P016

Overview of the Safety Profile of Efgartigimod Clinical Trials in Participants With Diverse IgG-Mediated Autoimmune Diseases

Tuan Vu,[1] Kelly Gwathmey,[2] Catherine M. Broome,[3] Matthias Goebeler,[4] Hiroyuki Murai,[5] Zsuzsanna Bata-Csörgo,[6] Adrian Newland,[7] Peter Ulrichts,[8] Rene Kerstens,[8] Jeffrey T. Guptill,[8] Sofiane Agha,[8] Ming Jiang,[8] James F. Howard Jr[9]

[1]Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, USA; [2]Department of Neurology, Virginia Commonwealth University, Richmond, VA, USA; [3]Department of Medicine, Georgetown University, Washington, DC, USA; [4]Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, Würzburg, Germany; [5]Department of Neurology, School of Medicine, International University of Health and Welfare, Narita, Japan; [6]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary; [7]Centre for Haematology, Barts and the London School of Medicine & Dentistry, Queen Mary University of London, London, UK; [8]argenx, Ghent, Belgium; [9]Department of Neurology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

BACKGROUND

Efgartigimod: Engineered IgG1 Fc Fragment[1–5]

- 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 other immunoglobulins
  - No reduction in albumin or increase in cholesterol levels

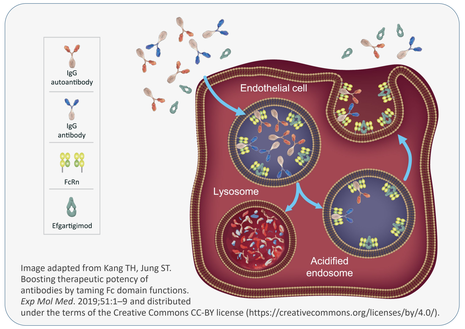
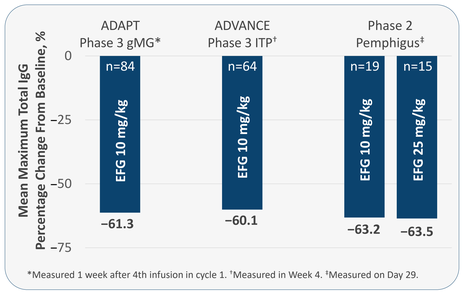


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

- FcRn blockade with EFG does not lead to complete IgG removal[2,5]
- Participants treated with EFG for various IgG-mediated autoimmune disorders showed a mean maximum reduction of 60.1–63.5% in total IgG levels[4,6–8]
- EFG treatment did not lead to any abnormal infection patterns compared with placebo, and most infections were mild to moderate in severity[4,6–8]

Mean Maximum Reduction in Total IgG Levels From Baseline Upon Treatment With EFG



*Measured 1 week after 4th infusion in cycle 1. †Measured in Week 4. ‡Measured on Day 29.

RESULTS

Generalized Myasthenia Gravis

- **Phase 3 ADAPT**[4]
- **EFG:** n=84
  Placebo: n=83
- **EFG 10 mg/kg IV**
- **Study duration: up to 26 weeks**
  - Initiation – cycles of 4 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:**
  - Acetylcholinesterase inhibitors (EFG: 85%; placebo: 81%)
  - Corticosteroids (EFG: 71%; placebo: 81%)
  - NSISTs (EFG: 61%; placebo: 61%)

Generalized Myasthenia Gravis OLE

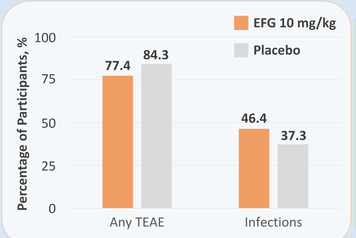
- **Phase 3 ADAPT+ OLE**
  3-year maximum
- **EFG:** N=151 rolled over from ADAPT; 145 received ≥1 dose
- **EFG 10 mg/kg IV**
- **Study duration and dosing:**
  - Maximum 19 cycles
  - Subsequent cycles administered according to individual clinical response (MG-ADL score) at least 7 weeks from initiation of previous cycle
- **Concomitant therapy at baseline:**
  - Acetylcholinesterase inhibitors (86%)
  - Corticosteroids (77%)
  - NSISTs (61%)

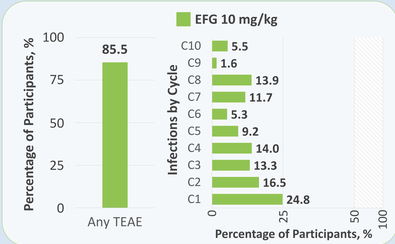
Primary Immune Thrombocytopenia

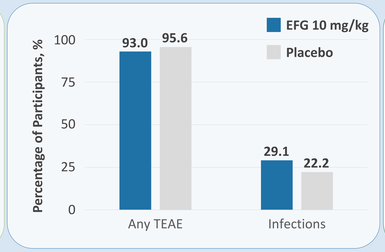
- **Phase 3 ADVANCE IV**
- **EFG:** n=86
  Placebo: n=45
- **EFG 10 mg/kg IV**
- **Study duration: 24 weeks**
  - Weeks 1–4: weekly dosing
  - Weeks 4–15: weekly or every-other-week* dosing
  - Weeks 16–24: continued based on Week 15 dosing
- **Concomitant therapy at baseline:**
  - Corticosteroids (EFG: 26%; placebo: 27%)
  - TPO-RA (EFG: 23%; placebo: 20%)
  - NSISTs (EFG: 9%; placebo: 13%)
  - Danazol (EFG: 2%; placebo: 2%)

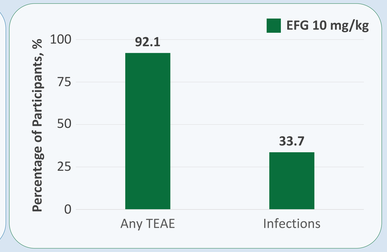
Primary Immune Thrombocytopenia OLE

- **Phase 3 ADVANCE+ OLE: 4-year maximum**
- **EFG:** N=101 rolled over from ADVANCE (September 2022)
- **EFG 10 mg/kg IV**
- **Study duration: 52 weeks (extendable to 3 more 52-week periods)**
  - Dosing either weekly or every other week, continued from ADVANCE IV
  - Change in dosing frequency permitted from Visit 1
- **Concomitant therapy at baseline:**
  - Corticosteroids (27%)
  - TPO-RA (22%)
  - NSISTs (14%)









	Phase 3 ADAPT for gMG		Phase 3 ADAPT+ OLE for gMG	Pooled Data for gMG (Phase 2 [NCT02965573]/ADAPT/ADAPT+ OLE)	Phase 3 ADVANCE IV for Primary ITP		Phase 3 ADVANCE+ OLE for Primary ITP	Pooled Data for ITP (ADVANCE IV/ADVANCE IV+ OLE)
Event Rate*	**EFG 10 mg/kg IV (n=84) [34.9 PYFU]**	**Placebo IV (n=83) [34.5 PYFU]**	**EFG 10 mg/kg IV (N=145) [229.0 PYFU]**	**EFG 10 mg/kg IV (N=164) [263.9 PYFU]**	**EFG 10 mg/kg IV (n=86) [38.0 PYFU]**	**Placebo IV (n=45) [19.2 PYFU]**	**EFG 10 mg/kg IV (N=101) [69.1 PYFU]**	**EFG 10 mg/kg IV (N=124) [105.2 PYFU]**
≥1 TEAE	7.2	7.8	3.5	4.2	13.6	17.9	8.2	10.2
≥1 serious TEAE	0.1	0.3	0.2	0.2	0.3	0.4	0.3	0.3
Severe TEAEs (grade ≥3)	0.3	0.4	0.3	0.3	0.6	0.7	0.5	0.5
Discontinued due to AEs	0.2	0.1	0.1	0.08	0.1	0.05	0.01	0.05
Treatment-related TEAE	1.8	1.6	0.8	1.0	0.8	0.6	0.3	0.5
Infection	1.6	1.2	0.7	0.9	1.0	0.6	0.8	0.9

*Event rate calculated as number of events per participant-year of follow-up.

Phase 2 Pemphigus Open-Label Study[6]

- ≥1 treatment-emergent adverse event (TEAEs) were reported by 84% of participants receiving EFG 10 mg/kg (n=19) and 87% receiving EFG 25 mg/kg (n=15)
- Of the 32 adverse events (AEs) of special interest (infections and infestations), 7 (15.6%) events in 5 participants were considered related to study treatment; none led to study discontinuation, and all were mild to moderate in severity, except 1 case of pneumonia and 1 of tooth infection, both of which were grade 3
- No abnormal infection patterns were observed; 2 serious AEs were reported, which were assessed as unrelated to EFG (pneumonia and tibia fracture)

In all studies, EFG treatment did not lead to reductions in albumin or increases in cholesterol levels, which importantly avoids downstream cardiovascular risks seen with elevated cholesterol levels

EFG did not hamper generation of IgG responses but did transiently reduce IgG titers[9]

- Antigen-specific IgG responses to influenza, pneumococcal, and COVID-19 immunization were detected in participants with generalized myasthenia gravis (gMG) who received these vaccines while receiving EFG

KEY TAKEAWAYS

- **EFG, a first-in-class FcRn antagonist, has broadly demonstrated safety across multiple autoimmune conditions and 371 participant years of exposure in phase 3 trials**
- **EFG reduces IgG levels via FcRn blockade and does not lead to complete removal of IgG, nor does it impact IgG production**
- **Participants with various IgG-mediated autoimmune disorders demonstrated 60.1–63.5% reduction in total IgG levels when treated with EFG**
- **EFG 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 incidence rate did not increase with longer exposure**
- **EFG treatment did not decrease albumin or increase cholesterol levels**

EFG is approved for the treatment of gMG in adult patients positive for anti-acetylcholine receptor antibodies in the US and Europe, and for patients regardless of antibody status in Japan.

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ABBREVIATIONS AND FOOTNOTES

AE, adverse event; C, cycle number; EFG, efgartigimod; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; ITP, immune thrombocytopenia; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living; NSIST, nonsteroidal immunosuppressive therapy; OLE, open-label extension; PYFU, participant-year(s) follow-up; TEAE, treatment-emergent adverse event; TPO-RA, thrombopoietin receptor agonist.

*The dosing schedule could change to every other week from Weeks 4–15 in participants who achieved platelet counts of ≥100×10^9/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 <100×10^9/L for 2 consecutive weeks or <30×10^9/L for 1 week, or in participants who received rescue therapy.

DISCLOSURES AND ACKNOWLEDGMENTS

TV: Alexion, Amgen, argenx, Cartesian Therapeutics, Dianthus, ImmunAbs, Immunovant, Janssen/Momenta, Regeneron Pharmaceuticals, RemeGen, Sanofi, UCB; **KG:** Alexion, argenx, UCB, Xeris; **CMB:** Alexion, Apellis, argenx, Sanofi; **MG:** Almirall, argenx, Biotest, GlaxoSmithKline, Janssen, Leo Pharma, Lilly, Novartis, UCB; **HM:** Alexion, argenx, AstraZeneca, Chugai, Japan Blood Products Organization, Ministry of Health, Labour and Welfare of Japan, Roche, UCB; **ZB-C:** NFKI Hungary, Orvostovábbképzo Szemle, Sanofi Genzyme; **AN:** Amgen, Angle, argenx, Dova, Novartis, Ono Pharmaceutical, Rigel Pharmaceuticals, Shionogi; **PU, RK, JTG, SA, MJ:** Employees of argenx; **JFH:** AcademicCME, Ad Scientiam, Alexion, Amgen, AstraZeneca Rare Disease, argenx, Biologix, Cartesian Therapeutics, Centers for Disease Control and Prevention, CheckRare CME, F. Hoffmann-LaRoche Ltd, Medscape CME, Merck EMB Serono, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, Novartis, PCORI, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ Health CME, Regeneron Pharmaceuticals, Sanofi US, Toleranzia AB, UCB, Zai Lab.

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REFERENCES

1. Sesarman A, et al. *Cell Mol Life Sci.* 2010;67:2533–50. **2.** Ulrichts P, et al. *J Clin Invest*. 2018;128:4372–86. **3.** Vaccaro C, et al. *Nat Biotech.* 2005;23:1283–8. **4.** Howard JF Jr, et al. *Lancet Neurol.* 2021;20:526–36. **5.** Nixon AE, et al. *Front Immunol.* 2015;6:176. **6.** Goebeler M, et al. *Br J Dermatol.* 2022;186:429–39. **7.** Newland AC, et al. *Am J Hematol*. 2020;95:178–87. **8.** Broome CM, et al. Presented at the 64th ASH Annual Meeting and Exposition; December 10–13, 2022; New Orleans, LA. **9.** Guptill JT, et al. *Autoimmunity.* 2022;55:620–31.