ADHERE stage B placebo SC; 'Lymphadenitis' (n=1), 'Eye movement disorder' (n=1), 'Asthenia' (n=1), 'Hepatic function abnormal' (n=1), 'COVID-19' (n=1), 'Chronic inflammatory demyelinating polyradiculoneuropathy' (n=4) and 'Cranial nerve disorder' (n=1) in ADHERE+. ‡Injection site reactions are defined as adverse events in the Medical Dictionary for Regulatory Activities high-level term *Injection site reactions* regardless of the time of adverse event onset relative to an injection. §Fatal TEAEs: In ADAPT-SC+, 4 participants died due to TEAEs, but none were considered related to EFG PH20 SC by the investigator: Cardiac arrest (n=1), Renal cancer metastatic (n=1), Pulmonary mass (n=1), and concomitant COVID-19 and Respiratory failure (n=1); in ADHERE, 3 participants died due to TEAEs, but none were considered related to EFG PH20 SC by the investigator: Cardiac arrest (Stage A, n=1), CIDP deterioration (Stage A, n=1), and Pneumonia (Stage B, n=1); in ADHERE+, 1 participant died due to CIDP deterioration which was considered related to EFG PH20 SC by the investigator.

Similar Rates of TEAEs Were Demonstrated in Participants With gMG and CIDP

Most TEAEs were mild to moderate in severity and no increase in the rate of TEAEs was observed with continued exposure during open-label extension trials

gMG | **CIDP**

Trial	ADAPT-SC		ADAPT-SC+
Population	**EFG PH20 SC** (n=55; PYFU=10.73)	**EFG IV** (n=55; PYFU=10.53)	**EFG PH20 SC** (N=179; PYFU=193.4)
Most commonly observed TEAEs (≥10%)	**%** [ER*]	**%** [ER*]	**%** [ER*]
Injection site erythema	**12.7** [0.7]	**0**	**29.1** [1.7]
COVID-19	**3.6** [0.2]	**0**	**22.3** [0.2]
Headache	**12.7** [0.9]	**12.7** [1.0]	**20.1** [0.6]
Nasopharyngitis	**0**	0	**15.6** [0.2]
Diarrhoea	**1.8** [0.5]	**5.5** [0.3]	**13.4** [0.2]
Injection site pain	**5.5** [0.3]	**0**	**11.7** [0.2]
Injection site pruritus	**9.1** [0.5]	**0**	**10.6** [0.2]
Injection site bruising	**7.3** [0.4]	**0**	**10.1** [0.2]
Injection site rash	**14.5** [1.3]	**0**	**8.4** [0.1]
Myasthenia gravis	**10.9** [0.7]	**1.8** [0.1]	**7.8** [0.1]

CIDP, chronic inflammatory demyelinating polyneuropathy; EFG, efgartigimod; gMG, generalised myasthenia gravis; IV, intravenous; PH20, recombinant human hyaluronidase PH20; PYFU, patient-year(s) of follow-up; SC, subcutaneous; TEAE, treatment-emergent adverse event.

*Event rates were calculated as the number of events divided by the PYFU. AEs were included if observed at ≥10% across any singular trial (ADAPT-SC or ADAPT-SC+) but may not be ≥10% across all trials included. ADAPT-SC+ data cut-off: 01 December 2022.

Similar Rates of TEAEs Were Demonstrated in Participants With gMG and CIDP

Most TEAEs were mild to moderate in severity and no increase in the rate of TEAEs was observed with continued exposure during open-label extension trials

gMG | **CIDP**

Trial	**ADHERE**			**ADHERE+**
Population	Stage A **EFG PH20 SC** (N=322; PYFU=46.9)	Stage B **EFG PH20 SC** (n=111; PYFU=56.7)	Stage B **Placebo SC** (n=110; PYFU=42.1)	**EFG PH20 SC** (N=228; PYFU=137.4)
Most commonly observed TEAEs (≥10%)	**%** [ER*]	**%** [ER*]	**%** [ER*]	**%** [ER*]
Injection site erythema	**10.2** [1.1]	**5.4** [0.1]	**0**	**3.1** [0.1]
COVID-19	**2.2** [0.2]	**17.1** [0.4]	**12.7** [0.3]	**13.6** [0.2]
Upper respiratory tract infection	**3.4** [0.3]	**1.8** [0.05]	**10.0** [0.3]	**6.1** [0.1]

CIDP, chronic inflammatory demyelinating polyneuropathy; EFG, efgartigimod; gMG, generalised myasthenia gravis; IV, intravenous; PH20, recombinant human hyaluronidase PH20; PYFU, patient-year(s) of follow-up; SC, subcutaneous; TEAE, treatment-emergent adverse event.

*Event rates were calculated as the number of events divided by the PYFU. AEs were included if observed at ≥10% across any singular trial (ADHERE or ADHERE+) but may not be ≥10% across all trials included. ADHERE+ data cut-off: 15 June 2023.

Conclusions

- Efgartigimod PH20 SC blocks FcRn to reduce IgG autoantibody levels, and its safety has been investigated in participants with gMG and CIDP across ADAPT-SC/ADAPT-SC+ OLE and ADHERE/ADHERE+ OLE, respectively
- Efgartigimod PH20 SC was well tolerated in participants with gMG and CIDP, demonstrating a consistent safety profile with similar rates of TEAEs observed across indications and dosing regimens
- Most TEAEs were mild to moderate in severity, and no increase in the rate of TEAEs was observed with continued exposure during open-label extension trials

CIDP, chronic inflammatory demyelinating polyneuropathy; FcRn, neonatal Fc receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; OLE, open-label extension; PH20, recombinant human hyaluronidase PH20; SC, subcutaneous; TEAE, treatment-emergent adverse event.