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

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KEY TAKEAWAYS

- Efgartigimod reduces IgG levels via FcRn blockade and does not lead to complete removal of IgG, nor does it impact IgG production or levels of albumin or cholesterol
- The safety of efgartigimod PH20 SC has been investigated in participants with gMG and CIDP across the ADAPT-SC/ADAPT-SC+ open-label extension (OLE; data cutoff: Dec 1, 2022) and ADHERE/ADHERE+ OLE (data cutoff: Jun 15, 2023) trials, respectively
- Efgartigimod PH20 SC was well tolerated in participants with gMG and CIDP, demonstrating a consistent safety profile with similar TEAE rates 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 to efgartigimod PH20 SC during OLE trials
- The rates of discontinuation due to TEAEs and serious infections were consistently low across trials of efgartigimod PH20 SC in participants with gMG and CIDP

BACKGROUND

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

Efgartigimod: Engineered IgG1 Fc Fragment

- 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[3]
- 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:[3–7]
  - Targeted reduction of all IgG subtypes
  - No impact on other immunoglobulins
  - No reduction in albumin or increase in cholesterol levels

Efgartigimod Mechanism of Action

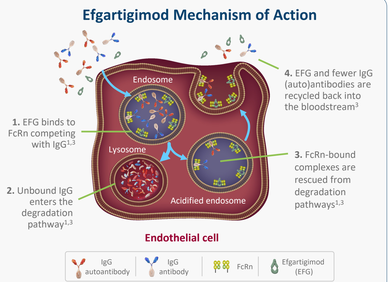

Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

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

RESULTS

- Participants treated with efgartigimod IV across registrational and phase 3 trials in IgG-mediated disorders showed a mean maximum reduction of 60.1–63.5% in total IgG levels from baseline[5,10–12]
- In ADAPT-SC, efficacy of efgartigimod PH20 SC was comparable to efgartigimod IV, with a reduction in mean total IgG levels from baseline of 66.4%[13]

Generalized Myasthenia Gravis

ADAPT-SC Phase 3 (NCT04735432; complete)[13]

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

Study duration:
- 10 weeks

Participants:
- Efgartigimod PH20 SC: n=55
- Efgartigimod IV: n=55

Primary end point:
- To demonstrate noninferiority of efgartigimod PH20 SC vs efgartigimod IV (reduction in total IgG from baseline at day 29)

ADAPT-SC+ OLE (NCT04818671; ongoing)[13,14]

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

Study duration:
- ≤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 efgartigimod PH20 SC

adapt SC myasthenia gravis study

	ADAPT-SC				ADAPT-SC+	
	Efgartigimod PH20 SC (n=55; PYFU=10.73)		Efgartigimod IV (n=55; PYFU=10.53)		Efgartigimod PH20 SC (N=179; PYFU=193.4)	
	%	ER*	%	ER*	%	ER*
Any TEAE	67.3	**12.4**	50.9	**7.6**	84.9	**9.0**
Any SAE	14.5	**0.9**	7.3	**0.5**	18.4	**0.3**
Any severe TEAE (or grade ≥3)	16.4	**1.0**	7.3	**0.5**	20.1	**0.4**
Any treatment-related TEAE	43.6	**4.9**	21.8	**2.2**	53.6	**4.1**
Discontinued due to TEAEs†	3.6	**0.2**	0	**0**	2.2	**0.03**
Any TEAEs of ISRs‡	38.2	**3.6**	0	**0**	45.8	**3.2**
Any serious infection	1.8	**0.1**	0	**0**	2.2	**0.02**
Fatal TEAEs§	0	**0**	0	**0**	2.2	**0.03**
Most commonly observed TEAEs (≥10%)**						
Injection site erythema	12.7	**0.7**	0	**0**	29.1	**1.7**
COVID-19	3.6	**0.2**	0	**0**	22.3	**0.2**
Headache	12.7	**0.9**	12.7	**1.0**	20.1	**0.6**
Nasopharyngitis	0	**0**	0	**0**	15.6	**0.2**
Diarrhea	1.8	**0.5**	5.5	**0.3**	13.4	**0.2**
Injection site pain	5.5	**0.3**	0	**0**	11.7	**0.2**
Injection site pruritis	9.1	**0.5**	0	**0**	10.6	**0.2**
Injection site bruising	7.3	**0.4**	0	**0**	10.1	**0.2**
Injection site rash	14.5	**1.3**	0	**0**	8.4	**0.1**
Myasthenia gravis	10.9	**0.7**	1.8	**0.2**	7.8	**0.1**

*Event rates were calculated as the number of events divided by the PYFU. †TEAEs grouped under Preferred Terms leading to efgartigimod PH20 SC discontinuation were COVID-19 (n=1) and Myasthenia gravis (n=1) in ADAPT-SC efgartigimod 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+. ‡Injection site reactions are defined as AEs in the Medical Dictionary for Regulatory Activities high-level term Injection site reactions regardless of the time of AE onset relative to an injection. §Fatal TEAEs: In ADAPT-SC+, 4 participants died due to TEAEs, but none were considered related to efgartigimod 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). **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.

Chronic Inflammatory Demyelinating Polyneuropathy

ADHERE registrational (NCT04281472; complete)[15]

Dosing:
- Weekly dosing of efgartigimod PH20 SC 1000 mg or placebo SC (ADHERE stage B only)

Study duration:
- ≤60 weeks

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

Stage B – Double-blinded, placebo-controlled
- Efgartigimod 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 (NCT04280718; ongoing)[16]

Dosing:
- Weekly dosing of efgartigimod PH20 SC 1000 mg or placebo SC

Study duration:
- ≤2 years (ongoing)

Participants:
- Efgartigimod 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 efgartigimod PH20 SC

adhere chronic inflammatory demyelinating polyneuropathy study

	ADHERE						ADHERE+	
	Stage A Efgartigimod PH20 SC (N=322; PYFU=46.9)		Stage B Efgartigimod PH20 SC (n=111; PYFU=56.7)		Stage B Placebo SC (n=110; PYFU=42.1)		Efgartigimod PH20 SC (N=228; PYFU=137.4)	
	%	ER†	%	ER†	%	ER†	%	ER†
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 severe TEAE (or grade ≥3)	7.8	**0.6**	6.3	**0.1**	6.4	**0.2**	11.0	**0.3**
Any treatment-related TEAE	31.4	**5.5**	24.3	**1.1**	20.0	**1.5**	23.7	**0.9**
Discontinued due to TEAEs‡	6.8	**0.5**	2.7	**0.05**	0.9	**0.02**	3.9	**0.09**
Any TEAEs of ISRs§	19.3	**2.6**	14.4	**0.4**	6.4	**0.2**	9.6	**0.3**
Any serious infection	1.2	**0.09**	0.9	**0.02**	2.7	**0.1**	2.2	**0.04**
Fatal TEAEs**	0.6	**0.04**	0	**0**	0.9	**0.02**	0.4	**0.01**
Most commonly observed TEAEs (≥10%)††								
Injection site erythema	10.2	**1.1**	5.4	**0.1**	0	**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**

*aINCAT deterioration was defined as an increase of ≥1 points in aINCAT score compared with stage B baseline. †Event rates were calculated as the number of events divided by the PYFU. ‡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 SC; 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+. §Injection site reactions are defined as AEs in the Medical Dictionary for Regulatory Activities high-level term Injection site reactions regardless of the time of AE onset relative to an injection. **Fatal TEAEs: In ADHERE, 3 participants died due to TEAEs, but none were considered related to efgartigimod 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 efgartigimod PH20 SC by the investigator. ††AEs were included if observed at ≥10% across any singular trial (ADHERE or ADHERE+) but may not be ±10% across all trials included.

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 Europe, and 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.

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ABBREVIATIONS

AChR, acetylcholine receptor; AE, adverse event; aINCAT, adjusted Inflammatory Neuropathy Cause and Treatment; CIDP, chronic inflammatory demyelinating polyneuropathy; ECI, evidence of clinical improvement; ER, event rate; Fc, fragment crystallizable; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; ISR, injection site reaction; IV, intravenous; OLE, open-label extension; PH20, recombinant human hyaluronidase PH20; PYFU, patient-year(s) of follow-up; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

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