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# Sex-Specific Analysis of Efgartigimod Efficacy in Patients With gMG: Subanalysis of the Randomized, Phase 3 ADAPT Trial

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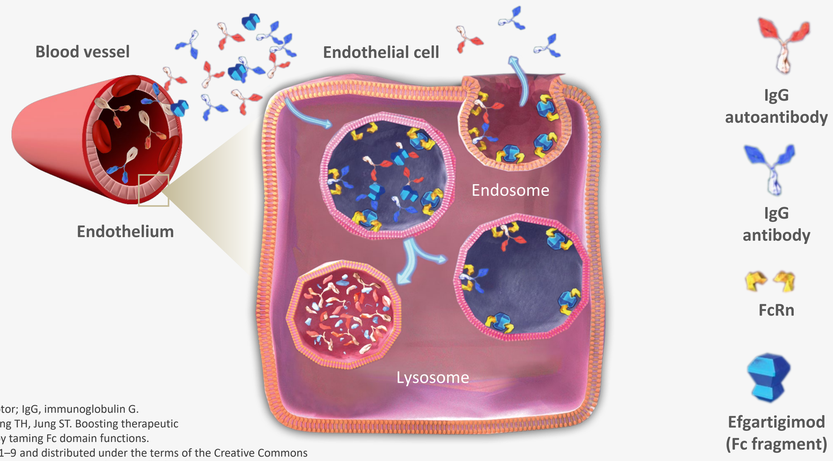
## INTRODUCTION

- Generalized myasthenia gravis (gMG) is a rare, chronic autoimmune disease that leads to potentially life-threatening muscular weakness.[1]
- Epidemiologic and clinical indicators point to a relevant role of sex in myasthenia gravis (MG). For example, early-onset MG is more frequent in female patients, whereas late-onset MG is more frequent in male patients. Hence, female patients show higher rates of thymus hyperplasia compared with male patients. Furthermore, female patients with MG have been found to have a lower quality of life, higher impairment in activities of daily living, and a higher risk of myasthenic exacerbations compared with male patients with MG.[2]
- Efgartigimod is a human immunoglobulin G (IgG) 1 antibody Fc fragment that blocks the neonatal Fc receptor, thereby decreasing IgG levels, including those of pathogenic IgG autoantibodies.[3,4]

### Efgartigimod Mechanism of Action: Blocking Neonatal Fc Receptor




FcRn, neonatal Fc receptor; IgG, immunoglobulin G.
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/).

- The pivotal ADAPT trial demonstrated that efgartigimod treatment resulted in clinically meaningful improvements in gMG-specific outcome measures in acetylcholine receptor antibody–positive (AChR-Ab+) patients.[4]
- The Sex and Gender Equity in Research (SAGER) guidelines recommend a systematic approach to the reporting of sex and gender in clinical trials and research,[5] which is of particular importance in gMG, a condition that demonstrates significant differences in disability and disease course between female and male patients.

## OBJECTIVE

- This analysis aimed to identify any potential sex-specific differences in outcomes between patients with gMG receiving efgartigimod or placebo.

## METHODS

- ADAPT (NCT03669588) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial in patients with gMG (MG-ADL total score of ≥5 points at screening and baseline, with ≥50% of the total score attributed to nonocular symptoms), regardless of autoantibody status.
- Patients received efgartigimod (10 mg/kg) or matching placebo administered as 4 infusions per cycle (1 infusion per week), repeated as needed depending on clinical response.
- The primary endpoint was percentage of AChR-Ab+ patients who were MG-ADL responders (defined as having a ≥2-point reduction [improvement] in MG-ADL total score vs baseline, sustained for ≥4 weeks) in the first treatment cycle.
- Secondary endpoints included proportion of Quantitative Myasthenia Gravis (QMG) responders (defined as having a ≥3-point reduction [improvement] in total QMG score vs baseline, sustained for ≥4 consecutive weeks) in the first treatment cycle.
- In this analysis, only AChR-Ab+ patients receiving a stable dose of ≥1 gMG treatment were included. The outcomes were analyzed by Zelen's Exact Test for homogeneous odds ratios between sex subgroups.

## RESULTS

### Patients

- Overall, 129 AChR-Ab+ patients were analyzed, of whom 86 (66.7%) were female.
- At baseline, female patients were younger, had a lower body mass index, had a longer duration since gMG diagnosis, and had undergone a thymectomy more often compared with male patients (**Table 1**).
- Female patients also had higher disease severity, as measured by the QMG score, than male patients at baseline (**Table 1**).

### Efficacy

- Following treatment with efgartigimod or matching placebo, no significant sex-specific treatment differences in MG-ADL or QMG response were observed (**Table 2**).

### Safety

- Regardless of sex, efgartigimod was well tolerated and safety profiles were generally similar between female and male AChR-Ab+ patients with gMG (**Table 3**).

**TABLE 1** Demographics and Baseline Disease Characteristics in the AChR-Ab+ Population, by Sex at Birth

| | Female (n=86) | Male (n=43) |
|---|---|---|
| **Age**, mean (SD), years | 42.9 (14.3) | 54.8 (14.5) |
| **Number of years since diagnosis**, mean (SD) | 9.95 (8.40) | 8.02 (7.74) |
| **BMI**, mean (SD), kg/m$^2$ | 26.28 (6.13) | 31.77 (7.57) |
| **Thymectomy performed for gMG**, n (%) | 56 (65.1) | 19 (44.2) |
| **MGFA class at screening**, n (%) | | |
| 2-2A | 20 (23.3) | 8 (18.6) |
| 2-2B | 15 (17.4) | 10 (23.3) |
| 3-3A | 24 (27.9) | 10 (23.3) |
| 3-3B | 25 (29.1) | 12 (27.9) |
| 4-4A | 2 (2.3) | 2 (4.7) |
| 4-4B | 0 | 1 (2.3) |
| **MG-ADL score at baseline**, mean (SD) | 8.8 (2.2) | 8.8 (2.6) |
| **QMG score at baseline**, mean (SD) | 16.3 (4.8) | 14.3 (4.4) |
| **NSIST use at baseline**, n (%) | 52 (60.5) | 25 (58.1) |

AChR-Ab+, acetylcholine receptor antibody-positive; BMI, body mass index; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NSIST, nonsteroidal immunosuppressive therapy (azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate, tacrolimus [in mono- or combination therapy]); QMG, Quantitative Myasthenia Gravis.

**TABLE 2** MG-ADL and QMG Responders During the First Cycle in the AChR-Ab+, Modified Intent-to-Treat Population and by Sex at Birth

| | Overall AChR-Ab+ Population | | | Female (n=86) | | Male (n=43) | | |
|---|---|---|---|---|---|---|---|---|
| **Endpoint**, n (%) | Efgartigimod (n=65) | Placebo (n=64) | Between-Treatment Analysis OR (95% CI)* | Efgartigimod (n=46) | Placebo (n=40) | Efgartigimod (n=19) | Placebo (n=24) | Between-Sex Subgroup Analysis† |
| **MG-ADL responders** | 44 (67.7) | 19 (29.7) | 4.95 (2.21–11.53) *P*<.0001 | 31 (67.4) | 13 (32.5) | 13 (68.4) | 6 (25.0) | *P*=.7014 |
| **QMG responders** | 41 (63.1) | 9 (14.1) | 10.84 (4.18–31.20) *P*<.0001 | 26 (56.5) | 7 (17.5) | 15 (78.9) | 2 (8.3) | *P*=.1595 |

AChR-Ab+, acetylcholine receptor antibody-positive; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living; OR, odds ratio; QMG, Quantitative Myasthenia Gravis.
*Treatment effect was tested using exact conditional logistic regression. †Homogenous ORs were tested using Zelen's Exact Test.

**TABLE 3** Summary of TEAEs in the AChR-Ab+ Safety Population, by Sex at Birth

| | Female (n=86) | | Male (n=43) | |
|---|---|---|---|---|
| **Patients with event**, n (%) | Efgartigimod (n=46) | Placebo (n=40) | Efgartigimod (n=19) | Placebo (n=24) |
| **Any TEAE** | 34 (73.9) | 33 (82.5) | 15 (78.9) | 21 (87.5) |
| **Any serious TEAE** | 2 (4.3) | 1 (2.5) | 1 (5.3) | 5 (20.8) |
| **Any grade ≥3 TEAE** | 5 (10.9) | 2 (5.0) | 1 (5.3) | 5 (20.8) |
| **Any TEAE of special interest** | 21 (45.7) | 16 (40.0) | 8 (42.1) | 6 (25.0) |
| **Any infusion-related reaction** | 1 (2.2) | 3 (7.5) | 1 (5.3) | 2 (8.3) |
| **Any TEAE deemed treatment related* by the principal investigator** | 13 (28.3) | 10 (25.0) | 7 (36.8) | 5 (20.8) |
| **Any procedure-related TEAE** | 0 | 0 | 1 (5.3) | 0 |
| **Any serious treatment-related TEAE** | 1 (2.2) | 0 | 1 (5.3) | 0 |
| **Any TEAE leading to treatment discontinuation** | 2 (4.3) | 0 | 0 | 3 (12.5) |
| **Any TEAE leading to death** | 0 | 0 | 0 | 0 |

AChR-Ab+, acetylcholine receptor antibody-positive; TEAE, treatment-emergent adverse event.
*"Treatment related" is defined as at least possibly drug related according to the investigator, or as a missing drug relatedness.

## CONCLUSION

- **These analyses support the conclusion that efgartigimod treatment is well tolerated and results in consistent improvement across gMG-specific outcome measures, irrespective of patient sex at birth.**

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