315

Long-term Safety and Efficacy of Efgartigimod in Patients With Generalized Myasthenia Gravis

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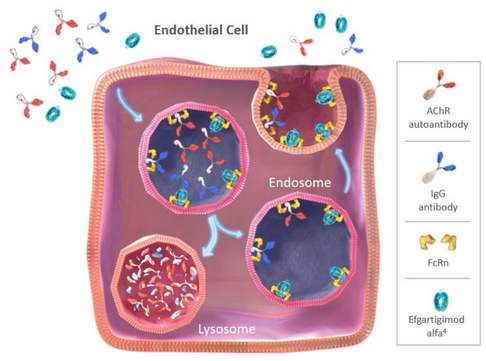
Introduction

- Neonatal Fc receptor (FcRn) recycles immunoglobulin G (IgG), extending its half-life and maintaining serum concentration[1]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity to FcRn (**Figure 1**)[2]
- Efgartigimod 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 IgM or IgA
  - No reduction in albumin levels
  - No increase in cholesterol

Figure 1. Efgartigimod Mechanism of Action: Blocking FcRn

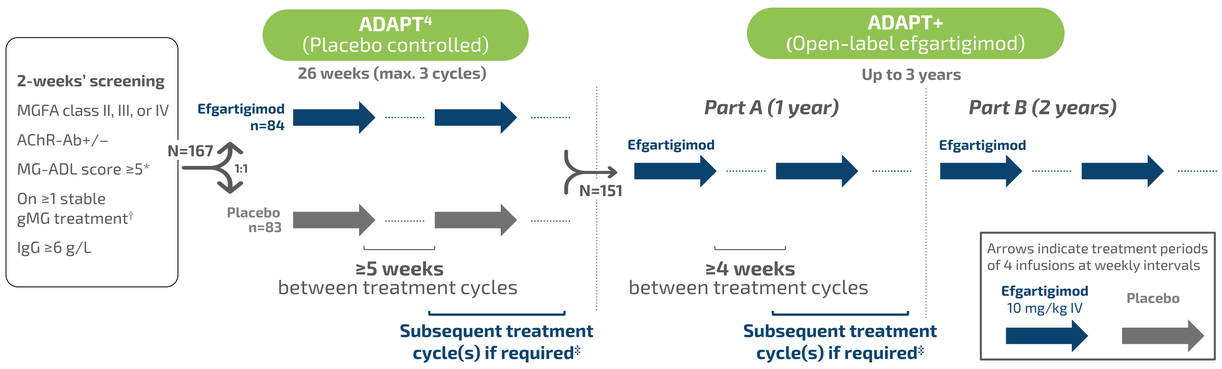


FcRn, neonatal Fc receptor; IgG, immunoglobulin G.
Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

Methods

- In the ADAPT study (**Figure 2**), the time between treatment cycles was ≥5 weeks (≥8 weeks from the first infusion) and there were a maximum of 3 cycles
- In the ADAPT+ study (**Figure 2**), the time between treatment cycles was ≥4 weeks (≥7 weeks from the first infusion) and there were a maximum of 17 cycles (as of the January 31, 2022, data cut-off)
- A total of 151 patients rolled over to the open-label extension (ADAPT+) and 145 had received ≥1 dose as of January 31, 2022; the remaining patients either were still responding from their last cycle during ADAPT or had dropped out between roll-over and the point at which they would have received their first dose in ADAPT+

Figure 2. Study Design

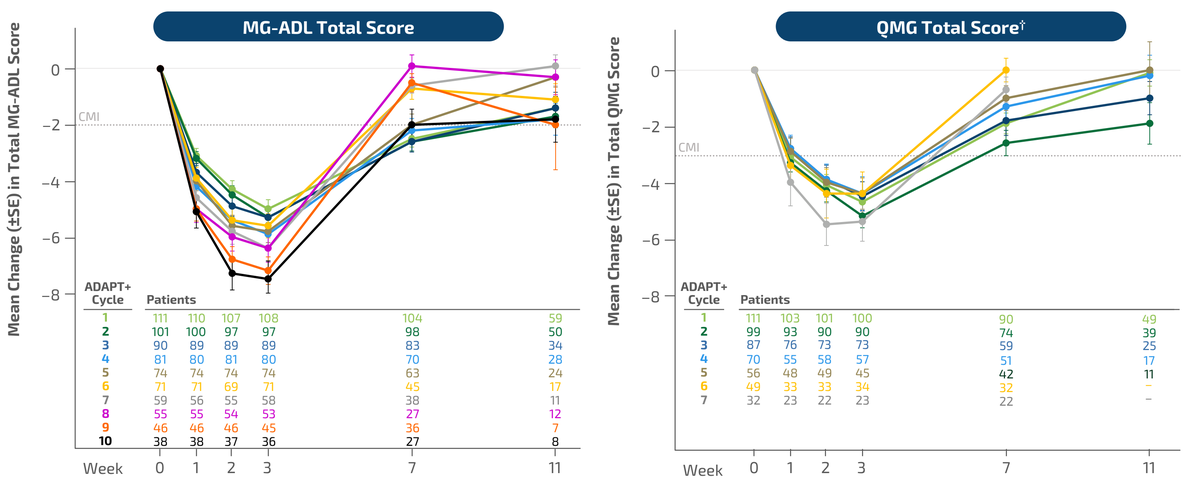


AChR-Ab+/–, acetylcholine receptor antibody positive or negative; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IV, intravenous; max., maximum; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America.
*50% of the score attributed to nonocular items.
†Acetylcholinesterase inhibitors, steroids, and/or nonsteroidal immunosuppressive therapy (for the duration of the trial).
‡Based on clinical evaluation. Patients needed to have an MG-ADL score ≥5 (>50% for nonocular items) and a reduction in MG-ADL total score of <2 points from study/cycle baseline to be eligible to receive a new cycle.

Results

- Consistent reduction in IgG levels were observed in ADAPT+ in both the overall and the acetylcholine receptor antibody–positive (AChR-Ab+) populations, with the greatest observed improvement at Week 3
- Efgartigimod demonstrated repeatable and sustained improvement in both Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scores over multiple cycles in ADAPT+ in the AChR-Ab+ population (**Figure 3**)
- The proportion of patients with increasing MG-ADL or QMG improvement over multiple cycles is shown in **Figure 4**

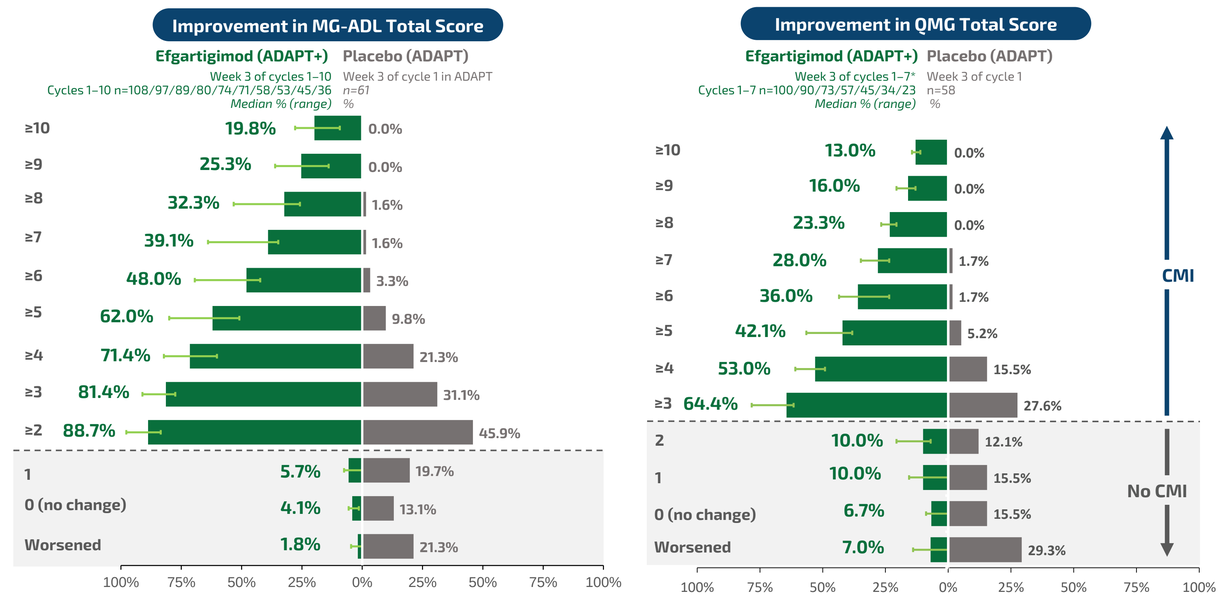
Figure 3. Mean Change From Cycle Baseline by Cycle* (Efgartigimod + Current Treatment) in MG-ADL Total Score and QMG Total Score in the AChR-Ab+ Population



AChR-Ab+, acetylcholine receptor antibody positive; CMI, clinically meaningful improvement; MG-ADL, Myasthenia Gravis Activities of Daily Living; SE, standard error; QMG, Quantitative Myasthenia Gravis.
*Mean (SE) total MG-ADL and QMG scores in the AChR-Ab+ population at baseline were 9.5 (0.29) and 15.3 (0.54), respectively. †QMG scores were required to be collected only during part A (year 1) of ADAPT+.

Results

Figure 4. Proportion of Patients With Increasing MG-ADL or QMG Improvement Over Multiple Cycles in the AChR-Ab+ Population



AChR-Ab+, acetylcholine receptor antibody positive; CMI, clinically meaningful improvement; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis.
*Only cycles with data up to Week 11 are included.

- The safety summary is shown in **Table 1**
- Most adverse events (AEs) in the ADAPT and ADAPT+ trials were mild to moderate in severity, including infusion-related reactions
- In ADAPT+, 15.2% (22/145) of patients had COVID-19 or COVID-19–related pneumonia; 2 AEs were grade ≥3
- Deaths in ADAPT+ are listed in **Table 2**

Table 1. Safety Summary

	ADAPT				ADAPT+	
	Placebo (n=83) (34.51 PY)		Efgartigimod (n=84) (34.86 PY)		Efgartigimod (n=145) (217.55 PY)	
	Events/PY	n (%)	Events/PY	n (%)	Events/PY	n (%)
Any AE	7.8	70 (84)	7.2	65 (77)	3.6	123 (85)
Any SAE	0.3	7 (8)	0.1	4 (5)	0.2	34 (23)
≥1 infusion-related reaction event	0.3	8 (10)	0.1	3 (4)	0.1	15 (10)
Any infection AE	1.2	31 (37)	1.6	39 (46)	0.8	80 (55)
Discontinued study treatment due to AEs	0.1	3 (4)	0.2	3 (4)	0.1	12 (8)
Any severe AE (grade ≥3)	0.4	8 (10)	0.3	9 (11)	0.3	38 (26)
Death	–	0 (0)	–	0 (0)	<0.1	5 (3)
Most frequent AEs						
Nasopharyngitis	0.5	15 (18)	0.3	10 (12)	0.1	20 (14)
Upper respiratory tract infection	0.2	4 (5)	0.3	9 (11)	<0.1	6 (4)
Urinary tract infection	0.1	4 (5)	0.3	8 (10)	0.1	13 (9)
Headache	1.1	23 (28)	1.2	24 (29)	0.5	36 (25)
Nausea	0.4	9 (11)	0.2	7 (8)	0.1	9 (6)
Diarrhea	0.4	9 (11)	0.2	6 (7)	0.1	14 (10)
COVID-19	–	–	–	–	0.1	22 (15)
Arthralgia	<0.1	1 (1)	0.1	2 (2)	0.1	12 (8)

AE, adverse event; PY, patient year(s); SAE, serious adverse event.

Table 2. Non–Treatment-Related Deaths (per Investigator)

Age, Years/Sex	Cause of Death	Infusions, n	Comorbidities and/or Medical History
72/F	Unknown; preexisting CV disease; autopsy confirmed coronary artery atherosclerosis and cardiomegaly	4 ADAPT 9 ADAPT+	Pulmonary embolism, chronic obstructive pulmonary disease, hypertension, hypokalemia, and colon bladder fistula
79/M	MG crisis and progression of underlying disease	8 ADAPT 4 ADAPT+	*Escherichia coli* pneumonia, aspiration pneumonitis, and acute respiratory failure
66/F	Malignant lung neoplasm (stage IV)	4 ADAPT 8 ADAPT+	Asthma, squamous cell carcinoma, histoplasmosis, diabetes mellitus, hypercholesterolemia, macular degeneration, hypertension, and bundle branch block
55/M	Acute MI; severe peripheral coronary artery atherosclerosis; stent implantation; myofibrosis; pulmonary hypertension and fibrous plaques of the pulmonary artery	8 ADAPT (PBO) 16 ADAPT+	Anemia, subarachnoid hemorrhage, and tibia fracture
62/M	Septic shock/COVID-19 pneumonia	8 ADAPT 16 ADAPT+	Chronic venous insufficiency, arterial hypertension, deep vein thrombosis, rheumatoid arthritis, and paroxysmal atrial fibrillation

CV, cardiovascular; F, female; M, male; MI, myocardial infarction; MG, myasthenia gravis, PBO, placebo.

Summary

The safety profile observed during long-term treatment with efgartigimod in ADAPT+ mirrored that seen during ADAPT, even though the study was conducted during the COVID-19 global pandemic

This analysis suggests that long-term treatment with efgartigimod is efficacious, providing consistent and repeatable clinically meaningful improvement in function and strength while remaining well tolerated

ADAPT+ is a planned, 3-year study and is ongoing

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