Phase 3 Trial Investigating Impact of Intravenous Efgartigimod in Anti-Acetylcholine Receptor Antibody–Negative Generalized Myasthenia Gravis

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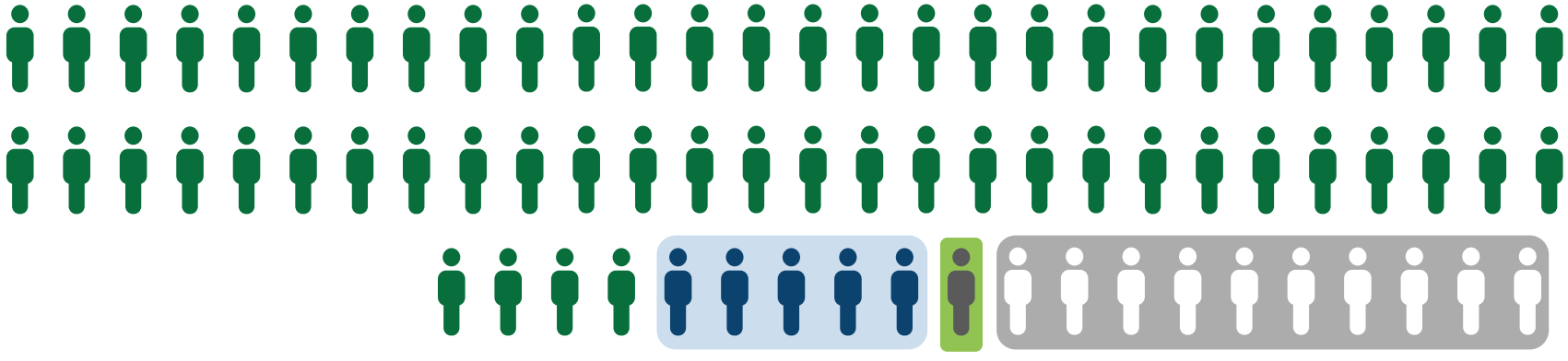
Prevalence of IgG Autoantibody Subtypes

AChR[1,2]
IgG1 and IgG3
≈80–85% of patients with MG



MuSK[1,3]
IgG4
≈5–10% of patients with MG

LRP4[1,3]
IgG1 and IgG2
≈1%–5% of patients with MG

Triple Seronegative[3-5]
No detectable autoantibodies against: AChR, MuSK, LRP4
≈10% of patients with MG

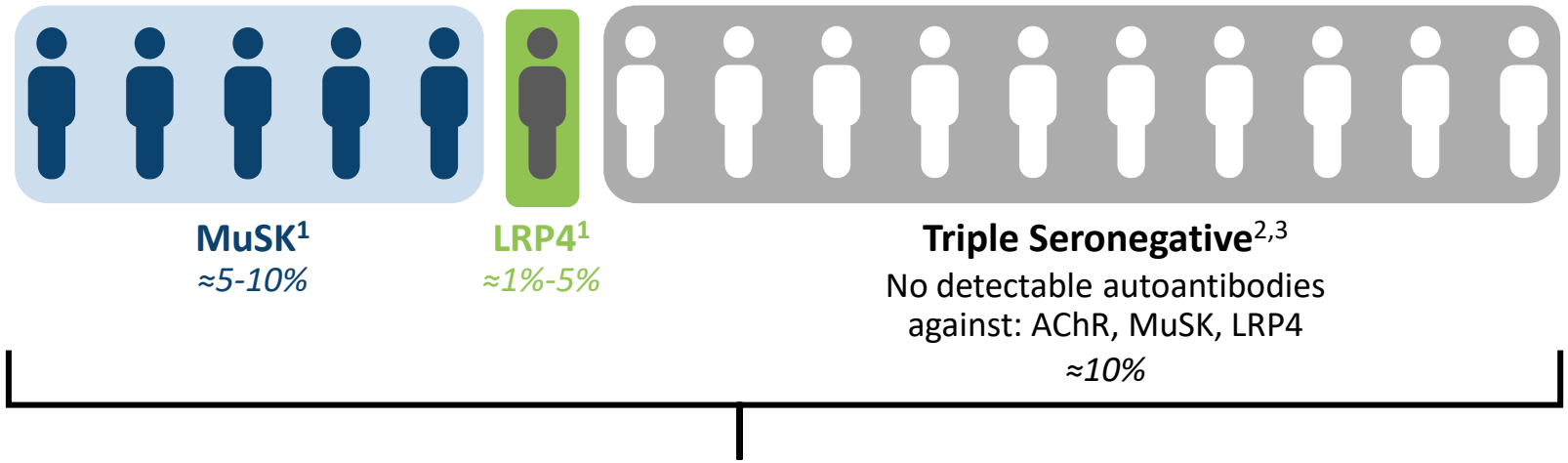
Possible reasons for testing negative

- Autoantibody levels below detection limits
- Autoantibodies against epitopes not detected by assay
- Autoantibodies against unknown targets

AChR, acetylcholine receptor; IgG, immunoglobulin G; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle-specific tyrosine kinase.

1. Behin A, Le Panse R. *J Neuromuscul Dis*. 2018;5(3):265-277. **2.** Gilhus NE, et al. *Nat Rev Dis Primers.* 2019;5(1):30. **3.** Gilhus NE, et al. *Nat Rev Neurol*. 2016;12(5):259-268. **4.** Gilhus NE. *N Engl J Med*. 2016;375(26):2570-2581. **5.** Leite MI, et al. *Brain*. 2008;131(7):1940-1952.

Clinical Challenges in the Management of AChR-Ab Seronegative gMG



- AChR-Ab seronegative gMG affects a heterogenous and potentially difficult to diagnose and treat patient population with high unmet clinical need who have historically been excluded from clinical trials[4-8]
- The Phase 3 ADAPT SERON clinical trial (NCT06298552) is currently ongoing to evaluate the safety and efficacy of efgartigimod IV in patients with AChR-Ab seronegative gMG

AChR-Ab; acetylcholine receptor antibody; IV, intravenous; gMG, generalized myasthenia gravis; LRP4, low-density lipoprotein receptor-related protein 4; MuSK, muscle-specific tyrosine kinase.

1. Behin A, et al. *J Neuromuscul Dis*. 2018;5(3):265-277**. 2.** Gilhus NE, et al. *Nat Rev Neurol*. 2016;12(5):259-268. **3.** Gilhus NE. *N Engl J Med*. 2016;375(26):2570-2581. **4.** Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526-536. **5.** Gilhus NE, Verschuuren JJ. *Lancet Neurol.* 2015;14(10):1023-1036. **6.** Vu T, et al. *NEJM Evid.* 2022;1(5):1-12. **7.** Howard JF Jr, et al. *Lancet Neurol.* 2017;16(12):976-986. **8.** Evoli A, et al. *Neuromuscul Disord.* 2024;44:104468.

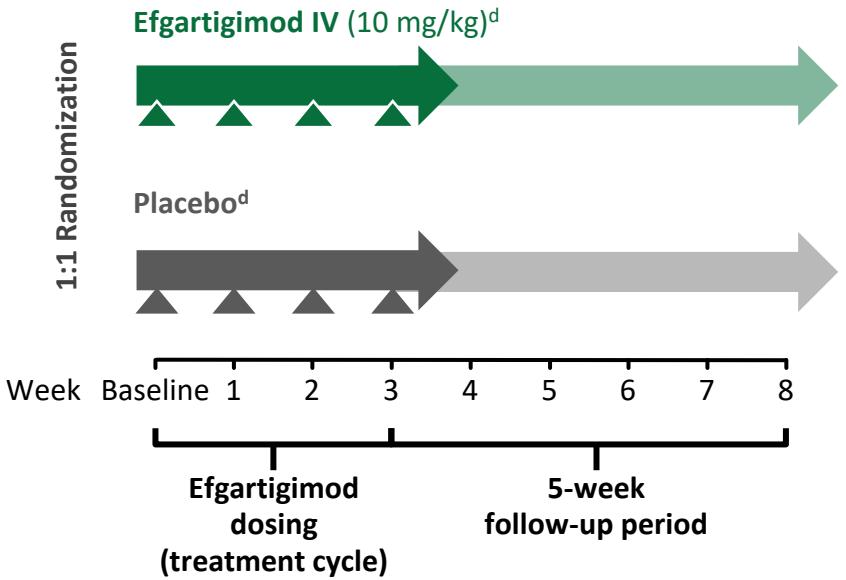
ADAPT SERON Study Design

Total enrollment:
119 AChR-Ab Seronegative Participants With Confirmed Acquired gMG Diagnosis Reviewed by MG Diagnostic Adjudication Committee

Screening
≤5 weeks

- Adults with AChR-Ab seronegative gMG
- MGFA Class II, III, or IV
- MG-ADL score of ≥5 at screening[b]
- On a stable dose of current treatment for gMG[c]
- Once eligibility was confirmed, participants were stratified by MuSK-Ab status

Part A
8 weeks



Part B, OLE
(Ongoing, ≤2 years)[a]

Cycles 1 and 2 of Part B

Efgartigimod IV (10 mg/kg)[d]

Efgartigimod treatment
- 4 once-weekly infusions

Time between cycles
- 4 weeks

Cycle 3 of Part B and onward

Efgartigimod IV (10 mg/kg)[d]

Efgartigimod treatment
- 4 once-weekly infusions

Time between cycles
- Individualized based on clinical response[e]

AChR-Ab; acetylcholine receptor antibody; AChEI, acetylcholinesterase inhibitor; IMP, investigational medical product; IV, intravenous; gMG, generalized myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MuSK-Ab, anti–muscle-specific kinase antibody; NSIST, nonsteroidal immunosuppressive therapy; OLE, open label extension. [a]Retention rate after Part A was 96% and 92% of participants are ongoing in part B as of most recent data cut. [b]>50% of the score attributed to nonocular items. [c]AChEI, steroids, and/or NSIST. [d]Triangles indicate efgartigimod or placebo administration. [e]Time between cycles will be no shorter than 7 days since previous efgartigimod IV infusion.

Part A

Baseline Demographics and Clinical Characteristics[a]

	Efgartigimod IV (n=58)	Placebo (n=61)
Age, years, mean (SD)	50.6 (13.4)	51.7 (13.0)
Age category, n (%)		
18-<65 years	49 (84.5)	50 (82.0)
≥65 years	9 (15.5)	11 (18.0)
Female sex, n (%)	44 (75.9)	46 (75.4)
Race, n (%)		
Asian	8 (13.8)	8 (13.3)
Black or African American	1 (1.7)	2 (3.3)
White	48 (82.8)	46 (76.7)
Other	1 (1.7)	4 (6.7)
Time since diagnosis, years, mean (SD)	5.7 (6.2)	6.5 (7.8)
Prior thymectomy, n (%)	14 (24.1)	4 (6.6)
MGFA classification at screening, n (%)		
Class II	17 (29.3)	23 (37.7)
Class III	38 (65.5)	35 (57.4)
Class IV	3 (5.2)	3 (4.9)

	Efgartigimod IV (n=58)	Placebo (n=61)
MG-ADL total score at baseline, mean (SD)	9.9 (3.2)	9.4 (3.3)
QMG total score at baseline, mean (SD)	14.1 (5.9)	14.8 (5.1)
Antibody serostatus, n (%)		
MuSK-Ab+	20 (34.5)	20 (32.8)
LRP4-Ab+	6 (10.3)	0
Triple seronegative	32 (55.2)	41 (67.2)
Baseline MG therapy, n (%)		
Any steroid	39 (67.2)	37 (60.7)
Any NSIST	31 (53.4)	22 (36.1)
Any AChEi	46 (79.3)	47 (77.0)
Only AChEi	11 (19.0)	13 (21.3)

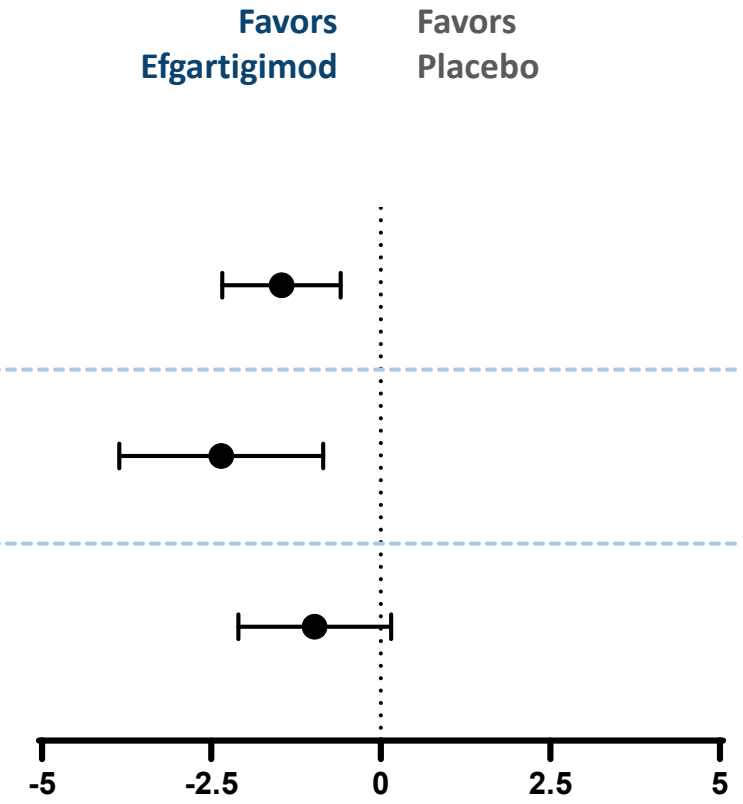
IV, intravenous; gMG, generalized myasthenia gravis; LRP4-Ab, anti–low-density lipoprotein receptor-related protein 4 antibody; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MuSK-Ab, anti–muscle-specific kinase antibody.

[a]The denominator for the percentage calculation was the number of participants per arm, excluding missing values. Baseline was defined as the last available nonmissing value before the first IMP administration. [b]Participants were excluded if they received a thymectomy <3 months before screening or if thymectomy was planned during the study.

Part A

Efgartigimod Demonstrated a Significant Improvement in MG-ADL Total Score at Week 4 Compared With Placebo (Primary Endpoint)[a]

Population	Efgartigimod IV	Placebo	Efgartigimod IV vs placebo	
	LS mean (90% CI)	LS mean (90% CI)	LS mean (90% CI)	*P* value
Overall (N=118)	-3.35 (-3.98 to -2.72)	-1.90 (-2.51 to -1.28)	-1.46 (-2.33 to -0.58)	0.007
MuSK-Ab seropositive (n=40)	-4.24 (-5.31 to -3.17)	-1.89 (-2.96 to -0.82)	-2.35 (-3.86 to -0.85)	0.01
Triple seronegative (n=73)	-2.80 (-3.65 to -1.94)	-1.82 (-2.56 to -1.08)	-0.98 (-2.10 to 0.15)	0.15



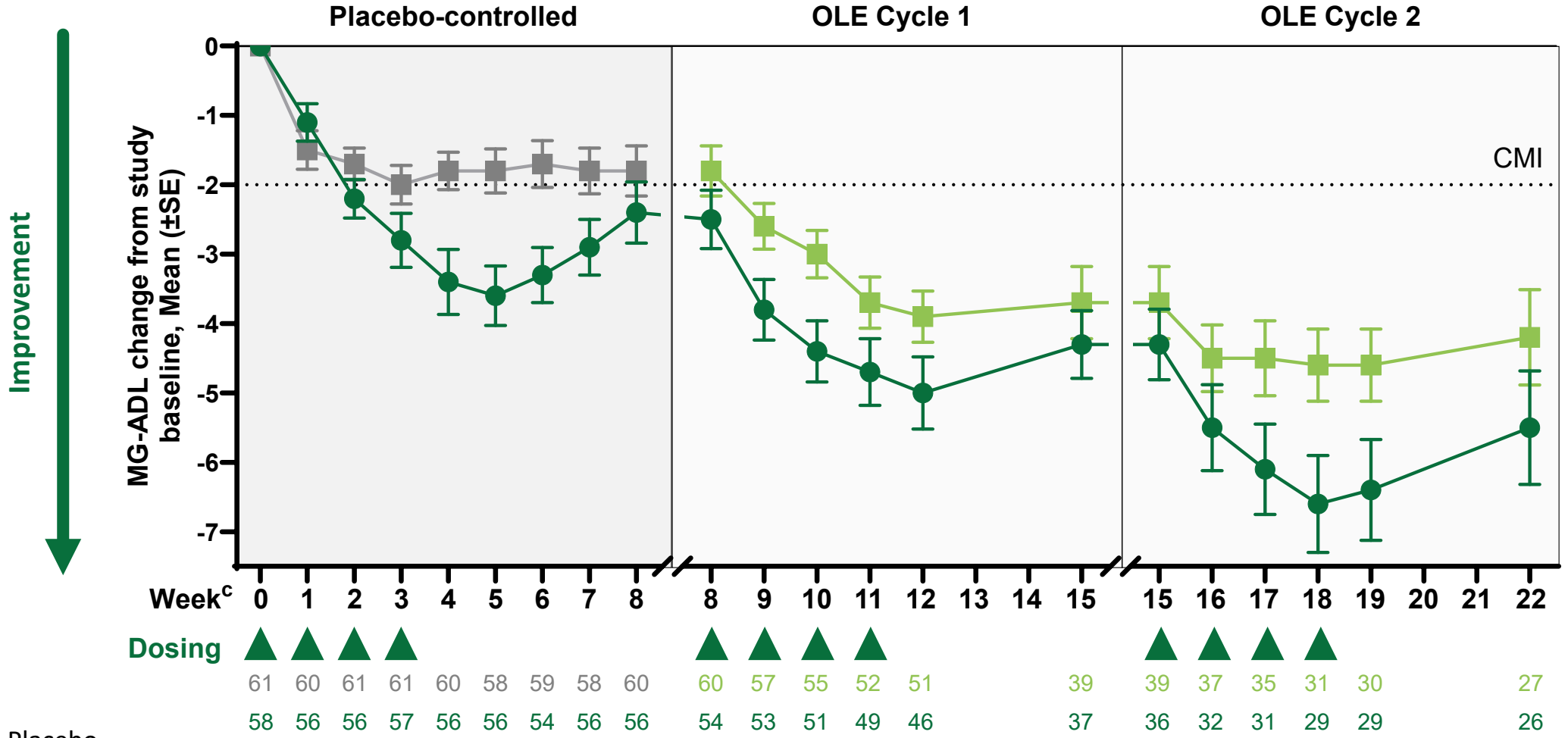
- Mean MG-ADL total score change from baseline to Week 4 in the LRP4-Ab seropositive population (n=5) was -2.8 (1.8)[b]

LRP4-Ab, low-density lipoprotein receptor-related protein 4 antibody; LS, least squares; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living; MMRM, mixed model for repeated measures; MuSK-Ab, anti–muscle-specific kinase antibody.

[a]An MMRM was used with treatment, analysis visit, treatment by analysis visit interaction, and MuSK-Ab serostatus as fixed effects, with baseline MG-ADL total score value as covariate. An unstructured covariance matrix for the error terms was assumed for modeling within-participant correlation. The 2-sided CI and 2-sided *P* value are presented for overall population and 2-sided nominal *P* value for subgroups (MuSK-Ab seropositive, triple seronegative). Baseline was defined as the last available nonmissing value before the first IMP administration. [b]Due to the small sample size within the LRP4-Ab subgroup, it was not possible to generate reliable estimates from the model.

Parts A/B

Efgartigimod Demonstrated Further Improvements in MG-ADL Total Score Across Subsequent Cycles in the Overall AChR-Ab Seronegative Population[a,b]

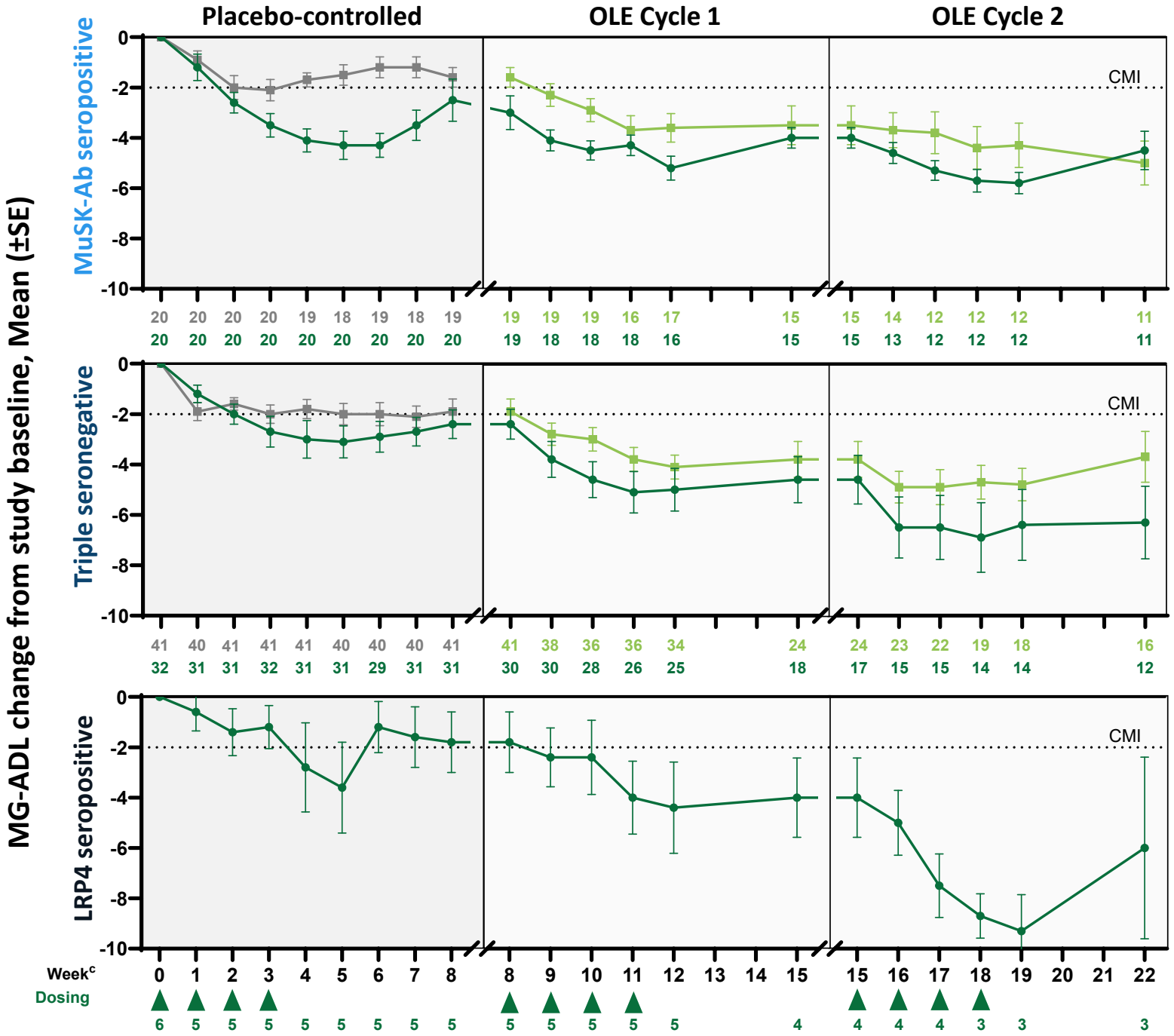


CMI, clinically meaningful improvement; MG-ADL, Myasthenia Gravis Activities of Daily Living.
[a]Study baseline was defined as the last available nonmissing value before the first IMP administration. [b]Participant numbers vary over time due to discontinuations, missed assessments, or participants not reaching the scheduled timepoint. [c]Weeks are presented as time from the study's start. Weeks 8 and 15 are repeated to accurately represent the participants included in the analysis at the beginning and end of each cycle.

Parts A/B

Efgartigimod Demonstrated Further Improvements in MG-ADL Total Score Across Subsequent Cycles in MuSK-Ab+, LRP4-Ab+, and Triple Seronegative gMG[a,b]

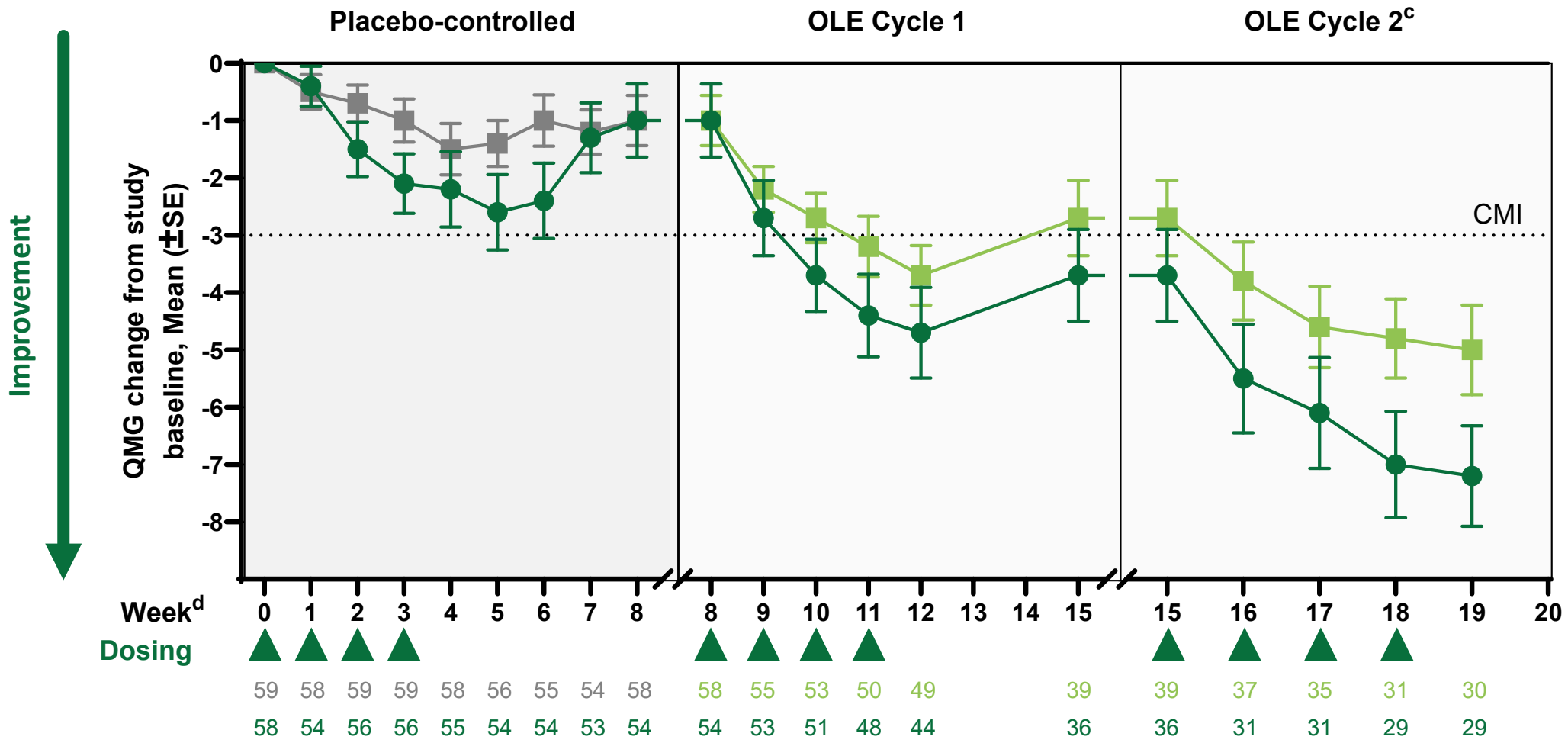
- Placebo
- Efgartigimod (EFG-EFG)
- Efgartigimod (PBO-EFG)



CMI, clinically meaningful improvement; gMG, generalized myasthenia gravis; LRP4-Ab, low-density lipoprotein receptor-related protein 4 antibody; MG-ADL, Myasthenia Gravis Activities of Daily Living; MuSK-Ab, anti–muscle-specific kinase antibody. [a]Study baseline was defined as the last available nonmissing value before the first IMP administration. [b]Participant numbers vary over time due to discontinuations, missed assessments, or participants not reaching the scheduled timepoint. [c]Weeks are presented as time from the study's start. Weeks 8 and 15 are repeated to accurately represent the participants included in the analysis at the beginning and end of each cycle.

Parts A/B

Efgartigimod Demonstrated Further Improvements in QMG Total Score Across Subsequent Cycles in the Overall AChR-Ab Seronegative Population[a,b]

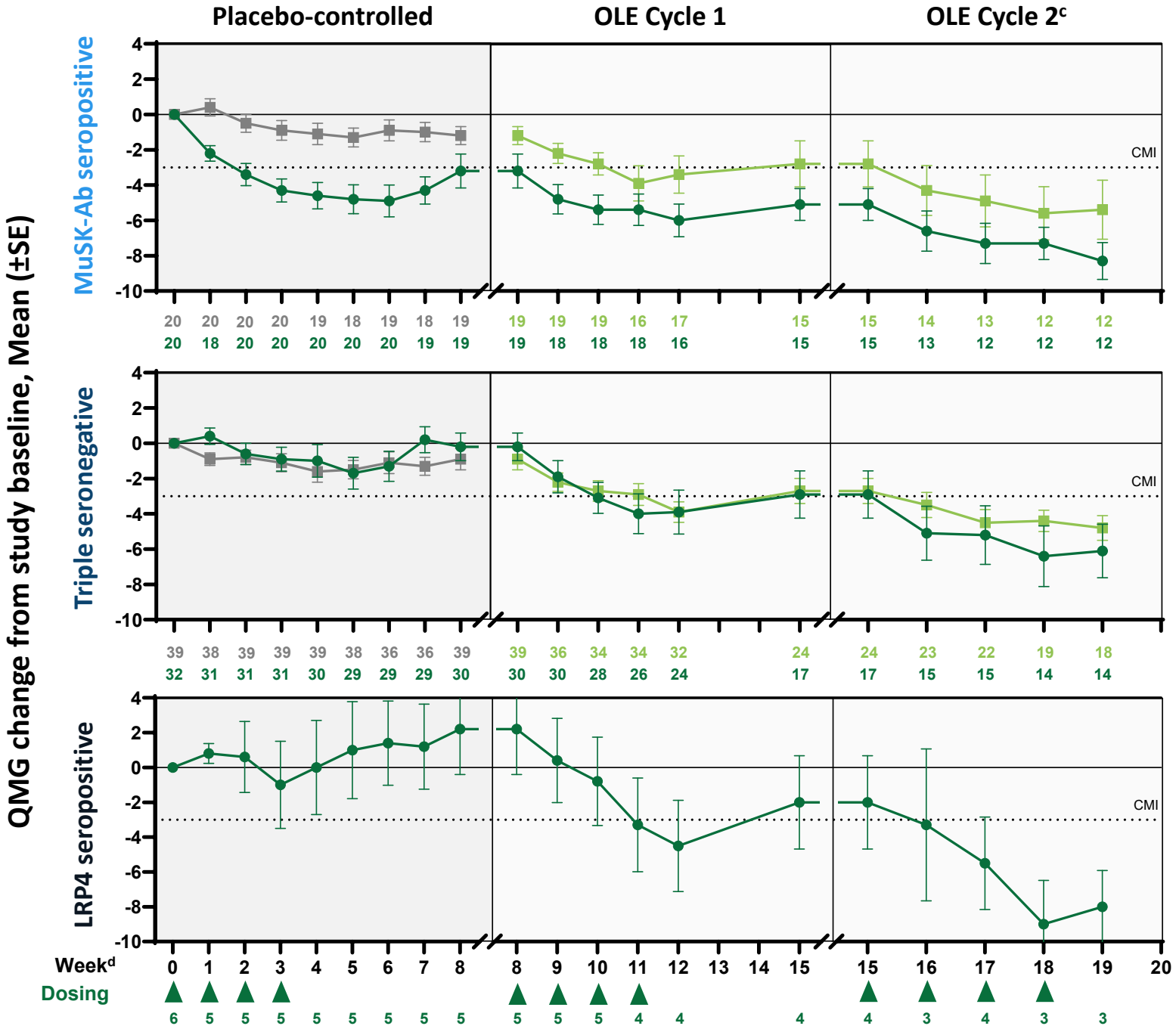


CMI, clinically meaningful improvement; QMG, Quantitative Myasthenia Gravis.
[a]Study baseline was defined as the last available nonmissing value before the first IMP administration. [b]Participant numbers vary over time due to discontinuations, missed assessments, or participants not reaching the scheduled timepoint. [c]Per the study protocol, QMG was only measured through week 4 of the second cycle of Part B. [d]Weeks are presented as time from the study's start. Weeks 8 and 15 are repeated to accurately represent the participants included in the analysis at the beginning and end of each cycle.

Parts A/B

Efgartigimod Demonstrated Improvements in QMG Total Score Across Subsequent Cycles in MuSK-Ab+, LRP4-Ab+, and Triple Seronegative gMG[a,b]

- Placebo
- Efgartigimod (EFG-EFG)
- Efgartigimod (PBO-EFG)



gMG, generalized myasthenia gravis; LRP4-Ab, low-density lipoprotein receptor-related protein 4 antibody; MG-ADL, Myasthenia Gravis Activities of Daily Living; MuSK-Ab, anti–muscle-specific kinase antibody; QMG, Quantitative Myasthenia Gravis.

[a]Study baseline was defined as the last available nonmissing value before the first IMP administration. [b]Participant numbers vary over time due to discontinuations, missed assessments, or participants not reaching the scheduled timepoint. [c]Per the study protocol, QMG was only measured through week 4 of the second cycle of Part B. [d]Weeks are presented as time from the study's start. Weeks 8 and 15 are repeated to accurately represent the participants included in the analysis at the beginning and end of each cycle.

Parts A/B

Efgartigimod Was Well Tolerated With No New Safety Signals Identified

	Part A				Parts A/B	
	Efgartigimod IV (N=58; PYFU=9.0)		Placebo (N=61; PYFU=9.5)		Total EFG IV (N=118, PYFU=39.2)	
	n (%)	ER[a]	n (%)	ER[a]	n (%)	ER[a]
≥1 TEAE	36 (62.1)	10.3	30 (49.2)	10.9	78 (66.1)	7.2
≥1 Serious TEAE	3 (5.2)	0.7	1 (1.6)	0.1	10 (8.5)	0.5
≥1 Fatal TEAE[b]	1 (1.7)	0.2	1 (1.6)	0.1	2 (1.7)	0.1
≥1 Grade ≥3 TEAE	3 (5.2)	0.7	1 (1.6)	0.5	13 (11.0)	0.6
≥1 Infection event	19 (32.8)	2.5	12 (19.7)	1.6	34 (28.8)	1.3
≥1 IRR event[c]	1 (1.7)	0.1	3 (4.9)	0.3	8 (6.8)	0.3
Discontinued due to TEAEs	0	0	0	0	4 (3.4)	0.2
Most frequent TEAEs[d]						
Upper respiratory tract infection	5 (8.6)	0.6	3 (4.9)	0.3	9 (7.6)	0.3
Nausea	4 (6.9)	0.8	3 (4.9)	0.3	9 (7.6)	0.3
Headache	3 (5.2)	0.6	7 (11.5)	1.3	13 (11.0)	0.4
Urinary tract infection	3 (5.2)	0.3	3 (4.9)	0.4	7 (5.9)	0.2
Fatigue	2 (3.4)	0.6	5 (8.2)	0.7	5 (4.2)	0.2

AE, adverse event; IRR, infusion-related reaction; IV, intravenous; MG, myasthenia gravis; PYFU, participant years of follow-up; TEAE, treatment-emergent adverse event.
[a]ER was calculated as the number of events/PYFU. [b]Causes of death included large intestine hemorrhage (Part A, efgartigimod IV group), MG crisis (Part A, placebo group), and sudden unexplained death (Part B, efgartigimod IV group). [c]No anaphylactic reactions were observed. [d]≥5% of participants in either arm.

Parts A/B

Efgartigimod Was Well Tolerated With No New Safety Signals Identified (cont'd)

- The overall safety data was consistent with other studies with efgartigimod
- Most TEAEs were mild to moderate in severity
  - Serious TEAEs occurred in 8.5% of participants overall
- Three participants died during the study[a]
  - Two in Part A – 1 in the efgartigimod group and 1 in the placebo group, neither deemed related to treatment
  - One in Part B potentially related to efgartigimod by the investigator
- Frequency of infection events was not increased with subsequent treatment
- There were no TEAEs that led to treatment discontinuation in either group in Part A and discontinuation owing to TEAEs remained low in Part B
- No decreases in albumin were observed with efgartigimod treatment

AChR-Ab; acetylcholine receptor antibody; gMG generalized myasthenia gravis; MG, myasthenia gravis; TEAE, treatment-emergent adverse event.
[a]The fatal events in Part A were MG crisis (placebo) and large intestine hemorrhage (efgartigimod), neither related to treatment. The fatal TEAE in Part B occurred unexpectedly. No autopsy was performed, but the fatality was considered by the investigator to be possibly related to efgartigimod treatment.

KEY TAKEAWAYS

The primary endpoint of ADAPT SERON was met, with a statistically significant improvement in MG-ADL total score at week 4 in AChR-Ab seronegative participants treated with efgartigimod IV versus placebo. Treatment with efgartigimod IV also resulted in a clinically meaningful reduction from baseline in MG-ADL total score at week 4

Improvements in MG-ADL and QMG across subsequent cycles were observed in the overall population and in the MuSK-Ab+, LRP4-Ab+, and triple seronegative subgroups

Results from ADAPT SERON demonstrate that **pathogenic IgGs may be an underlying driver** of gMG across patient subtypes, regardless of autoantibody status[1-3]

Efgartigimod was well tolerated with no new safety signals observed

AChR-Ab; acetylcholine receptor antibody; IV, intravenous; gMG, generalized myasthenia gravis; LRP4, low-density lipoprotein receptor-related protein 4; MG-ADL, Myasthenia Gravis Activities of Daily Living; MuSK-Ab, anti–muscle-specific kinase antibody.

1. Behin A, Le Panse R. *J Neuromuscul Dis*. 2018;5(3):265-277. **2.** Hoch W, et al. *Nat Med.* 2001;7(3):365-368. **3.** Shen C, et al. *J Clin Invest.* 2013;123(12):5190-5202.