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

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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

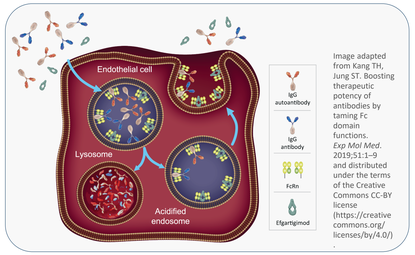
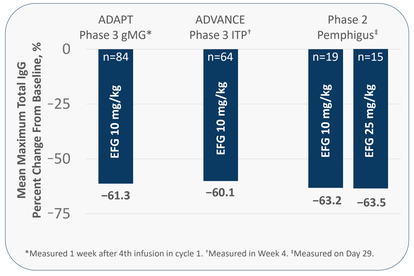


Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

- FcRn blockade with EFG does not lead to complete IgG removal[2,5]
- Patients treated with EFG 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

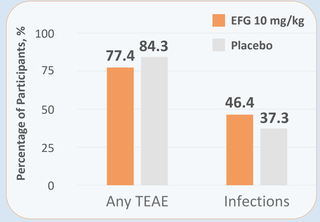
- **Phase 3 ADAPT+ OLE: 3-year maximum**
- **EFG:** N=151 rolled over from ADAPT; n=145 received ≥1 dose
- **EFG 10 mg/kg IV**
- **Study duration and dosing:**
  - Maximum 19 cycles
  - Subsequent cycles administered according to individual clinical response (MG-ADL score) at least 7 weeks from initiation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

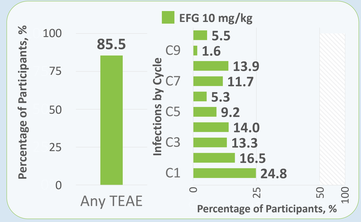
Primary Immune Thrombocytopenia

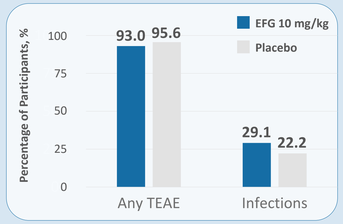
- **Phase 3 ADVANCE IV**
- **EFG:** n=86
  Placebo: n=45
- **EFG 10 mg/kg IV**
- **Study duration: 24 weeks**
  - Weeks 1–4: weekly dosing
  - Weeks 4–15: weekly or every-other-week* dosing
  - Weeks 16–24: continued based on Week 15 dosing
- **Concomitant therapy at baseline:**
  - Corticosteroids (EFG: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

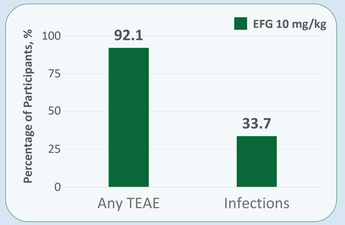
Primary Immune Thrombocytopenia OLE

- **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	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 treatment-emergent adverse event (TEAE) was 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 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 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

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 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 a 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 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; PY, patient-year(s); 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 ≥100×10⁹/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. †Incidence rate calculated as number of events per patient-year of follow-up.

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