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

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KEY TAKEAWAYS

- Efgartigimod, a first-in-class FcRn antagonist, has broadly demonstrated safety across multiple autoimmune conditions and 398.8 participant years of exposure in phase 3 trials
- 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
- Participants with various IgG-mediated autoimmune disorders demonstrated ~60% reduction in total IgG levels when treated with efgartigimod
- Efgartigimod was well tolerated with comparable TEAE rates to placebo across multiple IgG-mediated autoimmune disorders, dosing regimens, and exposure times
- Most TEAEs, including infections, were mild to moderate in severity, and event rate did not increase with longer exposure

BACKGROUND

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[2]
- Efgartigimod was designed to outcompete endogenous IgG, preventing recycling and promoting lysosomal degradation of IgG, without impacting its production:[2–6]
  - Targeted reduction of all IgG subtypes
  - No impact on other immunoglobulins
  - No reduction in albumin or increase in cholesterol levels

Efgartigimod Mechanism of Action

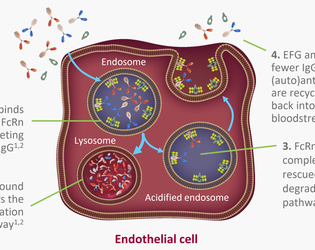

Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

Participants treated with efgartigimod across trials in IgG-mediated disorders showed a mean maximum reduction of 55.9–67.6% in total IgG levels[4,6–9]

Efgartigimod did not hamper generation of IgG responses but did transiently reduce IgG titers, enabling patients to retain ability to mount an immune response[10]

- Antigen-specific IgG responses to influenza, pneumococcal, and COVID-19 immunisation were detected in participants with gMG who received these vaccines while receiving efgartigimod

RESULTS

Generalised Myasthenia Gravis

Phase 3 ADAPT (NCT03669588; complete)[4]

- **EFG:** n=84
- **Placebo:** n=83
- **EFG 10 mg/kg IV**
- **Study duration: up to 26 weeks**
  - Initiation—cycles of 4 once-weekly infusions
  - Subsequent cycles administered according to individual clinical response (MG-ADL score) at least 8 weeks from initiation of previous cycle
- **Concomitant therapy at baseline**
  - AChEIs (EFG: 85%; placebo: 81%)
  - Corticosteroids (EFG: 71%; placebo: 81%)
  - NSISTs (EFG: 61%; placebo: 61%)
- **Mean maximum reduction in total IgG levels (SE) from baseline at Week 4, cycle 1 (AChR-Ab+ only):**
  - EFG: −61.3% (0.92); Placebo: 0.6% (2.67)

Phase 3 ADAPT+ OLE (NCT03770403; complete)[9]

- **EFG:** N=151 rolled over from ADAPT; 145 received ≥1 dose
- **EFG 10 mg/kg IV**
- **Study duration and dosing**
  - Maximum 19 cycles (3-year maximum)
  - Subsequent cycles administered according to individual clinical response (MG-ADL score) at least 7 weeks from initiation of previous cycle
- **Concomitant therapy at baseline**
  - AChEIs (86%)
  - Corticosteroids (77%)
  - NSISTs (61%)
- **Mean maximum reduction in total IgG levels (SE) from baseline at Week 3, cycle 1 (AChR-Ab+ only):**
  - EFG: −55.9% (1.15)*

Phase 3b ADAPT NXT OLE (NCT04980495; ongoing)

- **EFG:** N=69 (fixed cycles, n=17; Q2W, n=52)
- **EFG 10 mg/kg IV**
  - Fixed cycles (4 weekly infusions; 4 weeks between cycles)
  - Q2W
- **Study duration**
  - Part A (regimen comparison period): 21 weeks
  - Part B (extension period): up to 105 weeks
- **Concomitant therapy at baseline**
  - AChEIs (fixed cycles: 71%; Q2W: 94%)
  - Corticosteroids (fixed cycles: 59%; Q2W: 59%)
  - NSIDs (fixed cycles: 47%; Q2W: 37%)
- **Mean maximum reduction in total IgG levels (SE) from baseline at Week 4, cycle 1:**
  - Fixed cycles: −64.8% (1.90); Q2W: −67.6% (1.08)

	Phase 3 ADAPT for gMG				Phase 3 ADAPT+ OLE for gMG		Pooled Data for gMG (Phase 2 [NCT02965573]/ ADAPT/ADAPT+ OLE)	
	EFG 10 mg/kg IV (n=84; PYFU=34.9)		Placebo IV (n=83; PYFU=34.5)		EFG 10 mg/kg IV (N=145; PYFU=229.0)		EFG 10 mg/kg IV (N=164; PYFU=263.9)	
	n (%)	ER†	n (%)	ER	n (%)	ER†	n (%)	ER†
Any TEAE	65 (77.4)	7.22	70 (84.3)	7.83	124 (85.5)	3.5	143 (87.2)	4.17
Any serious TEAE	4 (4.8)	0.11	7 (8.4)	0.29	36 (24.8)	0.2	38 (23.2)	0.21
Any serious infection	0 (0)	–	1 (1.2)	0.03	9 (6.2)	0.05	9 (5.5)	0.04
Severe TEAEs (grade ≥3)	9 (10.7)	0.29	8 (9.6)	0.35	40 (27.6)	0.3	43 (26.2)	0.31
Discontinued due to TEAEs	3 (3.6)	0.20	3 (3.6)	0.09	12 (8.3)	0.06	15 (9.1)	0.08
Treatment-related TEAEs	26 (31.0)	1.8	22 (26.5)	1.57	44 (30.3)	0.8	66 (40.2)	0.99
Fatal TEAEs	0 (0)	–	0 (0)	–	5 (3.4)‡	0.02	5 (3.0)‡	0.02
Most frequent TEAEs§								
COVID-19	0 (0)	–	0 (0)	–	18 (12.4)	0.08	18 (11.0)	0.07
Diarrhoea	6 (7.1)	0.17	9 (10.8)	0.41	14 (9.7)	0.08	20 (12.2)	0.10
Headache	24 (28.6)	1.15	23 (27.7)	1.13	36 (24.8)	0.45	59 (36.0)	0.56
Nasopharyngitis	10 (11.9)	0.34	15 (18.1)	0.49	20 (13.8)	0.10	28 (17.1)	0.14
Nausea	7 (8.3)	0.20	9 (10.8)	0.43	9 (6.2)	0.06	16 (9.8)	0.08
Upper respiratory tract infection	9 (10.7)	0.32	4 (4.8)	0.14	6 (4.1)	0.03	13 (7.9)	0.07
Urinary tract infection	8 (9.5)	0.26	4 (4.8)	0.12	13 (9.0)	0.08	19 (11.6)	0.10

	Phase 3 ADAPT NXT for gMG EFG 10 mg/kg IV (Part A)					
	Fixed cycles (n=17; PYFU=6.9)		Q2W (n=52; PYFU=20.9)		Total population (n=69; PYFU=27.8)	
	n (%)	ER†	n (%)	ER†	n (%)	ER†
Any TEAE	16 (94.1)	12.03	43 (82.7)	10.10	59 (85.5)	10.56
Any serious TEAE	1 (5.9)	0.43	7 (13.5)	0.33	8 (11.6)	0.36
Any serious infection	1 (5.9)	0.14	2 (3.8)	0.10	3 (4.3)	0.11
Severe TEAEs (grade ≥3)	3 (17.6)	1.30	7 (13.5)	0.43	10 (14.5)	0.65
Discontinued due to TEAEs	0 (0)	–	1 (1.9)	0.05	1 (1.4)	0.04
Treatment-related TEAEs	8 (47.1)	3.04	12 (23.1)	2.73	20 (29.0)	2.81
Fatal TEAEs	0 (0)	–	0 (0)	–	0 (0)	–
Most frequent TEAEs‖						
COVID-19	2 (11.8)	0.29	11 (21.2)	0.53	13 (18.8)	0.47
Headache	5 (29.4)	1.16	8 (15.4)	0.62	13 (18.8)	0.76
Upper respiratory tract infection	2 (11.8)	0.43	5 (9.6)	0.38	7 (10.1)	0.40

*In ADAPT+, no data on IgG reduction was captured at Week 4, when maximal IgG reduction occurs. †Event rate (ER) calculated as events/PYFU. ‡None of the 5 deaths (acute myocardial infarction, lung carcinoma, MG crisis, septic shock, coronary artery atherosclerosis/cardiomegaly) in ADAPT+ were related to efgartigimod administration per the principal investigator. §Most frequent TEAEs occurring in more than ≥10% of participants per trial. ‖Most frequent TEAEs occurring in more than ≥10% of total population.

Immune Thrombocytopenia

Phase 3 ADVANCE (NCT04188379; complete)[8]

- **EFG:** n=86
- **Placebo:** n=45
- **EFG 10 mg/kg IV**
- **Study duration: 24 weeks**
  - Weeks 1–4: weekly dosing
  - Weeks 4–15: weekly or Q2W* dosing
  - Weeks 16–24: based on Week 15 dosing
- **Concomitant therapy at baseline**
  - Corticosteroids (EFG: 26%; placebo: 27%)
  - NSISTs (EFG: 9%; placebo: 13%)
  - TPO-RA (EFG: 23%; placebo: 20%)
  - Danazol (EFG: 2%; placebo: 2%)
- **Mean maximum reduction in total IgG levels (SE) from baseline at Week 4, cycle 1:**
  - EFG: −60.1% (3.65); Placebo: 2.8% (4.13)

Phase 3 ADVANCE+ OLE (NCT04225156; ongoing)

- **EFG:** N=101 rolled over from ADVANCE IV
- **EFG 10 mg/kg IV**
- **Study duration: 52 weeks (extendable to 3 more 52-week periods)**
  - Dosing either weekly or Q2W; continued from ADVANCE IV
  - Change in dosing frequency permitted from Visit 1
- **Concomitant therapy at baseline**
  - Corticosteroids (27%)
  - NSISTs (14%)
  - TPO-RA (22%)
- **Mean maximum reduction in total IgG levels (SE) from ADVANCE IV baseline at Week 4, cycle 1:**
  - EFG: −65.3% (1.15)

	Phase 3 ADVANCE IV for Primary ITP				Phase 3 ADVANCE+ OLE for Primary ITP		Pooled Data for ITP (ADVANCE IV/ ADVANCE IV+ OLE)	
	EFG 10 mg/kg IV (n=86; PYFU=38.0)		Placebo IV (n=45; PYFU=19.2)		EFG 10 mg/kg IV (N=101; PYFU=69.1)		EFG 10 mg/kg IV (N=124; PYFU=105.2)	
	n (%)	ER†	n (%)	ER	n (%)	ER†	n (%)	ER†
Any TEAE	80 (93.0)	13.56	43 (95.6)	17.87	93 (92.1)	8.18	118 (95.2)	10.21
Any serious TEAE	7 (8.1)	0.32	7 (15.6)	0.42	12 (11.9)	0.30	19 (15.3)	0.29
Any serious infection	2 (2.3)	0.05	2 (4.4)	0.10	1 (1.0)	0.03	2 (1.6)	0.03
Severe TEAEs (grade ≥3)	11 (12.8)	0.58	9 (20.0)	0.68	16 (15.8)	0.54	26 (21.0)	0.52
Discontinued due to TEAEs	4 (4.7)	0.11	1 (2.2)	0.05	1 (1.0)	0.01	5 (4.0)	0.05
Treatment-related TEAEs	15 (17.4)	0.79	10 (22.2)	0.94	11 (10.9)	0.26	20 (16.1)	0.47
Fatal TEAEs	0 (0)	–	0 (0)	–	3 (3.0)‡	0.04	3 (2.4)‡	0.03
Most frequent TEAEs of interest‡								
Haematuria	14 (16.3)	0.79	7 (15.6)	0.63	7 (6.9)	0.26	17 (13.7)	0.44
Headache	14 (16.3)	0.53	6 (13.3)	1.15	10 (9.9)	0.23	21 (16.9)	0.34
Petechiae	13 (15.1)	0.55	12 (26.7)	1.04	17 (16.8)	0.45	24 (19.4)	0.50

*The dosing schedule could change to every other week from Weeks 4–15 in participants who achieved platelet counts of ≥100×10⁹/L for 3 out of 4 consecutive weeks, including the last of these weeks. Treatment could change from every other week to weekly in participants whose platelet counts decreased to <100×10⁹/L for 2 consecutive weeks or <30×10⁹/L for 1 week, or in participants who received rescue therapy. †Event rate calculated as events/PYFU. ‡None of the 3 deaths (cerebral haemorrhage, femur fracture, pulmonary fibrosis) in ADVANCE+ were related to efgartigimod administration per the principal investigator. Most frequent TEAEs of interest occurring in more than ≥10% of participants in ADVANCE IV.[8]

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

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ABBREVIATIONS

AChEI, acetylcholinesterase inhibitor; AChR, acetylcholine receptor; COVID-19, coronavirus disease 2019; EFG, efgartigimod; EMEA, Europe, Middle East, and Africa; ER, event rate; Fc, fragment crystallisable; FcRn, neonatal Fc receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; ITP, immune thrombocytopenia; IV, intravenous; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; NSID, nonsteroidal immunosuppressive drug; NSIST, nonsteroidal immunosuppressive therapy; OLE, open-label extension; PYFU, participant-year(s) follow-up; Q2W, every 2 weeks; SE, standard error; TEAE, treatment-emergent adverse event; TPO-RA, thrombopoietin receptor agonist.

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AM: Alexion, argenx, axunio, Grifols, Hormosan, Janssen, Merck, Novartis, Octapharma, UCB; **KG:** Alexion, argenx, UCB, Xeris Pharmaceuticals; **CMB:** Alexion, Apellis, argenx, Sanofi; **MG:** Almirall, argenx, Biotest, GSK, Janssen, LEO Pharma, Lilly, Novartis, UCB; **HM:** Alexion, argenx, Chugai, Japan Blood Products Organization, Roche, UCB; **ZBC:** NKFIH Hungary, Orvostovábbképzo Szemle, Sanofi Genzyme Hungary; **AN:** Amgen, Angle, argenx, Dova, Novartis, Ono, Rigel, Shionogi; **PU, RK, JTG, SA, and MJ:** Employees of argenx; **JFH:** AcademicCME, Ad Scientiam, Alexion, AstraZeneca Rare Disease, argenx, Biologix Pharma, Cartesian Therapeutics, Centers for Disease Control and Prevention, CheckRare CME, F. Hoffmann-LaRoche Ltd, Amgen, Medscape CME, Merck EMD Serono, MGFA, Muscular Dystrophy Association, National Institutes of Health, NMD Pharma, Novartis, PCORI, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, Tolerancia AB, UCB, Zai Lab; **KGC:** Alexion, Alnylam, Amicus, argenx, Biogen, CSL Behring, Ipsen, Janssen, Roche, UCB.

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