UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Azienda Ospedaliera Universitaria Federico II
Integrata con il Servizio Sanitario Regionale

Nuovi Approcci Terapeutici nelle Malattie Neurologiche: Miastenia Gravis

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Disclosures

- Public Speaking honoraria from: Biogen, Mylan, Novartis, Roche, Sanofi, Teva
- Served on Advisory Boards for: Almirall, Argenx, Avexis, Forward Pharma, Merk, Novartis, Pomona, Roche, Sanofi
- Principal Investigator for: Alexion (ECU-NMO-301/302, ECU-MG-301/302), Argenx (Adapt, Adapt+), Novartis (Asclepios)

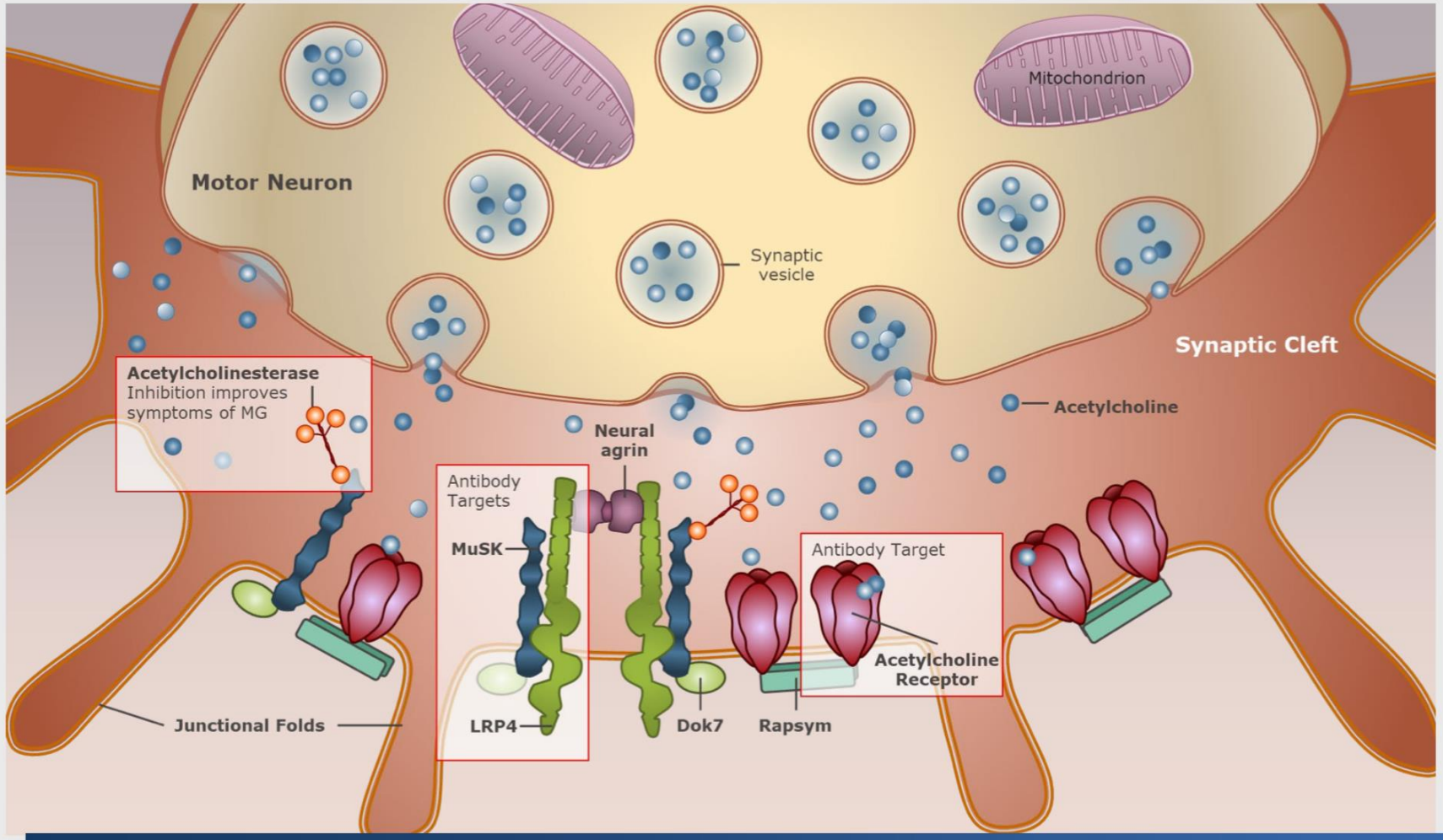
Myasthenia Gravis (MG) is an autoimmune disease of the NMJ[1]

- MG is a severe neuromuscular autoimmune disorder[1]
- Prevalence of MG ranges from 15 to 179 cases per million[2]
  - 41,000 to 84,000 patients in the United States[3,4]
- Corticosteroids and other immunomodulatory drugs are used to manage MG[1]
- However, despite adequate dosing of multiple immunosuppressant therapies, some patients with MG are refractory to treatment [1]
- Patients with refractory gMG have marked limb weakness as well as ocular, respiratory, and bulbar impairment[5]
- 10 to 15% of patients with MG have refractory gMG[6,7]

gMG, generalized myasthenia gravis; NMJ, neuromuscular junction.

1. Howard JF, et al. *Muscle Nerve.* 2013;48:76-84. **2.** Carr AS, et al. BMS Neurol. 2010;10:46. doi: 10.1186/1471-2377-10-46. **3.** Breiner A, et al. *Neuromuscul Disord.* 2016;26(1):41-46. **4.** Lee HS, et al. *Yonsei Med J.* 2016;57(2):419-425. **5.** Howard JF, et al. Poster presented at: American Academy of Neurology; Boston, MA; April 22-28, 2017. Poster 012. **6.** Silvestri NJ, Wolfe GI. *Clin Neuromuscul Dis.* 2014;15(4):167-178. **7.** Suh J, et al. *Yale J Biol Med.* 2013;86:255-260.

IgG autoantibodies are Key Mediators of MG Pathophysiology



Neuromuscular junction proteins targeted by autoantibodies:

- Acetylcholine receptor (IgG1, IgG3)
- Muscle-specific kinase (MuSK, IgG4)
- Lipoprotein receptor-related peptide 4 (LRP4, IgG1)
- Other targets may include agrin, collagen Q, cortactin

IgG autoantibodies are directly pathogenic in MG by targeting receptors and proteins of the NMJ[1,2]

Dok7: docking protein 7; IgG: immunoglobulin G; LRP4: lipoprotein receptor-related peptide 4; MG: myasthenia gravis; MuSK: muscle-specific kinase; NMJ: neuromuscular junction.

Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S, *et al*. Myasthenia gravis - autoantibody characteristics and their implications for therapy. *Nat Rev Neurol*. 2016 May;12(5):259-68.

IgG Autoantibodies are Directly Pathogenic in MG

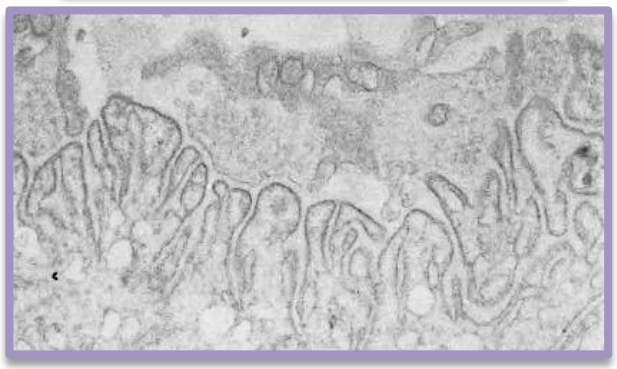
IgG autoantibodies cause:

- Functional blockade of AChRs
- Accelerated degradation of AChR
- Complement-mediated damage

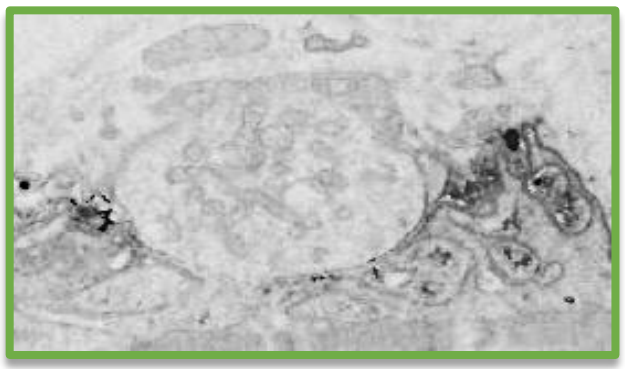
→ **Reduced functioning AChR Receptors**

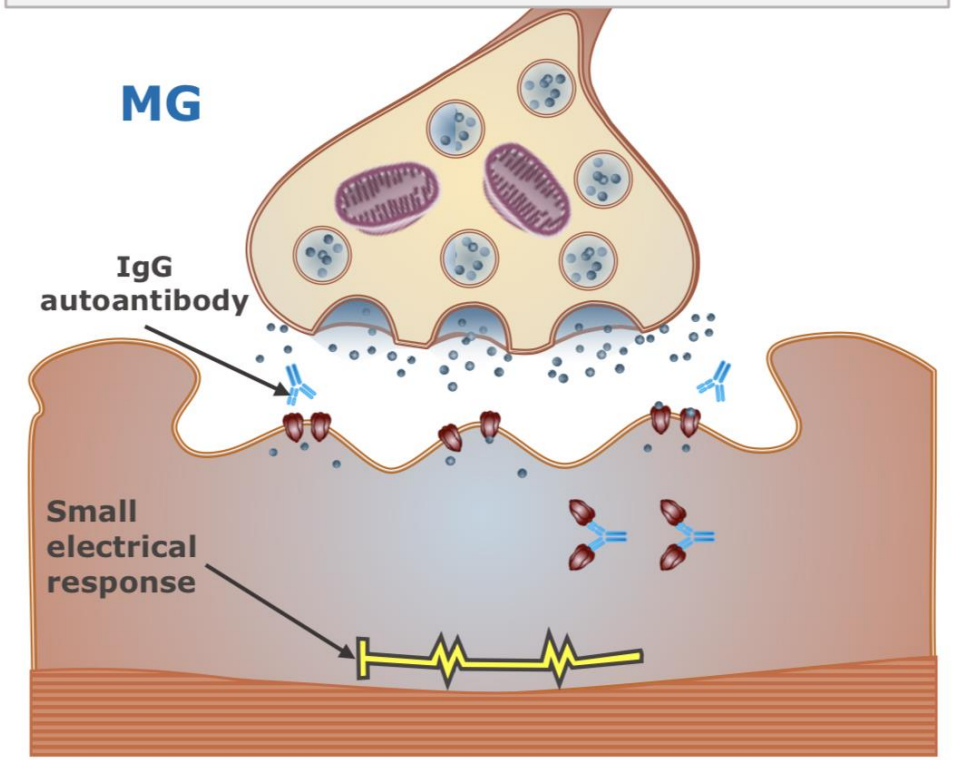
→ **Loss of structural integrity of NMJ**

Electron micrograph of NMJ with postsynaptic folds



Electron micrograph of C9 localization at the NMJ with altered morphology





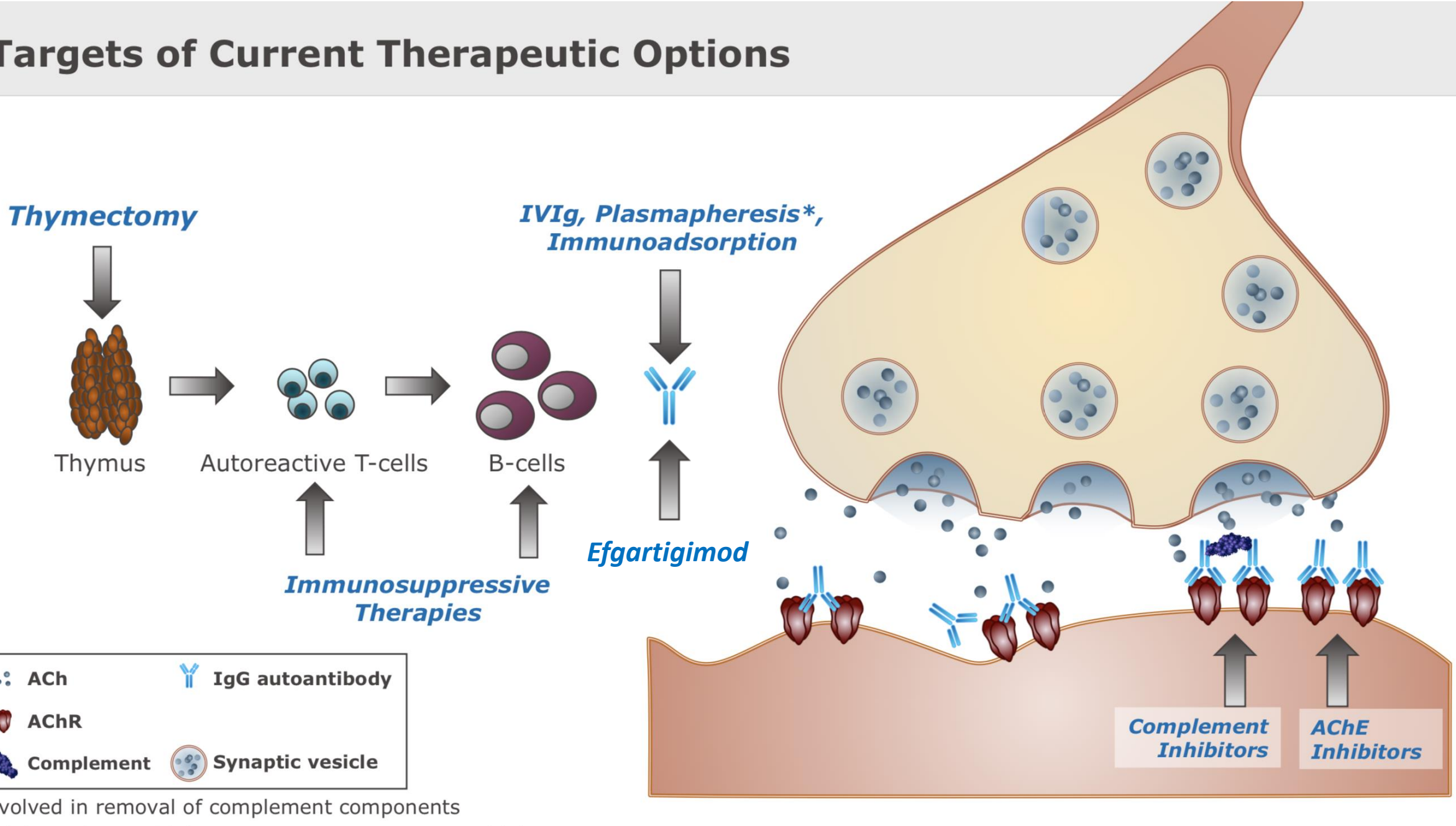
Impaired Neuromuscular Transmission

ACh: acetylcholine; AChR: acetylcholine receptor; IgG: immunoglobulin G; MG: myasthenia gravis; NMJ: neuromuscular junction.

Adapted from Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Joscalzo J. Harrison's Principles of Internal Medicine, 19th Edition. www.accessmedicine.com McGraw-Hill Education.

Engel AG, et al. *Mayo Clin Proc.* 1977;52:267-280. Sahashi K, et al. *J Neuropathol Exp Neurol.* 1980:39:160-172.

Targets of Current Therapeutic Options



* Also involved in removal of complement components

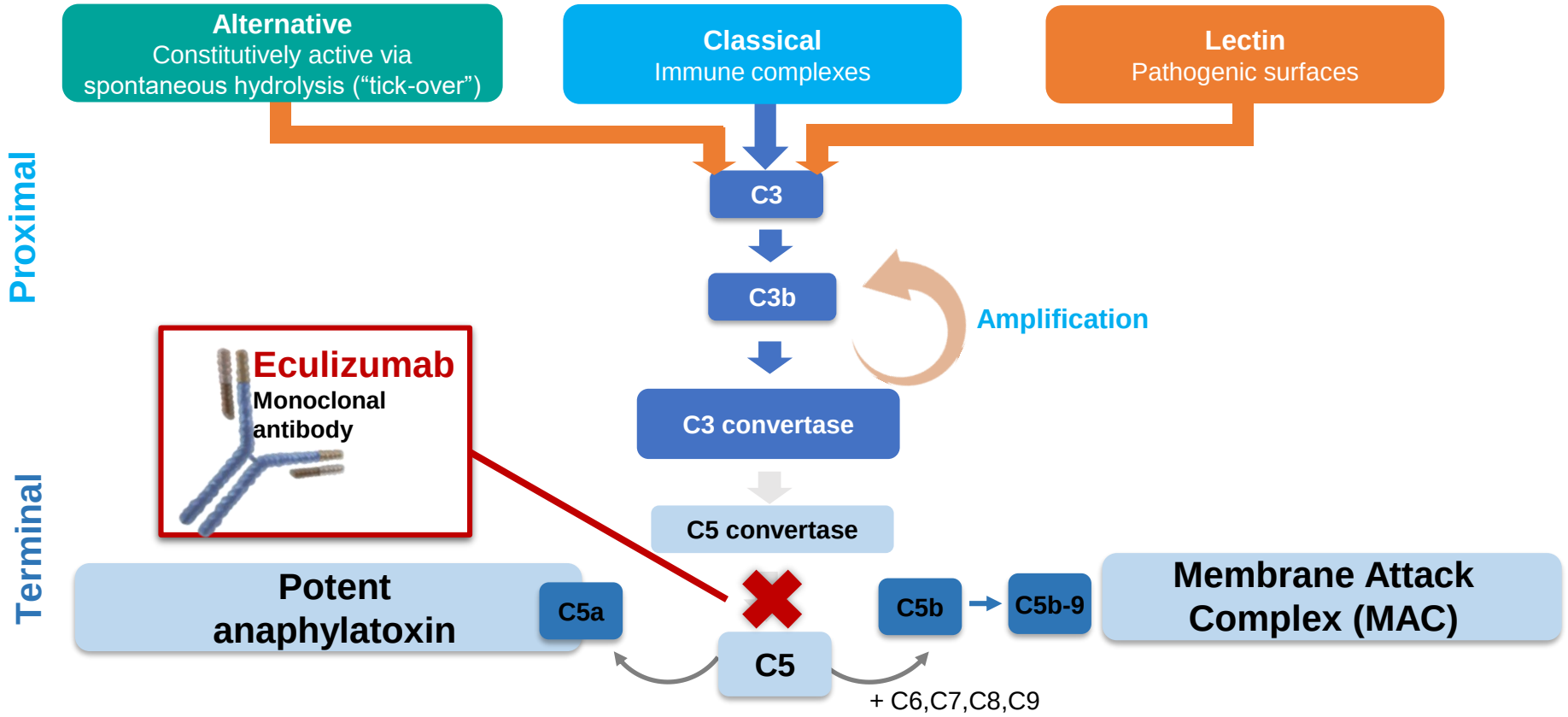
ACh: acetylcholine; AChE: acetylcholinesterase; IVIg: intravenous immunoglobulin

Howard Jr JF. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology 2019;92:e1-e13.
Mantegazza R, Bonanno S, Camera G, Antozzi C. Current and emerging therapies for the treatment of myasthenia gravis. *Neuropsychiatr Dis Treat*. 2011;7:151–160. doi:10.2147/NDT.S8915
Reeves H, Winters J. The mechanisms of action of plasma exchange.British Journal of Haematology, 2014, 164, 342–351

Eculizumab e Miastenia Gravis

Eculizumab Binds C5 and Inhibits Terminal Complement Activity[1-4]

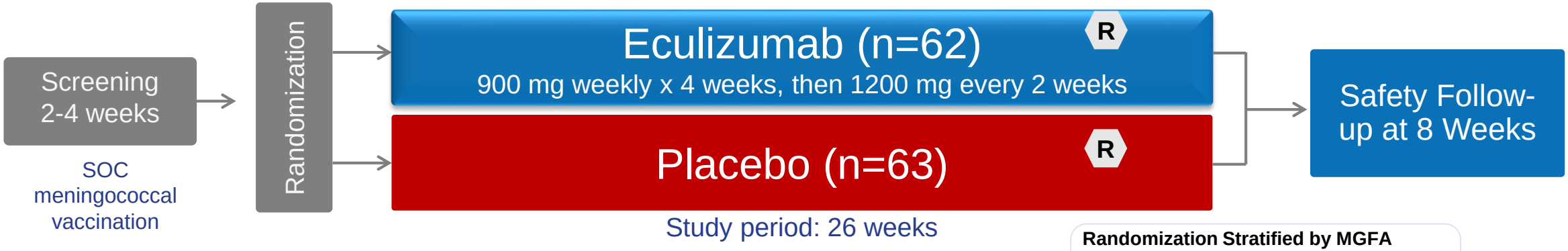
- Eculizumab blocks terminal complement activation[1]
  - Humanized murine monoclonal antibody that targets C5[5]



C5b(T), thrombin-generated C5b; MAC, membrane attack complex.

1. Walport MJ. *N Engl J Med.* 2001;344(14):1058-1066. 2. Murphy K. Innate immunity: the first lines of defense. In: Scobie J, et al, eds. *Janeway's Immunobiology.* 8th ed. New York, NY: Garland Science; 2012:37-73. 3. Kelly R, et al. *Ther Clin Risk Manag*. 2009;5:911-921. 4. Soliris [prescribing information]. New Haven, CT: Alexion Pharmaceuticals, Inc.; 2017. **5.** Howard JF, et al. *Muscle Nerve*. 2013;48(1):76-84.

REGAIN Clinical Study Design (ECU-MG-301)



R **Rescue due to Clinical Deterioration**
Rescue therapy was permitted if a patient experienced clinical deterioration as defined by the protocol.[a] Patient could remain in the trial.

Randomization Stratified by MGFA
Classification at Screening:

MGFA IIa/IIIa	MGFA IIb/IIIb
MGFA IVa	MGFA IVb

- Key Inclusion Criteria
  - MGFA clinical classification: class II to IV at screening
  - Positive serologic test for anti-AChR antibodies at screening
  - Failed prior therapy over ≥1 year with
    - ≥2 ISTs OR
    - ≥1 IST and required chronic PLEX or IVIg
  - MG-ADL total score ≥6 at screening and randomization (Day 1)

Dosing Selection

Full Inclusion Criteria

Full Exclusion Criteria

- Patients could continue to receive a stable dose of the IST they were taking at the time of study entry, but no new ISTs and no changes in IST dosage were permitted during the study

anti-AChR, antibodies to acetylcholine receptor; IST, immunosuppressive therapy; IVIg, intravenous immunoglobin; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; PLEX, plasma exchange; SOC, standard of care.
[a]Supplemental study drug (600 mg eculizumab or placebo) was administered within 60 minutes after each plasmapheresis/PLEX rescue session.

Howard JF , et al. Lancet Neurol 2017;16(12):976-986

History of Treatment/Therapy Before REGAIN Entry

Medication/Treatment	Eculizumab (n=62)	Placebo (n=63)
Corticosteroids, n (%)	58 (93.5)	62 (98.4)
Azathioprine, n (%)	47 (75.8)	47 (74.6)
Mycophenolate mofetil, n (%)	27 (43.5)	29 (46.0)
Cyclosporine, n (%)	17 (27.4)	18 (28.6)
Tacrolimus, n (%)	6 (9.7)	8 (12.7)
Methotrexate, n (%)	5 (8.1)	8 (12.7)
Rituximab, n (%)	7 (11.3)	7 (11.1)
Cyclophosphamide, n (%)	3 (4.8)	3 (4.8)
IVIg, n (%)	51 (82.3)	48 (76.2)
Plasma exchange, n (%)	31 (50.0)	29 (46.0)

IVIg, intravenous immunoglobin.

Howard JF , et al. Lancet Neurol 2017;16(12):976-986

Concomitant Medications on Day 1 of REGAIN Study

Medication/Treatment	Eculizumab (n=62)	Placebo (n=63)
Anticholinesterase, n (%)	58 (93.5)	53 (84.1)
Corticosteroids, n (%)	49 (79.0)	51 (81.0)
Proton pump inhibitors, n (%)	33 (53.2)	33 (52.4)
Immunosuppressants other than prednisone, n (%)	55 (88.7)	52 (82.5)
Azathioprine	20 (32.3)	21 (33.3)
Methotrexate	4 (6.5)	4 (6.3)
Cyclosporine	8 (12.9)	9 (14.3)
Tacrolimus	3 (4.8)	4 (6.3)
Mycophenolate mofetil	18 (29.0)	16 (25.4)
Bisphosphonates	19 (30.6)	11 (17.5)
Thyroid hormones	8 (12.9)	8 (12.7)
Anti-depressants*	17 (27.4)	21 (33.3)

*Anti-depressants includes selective serotonin reuptake inhibitors and other anti-depressants.

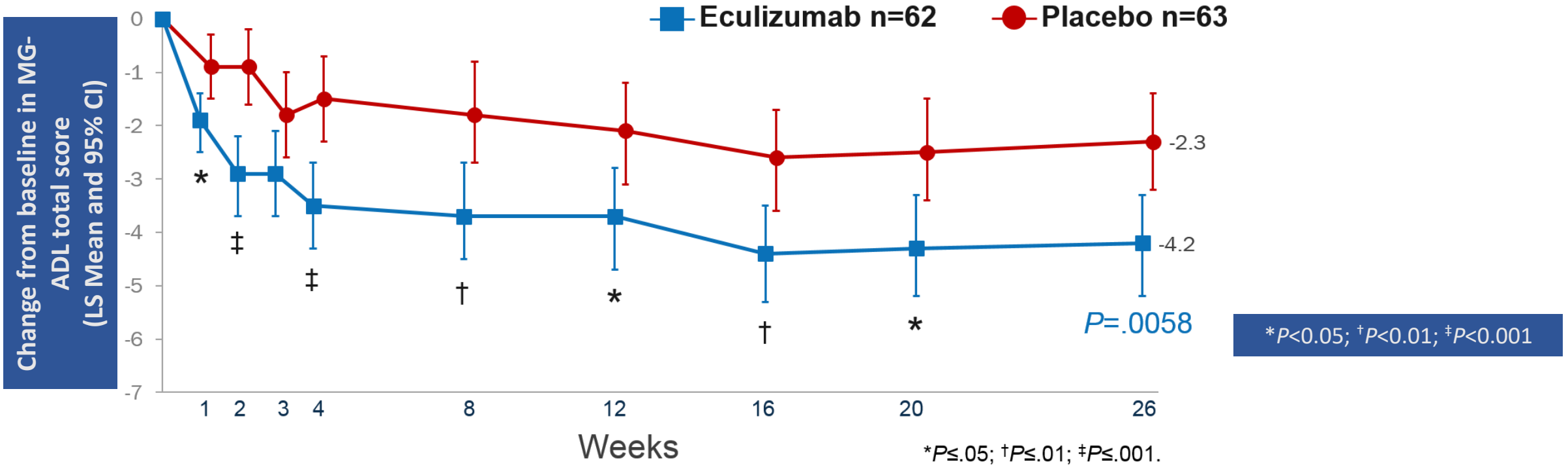
Howard JF , et al. Lancet Neurol 2017;16(12):976-986

Review of Efficacy Endpoint Measures

	MG Activities of Daily Living Profile (MG-ADL)[1,2]	Quantitative MG Scoring System (QMG)[1-3]
	Primary Endpoint	First Secondary Endpoint
	Patient-reported, physician-directed assessment	Physician-administered assessment
Method	▪ 8 question survey ▪ Each scored from 0 (normal) to 3 (most severe) ▪ Total scores range from 0 to 24	▪ 13 objective items ▪ Each scored from 0 (normal) to 3 (most severe) ▪ Total scores range from 0 to 39
Assessments	▪ Ocular/facial function (2 questions) ▪ Oropharyngeal function (3 questions) ▪ Respiratory function (1 question) ▪ Extremity function (2 questions)	▪ Ocular/facial function (3 measures) ▪ Oropharyngeal function (2 measures) ▪ Respiratory function (1 measure) ▪ Extremity/trunk muscle function (7 measures)
Duration	~10 minutes	~30 minutes

1. Howard JF , et al. Lancet Neurol 2017;16(12):976-986. **2.** Muppidi S. *J Clin Neuromuscul* Dis. 2017;18(3):135-146. **3.** Barohn RJ. The Quantitative Myasthenia Gravis (QMG) Test: The Manual. St Paul, MN: Myasthenia Gravis Foundation of America; 2000.

Repeated Measures of MG-ADL Total Score from Baseline to Week 26



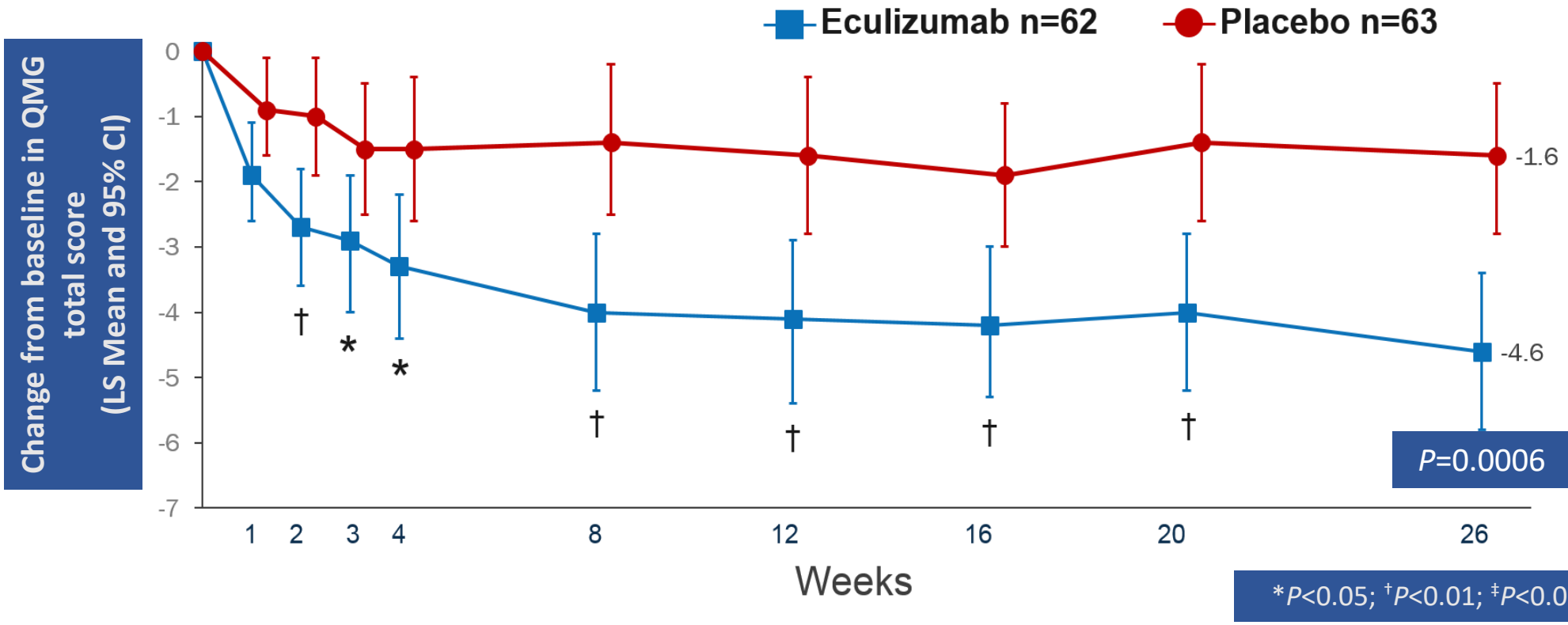
*P<0.05; †P<0.01; ‡P<0.001

- MG Activities of Daily Living (MG-ADL) profile is a patient-reported, 8-question survey that emphasizes the functional impact of muscle weakness
- The Kaplan-Meier estimate of the median (95% CI) time for patients in the placebo arm and the eculizumab arm to experience a 3-point improvement in MG-ADL total score was 54.0 (22.0, 71.0) days and 15.5 (9.0, 57.0) days, respectively

MG-ADL, myasthenia gravis activities of daily living.

Howard JF , et al. Lancet Neurol 2017;16(12):976-986

Repeated Measures of QMG Total Score from Baseline to Week 26

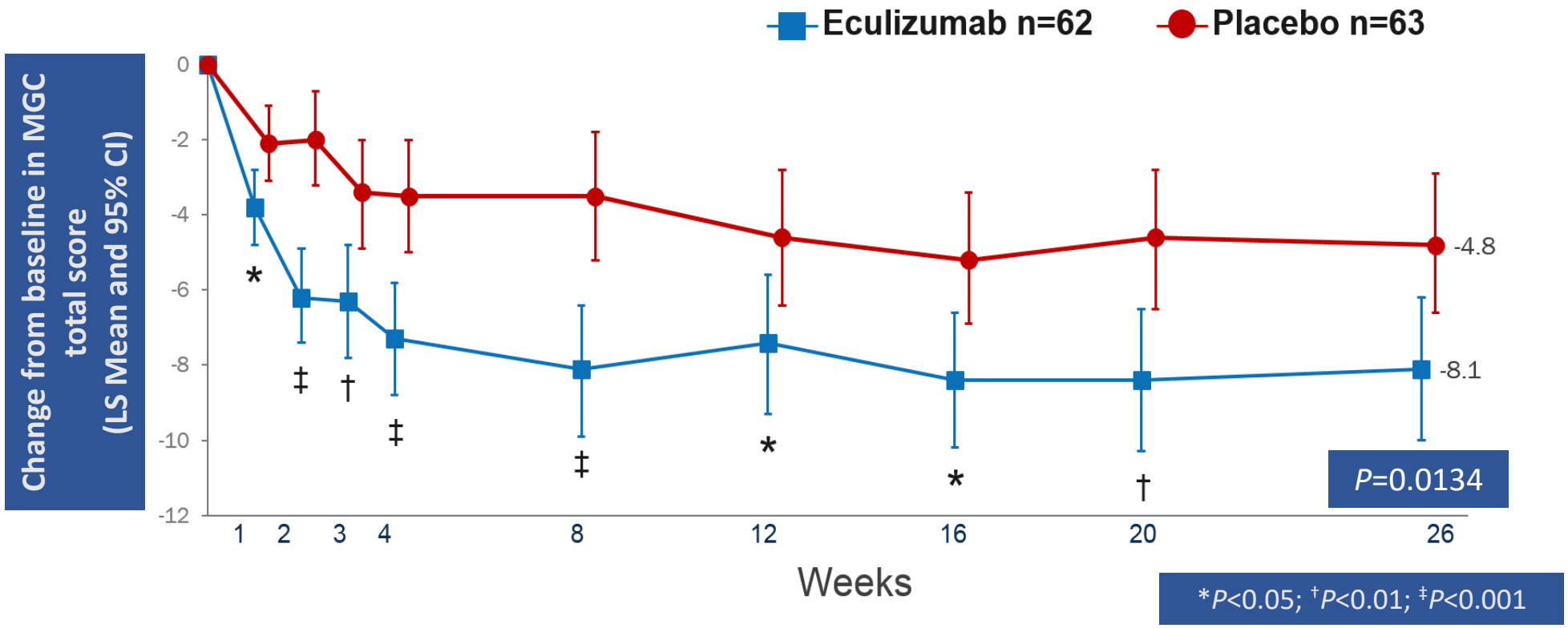


- Quantitative Myasthenia Gravis (QMG) test is physician-administered and assesses muscular weakness

QMG, quantitative myasthenia gravis.

Howard JF , et al. Lancet Neurol 2017;16(12):976-986

Repeated Measures of MGC Total Score from Baseline to Week 26

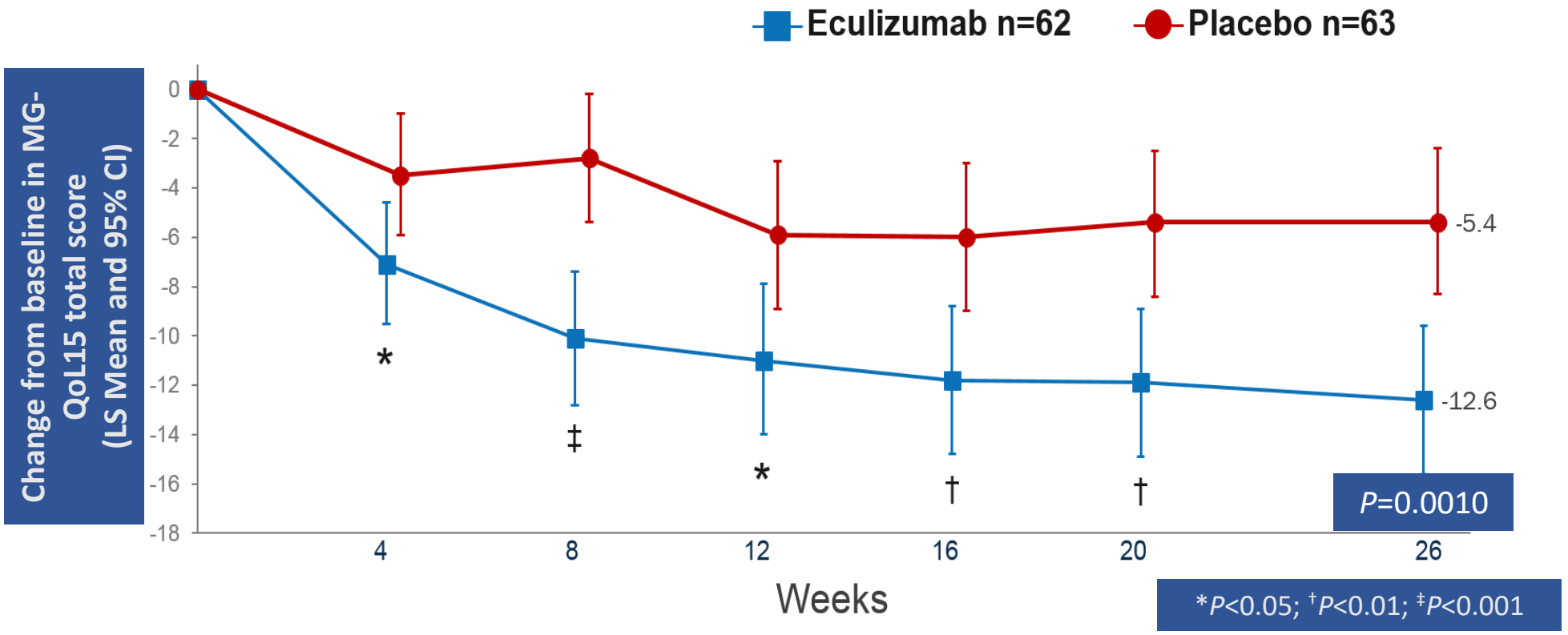


- MG Composite (MGC) scale is a mixed outcome measure that incorporates both physician-evaluated and patient-reported outcome items

MGC, myasthenia gravis composite.

Howard JF , et al. Lancet Neurol 2017;16(12):976-986

Repeated Measures of MG-QoL15 Total Score from Baseline to Week 26



- 15-item MG Quality of Life (MG-QOL15) scale is a brief, patient-reported survey designed to assess some aspects of quality of life related to MG

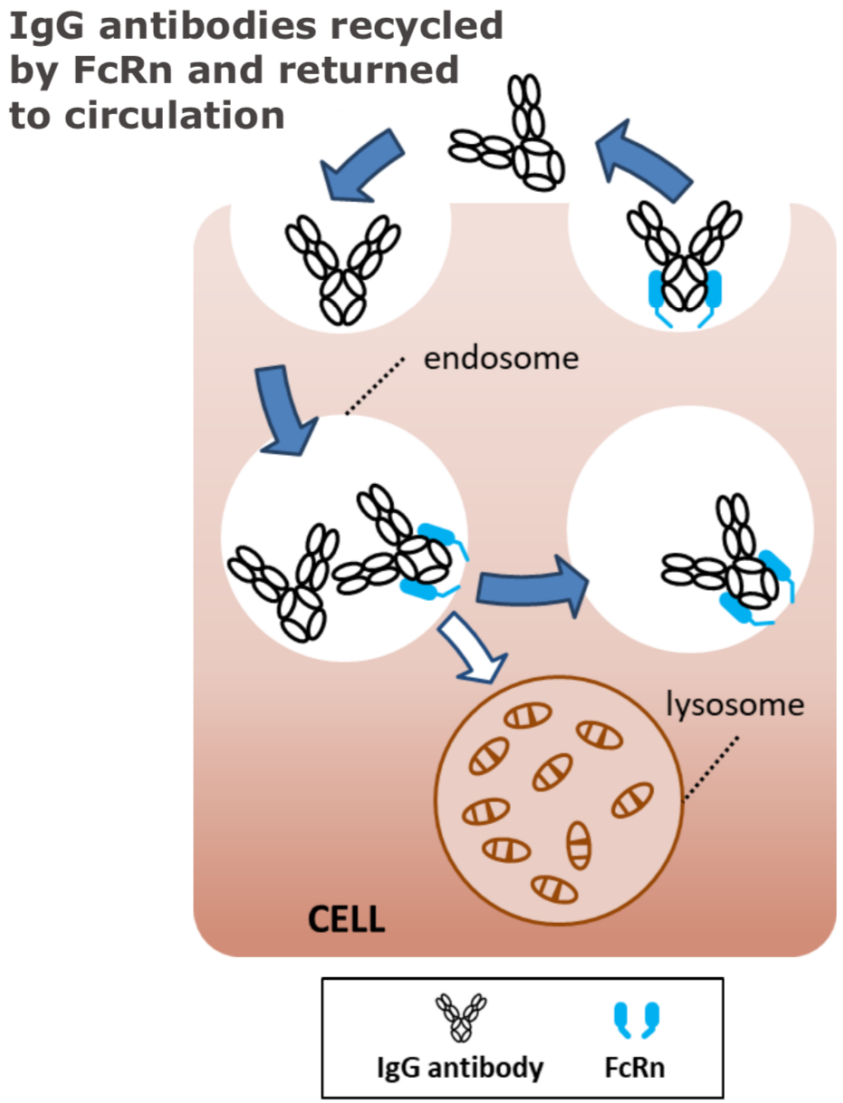
MG-QoL15, myasthenia gravis quality of life

Howard JF , et al. Lancet Neurol 2017;16(12):976-986

Efgartigimod e Miastenia Gravis

Neonatal Fc Receptor (FcRn) is central to IgG regulation

- FcRn rescues immunoglobulin G (IgG) from degradation through a recycling pathway
- Due to FcRn recycling, IgGs have a longer half-life and are more abundant than other immunoglobulins
- FcRn prolongs half-life of pathogenic IgG
- FcRn is present in endothelial cells and myeloid cells; present throughout life
- Inhibition of FcRn is a rational potential therapeutic approach in autoimmune diseases mediated by pathogenic IgG antibodies

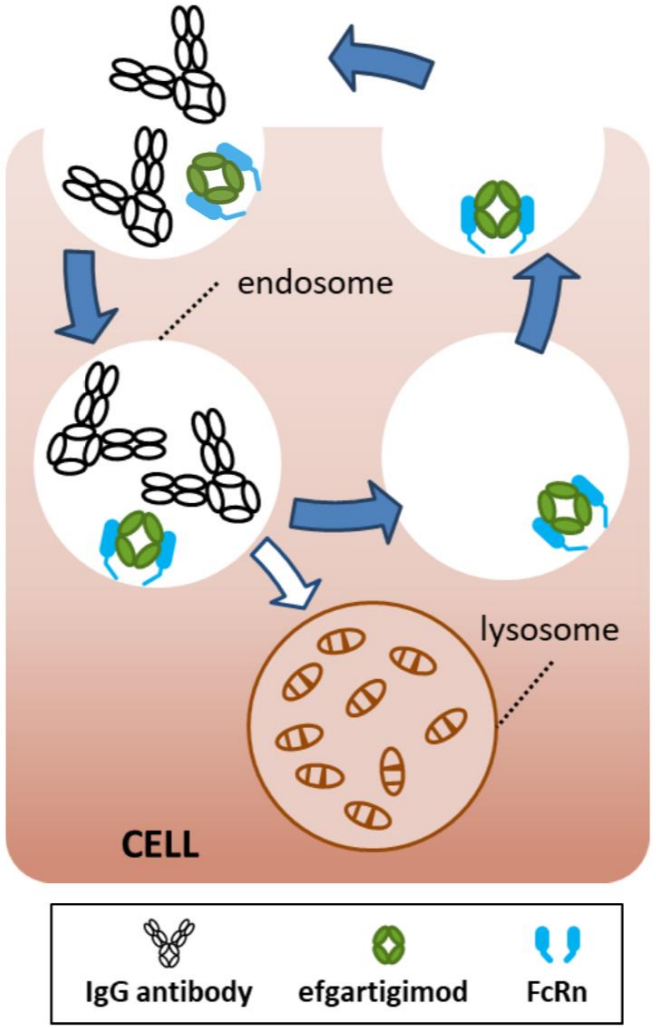


FcRn: neonatal fragment crystallizable receptor; IgG: immunoglobulin G.

Sesarman A, Vidarsson G, Sitaru C. The neonatal Fc receptor as therapeutic target in IgG-mediated autoimmune diseases. *Cell Mol Life Sci*. 2010 Aug;67(15):2533-50.

Efgartigimod* Mechanism of Action (MOA)

- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity to FcRn
- Binds in the same way as endogenous IgG, preserving characteristic pH-dependent binding
- Designed to outcompete endogenous IgG, preventing recycling, promoting IgG lysosomal degradation
- Phase 1 Data showed:
  - Targeted reduction of all IgG subtypes
  - No impact on IgM, IgA or albumin



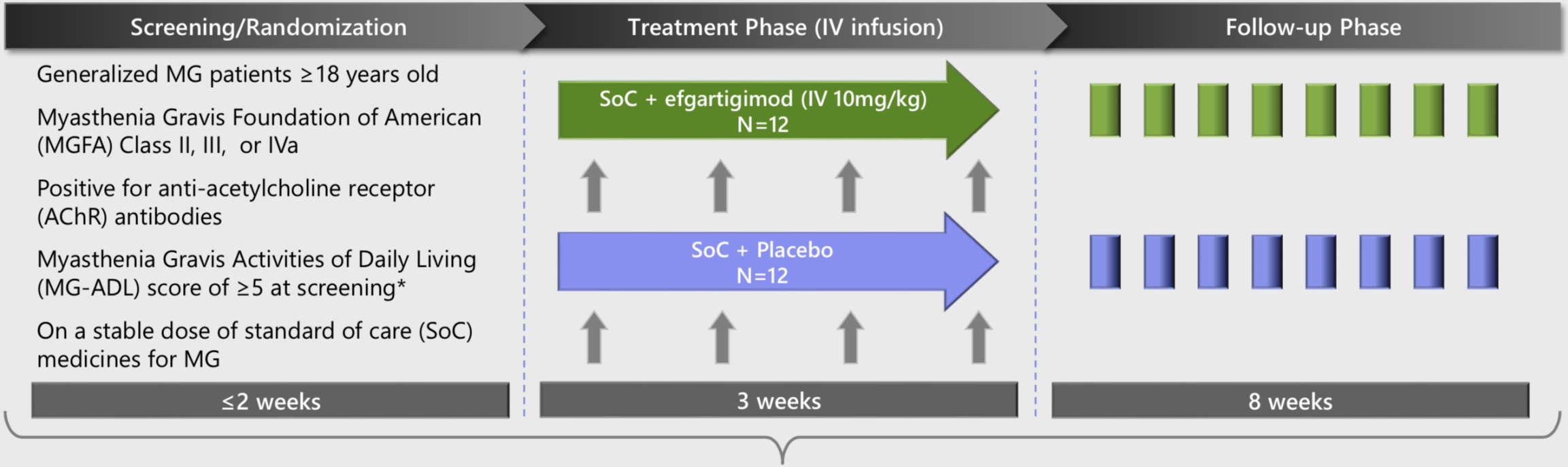
*efgartigimod is an investigational agent and has not been approved by the U.S. Food and Drug Administration or other regulatory agencies.

FcRn: Neonatal fragment crystallizable receptor; IgG: Immunoglobulin G;

Ulrichts P, Guglietta A, Dreier T, van Bragt T, Hanssens V, Hofman E, *et al.* Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. *J Clin Invest.* 2018. 128(10):4372-4386.

Efgartigimod
Phase II Clinical Trial Design

A randomized, double-blind, placebo-controlled, multicenter, proof-of-concept trial in MG



Primary Endpoint

Safety and Tolerability

Secondary Endpoints

Efficacy
MG-ADL; QMG; MGC; MG-QOL

PK/PD

Immunogenicity

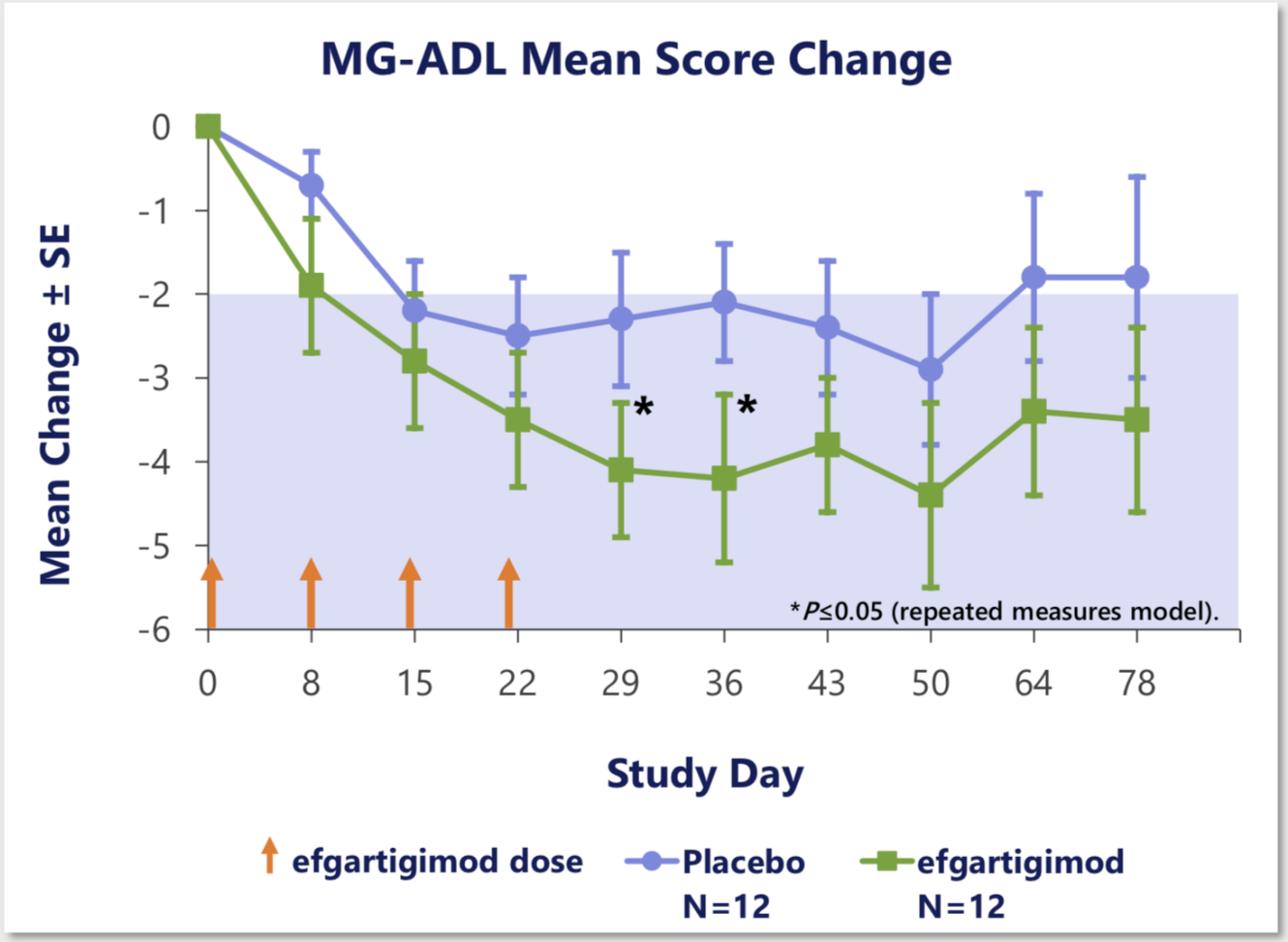
*>50% of the score attributed to non-ocular items.

MG: myasthenia gravis; MG-ADL: myasthenia gravis–activities of daily living; QMG: Quantitative MG scale; MGC: myasthenia gravis composite; MG-QoL: myasthenia gravis–quality of life survey; PK: pharmacokinetics; PD: pharmacodynamics.

Howard Jr JF. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology 2019;92:e1-e13.

Change in Mean MG-ADL Score

- A clinically meaningful reduction† in MG-ADL observed (reduction ≥2), sustained at end of study (Day 78)
- Clinical improvement consistent across clinical measures (MG-ADL, QMG, MGC, MG-QoL15)



*Clinical improvements reached statistical significance (*P*≤0.05 mixed repeated measures model)

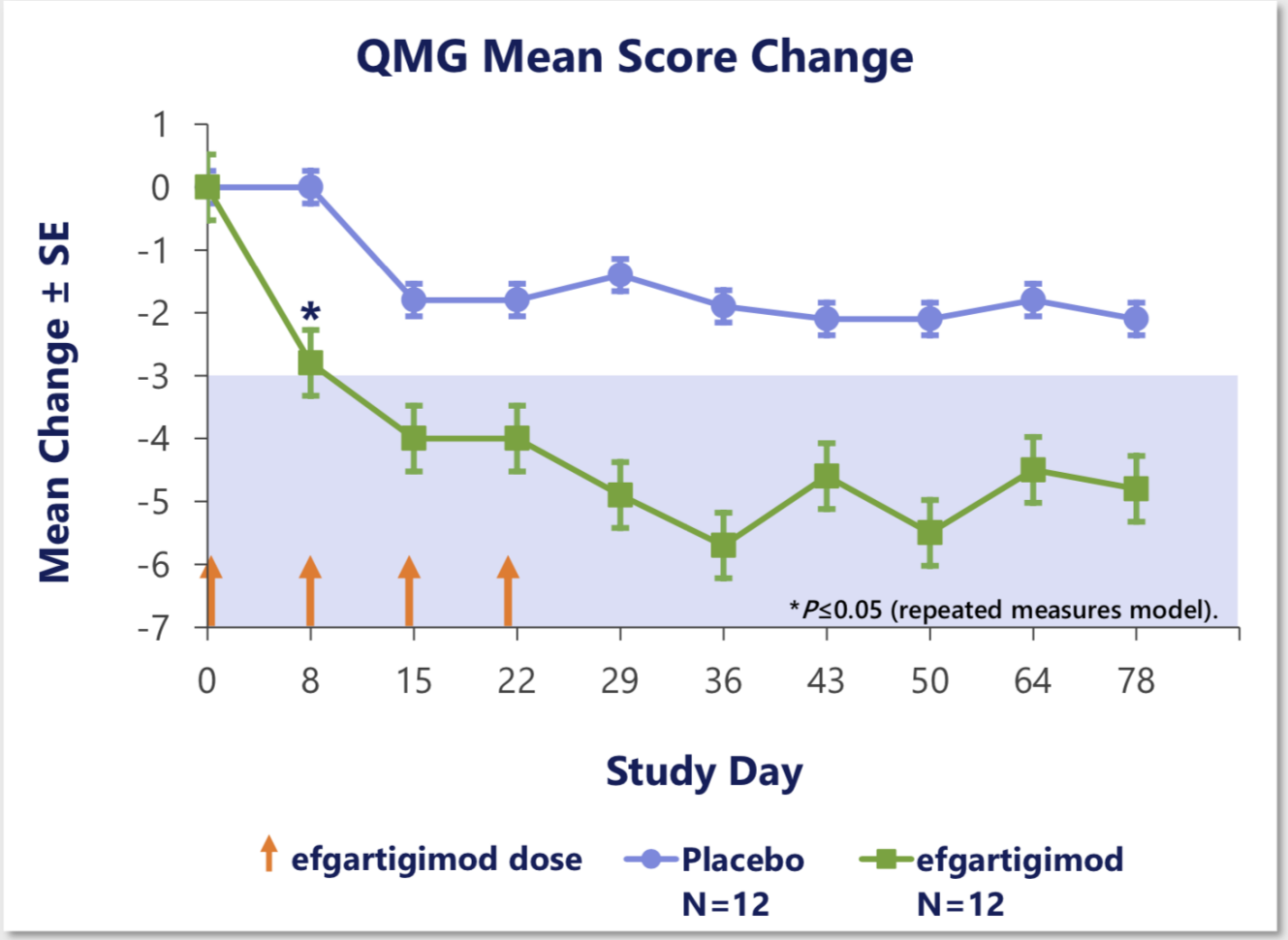
†Clinically meaningful as defined in study protocol

MG-ADL: myasthenia gravis activities of daily living; QMG: Quantitative MG scale; MGC: myasthenia gravis composite; MG-QoL: myasthenia gravis–quality of life survey; SE: standard error.

Howard Jr JF. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology 2019;92:e1-e13.

Change in Mean QMG Score

- A clinically meaningful reduction† was observed in QMG (reduction ≥3) and sustained at End of Study (Day 78)
- Clinical improvement consistent across clinical measures (MG-ADL, QMG, MGC, MG-QoL15)



*Clinical improvements reached statistical significance (*P*≤0.05 mixed repeated measures model).

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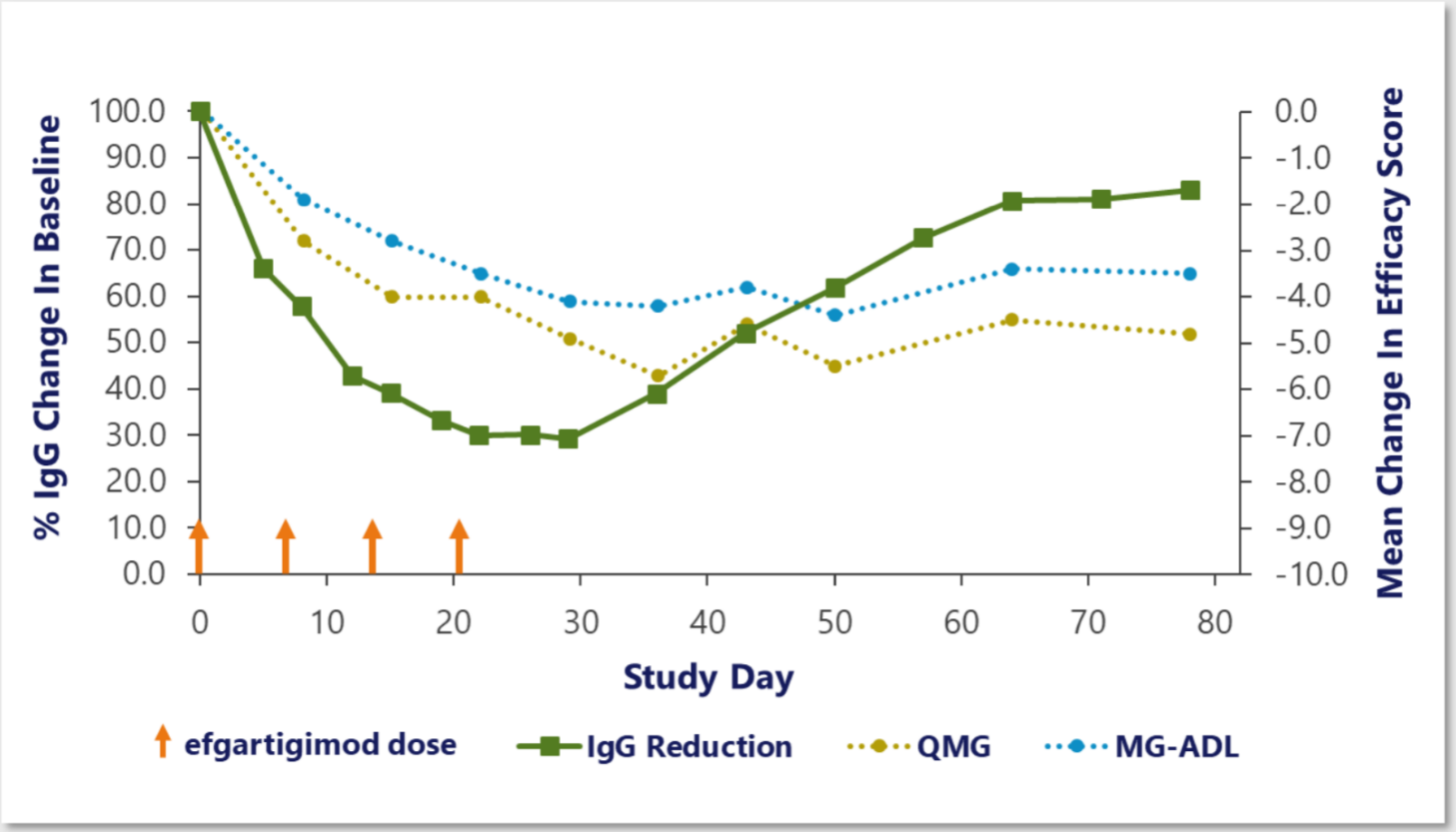
MG-ADL: myasthenia gravis activities of daily living; MGC: myasthenia gravis composite; MG-QoL: myasthenia gravis–quality of life survey; QMG: Quantitative MG scale; SE: standard error.

Howard Jr JF. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology 2019;92:e1-e13.

Change in IgG, Mean MG-ADL and Mean QMG Scores

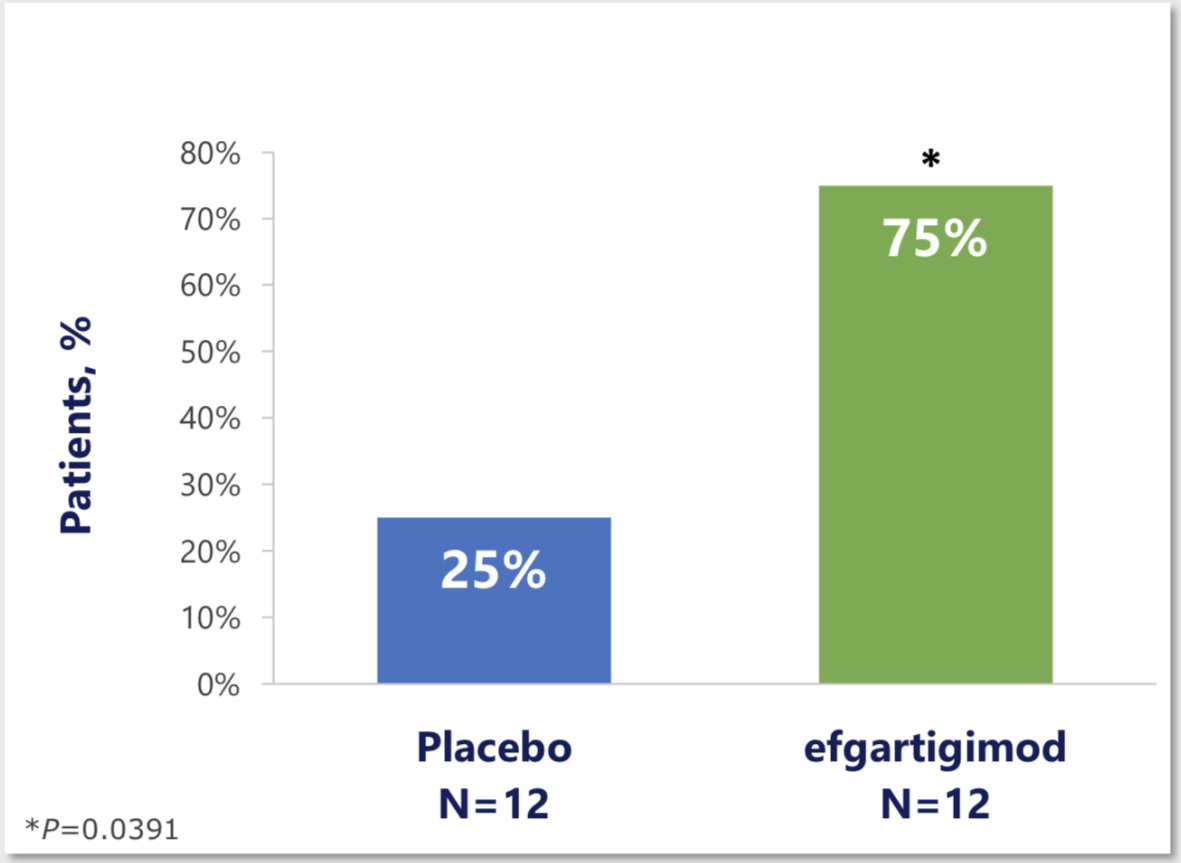
- Reduction of total IgG correlated with clinical improvement (mean change MG-ADL and mean change QMG scores; efgartigimod, n=12)
- However, clinical improvements lasted longer than total IgG reductions and persisted as total IgG level returned toward baseline values
  - This observation is being investigated in the current efgartigimod Phase III, placebo-controlled trial (ADAPT)



IgG: immunoglobulin G; MG-ADL: myasthenia gravis activities of daily living; QMG: quantitative MG test.

Howard Jr JF. A double-blind placebo-controlled study to evaluate the safety and efficacy of FcRn-antagonist ARGX-113 (efgartigimod) in generalized myasthenia gravis. Plenary session. AAN Annual Meeting, Los Angeles; April, 2018.

Patients with a Reduction in Total MG-ADL ≥2 for at Least 6 Weeks



- 75% of patients in the efgartigimod group showed a clinically meaningful improvement sustained for at least 6 consecutive weeks compared to 25% of patients in the placebo group

*P=0.0391

MG-ADL: myasthenia gravis activities of daily living.

Howard Jr JF. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. Neurology 2019;92:e1-e13.