Poster #132

Efficacy, Safety, and Tolerability of Efgartigimod in AChR-Ab– Patients With Generalized Myasthenia Gravis: Interim Analysis of ADAPT/ADAPT+ Studies

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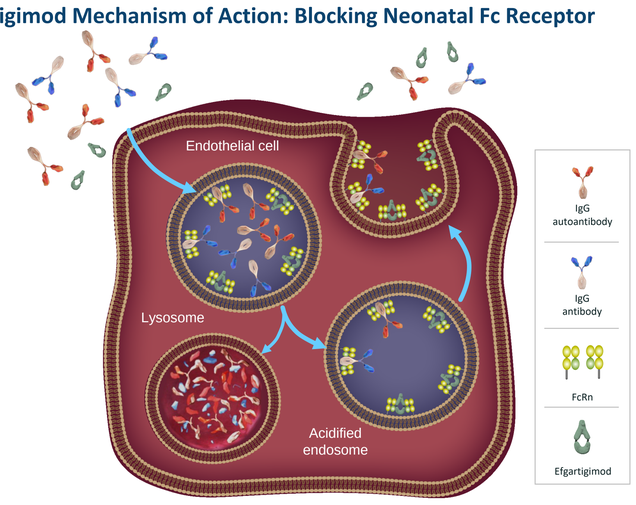
INTRODUCTION

Efgartigimod Mechanism of Action: Blocking Neonatal Fc Receptor



- FcRn recycles 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[2,3]
- Efgartigimod was designed to outcompete endogenous IgG, preventing recycling and promoting IgG lysosomal degradation without directly impacting its production[2-6]
  - Targeted reduction of all IgG subtypes
  - No impact on IgM or IgA
  - No reduction in albumin or increase in cholesterol levels

Clinical Challenges in the Management of AChR-Ab– gMG

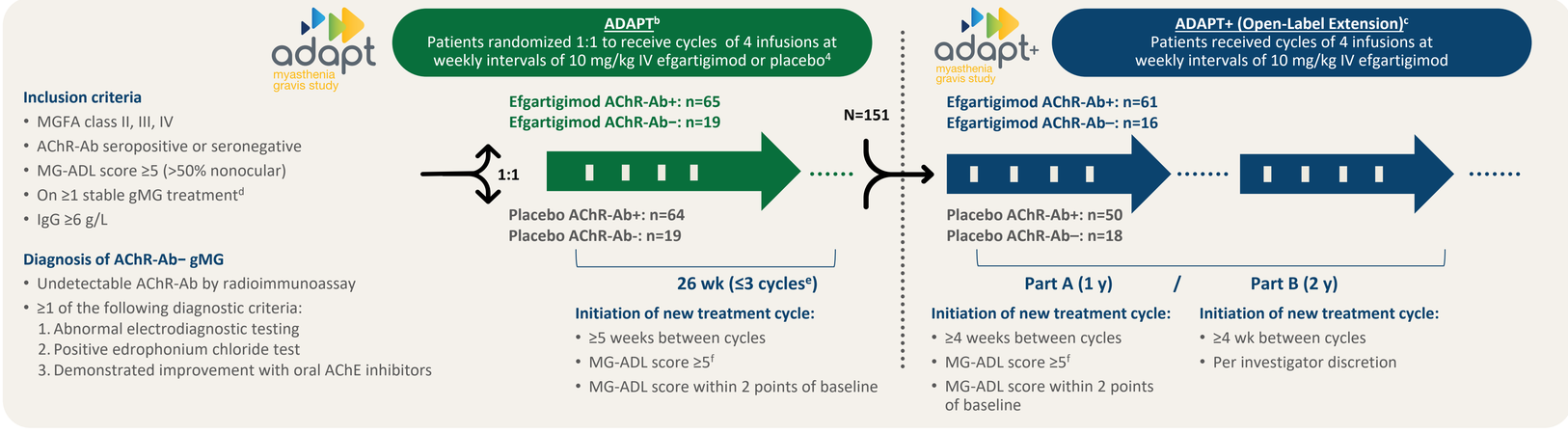
- Pathogenic IgG autoantibodies are detectable in most patients with gMG, typically targeting the AChR on skeletal muscle[7]
- 15%–20% of patients with gMG are AChR-Ab–, including ~4% with MuSK antibodies and ~2% with anti-LRP4 antibodies[8,9]
- Autoantibodies are detectable using highly sensitive cell-based assays in ~30% of patients without detectable autoantibodies by conventional assays[10]
- AChR-Ab– gMG affects a heterogenous and potentially difficult-to-diagnose patient population with high unmet clinical need who have historically been excluded from clinical trials[4,8,11,12]

SUMMARY

- ADAPT is the first gMG trial to include AChR-Ab– patients
- Clinically meaningful improvement in MG-ADL scores were observed in ADAPT+ patients across 10 treatment cycles
- AChR-Ab– and AChR-Ab+ patients treated with efgartigimod experienced similar response rates, although a higher response to placebo was observed in AChR-Ab– patients compared to AChR-Ab+[4]
- Long-term treatment with efgartigimod was well tolerated, with similar rates of AEs observed in ADAPT and ADAPT+ and no notable differences seen in AChR-Ab- patients
- While ADAPT was not powered to demonstrate statistical significance, patients who crossed over from placebo to efgartigimod during ADAPT+ demonstrated improvement in MG-ADL and QMG scores
- Additional studies assessing the efficacy of efgartigimod in AChR-Ab– patients are warranted

METHODS

ADAPT was a 26-week, global, multicenter, randomized, double-blind, placebo-controlled, phase 3 trial evaluating efgartigimod in patients with gMG. Participants who completed ADAPT were eligible to be rolled over to ADAPT+[4,a]

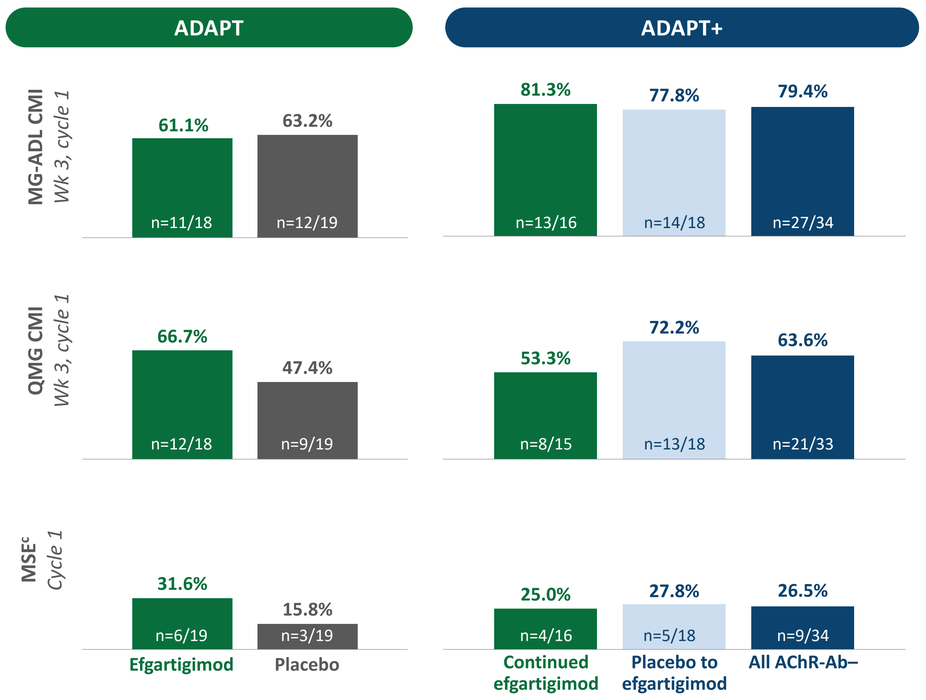


Note: Beige lines within arrows indicate day of efgartigimod infusion.
[a]Participants who required retreatment but were unable to complete a treatment cycle within the time frame of ADAPT were also eligible to be rolled over to ADAPT+. [b]The ADAPT study was started on August 22, 2018, and was completed on April 6, 2020. [c]The ADAPT+ study was started on March 1, 2019 and current data cutoff was January 31, 2022. [d]Acetylcholinesterase inhibitor, steroid +/or nonsteroidal immunosuppressive therapy. Patients could not change concomitant therapies in ADAPT or during dosing in Part A of ADAPT+. Physicians could change concomitant therapies between doses in Part A and at any time in Part B of ADAPT+. [e]≤3 cycles dosed at ≥8 weeks after initial cycle. [f]With >50% from nonocular items.

RESULTS

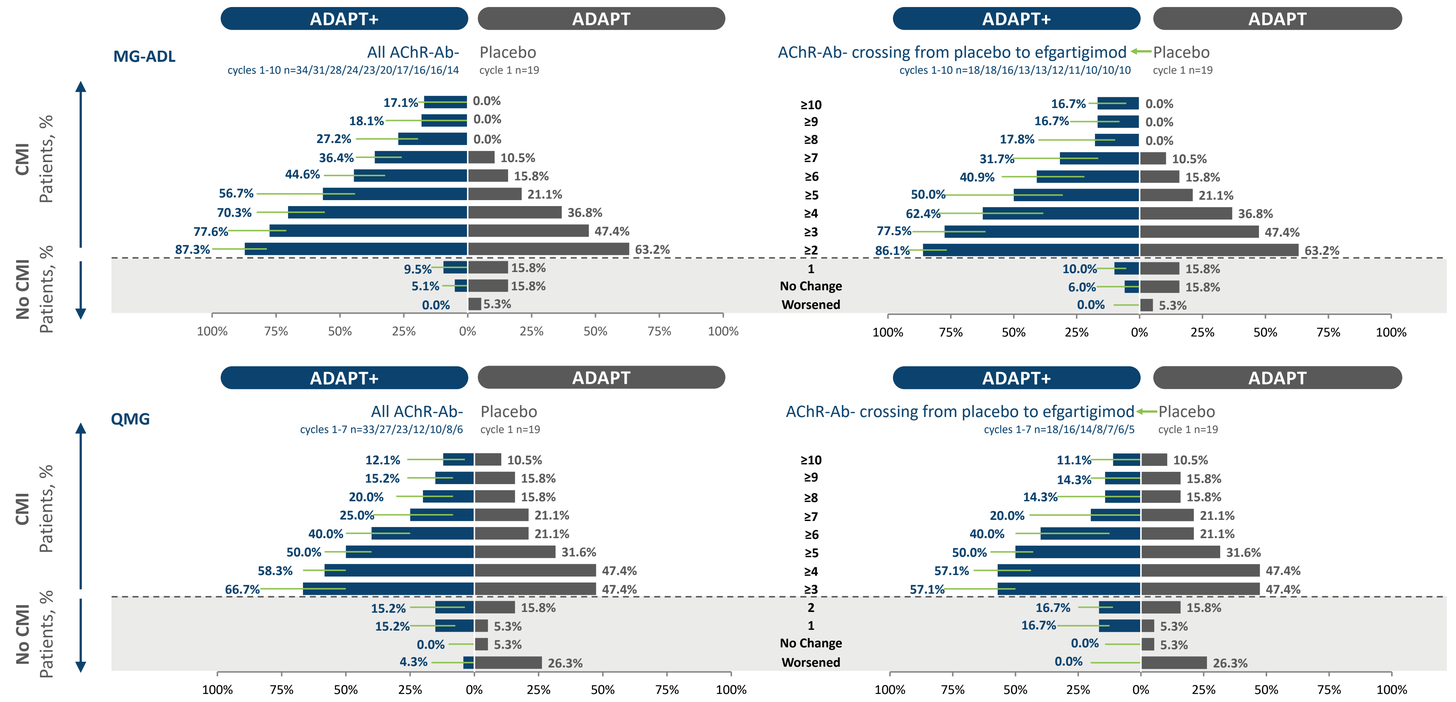
Efficacy of Efgartigimod in AChR-Ab– Patients

Figure 1. Proportion of AChR-Ab– Patients With CMI and MSE in ADAPT and ADAPT+[a,b]



[a]CMI defined as ≥2-point improvement in MG-ADL, and ≥3-point improvement in QMG. [b]MSE defined as an MG-ADL score of 0–1. [c]Study limitation: MSE was captured at any time during cycle 1. There were no study visits during weeks 4-6 in ADAPT+.

Figure 2. Proportion of AChR-Ab–Patients With Increasing Improvement in MG-ADL and QMG Scores of Cycles in ADAPT+ (WEEK 3[a,b])



[a]Cycles with data out to week 11 were included. [b]Study limitation: results don't preclude survivor bias.

Trial Participants

Table 1. Baseline Characteristics

Characteristic	AChR-Ab– Patients: Efgartigimod (n=19)	AChR-Ab– Patients: Placebo (n=19)
Age, mean (SD), y	50.2 (11.6)	44.8 (12.6)
Sex, female, n (%)	17 (89.5)	15 (78.9)
MuSK-Ab+, n (%)	3 (15.8)	3 (15.8)
Time since diagnosis, mean (SD), y	11.7 (11.5)	8.5 (5.2)
Mean (SD) MG-ADL score	9.7 (3.1)	9.8 (2.5)
Mean (SD) QMG score	16.6 (4.6)	16.5 (5.2)
MGFA class at screening, n (%)		
Class II	6 (31.6)	6 (31.5)
Class III	12 (63.2)	13 (68.4)
Class IV	1 (5.3)	0
Prior therapy with NSIST, n (%)	15 (78.9)	14 (73.7)
Baseline gMG therapies, n (%)		
Any NSIST[a]	11 (57.9)	14 (73.7)
Steroids	14 (73.7)	16 (84.2)
AChE Inhibitor	14 (73.7)	10 (52.6)

[a]NSIST: azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate, and/or tacrolimus.

Safety in Overall Trial Population

Table 2. AEs Summary

Treatment-Emergent AE	ADAPT: Placebo (N=83) [34.51 PY] IR[d]	ADAPT: Placebo (N=83) [34.51 PY] n (%)	ADAPT+: Efgartigimod (N=84) [34.86 PY] IR[d]	ADAPT+: Efgartigimod (N=84) [34.86 PY] n (%)	ADAPT+: Efgartigimod (N=145) [217.55 PY] IR[d]	ADAPT+: Efgartigimod (N=145) [217.55 PY] n (%)
AEs[a]	**7.8**	70 (84)	**7.2**	65 (77)	**3.6**	123 (85)
SAEs	**0.3**	7 (8)	**0.1**	4 (5)[b]	**0.2**	34 (23)[b]
≥1 Infusion-related reaction event	**0.3**	8 (10)	**0.1**	3 (4)	**0.1**	15 (10)
Infection AEs	**1.2**	31 (37)	**1.6**	39 (46)	**0.8**	80 (55)
Discontinued study treatment owing to AEs[c]	**0.1**	3 (4)	**0.2**	3 (4)	**0.1**	12 (8)
Severe AEs (grade ≥3)	**0.4**	8 (10)	**0.3**	9 (11)	**0.3**	38 (26)
Death[c]	-	0 (0)	-	0 (0)	**<0.1**	5 (3)
Most frequent AEs (>10%)						
Nasopharyngitis	**0.5**	15 (18)	**0.3**	10 (12)	**0.1**	20 (14)
URTI	**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[e]	-	0 (0)	-	0 (0)	**0.1**	22 (15)

[a]AEs were predominantly mild or moderate. [b]Only 1 SAE was considered treatment related per investigator. [c]None of the deaths in ADAPT+ were deemed related to efgartigimod administration per the principal investigator. [d]IR was calculated as number of events per total PYs of follow-up. [e]Includes all preferred terms of COVID-19, COVID-19 pneumonia, Coronavirus infection, SARS-COV-2 test positive.

ABBREVIATIONS: AChE, acetylcholinesterase; AChR-Ab, acetylcholine receptor antibody; AE, adverse event; CMI, clinically meaningful improvement; COVID-19, coronavirus 2019; FcRn, Neonatal Fc Receptor; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IR, incidence rate; IV, intravenous; MGFA, Myasthenia Gravis Foundation of America; MG-ADL, Myasthenia Gravis–Activities of Daily Living; MSE, minimal symptom expression; MuSK-Ab, muscle-specific kinase antibody; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; NSIST, nonsteroidal immunosuppressive therapy; POCRI, Patient-Centered Outcomes Research Institute; PY, patient year; QMG, Quantitative Myasthenia Gravis; SAE, serious adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

REFERENCES: **1.** Sesarman A, et al. *Cell Mol Life Sci.* 2010;67(15):2533-2550. **2.** Ulrichts P, et al. *J Clin Invest.* 2018;128(10):4372-4386. **3.** Vaccaro C, et al. *Nat Biotech.* 2005;23(10):1283-1288. **4.** Howard JF Jr, et al. *Lancet Neurol.* 2021;20(7):526-536. **5.** Nixon AE, et al. *Front Immunol.* 2015;6:176. **6.** Ward ES, et al. *Front Immunol.* 2022;13:892534. **7.** Behin A, Le Panse R. *J Neuromuscul Dis.* 2018;5(3):265-277. **8.** Gilhus NE, Verschuuren JJ. *Lancet Neurology.* 2015;14(10):1023-1036. **9.** Scuderi F, et al. *Lab Invest.* 2002;82(9):1139-1146. **10.** Damato V, et al. *J Neurol Neurosurg Psychiatry.* 2022;93(9):995-1000. **11.** Vu T, et al. *NEJM Evid.* 2022;1(5):1-12. **12.** Howard JF Jr, et al. *Lancet Neurol.* 2017;16(12):976-986.

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