PB1334

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

Michelle Sholzberg,[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 Medicine, University of Toronto, Toronto, ON, Canada; [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

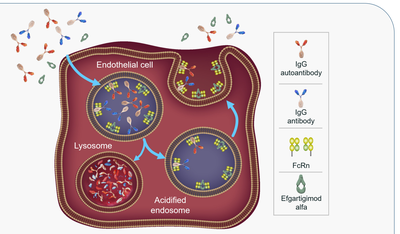
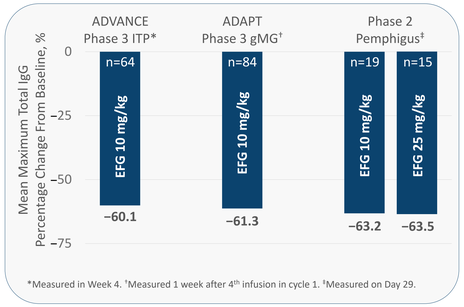


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

- FcRn blockade with EFG does not lead to complete IgG removal[2,5]
- Patients treated with EFG in 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 in Week 4. †Measured 1 week after 4th infusion in cycle 1. ‡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

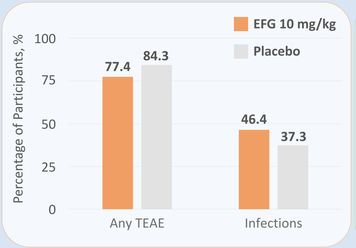
- **Phase 3 ADAPT+ OLE**
  3-year maximum
- **EFG:** N=151 rolled over from ADAPT; 145 received ≥1 dose
- **EFG 10 mg/kg IV**
- **Study duration and dosing:**
  - Maximum 19 cycles
  - Subsequent cycles administered according to individual clinical response (MG-ADL score) at least 7 weeks from initiation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

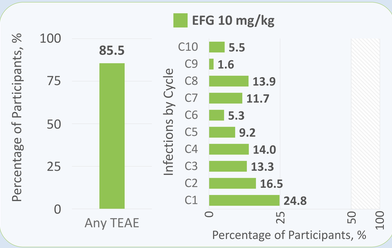
Primary Immune Thrombocytopenia

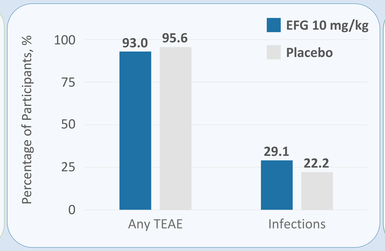
- **Phase 3 ADVANCE IV**
- **EFG:** n=86
  Placebo: n=45
- **EFG 10 mg/kg IV**
- **Study duration: 24 weeks**
  - Weeks 1–4: weekly dosing
  - Weeks 4–15: weekly or every-other-week* dosing
  - Weeks 16–24: continued based on Week 15 dosing
- **Concomitant therapy at baseline:**
  - Corticosteroids (EFG: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

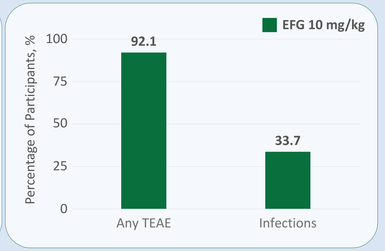
Primary Immune Thrombocytopenia

- **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	Phase 3 ADVANCE IV for Primary ITP		Phase 3 ADVANCE+ OLE for Primary ITP
Incidence Rate†	**EFG 10 mg/kg IV (n=84) [34.9 PY]**	**Placebo IV (n=83) [34.5 PY]**	**EFG 10 mg/kg IV (N=145) [229.0 PY]**	**EFG 10 mg/kg IV (n=86) [38.0 PY]**	**Placebo IV (n=45) [19.2 PY]**	**EFG 10 mg/kg IV (N=101) [69.1 PY]**
≥1 TEAE	7.2	7.8	3.5	13.6	17.9	8.2
≥1 serious TEAE	0.1	0.3	0.2	0.3	0.4	0.3
Severe TEAEs (grade ≥3)	0.3	0.4	0.3	0.6	0.7	0.5
Discontinued due to AEs	0.2	0.1	0.1	0.1	0.0	0.0
Infection	1.6	1.2	0.7	1.0	0.6	0.8
Thromboembolic events	0.03	0.03	0.02	0.00	0.00	0.05

- **Phase 2 Pemphigus Open-label Study**[6]
  - ≥1 TEAE was reported by 84% of participants receiving EFG 10 mg/kg (n=19) and 87% receiving EFG 25 mg/kg (n=15)
  - Of 32 AEs of special interest (infections and infestations), 7 events in 5 participants (15.6%) 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 tooth infection, which were both 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**
- **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 gMG who received these vaccines while receiving EFG

KEY TAKEAWAYS

- EFG reduces IgG levels via FcRn blockade and does not lead to complete removal of IgG nor does it impact IgG production
- Patients 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
- Most TEAEs, including infections, were mild to moderate in severity, and incidence rate did not increase with longer exposure
- EFG was well tolerated and demonstrated a consistent safety profile across varying dosing regimens and exposure times
- EFG treatment did not decrease albumin or increase cholesterol levels

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

Presented at the 31st Congress of the International Society on Thrombosis and Haemostasis; June 24–28, 2023; Montreal, Canada

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; NSIST, nonsteroidal immunosuppressive therapy; OLE, open-label extension; PY, patient-year; SAE, serious adverse event; 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. †Incidence rate calculated as number of events per patient-year of follow-up.

DISCLOSURES AND ACKNOWLEDGEMENTS

MS: Consultant: Band Therapeutics; Unrestricted research funding: Octapharma, Pfizer; Honoraria: Amgen, Novartis, Octapharma, Pfizer; **KG:** Consultant: Alexion Pharmaceuticals, argenx BVBA, Strongbridge, UCB; Honoraria: Alexion Pharmaceuticals; **CMB:** Honoraria: Alexion Pharmaceuticals, Apellis, argenx, Sanofi; **MG:** Consultant: Almirall, argenx (paid to institution); Honoraria: Biotest, GSK, Janssen, Leo Pharma, Lilly, Novartis, UCB; **HM:** Consultant: Alexion Pharmaceuticals, argenx, Roche, UCB; Honoraria: Japan Blood Products Organization, Chugai; **ZB-C:** Consultant: Sanofi-Genzyme Hungary; Honoraria: Orvostovábbképzo Szemle; Research funding: NKFI Hungary; **AN:** Consultant: Amgen, Angle, argenx, Dova, Novartis, Ono, Rigel, Shionogi; Research funding: Amgen, Novartis, Rigel; Honoraria: Amgen, Angle, argenx, Dova, Novartis, Ono, Rigel, Shionogi; Paid expert testimony: argenx, Rigel; **PU, RK, JTG, SA, MJ:** Employees of argenx; **JFH:** Research funding (paid to the institution): Alexion Pharmaceuticals, argenx BVBA, Cartesian Therapeutics, Ra Pharmaceuticals (now UCB Biosciences), Takeda Pharmaceuticals; Honoraria: Alexion Pharmaceuticals, argenx BVBA, F. Hoffman-LaRoche Ltd., Immunovant Inc., Ra Pharmaceuticals (now UCB Biosciences), Regeneron Pharmaceuticals, Sanofi US, Viela Bio Inc. (now Horizon Therapeutics). This work was supported by argenx, who designed and funded the analysis. Medical writing assistance was provided by Envision Pharma Group.

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. 64th ASH Annual Meeting and Exposition; December 10–13, 2022; New Orleans, LA. **9.** Guptill JT, et al. *Autoimmunity*. 2022;55:620–31.