
Advances
in Myasthenia Gravis
Emerging Biological Therapies and
Clinical Frontiers

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Disclosures

	Relationship with Commercial Entities	Other
Dr. Carolina Barnett-Tapia	Consultant: Alexion, Argenx, Johnson & Johnson, Novartis, NMD Pharma, UCB Clinical Trials: Alexion, argenx	Developer of the MGII, might receive royalties
Dr. Hans Katzberg	Consultant & Clinical Trials: Alexion, Alnylam, ArgenX, AstraZeneca, Biocryst, Cour, CSL Behring, Dyne, Dianthus, Johnson and Johnson, Merz, Octapharma, Roche, Takaeda, Terumo, UCB	N/A

Learning Objectives

After this session, you should be better able to:

- Discuss the mechanisms and clinical outcomes used to evaluate emerging biologic therapies in myasthenia gravis
- Describe novel biologic strategies beyond FcRn inhibition, including complement-targeted and CAR-T cell therapies
- Assess the clinical application and evolving role of FcRn inhibitors in the treatment of myasthenia gravis

Advances
in Myasthenia Gravis

Emerging Biological Therapies and
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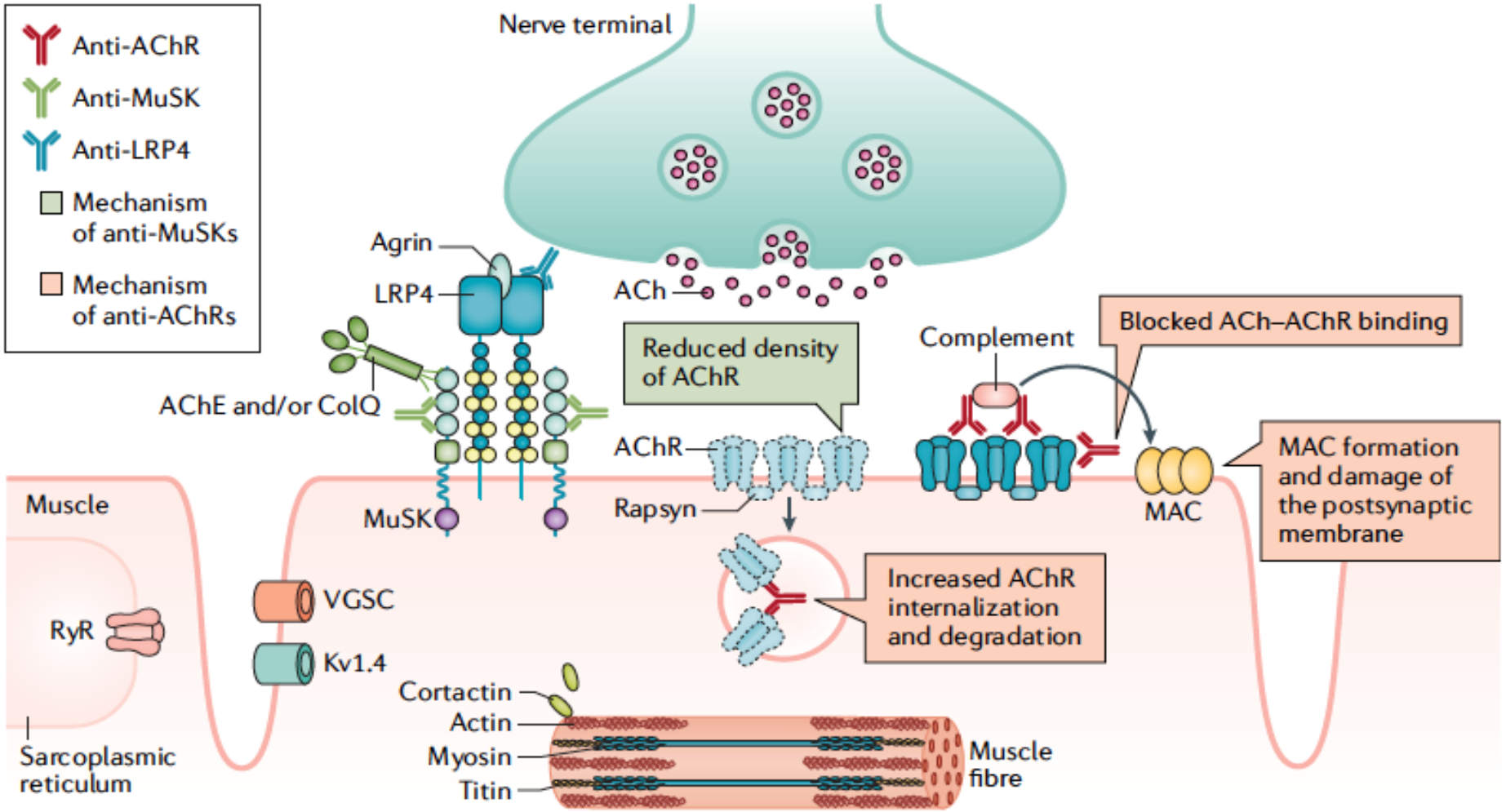
Current Treatment Landscape and Outcomes

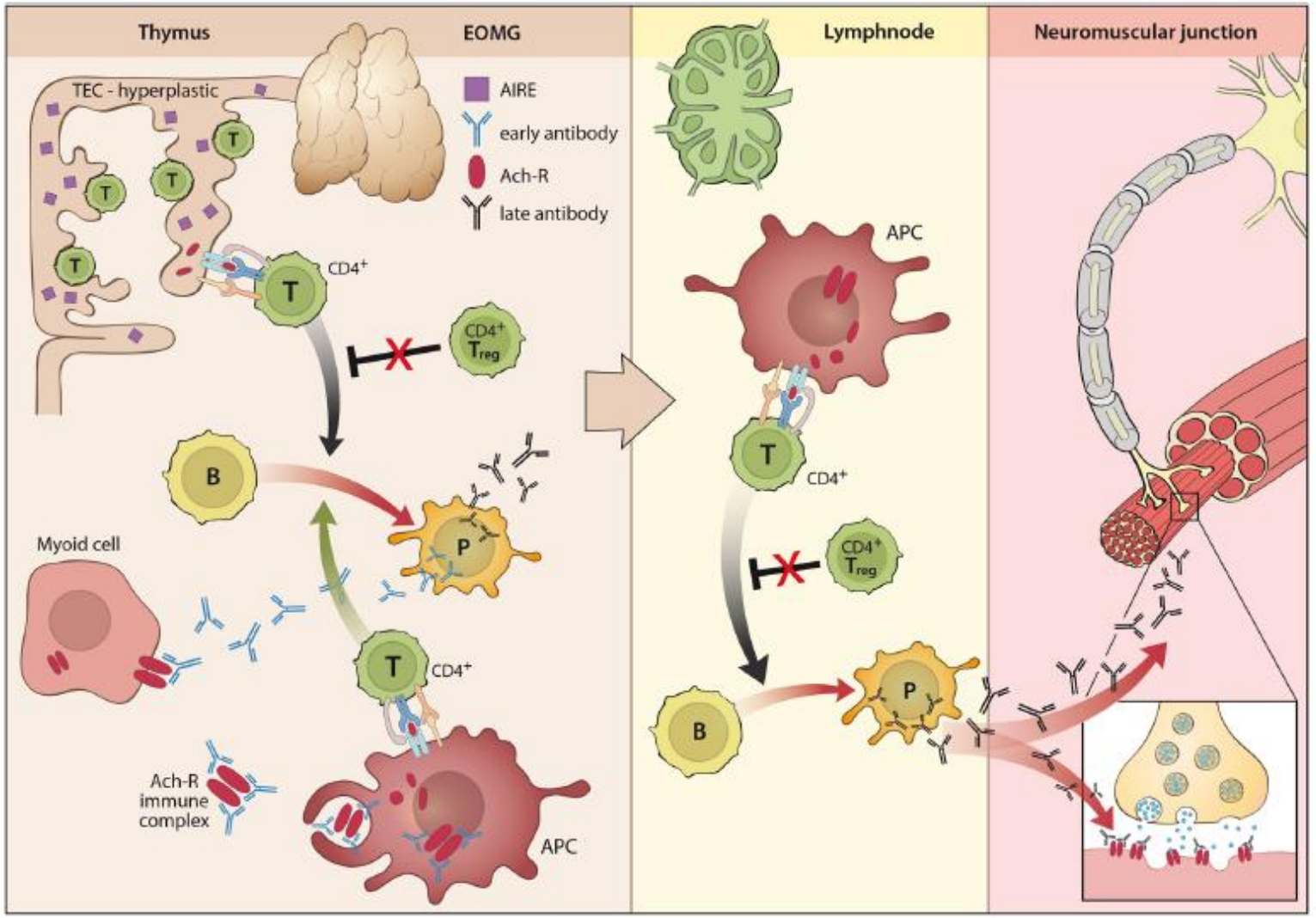
Carolina Barnett-Tapia MD, PhD

Neuromuscular junction targets in the pathogenesis of myasthenia gravis



Gilhus et al. Nature reviews 2019.

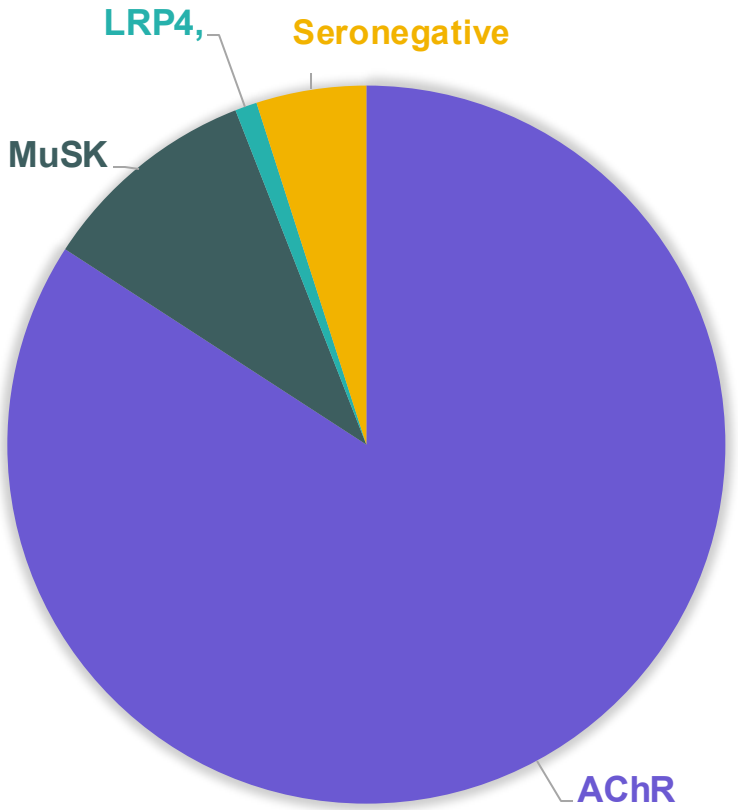
Overview of the Pathogenesis of Autoimmune MG



Melzer N, et al. J Neurol. 2016; 263(8): 1473-1494.

Poll #1: Approximately what percentage of patients with MG are positive for AChR antibodies?

Pathogenic Antibodies in Myasthenia



AChR Antibodies (IgG1 and IgG3) — **80-90%**
- Functional AChR inhibition
- Activate complement
- Degradation of AChR

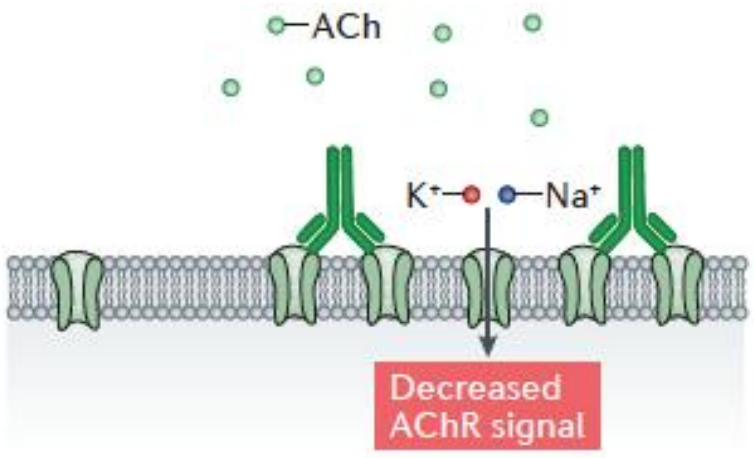
MuSK antibodies (IgG4) — **~10%**
- Inhibit MuSK activation
- Do not activate complement

LRP4 antibodies (IgG1) — **1%**

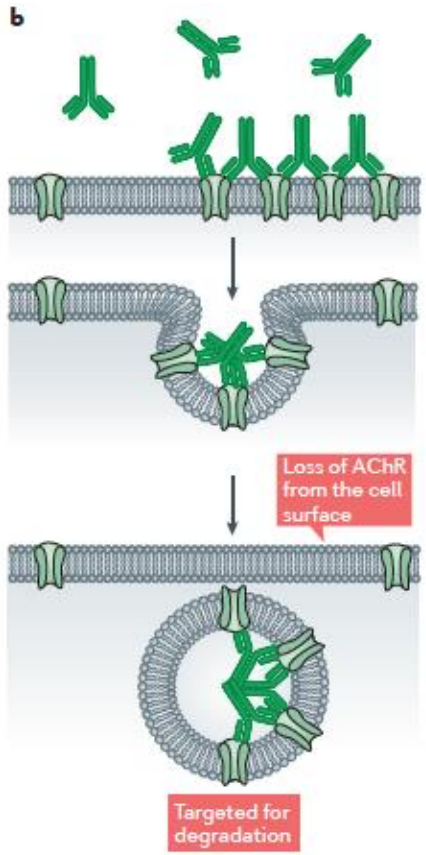
Seronegative — **5%**
- This number has been decreasing.
- Some seronegative may be positive with cell-based assay

1. Phillips WD, Vincent A. F1000Res 2016;5:F1000 Faculty Rev-1513; 2. Meriggioli MN, Sanders DB. Expert Rev Clin Immunol 2012;8:427–38; 3.

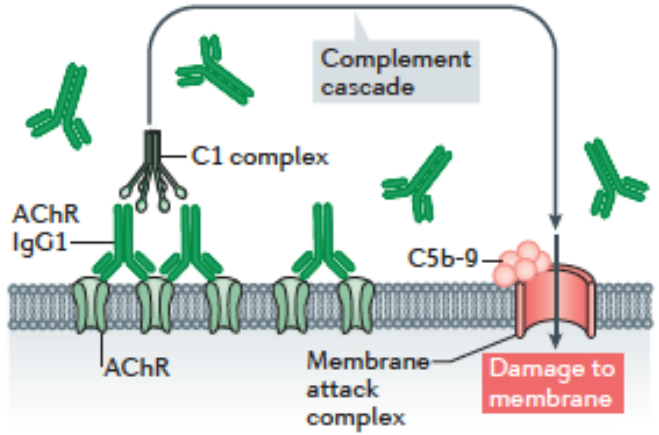
Pathogenic Mechanisms of AChR Antibodies in MG



Direct blocking of ACh current



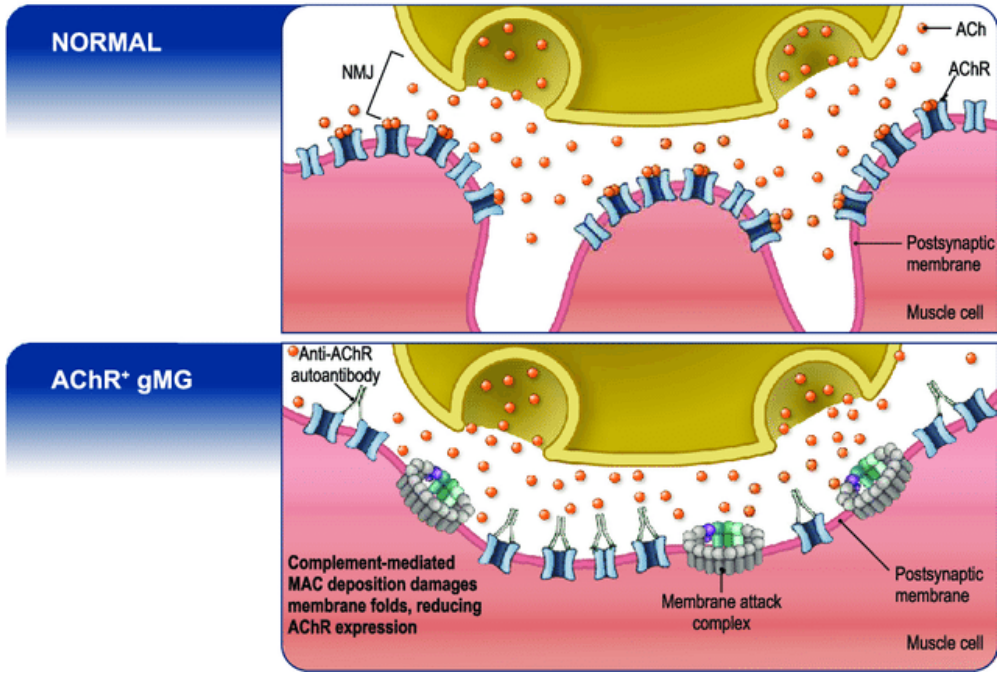
Internalization and degradation of ACRs



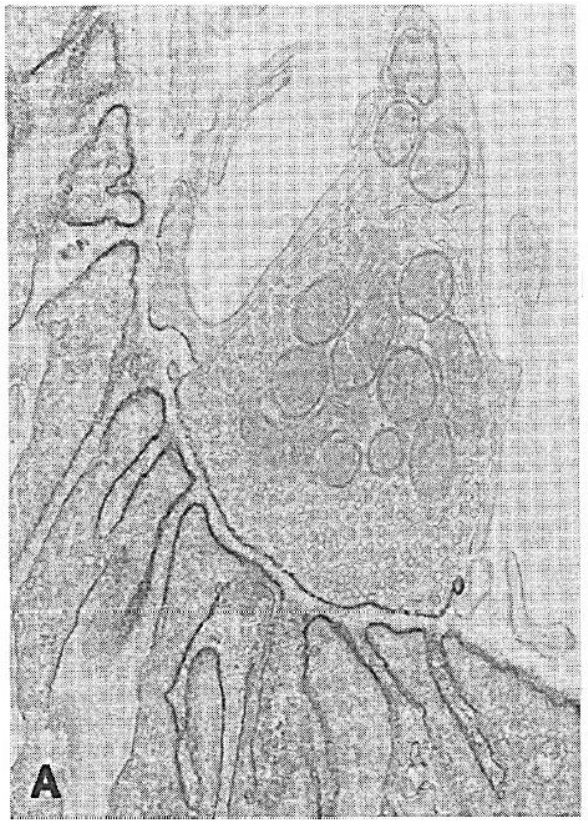
Complement deposit and muscle membrane damage

Crisp S, et al. Nature Reviews 2016;17:103-117

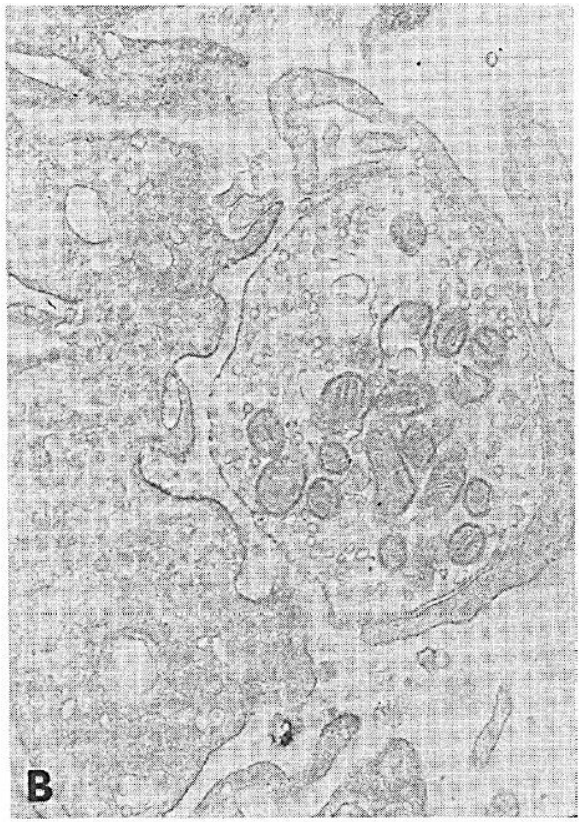
Destruction of the NMJ by Complement in AChR Ab+ MG



Healthy control

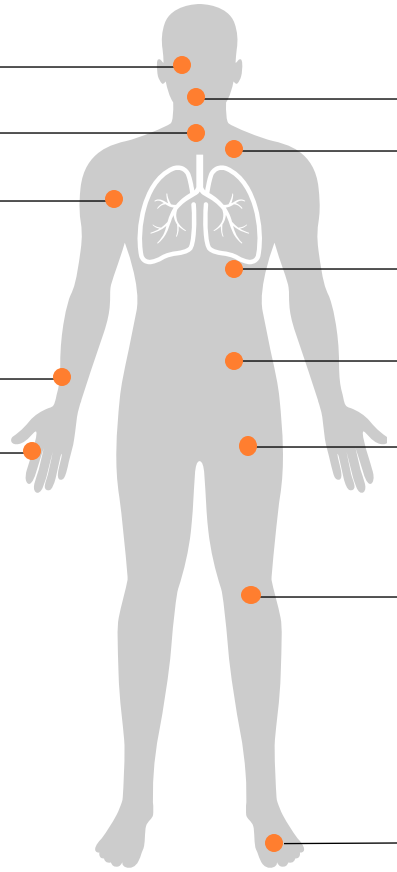


Myasthenia gravis



Howard JF. Exp Op. Invest Drugs. 2021;30(5):1-11
Engel A, JNNP. 1980;43:577-589

Fatigable Weakness



Ocular

Blurry or double vision
Eyelid drooping
Eye muscle weakness
Fatigability

Voice and Speech

Fatigability
Speech impairment
Voice quality/tone

Back/Shoulders

Fatigue
Pain
Spasms
Weakness

Arms

Cramps
Difficulty lifting
Fatigability
Fatigue
Pain
Spasms
Weakness
(e.g. picking things up)

Hands/Fingers

Dexterity
Fine motor skills
(e.g. grasping)
Fatigability
Loss of strength
Spasms

Neck

Fatigability
Pain holding head up
Weakness

Breathing

Fatigability
Shallow breathing
Shortness of breath

Core

Weakness

Hips

Fatigue
Pain
Spasms
Weakness

Legs/Feet

Cramps
Fatigability
Fatigue
Pain
Spasms
Twitches
Weakness

Chewing

Difficulty chewing
Jaw fatigue
Weakness

Swallowing

Choking
Aspirating
Vomiting

Lower Facial Muscles

Drooping
Difficulty making facial expressions

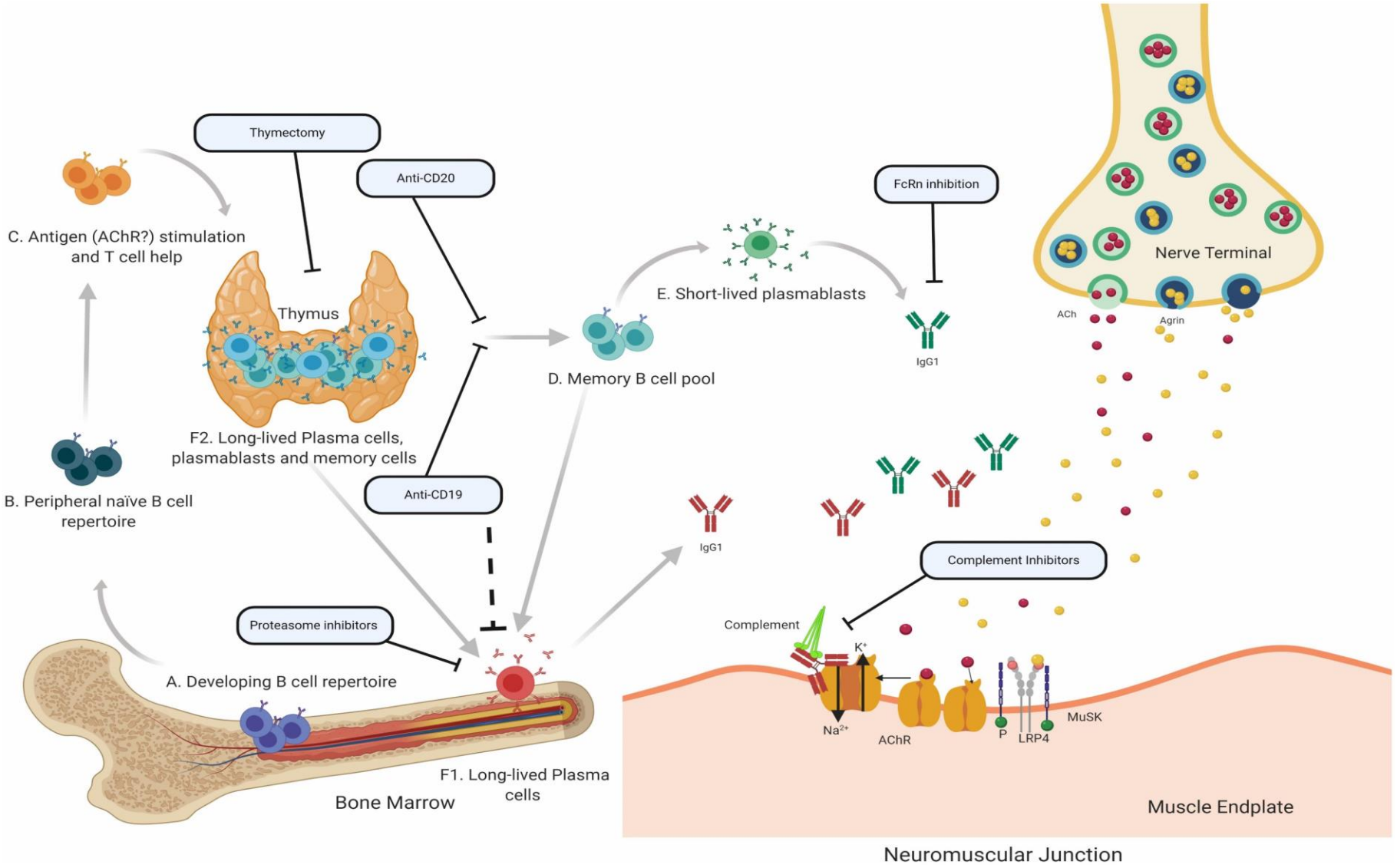
Overall Symptoms

(location unspecified, or described as a general experience)

Cognitive impairment (difficulty focusing, memory), **Fatigability (worsening of impairment), Mental fatigue (too exhausted to think or mentally motivate),** Pain (general muscle soreness or achiness), **Physical fatigue (lack of energy, a feeling of depletion, or lethargy)**, Weakness (overall strength)

Jackson K et al. Neurol Ther. 2022

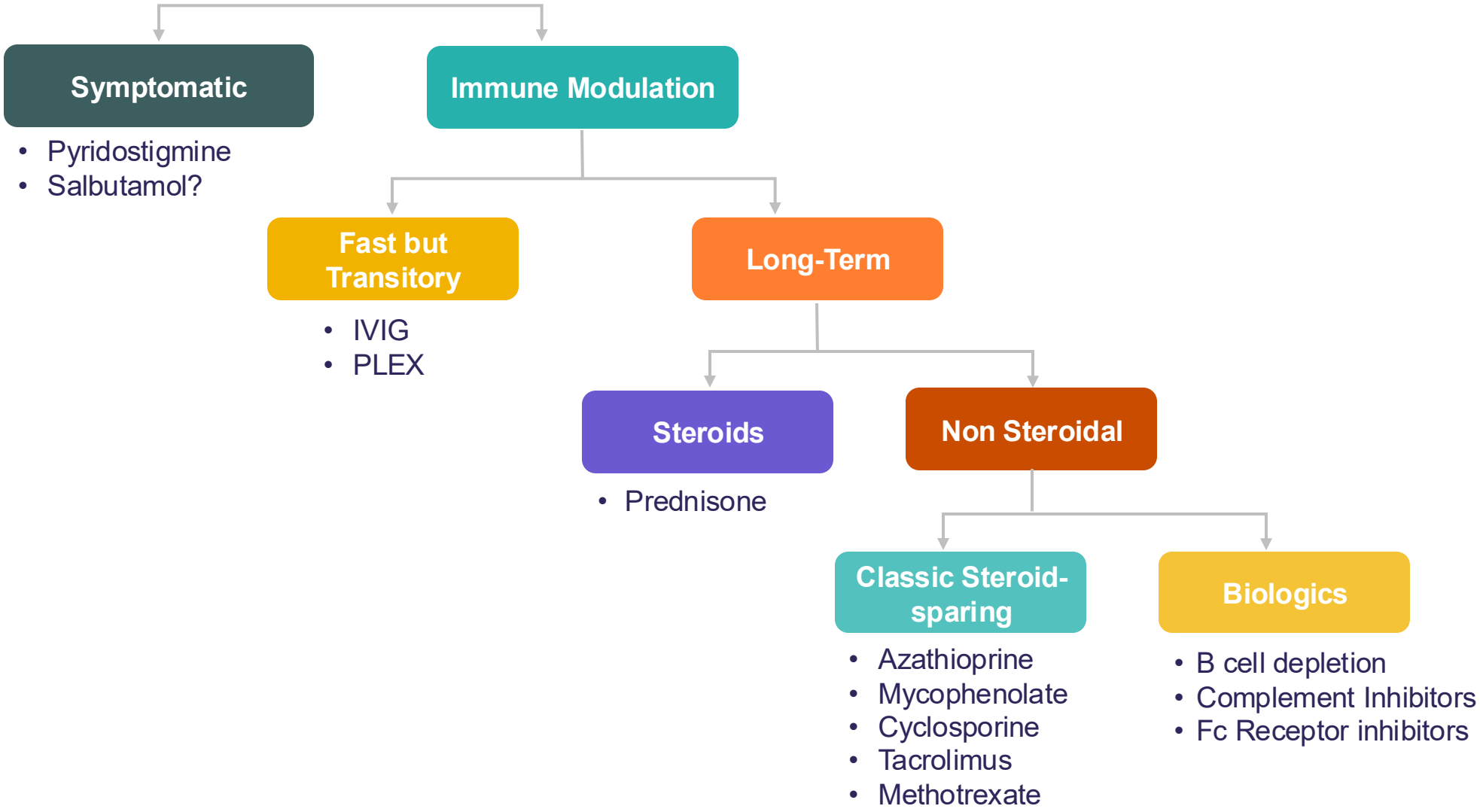
Therapeutic Approaches in Myasthenia Gravis



AChE inhibitors (symptomatic)

Fichtner et al. Frontiers Neurol. 2020;11.

Autoimmune MG: Pharmacologic Treatments



Long-Term Outcomes

MG-related mortality has decreased

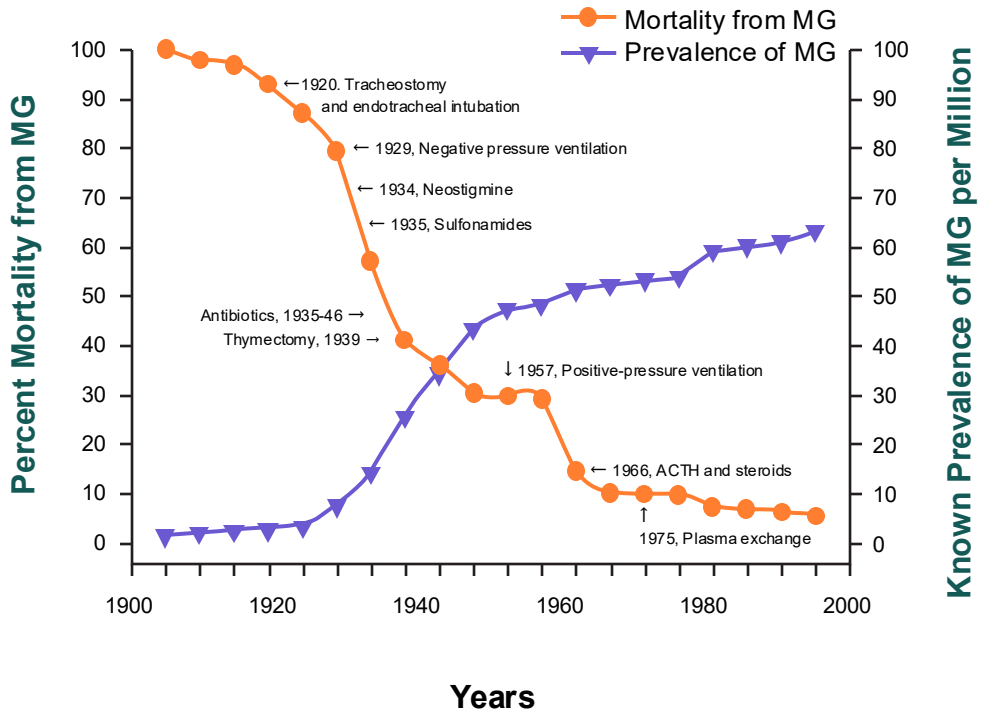
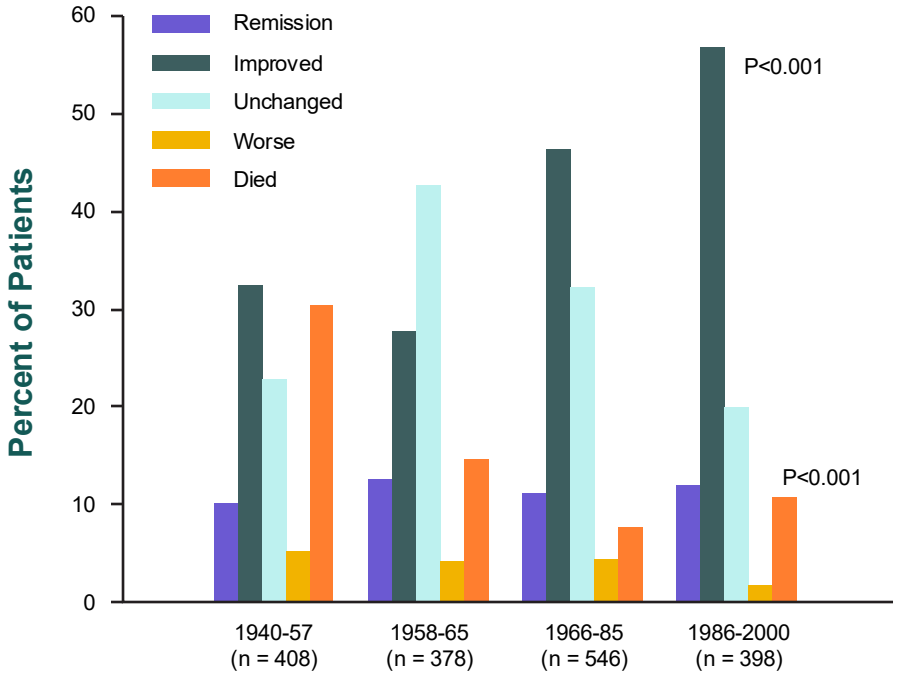


FIGURE 1. Known prevalence and mortality from MG during 1900 to 2000.

Most patients respond to treatment
Refractory MG ~ 5-10%



Grob, et al. Muscle Nerve. 2008;37(2):141–9.

Treatment Goals

To achieve best possible symptom control (ideally no symptoms) with minimal toxicity from interventions.

Multiple cohorts have shown than a large proportion of people with MG **are not meeting treatment goals**

How we measure outcomes in MG?

Quantitative Myasthenia Gravis Score
(QMGS)

Myasthenia Gravis Activities of Daily Living
(MG-ADL)

Myasthenia Gravis Composite
(MGC)

Myasthenia Gravis Impairment Index
(MGII)

Poll #2: Which of these scales do you use most often in your practice?

QMGS

Items	None	Mild	Moderate	Severe
Grade	**0**	**1**	**2**	**3**
Double vision (lateral gaze), sec	60	11-59	1-10	Spontaneous
Ptosis (upward gaze), sec	60	11-59	1-10	Spontaneous
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing, choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-#49	Dysarthria at #10-#29	Dysarthria at #9
Right arm outstretched (90 degrees, sitting), sec	240	90-239	10-89	0-9
Left arm outstretched (90 degrees, sitting), sec	240	90-239	10-89	0-9
Forced vital capacity	≥80%	65%-79%	50%-64%	<50%
Right hand grip, kg **Men** **Women**	 ≥45 ≥30	 15-44 10-29	 5-14 5-9	 0-4 0-4
Left hand grip, kg **Men** **Women**	 ≥35 ≥25	 15-34 10-24	 5-14 5-9	 0-4 0-4
Head, lifted (45%, supine), seconds	120	30-119	1-29	0
Right leg outstretched (45%-50%, supine), sec	100	31-99	1-30	0
Left leg outstretched (45%-50%, supine), sec	100	31-99	1-30	0
				Total QMG score (range, 0-39)

Barohn RJ, et al. Ann Y Acad Sci. 1998;841:769-772

MG-ADL

Grade	0	1	2	3	Score (0, 1, 2, 3)
1. Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking, necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total MG-ADL score (range, 0-24)	

Neurology 1999;52(7):1487-1489

Myasthenia Gravis Composite

Items	Scores			
Ptosis, upward gaze (physician examination)	**0 =** >45 s	**1 =** 11–45 s	**2 =** 1–10 s	**3 =** Immediate
Double vision on lateral gaze, left or right (physician examination)	**0 =** >45 s	**1 =** 11–45 s	**3 =** 1–10 s	**4 =** Immediate
Eye closure (physician examination)	**0 =** Normal	**0 =** Mild weakness (can be forced open with effort)	**1 =** Moderate weakness (can be forced open easily)	**2 =** Severe weakness (unable to keep eyes closed)
Talking (patient history)	**0 =** Normal	**2 =** Intermittent slurring or nasal speech	**4 =** Constant slurring or nasal but can be understood	**6 =** Difficult to understand speech
Chewing (patient history)	**0 =** Normal	**2 =** Fatigue with solid food	**4 =** Fatigue with soft food	**6 =** Gastric tube
Swallowing (patient history)	**0 =** Normal	**2 =** Rare episode of choking or trouble swallowing	**5 =** Frequent trouble swallowing (eg, necessitating changes in diet)	**6 =** Gastric tube
Breathing (thought to be caused by MG)	**0 =** Normal	**2 =** Shortness of breath with exertion	**4 =** Shortness of breath at rest	**9 =** Ventilator dependence
Neck flexion or extension (weakest) (physician examination)	**0 =** Normal	**1 =** Mild weakness	**3[a] =** Moderate weakness (ie, ≈50%±15%)	**4 =** Severe weakness
Shoulder abduction (physician examination)	**0 =** Normal	**2 =** Mild weakness	**4[a] =** Moderate weakness (ie, ≈50%±15%)	**5 =** Severe weakness
Hip flexion (physician examination)	**0 =** Normal	**2 =** Mild weakness	**4[a] =** Moderate weakness (ie, ≈50%±15%)	**5 =** Severe weakness
				Total MGC score (range, 0-50)

Neurology 2010:74;1434-1440

MGII

- 22 patient-reported items
- 6 examination items
- Total Score
- Ocular Score
- Generalized Score

MG Impairment Index (MGII)™ - Patient Questionnaire

Name: _____

Date: _____

INSTRUCTIONS:

Please answer the following questions regarding your symptoms. Only consider those that you think are related to myasthenia. Check the answer that best describes your symptoms over the past 2 weeks.

PROBLEMS WITH YOUR EYES: Please answer regarding the past 2 weeks.

1. Double vision throughout the day

Have you experienced episodes of double vision? If yes, at what time do they occur **(on average)**?	No Double Vision ☐ 0	Episodes only in the evenings ☐ 1	Episodes starting in the afternoons ☐ 2	Constant or present most of the day ☐ 3

2. Double vision with activities

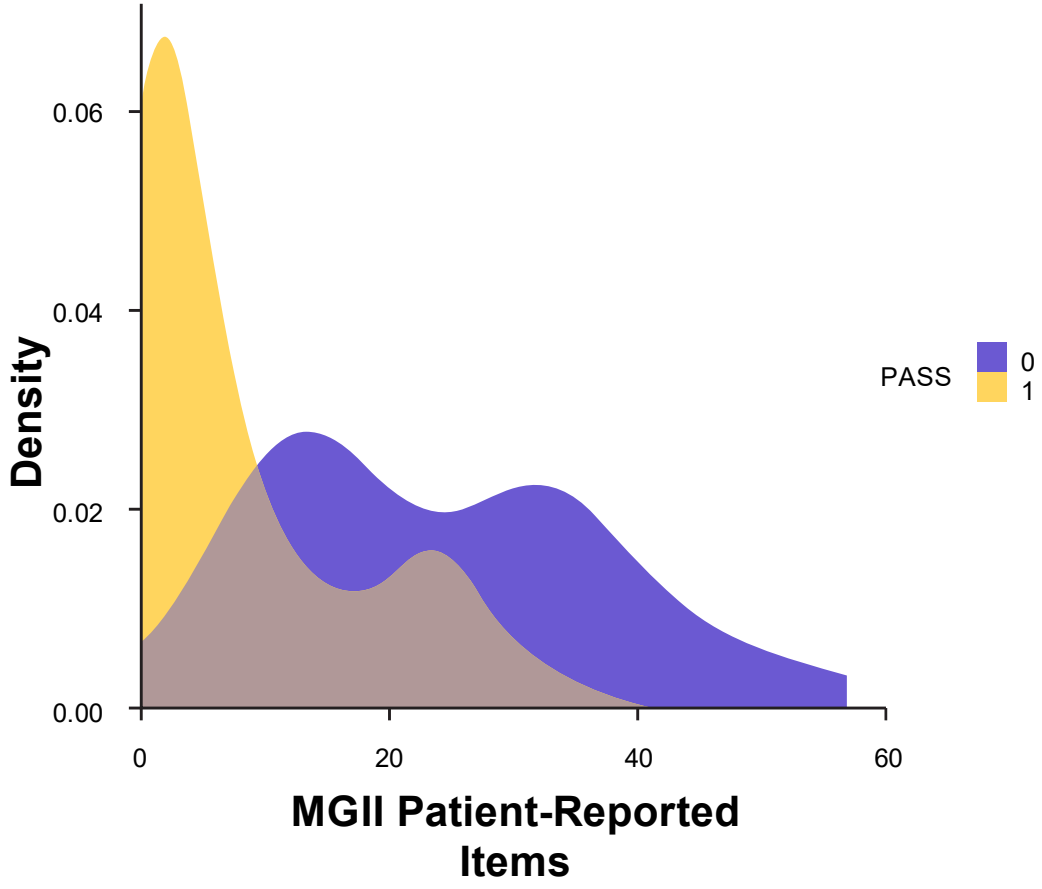
Have you experienced double vision with activities such as reading, driving, watching TV or using a computer? If yes, how long does it take **(on average)** before the double vision occurs?	No Double Vision ☐ 0	After more than 1 hour ☐ 1	After less than 1 hour, but not immediately ☐ 2	Constant double vision or it starts immediately ☐ 3

3. Severity of double vision

Have you experienced double vision? If yes, how severe has it been **(at your worst)**?	No Double Vision ☐ 0	Mild: it doesn't affect my daily activities ☐ 1	It affects my activities but no need to cover one eye ☐ 2	I need to cover one eye to be able to function ☐ 3

Many Patients Have High Disease Burden

32% MG patients self-reported to have unacceptable MG symptoms



Survey of patients from a tertiary academic referral centre in Canada

	No PASS (n = 37)	PASS (n= 80)
Age	59.6 ± 14	61.5 ± 14
Female	25 (68%)	42 (54%)
Duration >3 years	23 (62%)	57 (71%)
MGII-Questionnaire	**24.0± 13.7**	**7.8 ± 9.4**
MGII-Ocular	**8.1±5.5**	**2.4±3.7**
MGII-Generalized	**8.1±4.7**	**2.9±3.7**

Mendoza et al. Neurology 2020

Many Patients Have Unacceptable Disease Burden

	Unacceptable Symptoms (n = 164)	Acceptable Symptoms (n= 93)
Age	58.3 ± 16	58.9 ± 15
Female	**99 (60%)**	**38 (41%)**
Duration (months)	105±117	119±121
PDN Dose	**18±14**	**10±8**
QMGS	**10.9±5.7**	**4.7±3.3**
MGC	**9.9±6.9**	**2.4±2.5**
MG-ADL	**6.6± 3.7**	**1.3±1.6**
MG-QoL 15	**25.3±14**	**7.6±8.7**
Fatigue	**52.9±9.5**	**41.3±9.4**

Cohort of 257 MG patients

Tertiary Academic Centre in Canada

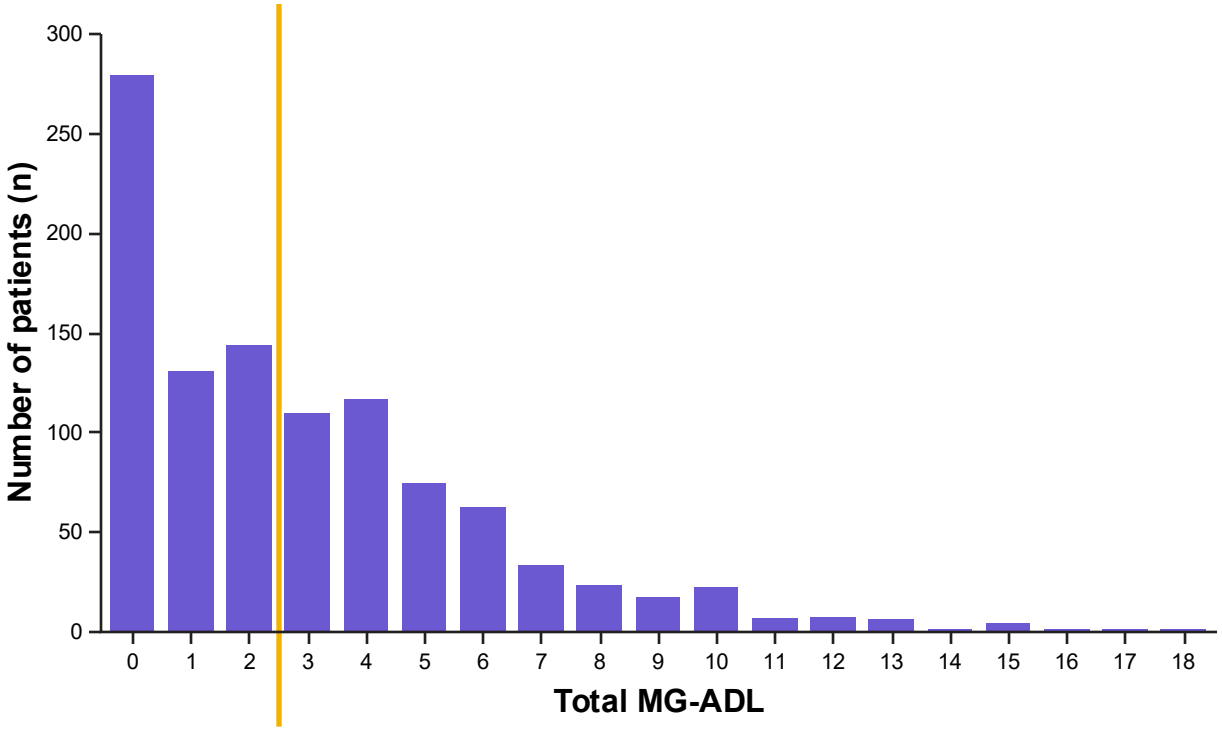
64% had unacceptable symptom burden

Mean disease duration was 8.8 years

Mendoza et al. Neurology 2020

Many Patients Have Unacceptable Disease Burden

Measures of Disease Activity by Myasthenia Gravis Activities of Daily Living (MG-ADL)



Acceptable Threshold

Patient-Reported Symptom Severity in a Nationwide Myasthenia Gravis Cohort

Cross-sectional Analysis of the Swedish GEMG Study

Malin Petersson, MD, Amalia Feresiadou, MD, Daniel Jons, MD, Andreea Ilinca, MD, PhD, Fredrik Lundin, MD, PhD, Rune Johansson, MD, Anna Budzianowska, MD, Anna-Karin Roos, MD, Viktor Kågström, MD, Martin Gunnarsson, MD, PhD, Peter Sundström, MD, PhD, Fredrik Piehl, MD, PhD, and Susanna Brauner, MD, PhD

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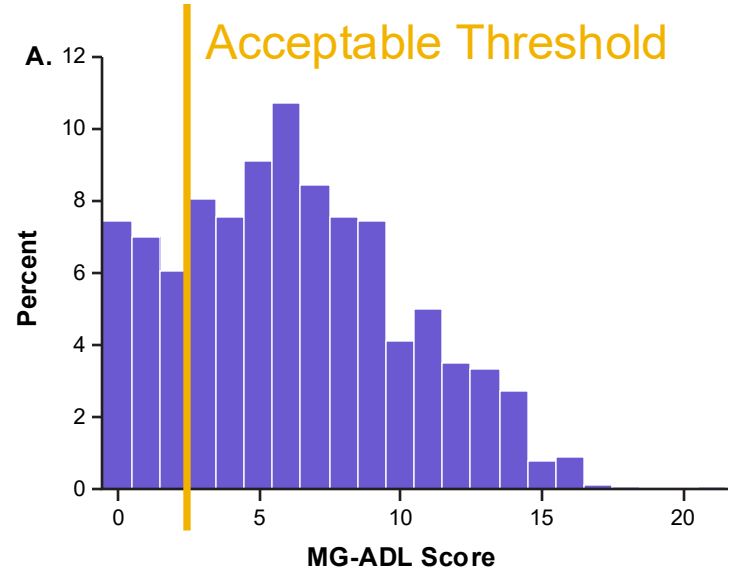
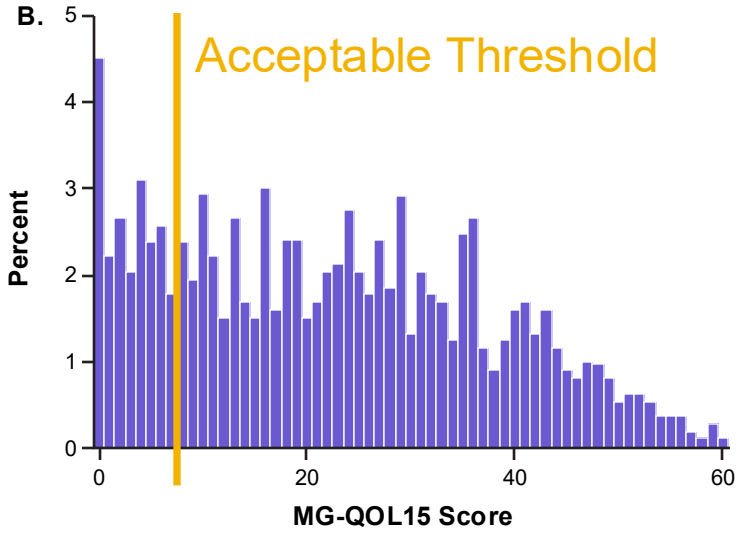
Neurology® 2021;97:e1382-e1391. doi:10.1212/WNL.0000000000012604

47% of patients were above MG-ADL cut point for patient-acceptable symptoms

Unacceptable Disease Burden

Many Patients Have Unacceptable Disease Burden





Received: 3 December 2018 | Revised: 5 August 2019 | Accepted: 30 August 2019
DOI: 10.1002/mus.26695

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Cross-sectional analysis of the Myasthenia Gravis Patient Registry: Disability and treatment

In this cohort, mean disease duration was 9 years

Limitations of Traditional Immunosuppressant Therapies

- **Nonselective**: Widespread suppression of immune system
- **Delayed response**: Can take months and up to a year
- Adverse events
- Monitoring of therapy
- Availability (e.g. PLEX, IVIG)

Patients' Experiences

Neurol Ther (2021) 10:1103–1125
https://doi.org/10.1007/s40120-021-00285-w

ORIGINAL RESEARCH

The Lived Experience of Myasthenia Gravis: A Patient-Led Analysis

Nancy Law · Kelly Davio · Melissa Blunck · Dawn Lobban · Kenza Seddik

Fluctuating & unpredictable symptoms

Treatment inertia, often resulting in under-treatment

Sense of disconnect with healthcare professionals

What did we learn from this analysis?

This international patient-led analysis of over 114 patient insights showed that living with myasthenia gravis significantly impacts many aspects of life.

Five themes that describe the experience of living with myasthenia gravis were articulated by the patient authors, including:

- living with fluctuating and unpredictable symptoms
- a constant state of adaptation, continual assessment and trade-offs in all aspects of life
- treatment inertia, often resulting in under-treatment
- a sense of disconnect with health care professionals
- feelings of anxiety, frustration, guilt, anger, loneliness and depression.

Summary

- Myasthenia Gravis is a treatable disease.
- Early diagnosis and treatment are associated with better outcomes
- Determining antibody subtype has implications for treatment.
- Most patients respond to standard of care treatments; however, a large number of patients still have disabling symptoms.
- Limitations are side effects and time to onset.
- There is a proportion of patients who are refractory to traditional therapies

Advances
in Myasthenia Gravis

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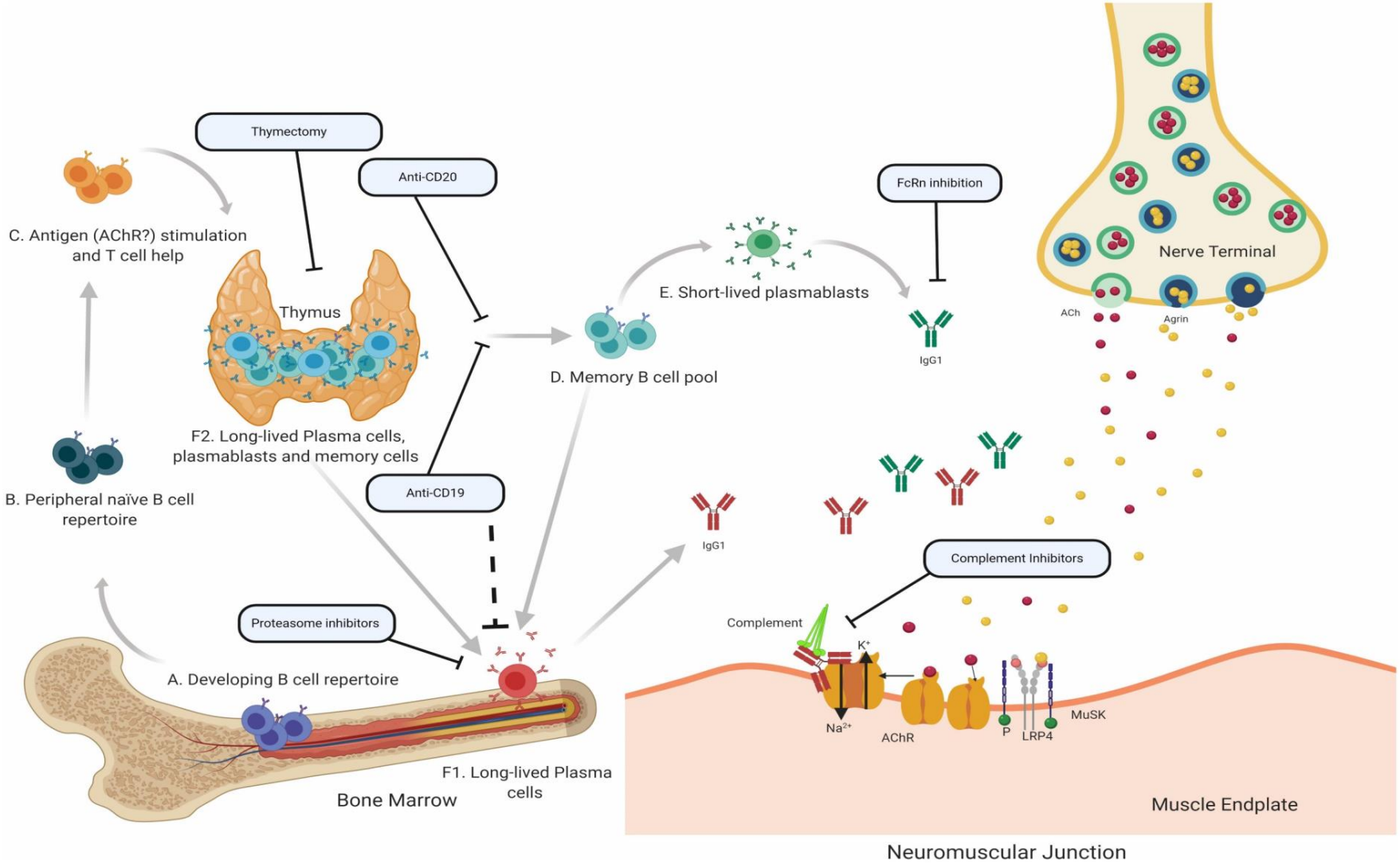
Clinical Frontiers

Novel Therapies for Myasthenia Gravis

Carolina Barnett-Tapia MD, PhD

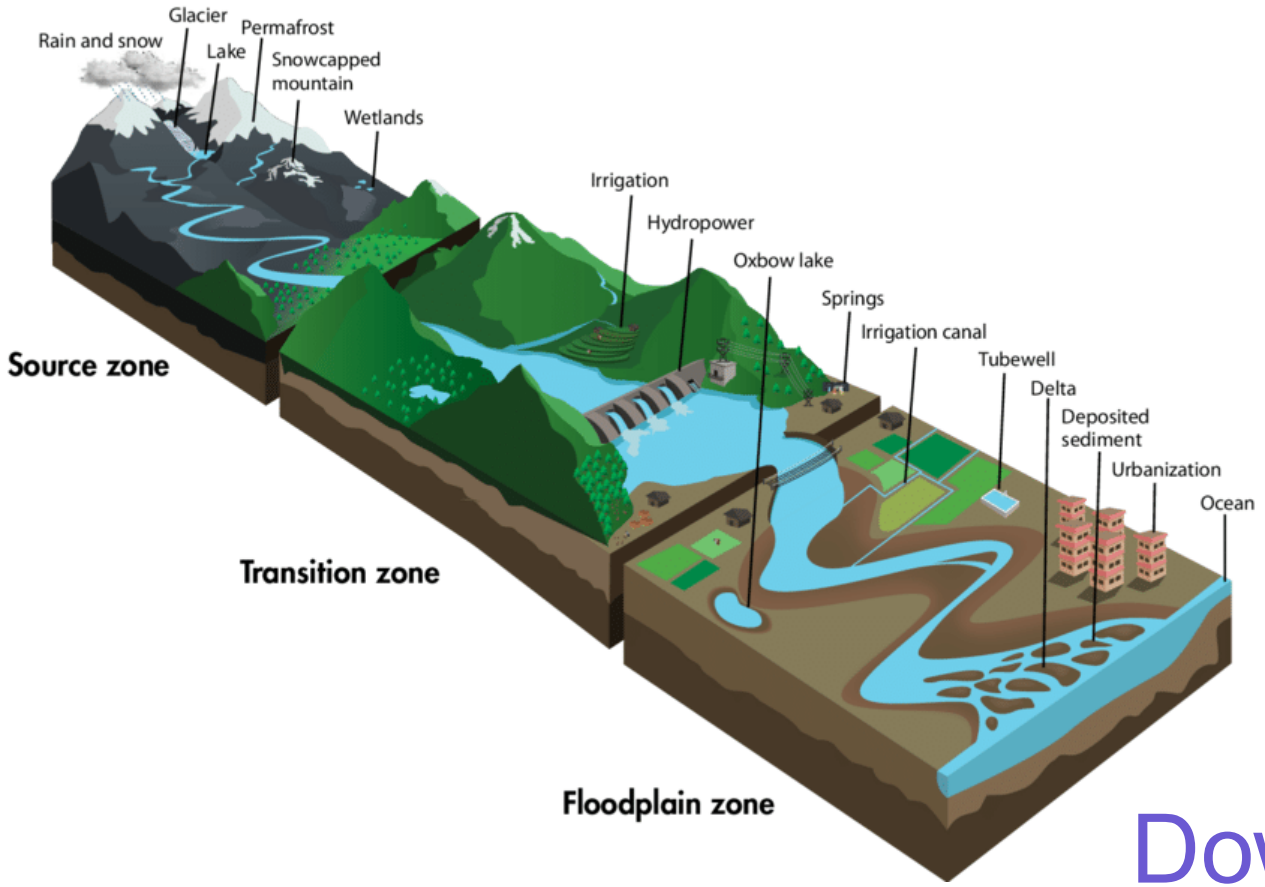
Therapeutic Approaches in Myasthenia Gravis



Fichtner et al. Frontiers Neurol. 2020;11.

Therapeutic Approaches in Myasthenia Gravis

Upstream



Downstream

Upstream and Downstream

Inhibit Antibody Production

B-cell depletion
Cell therapy

Remove Antibodies from Circulation

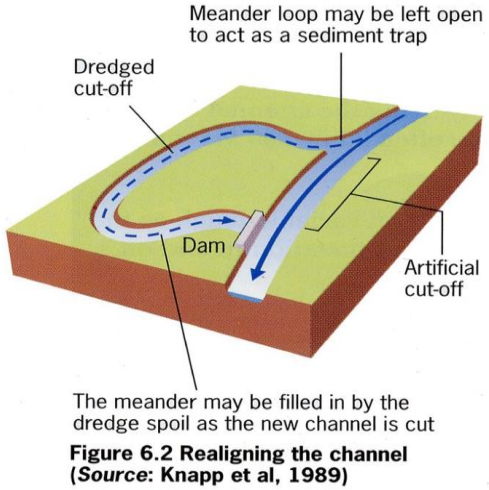


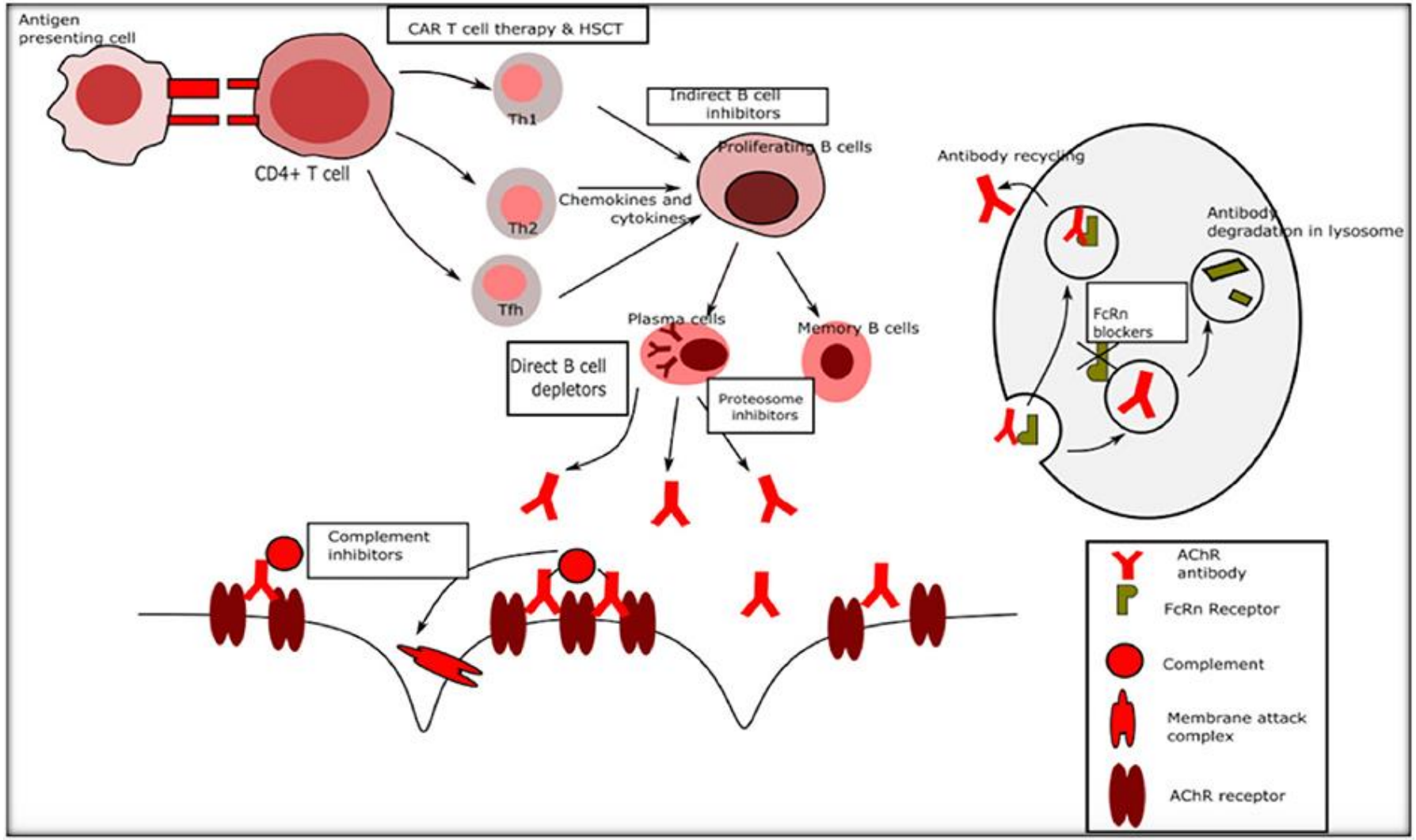
Figure 6.2 Realigning the channel (*Source*: Knapp et al, 1989)

- Plasma Exchange
- IVIG
- FcRn inhibitors

Prevent Antibody-mediated Damage

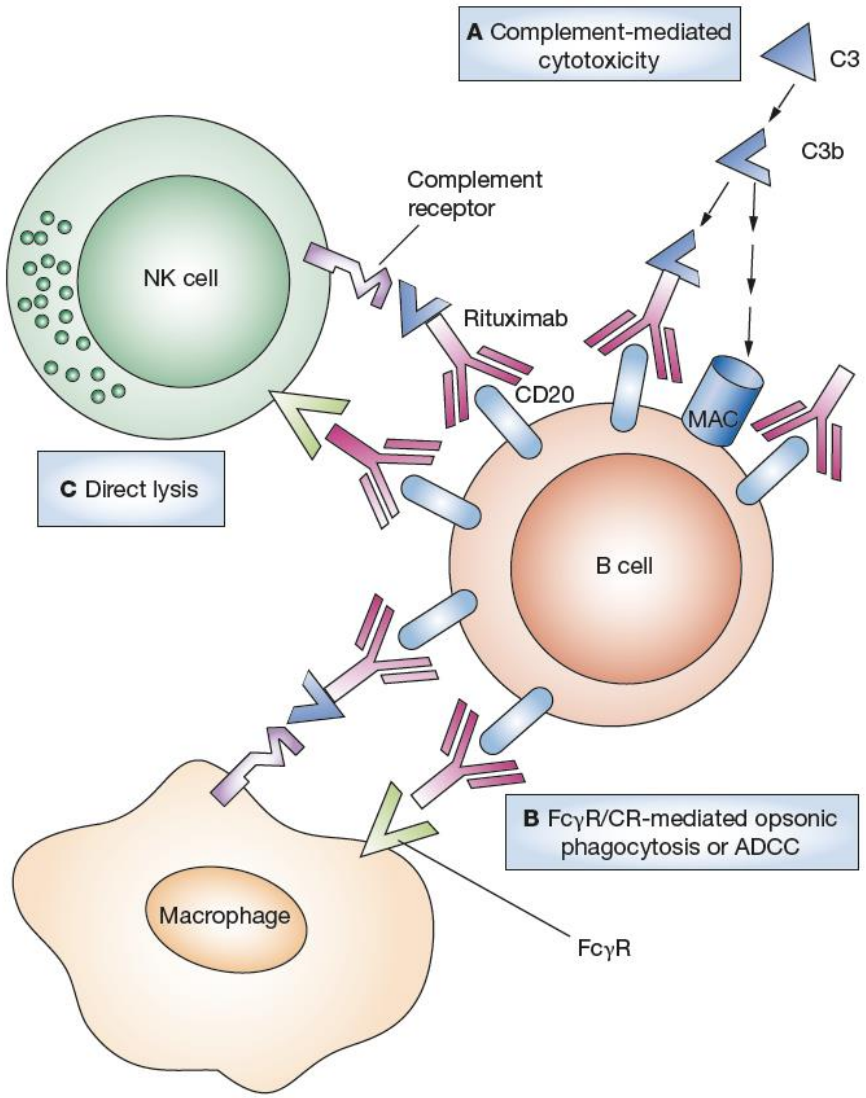
Complement inhibitors

Novel Treatments for MG



Menon et al. Frontiers Neurol. 2020;11:538.

B Cell Depletion – Rituximab



- Monoclonal antibody, CD20
- B-cell destruction
- Reduction antibody production

Poll #3: Have you used rituximab for the treatment of MG in your practice?

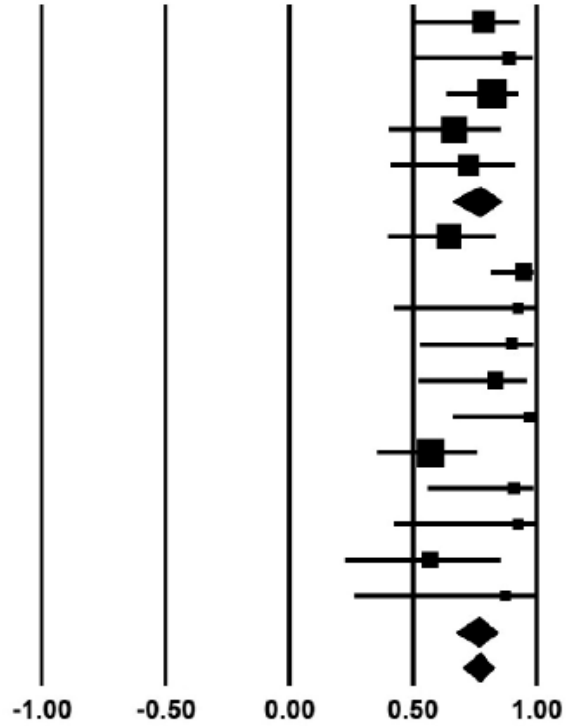
Rituximab – MuSK

- 56% RTX-treated patients had excellent outcome compared to 16% controls
- 29% RTX needed PDN vs 79% controls at follow-up
- NNT=2

Hehir et al. Neurology 2017.

Rituximab – AChRAb

Group by RTX dose	Study name	Statistics for each study: Event rate	Lower limit	Upper limit	Z-Value	p-Value
low dosage	Jing, S.	0.786	0.506	0.929	1.995	0.046
low dosage	Choi, K.	0.889	0.500	0.985	1.961	0.050
low dosage	Chan, F.	0.821	0.636	0.924	3.093	0.002
low dosage	Sun, F.	0.667	0.406	0.854	1.266	0.206
low dosage	Blum, S.	0.727	0.414	0.910	1.449	0.147
low dosage		0.771	0.661	0.853	4.357	0.000
routine dosage	Tess Litchman.	0.647	0.404	0.832	1.194	0.232
routine dosage	Topakian, R.	0.949	0.817	0.987	4.019	0.000
routine dosage	Singh, N.	0.929	0.423	0.996	1.748	0.081
routine dosage	Roda, R. H.	0.900	0.533	0.986	2.084	0.037
routine dosage	Landon-Cardinal, O.	0.833	0.523	0.958	2.078	0.038
routine dosage	Robeson, K. R.	0.971	0.664	0.998	2.436	0.015
routine dosage	Afanasiev, V.	0.571	0.360	0.760	0.652	0.514
routine dosage	Diaz-Manera, J.	0.909	0.561	0.987	2.195	0.028
routine dosage	Nowak, R. J.	0.929	0.423	0.996	1.748	0.081
routine dosage	Maddison, P.	0.571	0.230	0.856	0.377	0.706
routine dosage	Illa, I.	0.875	0.266	0.993	1.287	0.198
routine dosage		0.768	0.676	0.840	5.083	0.000
Overall		0.770	0.701	0.826	6.695	0.000



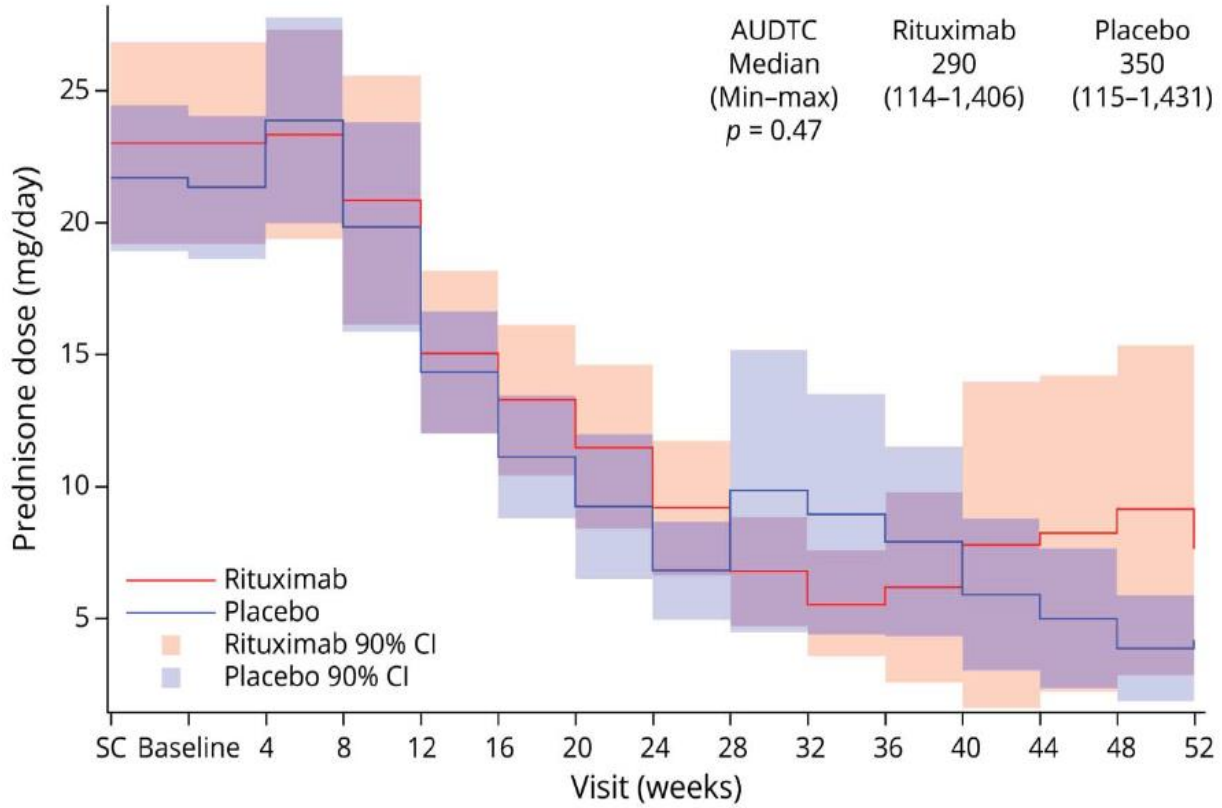
Meta Analysis

Fig. 2. Forest plot showing the efficacy of RTX in AChR-MG patients and 95% confidence interval (CI).

Rituximab – AChRAb

BeatMG

B Cell Targeted Treatment In Myasthenia Gravis: A Phase II Trial of Rituximab In Myasthenia Gravis



- **52 patients**: 25 RTX, 27 placebo
- No difference in prednisone dose or symptoms.

Nowak et al. Neurology 2021.

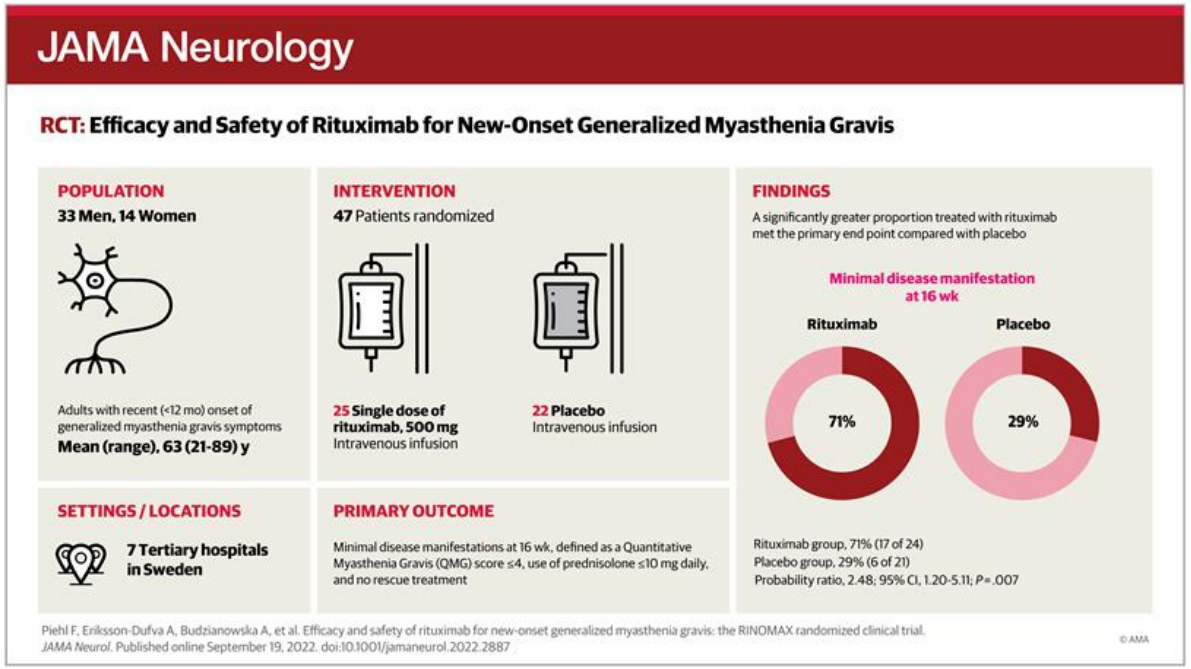
Rituximab – AChRAb

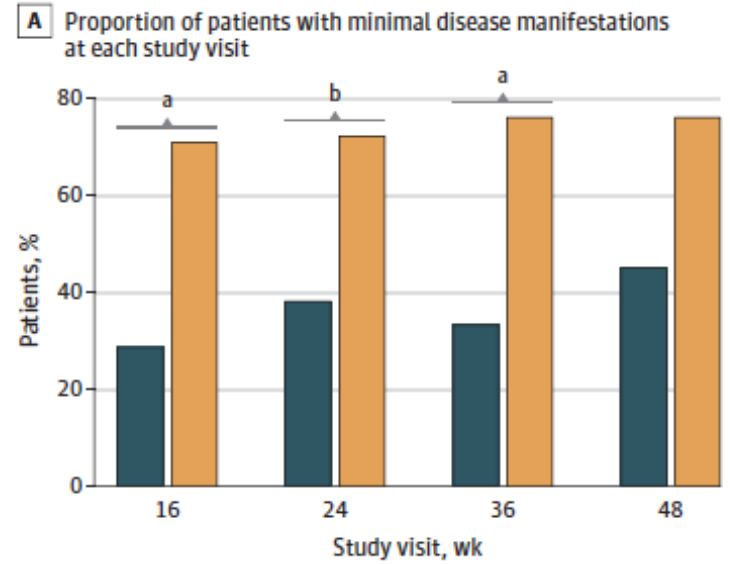
JAMA Neurology | Original Investigation

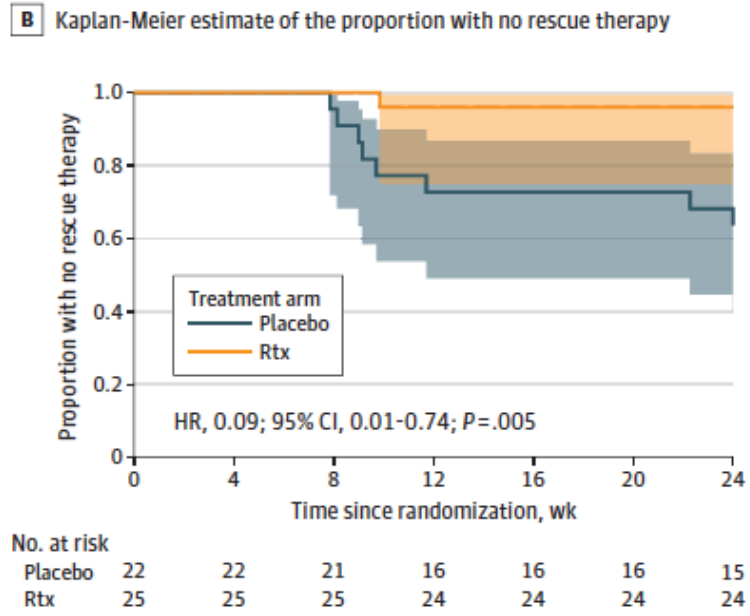
Efficacy and Safety of Rituximab for New-Onset Generalized Myasthenia Gravis

The RINOMAX Randomized Clinical Trial

Fredrik Piehl, MD, PhD; Ann Eriksson-Dufva, MD; Anna Budzianowska, MD, PhD; Amalia Feresiadou, MD; William Hansson, MD; Max Albert Hietala, MD, PhD; Irene Håkansson, MD, PhD; Rune Johansson, MD; Daniel Jons, MD; Ivan Kmezic, MD; Christopher Lindberg, MD, PhD; Jonas Lindh, MD, PhD; Fredrik Lundin, MD, PhD; Ingela Nygren, MD, PhD; Anna Rostedt Punga, MD, PhD; Rayomand Press, MD, PhD; Kristin Samuelsson, MD, PhD; Peter Sundström, MD, PhD; Oskar Wickberg, MD; Susanna Brauner, MD, PhD; Thomas Frisell, PhD







Inebilizumab – AChRAb and MuSK MG

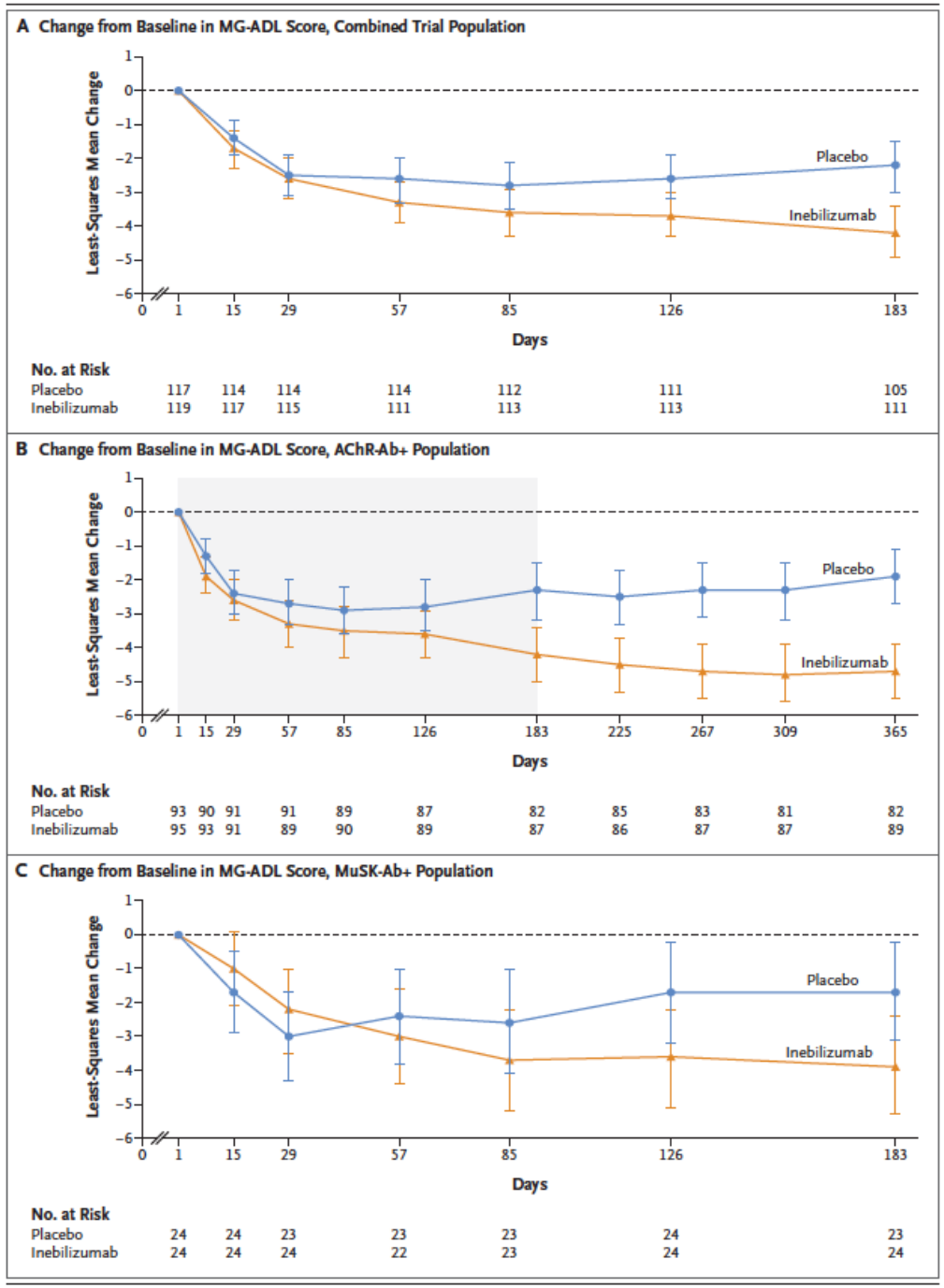
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Inebilizumab in Generalized Myasthenia Gravis

R.J. Nowak,[1] M. Benatar,[2] E. Ciafaloni,[3] J.F. Howard, Jr.,[4] M.I. Leite,[5] K. Utsugisawa,[6] J. Vissing,[7] M. Rojavin,[8] Q. Li,[8] F. Tang,[8] Y. Wu,[8] N. Rampal,[8] and S. Cheng,[8] for the MINT Investigators*

Monoclonal antibody, against CD19+ B cells



Published April 8, 2025 DOI: 10.1056/NEJMoa2501561

Complement Inhibition

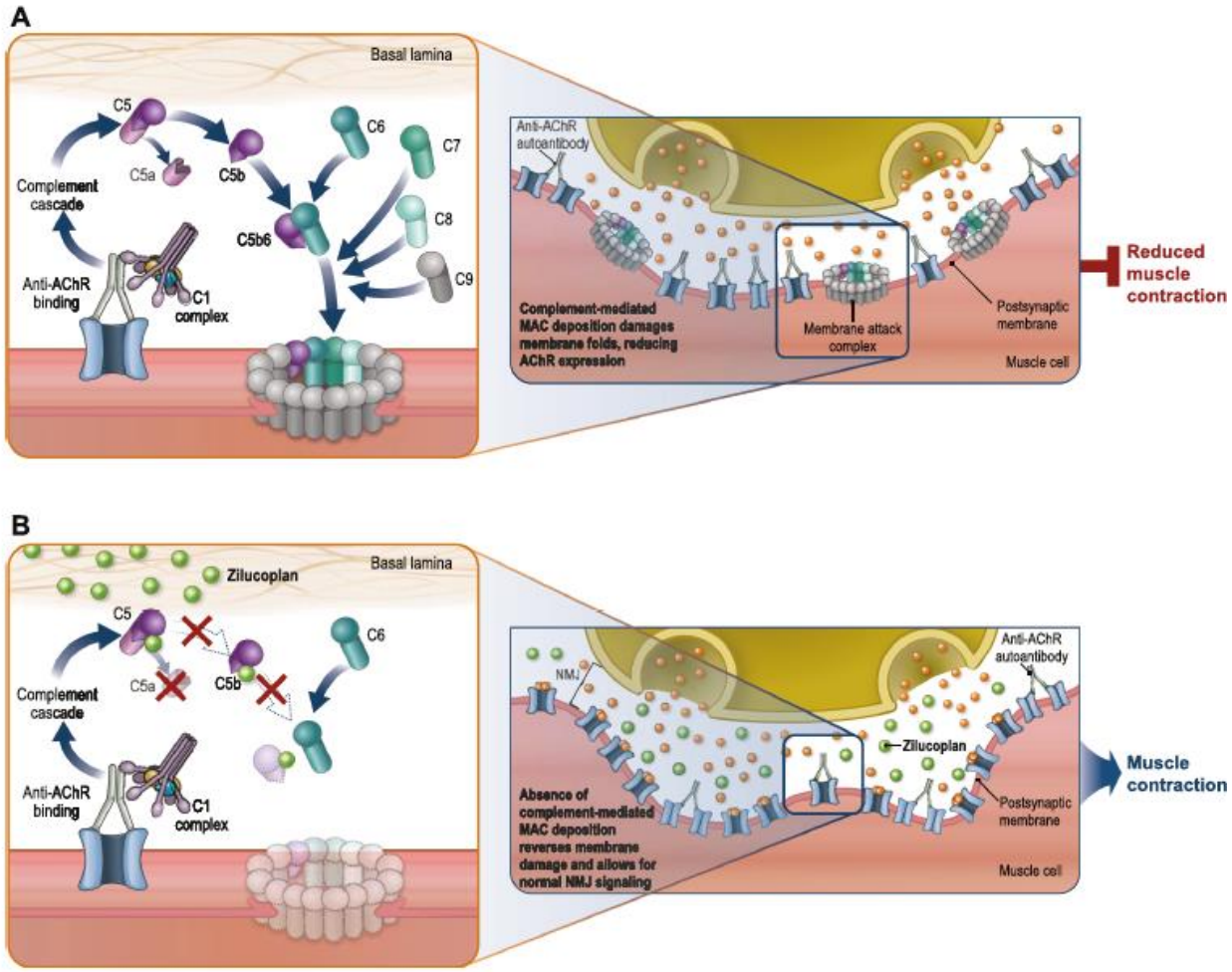


Figure 2. (A) Activation of the terminal complement cascade in gMG and (B) inhibition by zilucoplan. Graphics are schematic representations and are not true to scale. In panel A, cross-linking of AChRs by anti-AChR antibodies initiates the classical complement cascade, leading to cleavage of C5 and assembly of the MAC. In panel B, zilucoplan binds C5 at the location corresponding to C5b, thereby inhibiting both the cleavage of C5 and the binding of C6 to pre-formed C5b, thus preventing assembly of the MAC. ACh, acetylcholine; AChR, acetylcholine receptor; C[x], complement component [x]; gMG, generalized myasthenia gravis; MAC, membrane attack complex; NMJ, neuromuscular junction.

Complement inhibitors prevent downstream MAC assembly and secondary muscle destruction induced by complement.

Howard JF. Exp Op. Invest Drugs. 2021;30(5):1-11

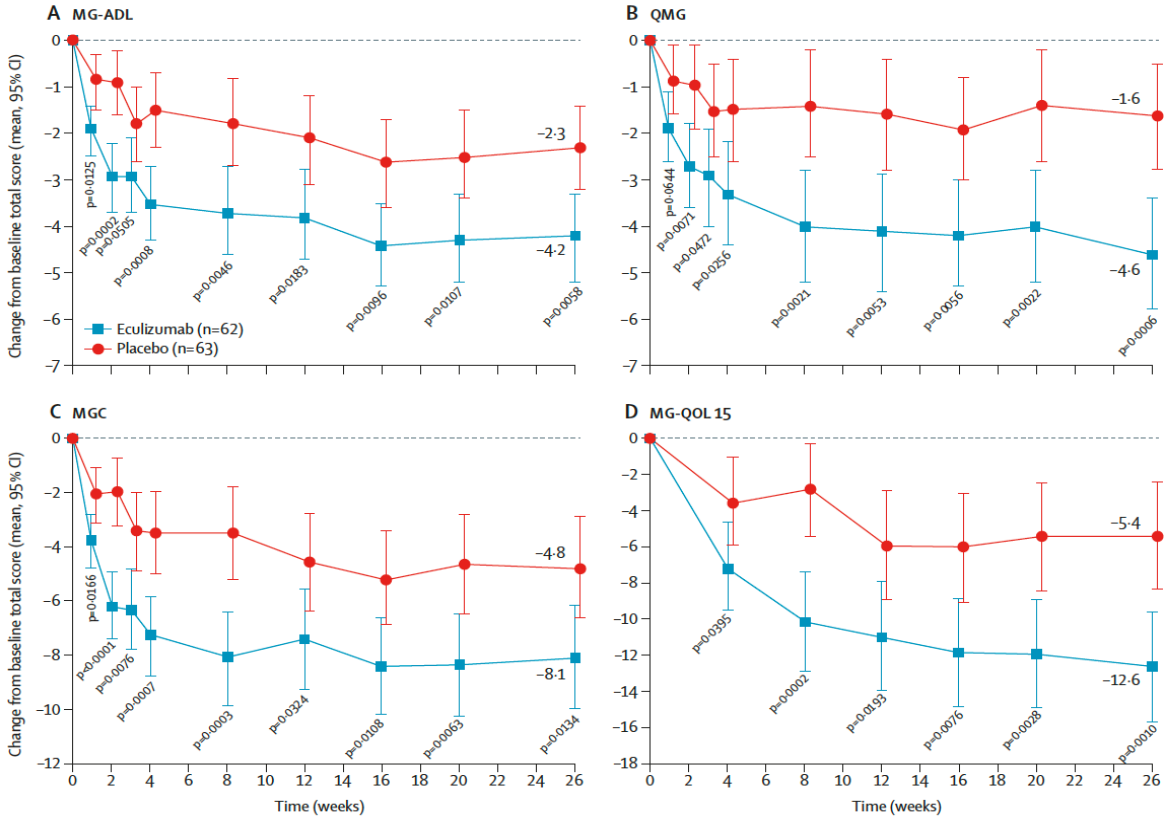
Complement Inhibition

Name	Route	Population	Status	Cost
Eculizumab **C5** **NCT01997229**	I.V. Weekly x 4, Then Q2 weeks	ACHRAb +, generalized Refractory disease	FDA, Health Canada approval Meningococcal vaccination	$$$
Ravalizumab **C5** **NCT03020293**	I.V. Every 2 weeks x 2, then every 8 weeks	ACHRAb +, generalized MGFA II-IV, MG-ADL ≥6	FDA, Health Canada approval Meningococcal vaccination	$?
Zilucoplan **C5 y C5b** **NCT04115293**	S.C 0.3 mg/Kg day	ACHRAb +, generalized MGFA II-IV, MG-ADL ≥6, QMGS≥12	FDA, Health Canada approval Meningococcal vaccination	$?

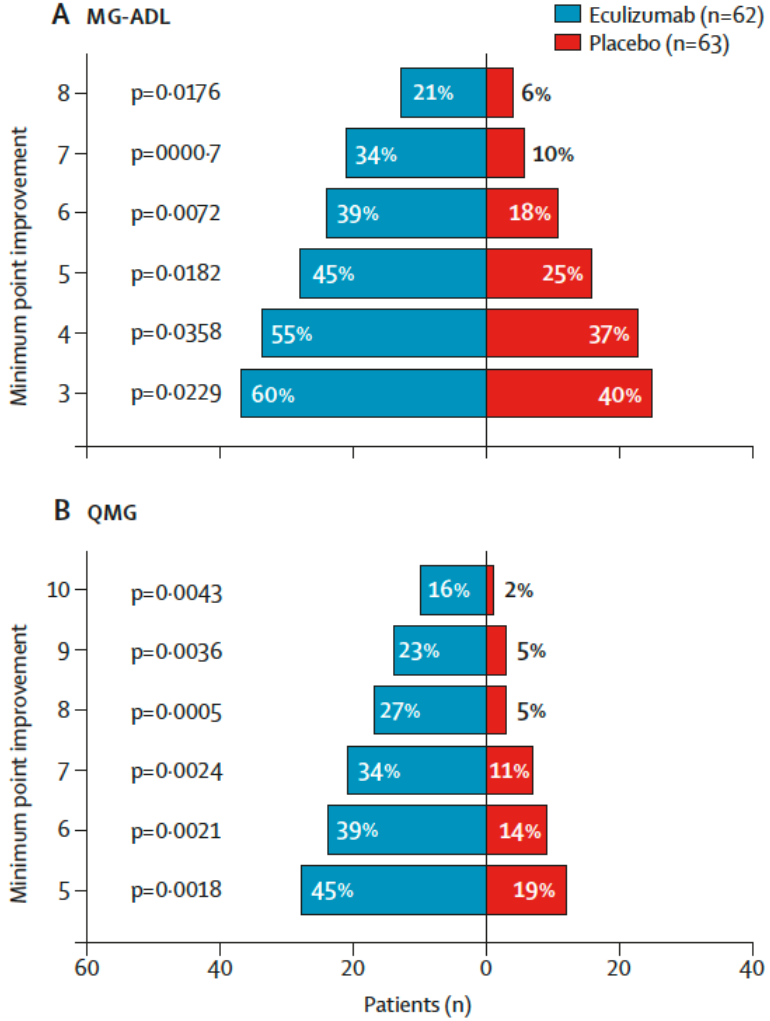
Eculizumab

Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

*James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group**



Refractory MG



Ravulizumab

NEJM Evidence

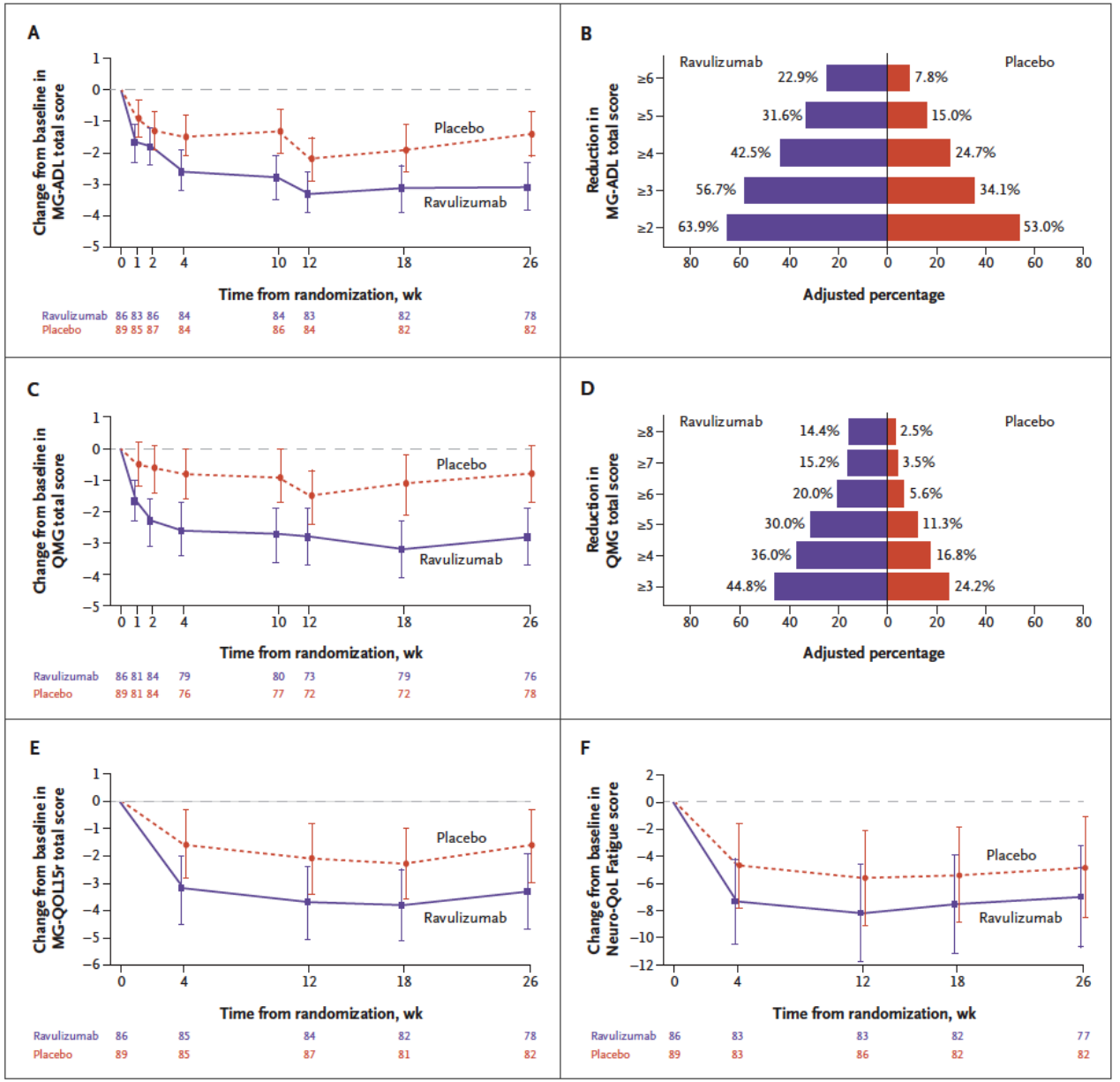
Published April 26, 2022
NEJM Evid 2022; 1 (5)
DOI: 10.1056/EVIDoa2100066

ORIGINAL ARTICLE

Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis

Tuan Vu, M.D.,[1] Andreas Meisel, M.D.,[2] Renato Mantegazza, M.D.,[3] Djillali Annane, M.D.,[4] Masahisa Katsuno, M.D.,[5] Rasha Aguzzi, M.S.,[6] Ahmed Enayetallah, M.D., Ph.D.,[6] Kathleen N. Beasley, Pharm.D.,[6] Nishi Rampal, M.D.,[6] James F. Howard, Jr., M.D.,[7] for the CHAMPION MG Study Group*

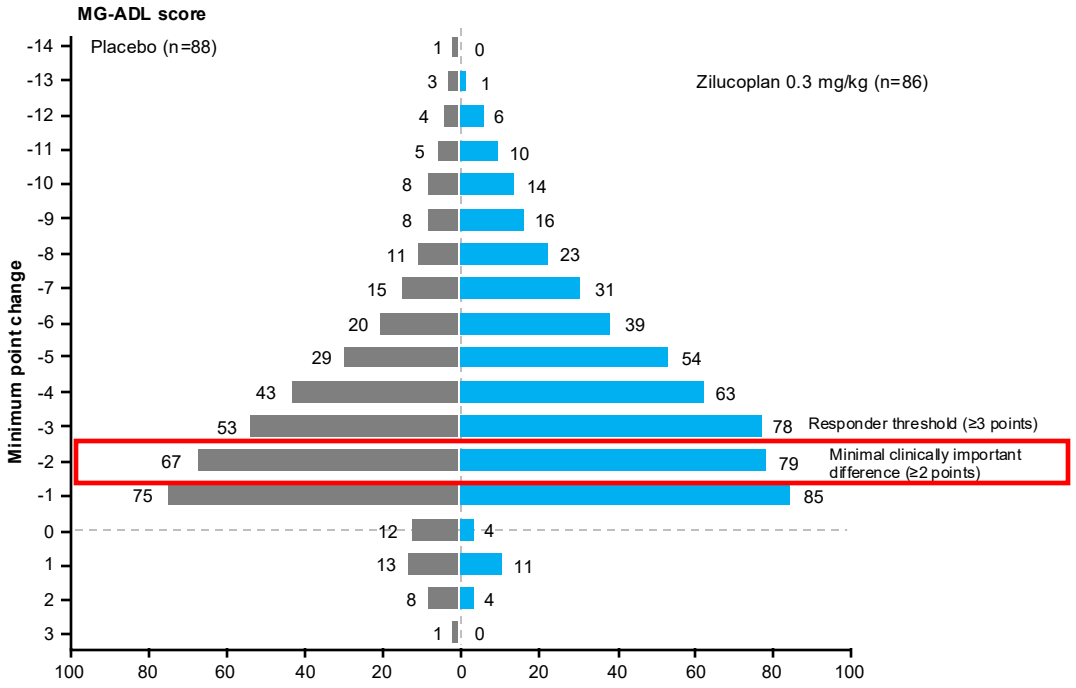
gMG Classes II-IV



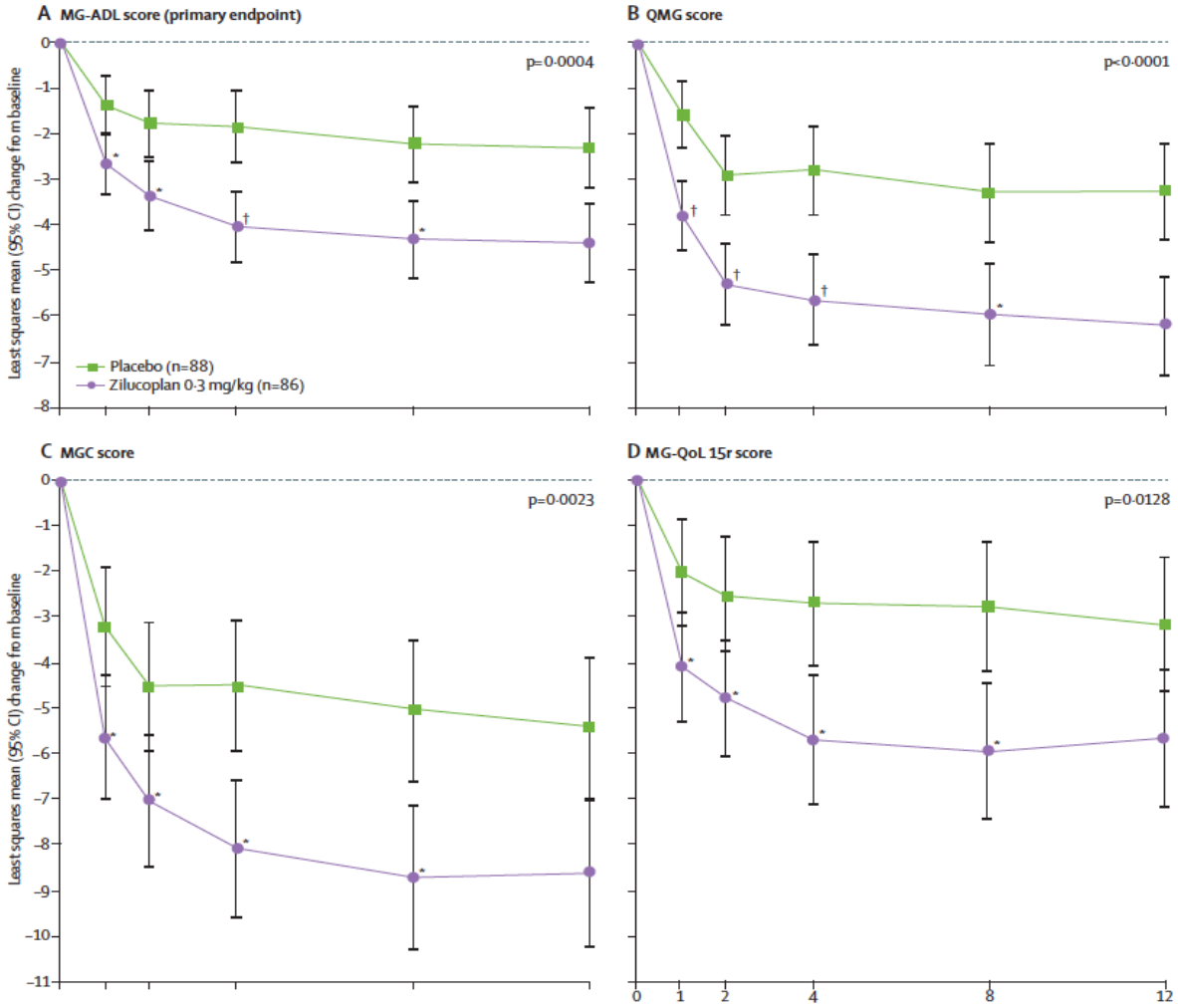
Zilucoplan

Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study

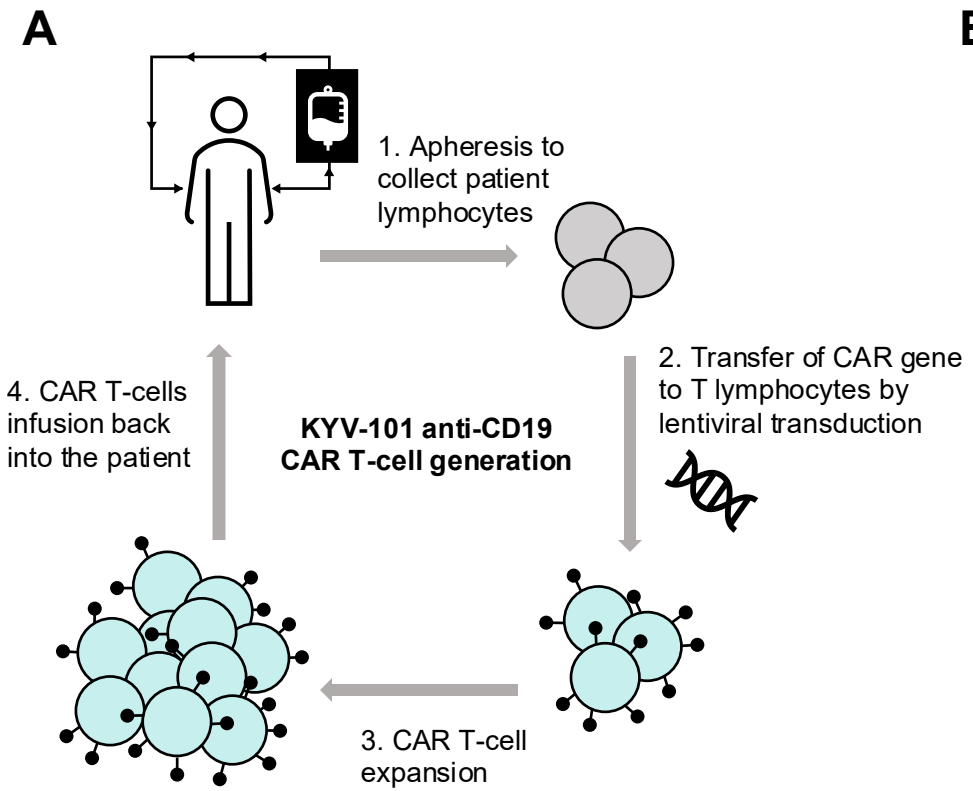
James F Howard Jr, Saskia Bresch, Angela Genge, Channa Hewamadduma, John Hinton, Yessar Hussain, Raul Juntas-Morales, Henry J Kaminski, Angelina Maniaol, Renato Mantegazza, Masayuki Masuda, Kumaraswamy Sivakumar, Marek Śmiłowski, Kimiaki Utsugisawa, Tuan Vu, Michael D Weiss, Małgorzata Zajda, Babak Boroojerdi, Melissa Brock, Guillemette de la Borderie, Petra W Duda, Romana Lowcock, Mark Vanderkelen, M Isabel Leite and the RAISE Study Team*

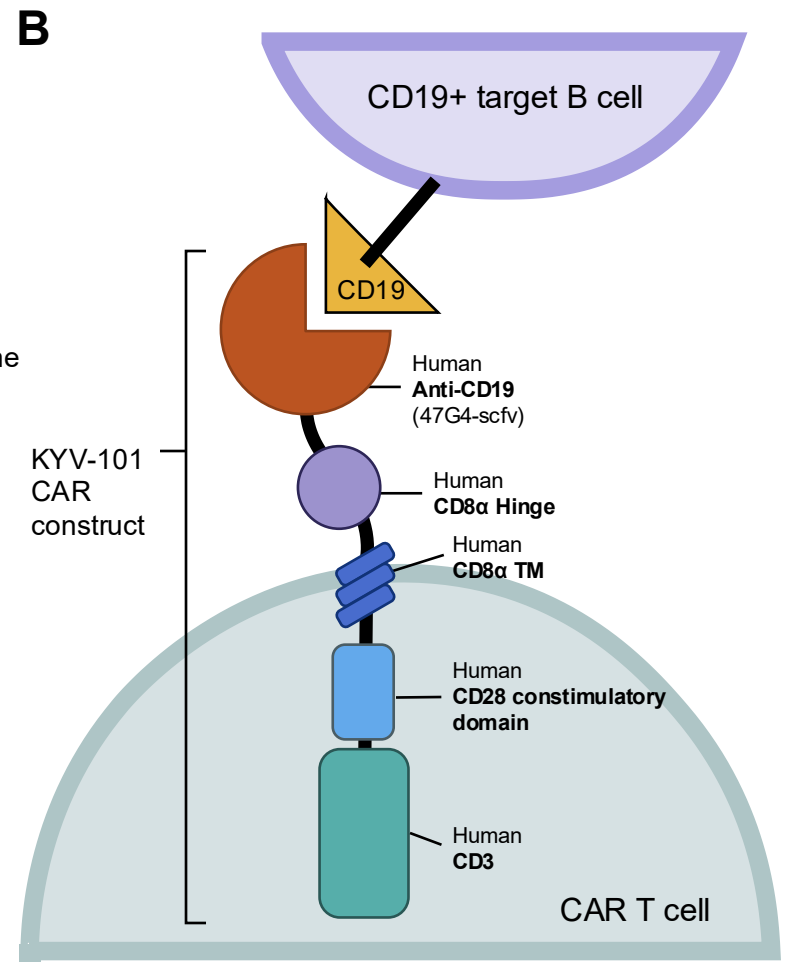


gMG Classes II-IV



Cell Therapy – CAR-T





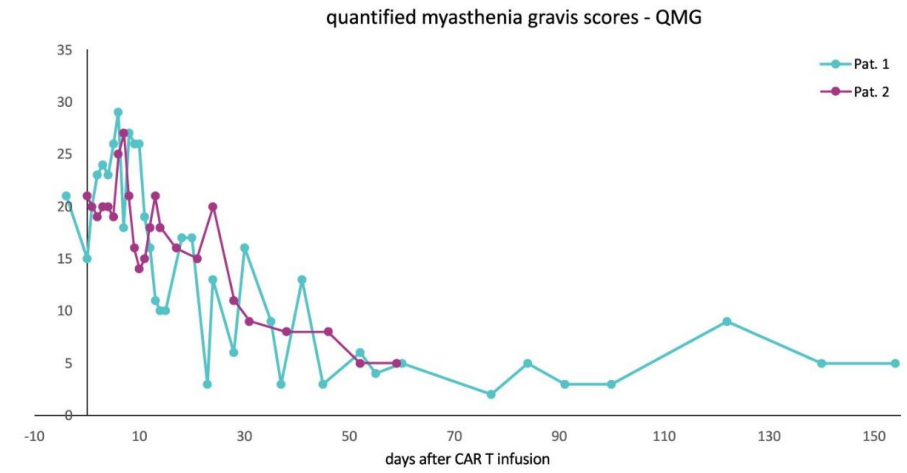
Chimeric Antigen Receptor (CAR) T cells

Modified to target specific cells

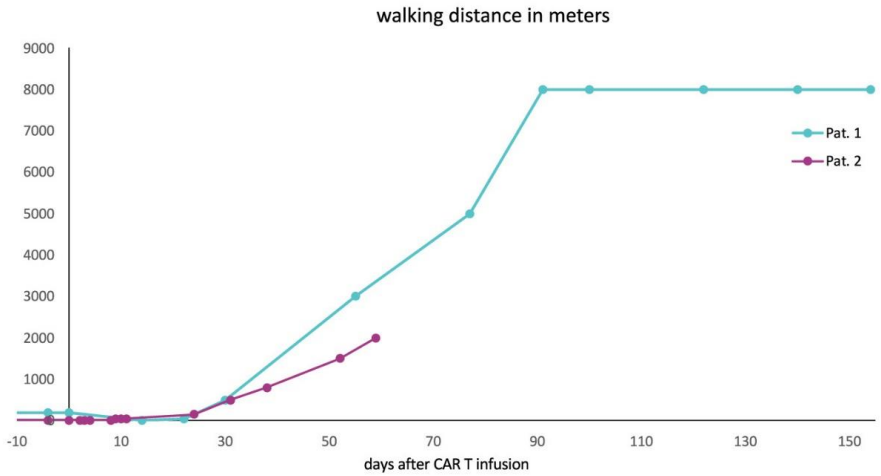
Motte, Jeremias et al. Neuron, Volume 112, Issue 11, 1757 - 1763.e2

Cell Therapy – CAR-T

A

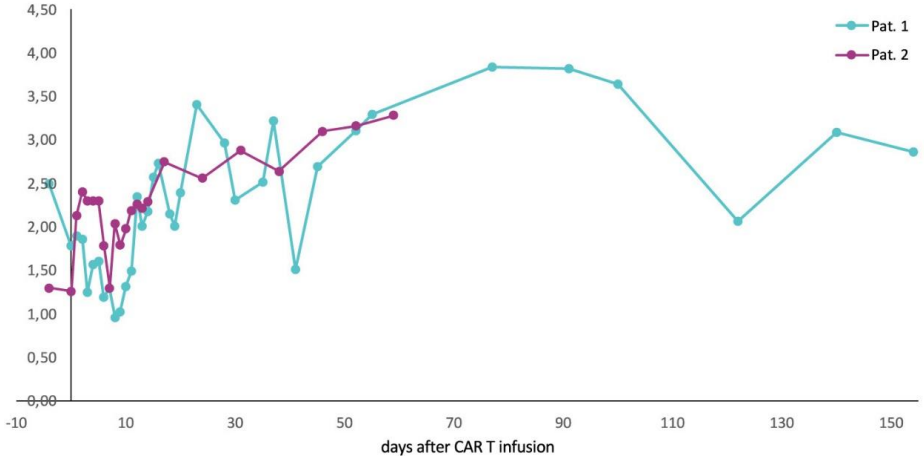


B

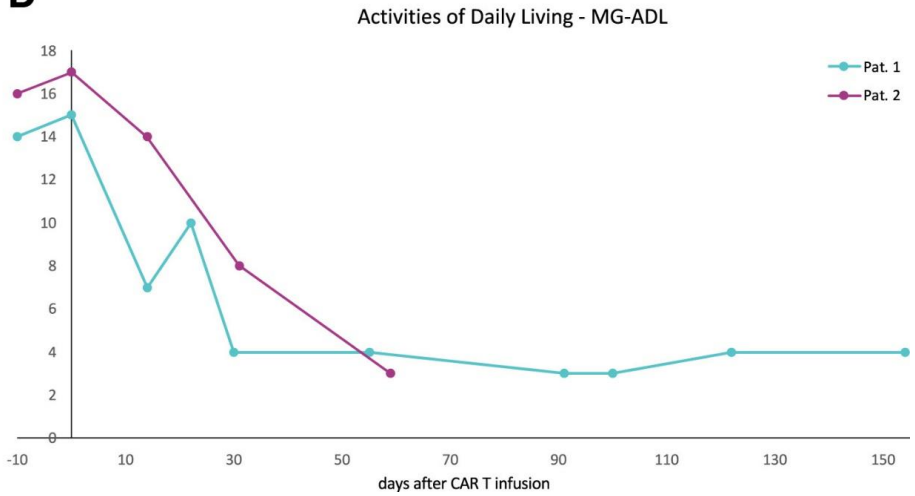


Patient with refractory MG

C



D



Motte, Jeremias et al. Neuron, Volume 112, Issue 11, 1757 - 1763.e2

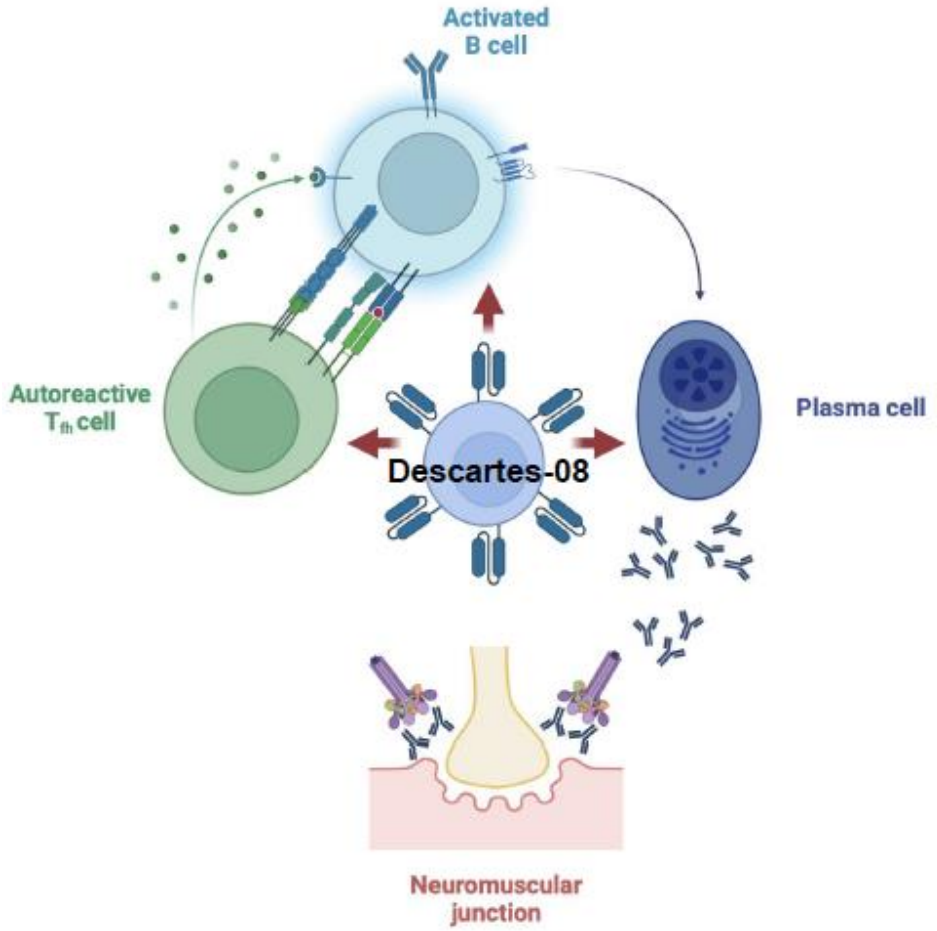
Cell Therapy – CAR-T

RNA-engineered chimeric antigen receptor T-cells (rCAR-T) areinherently safer than conventional (DNA-engineered) CAR-T

- rCAR-T leverages mRNA to achieve tunable duration, predictablePK, and controlled exposure
- No lymphodepletion (chemotherapy) needed
- All treatment is outpatient; can be done in community clinics

Descartes-08

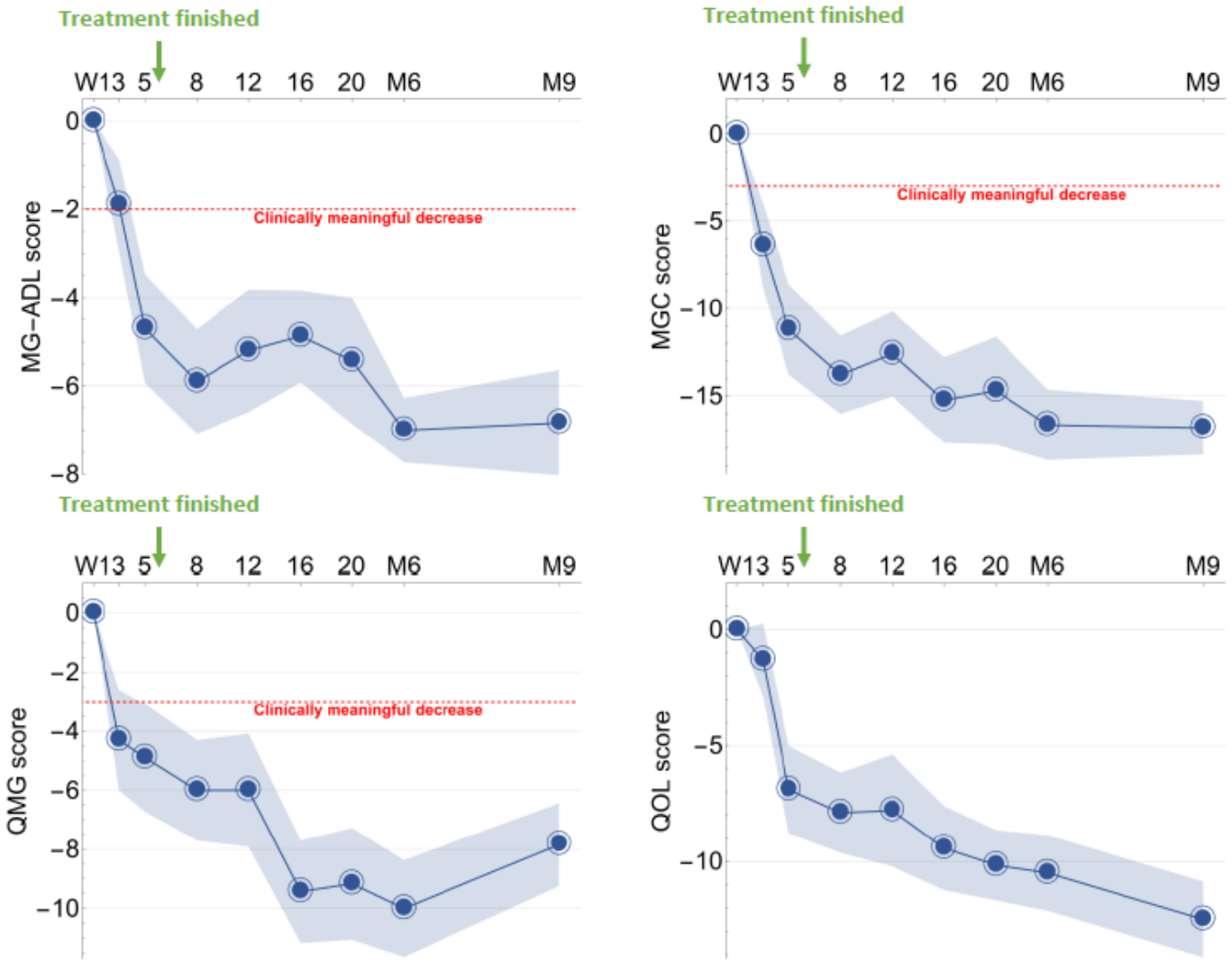
- CD8+ T cells
  - Enhanced killing and reduced inflammatory cytokine secretion versus pan T-cell approaches
- CAR binds BCMA
  - A highly specific plasma cell antigen
- Mechanism of action may be multi-modal
  - Direct: eliminate autoantibody-producing plasma cell clones
  - Indirect: inhibit autoreactive T-cell and B-cell clones



Cell Therapy – CAR-T

THE LANCET
Neurology
Volume 22, Issue 7, July 2023, Pages 578-590

Phase 3 study underway



Other MG treatments in the pipeline

Class	Agent	Population overview	Primary endpoint
IL-6 inhibitor	Tocilizumab NCT05067348	• MGFA II–IV gMG • MG-ADL ≥5, QMGS≥11 • AChR-Ab+	Change in QMGS from baseline
Inhibition of BAFF and APRIL	Telitacicept NCT05737160	• MGFA II-III • AChRAB and MuSK + • QMGS ≥ 8	Change in QMGS from baseline
B-cell and plasma cell targeting therapies	Remibrutinib (oral) BTK inhibitor NCT06744920	• MGFA II-IV • AChRAB and MuSK + • MG-ADL ≥6	Change in MG-ADL from baseline
	Blinatunomab (CD-19) NCT06836973	• MGFA I-IV, refractory • AChRAb, MuSK and LRP4 +	Change in MG-ADL from baseline
B-cell and T-cell targeting	Cladribine (oral) NCT06463587	• MGFA II-IV • AChRAb, MuSK and LRP4 + • MG-ADL ≥6	Change in MG-ADL from baseline
Comp. inhibitors	Gefurulimab NCT05556096	• MGFA II–IV AChR-Ab+ gMG • MG-ADL ≥6 • Meningococcal vaccination	Change in MG-ADL from baseline
	Pozelimab + Cemdisiran NCT05070858	• MGFA II–IV AChR-Ab+ gMG • MG-ADL ≥6 • Meningococcal vaccination	Change in MG-ADL from baseline
	Iptacopan (oral) NCT06517758	• MGFA II–IV AChR-Ab+ gMG • MG-ADL ≥6 • Meningococcal vaccination	Change in MG-ADL from baseline

Summary

- There are many potential targets for the treatment of gMG
- Antibody profile influences treatment selection
- Novel treatments for gMG are becoming more common – while this may improve outcomes, treatment decisions may become more complex

Advances
in Myasthenia Gravis

Emerging Biological Therapies and
Clinical Frontiers

Fc Inhibition Therapy in Myasthenia Gravis

Hans Katzberg MD, MSc

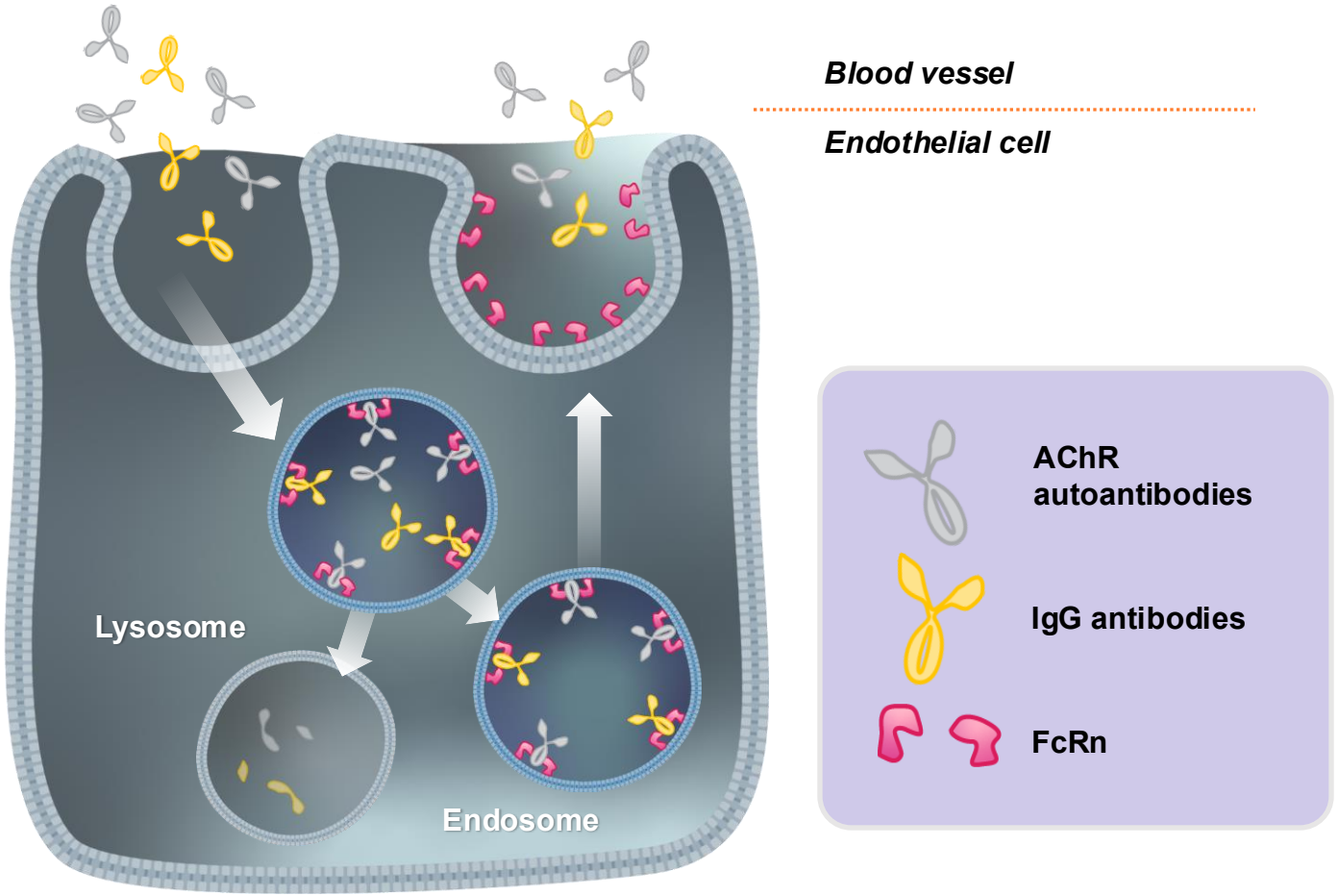
Outline

Review the pathophysiology of Fc receptor inhibition for treatment of myasthenia gravis (MG)

Understand the different Fc receptor inhibitor molecules in use and under investigation for treatment of MG

Poll #4: How do Fc receptor inhibitors work to improve disease states in myasthenia gravis?

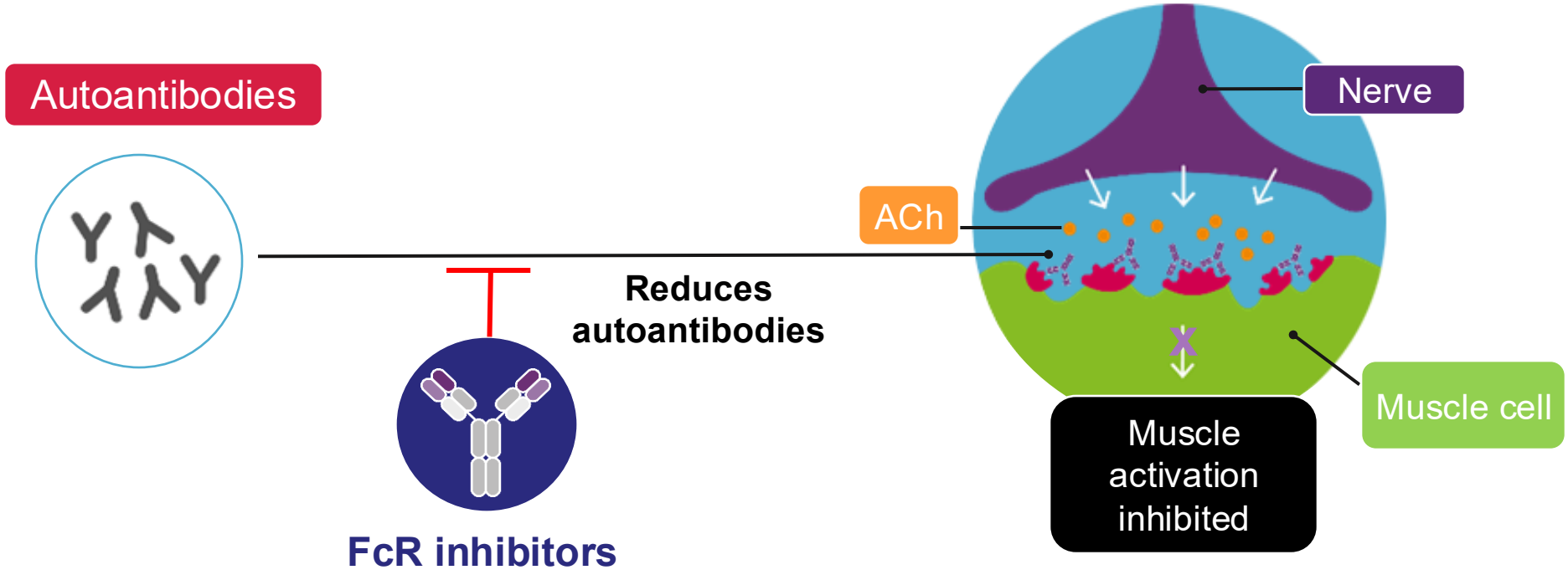
FcRn Plays a Key Role in gMG by Perpetuating IgG Antibodies



- FcRn binds IgG antibodies, preventing them from being destroyed in the lysosome
- In doing so, FcRn helps maintain high levels of circulating IgG antibodies, including AChR autoantibodies
- FcRn perpetuates the ability of AChR autoantibodies to attack structures such as AChR and damages the NMJ

FcR Inhibitors

Remove all IgG sub-classes (IgG1, IgG2, IgG3, and IgG4) and would therefore be expected to remove all known MG autoantibodies including AChR (IgG1) and MuSK (IgG4)



Poll #5: Which of the following statements about Fc receptor inhibitor molecules is correct?

Targeted Fc Receptor Inhibitor gMG therapies

	Efgartigomod	Rozanolixizumab	Nipocalimab	Batoclimab
Target	FcRn Blocker (fragment-based Ab)	FcRn blocker (full-length MAb)	FcRn blocker (full-length MAb)	FcRn blocker (full-length MAb)
Status	Approved (FDA/EMA/Health Canada)	Approved (FDA/EMA/Health Canada)	Approved by FDA; decisions pending from EMA, Health Canada	Ongoing phase 2 trials
gMG subtype	AChRAb+ gMG	AChRAb+ or MuSK+ gMG	AChRAb+	Unspecified gMG
ROA	IV infusion weekly for 4 weeks = 1 cycle, SC infusion being tested	Weight-based dosing weekly SC via infusion pump	IV load followed by IV infusion every 2 weeks	Weekly SC doses

Efgartigimod ADAPT Study Design in gMG

DESIGN

167 gMG patients

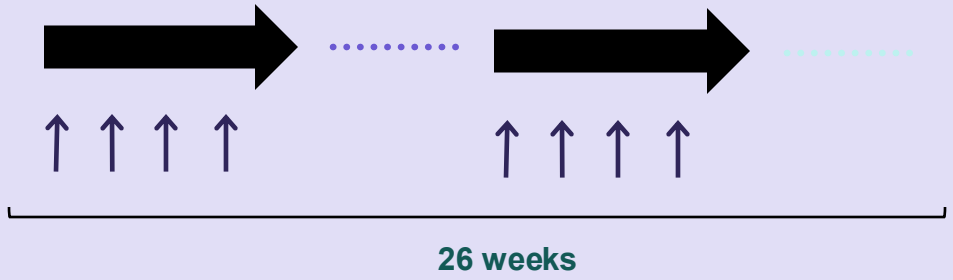
MGFA Class II, III, IV

AChR-antibody positive or negative

MG-ADL score ≥5 (>50% non-ocular)

On a minimum of one stable gMG treatment*

Patients randomized 1:1 to receive 10 mg/kg IV efgartigimod or placebo



Open Label Extension

Primary endpoint: MG-ADL responders (≥2-point improvement for ≥4 consecutive weeks) in AChR-Ab+ patients in cycle 1 (8 weeks)

DOSING

Treatment Cycles of 4 weekly IV infusions
(1 hour infusion)

All patients receive initial treatment cycle

Individualized treatment cycles
(*up to 3 cycles in 26 weeks*)

Time between cycles determined by duration of clinically meaningful improvement (CMI)

Retreatment criteria:

- ≥8 weeks since initiation of previous cycle
- Total MG-ADL ≥5 points (>50% non-ocular)
- For MG-ADL responders, no CMI in MG-ADL (i.e., <2-point reduction compared to start of cycle)

*(Acetylcholinesterase inhibitor, Steroid +/or Non-steroidal immunosuppressive therapy) gMG, generalized myasthenia gravis; IV, intravenous
Note: Patients requiring rescue therapy discontinued from the study treatment
Howard JF, Bril V, Vu T, et al. Lancet Neurology 2021; ClinicalTrials.gov identifier: NCT03669588. Updated February 8, 2022.Accessed May 11, 2023. https://clinicaltrials.gov/ct2/show/NCT03669588.

Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial

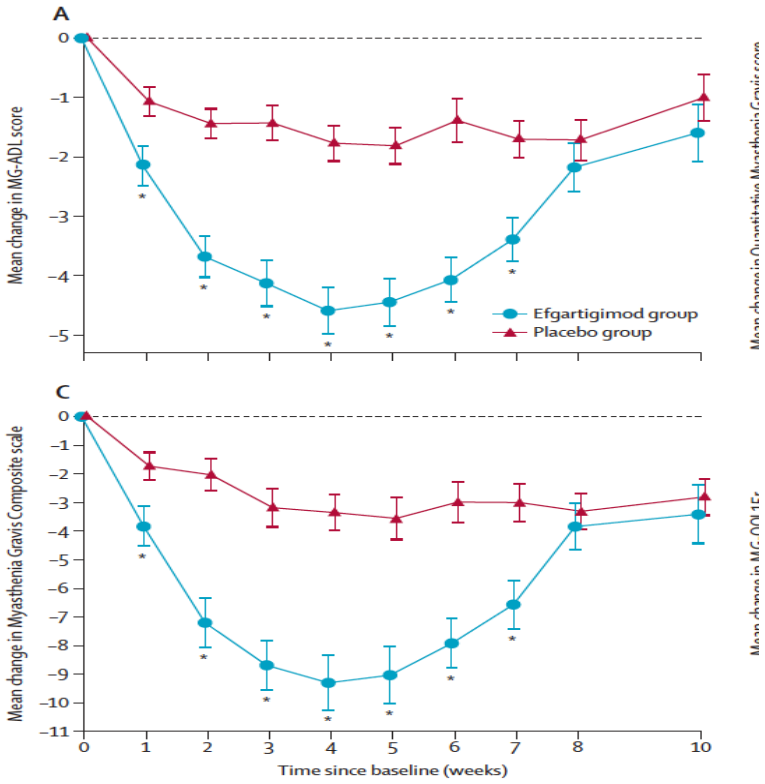
James F Howard Jr, Vera Bril, Tuan Vu, Chafic Karam, Stojan Peric, Temur Margania, Hiroyuki Murai, Malgorzata Bilinska, Roman Shakarishvili, Marek Smilowski, Antonio Guglietta, Peter Ulrichts, Tony Vangeneugden, Kimiaki Utsugisawa, Jan Verschuuren, Renato Mantegazza, and the ADAPT Investigator Study Group*

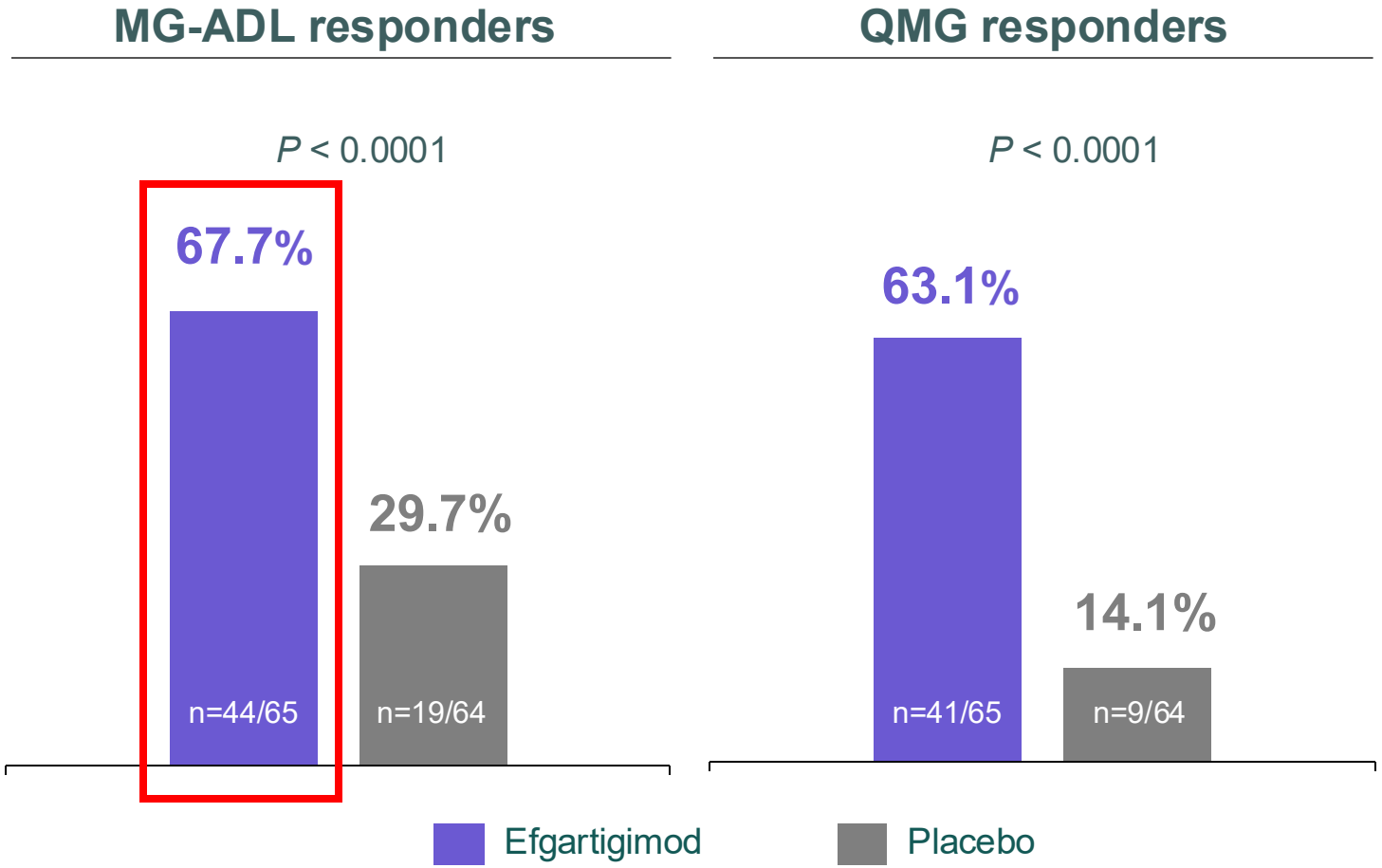
Primary

MG-ADL responder:
≥2-point improvement for at least four consecutive weeks during the first cycle*

Secondary

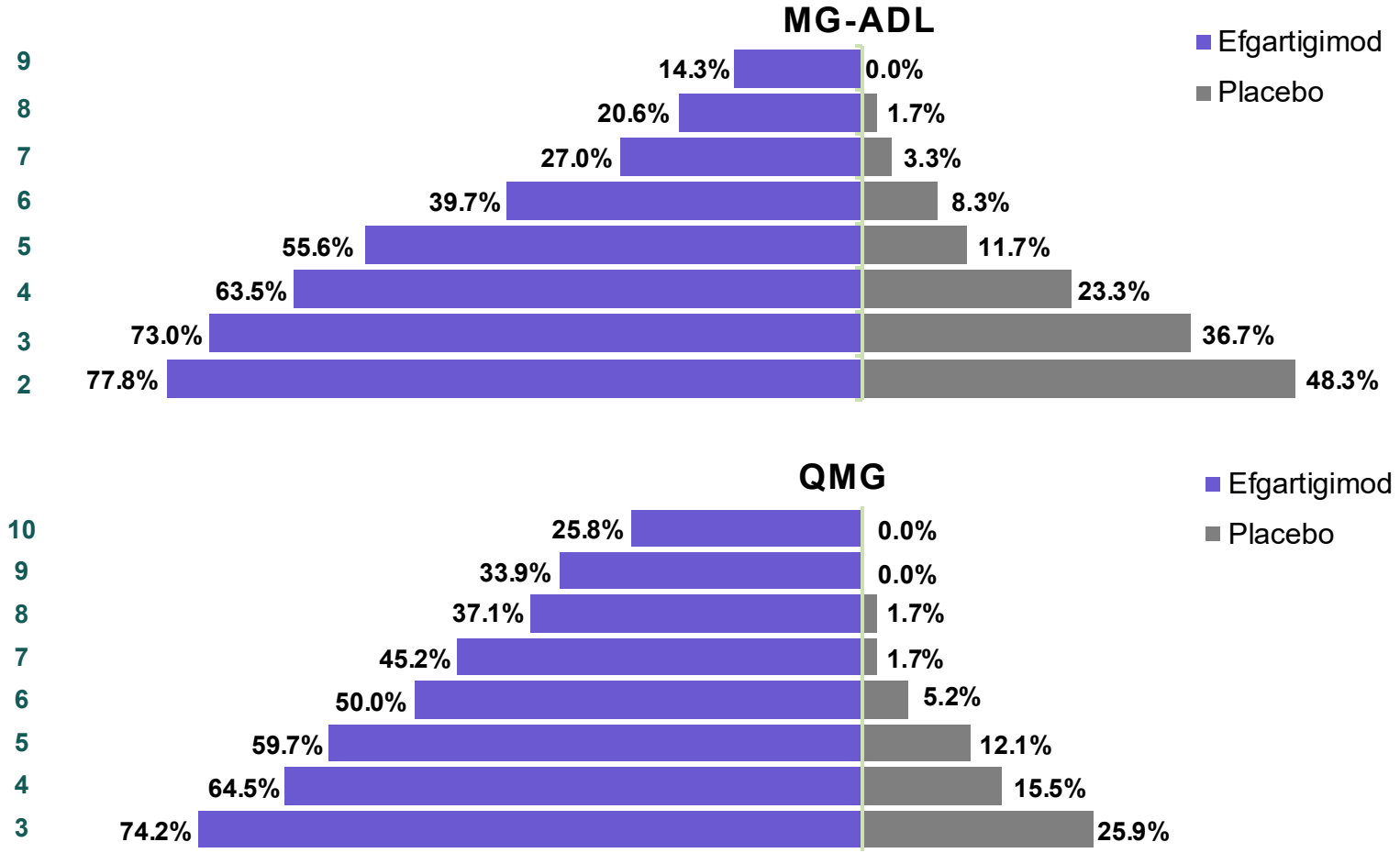
QMG responder:
≥3-point improvement for at least four consecutive weeks during the first cycle*



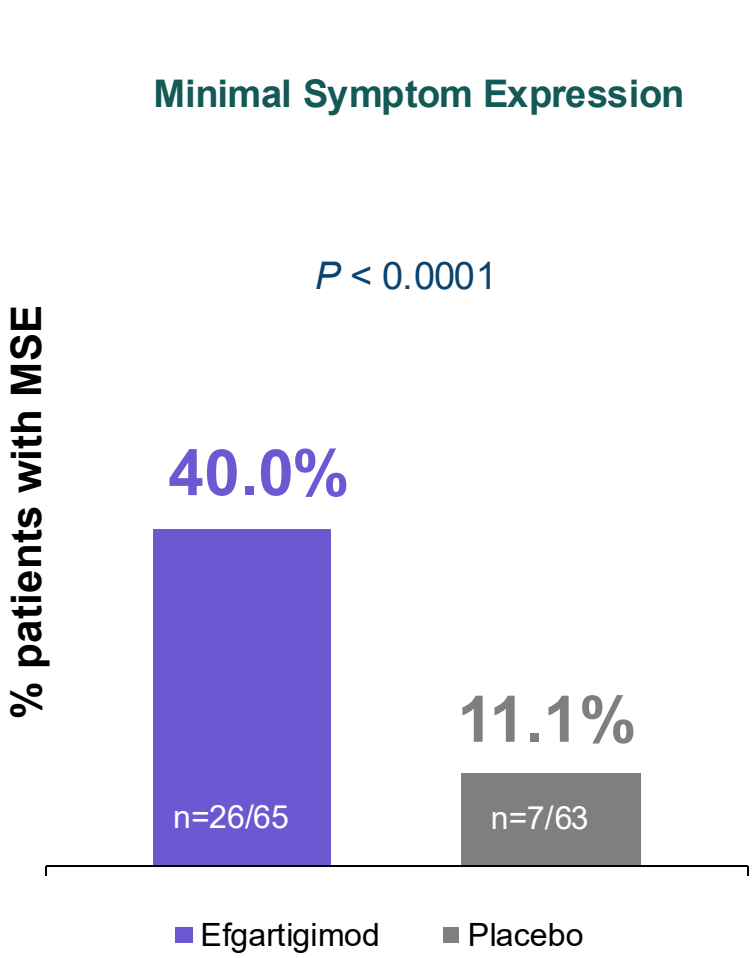


Proportion of patients with increasing MG-ADL and QMG improvement and achieving Minimal Symptom Expression (AChR-Ab+ patients, Cycle 1)

Proportion of patients with increasing thresholds of MG-ADL and QMG improvement at week 4*



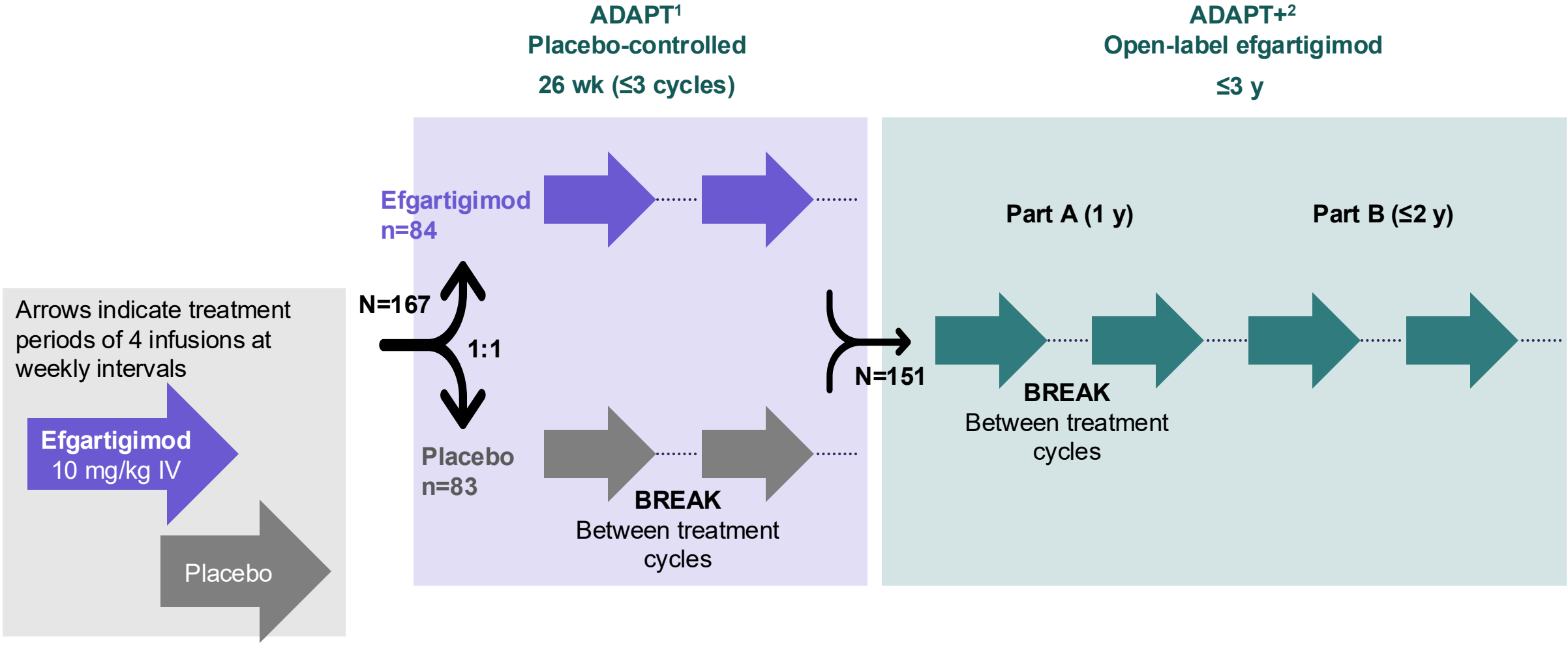
Proportion of patients with MSE (MG-ADL 0 or 1) any time during cycle 1



MSE, Minimal Symptom Expression
*One week after last infusion of cycle

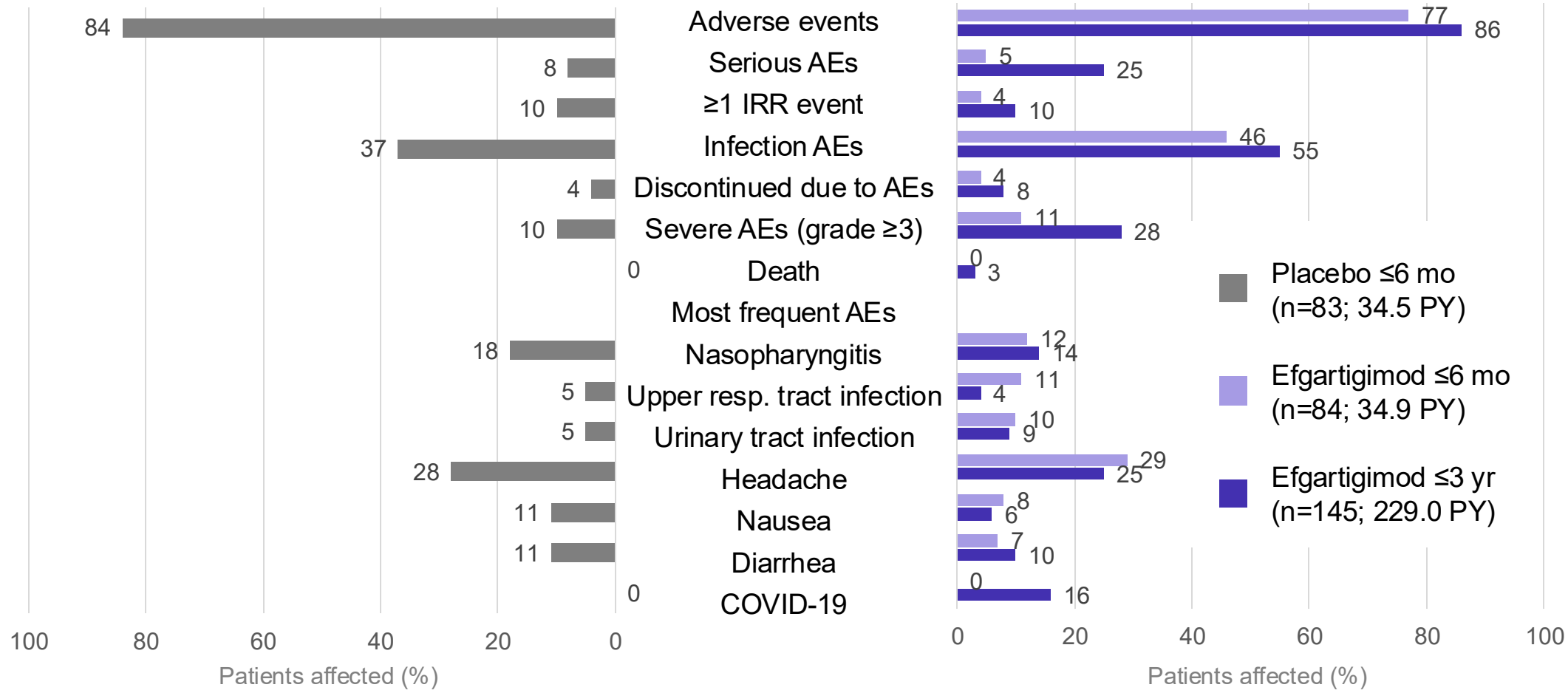
Howard JF, Bril V, Vu T, et al. Lancet Neurology 2021 Jul;20(7):526-536.; Vissing J, Jacob S, Fujita KP et al., J Neurol. 2020; 267(7): 1991–2001.

ADAPT/ADAPT+: Phase 3 trial for efgartigimod and OLE



1. Howard JF, et al. Lancet Neurol. 2021;20(7):526-536. 2. Howard JF, et al. Front. Neurol. 2024;14:1284444.

Efgartigimod Safety Data
Safety population, ADAPT (≤6 mo) and ADAPT+ (≥3 yr)



AE, adverse event; IRR, infusion-related reaction

ADAPT NXT Study Design

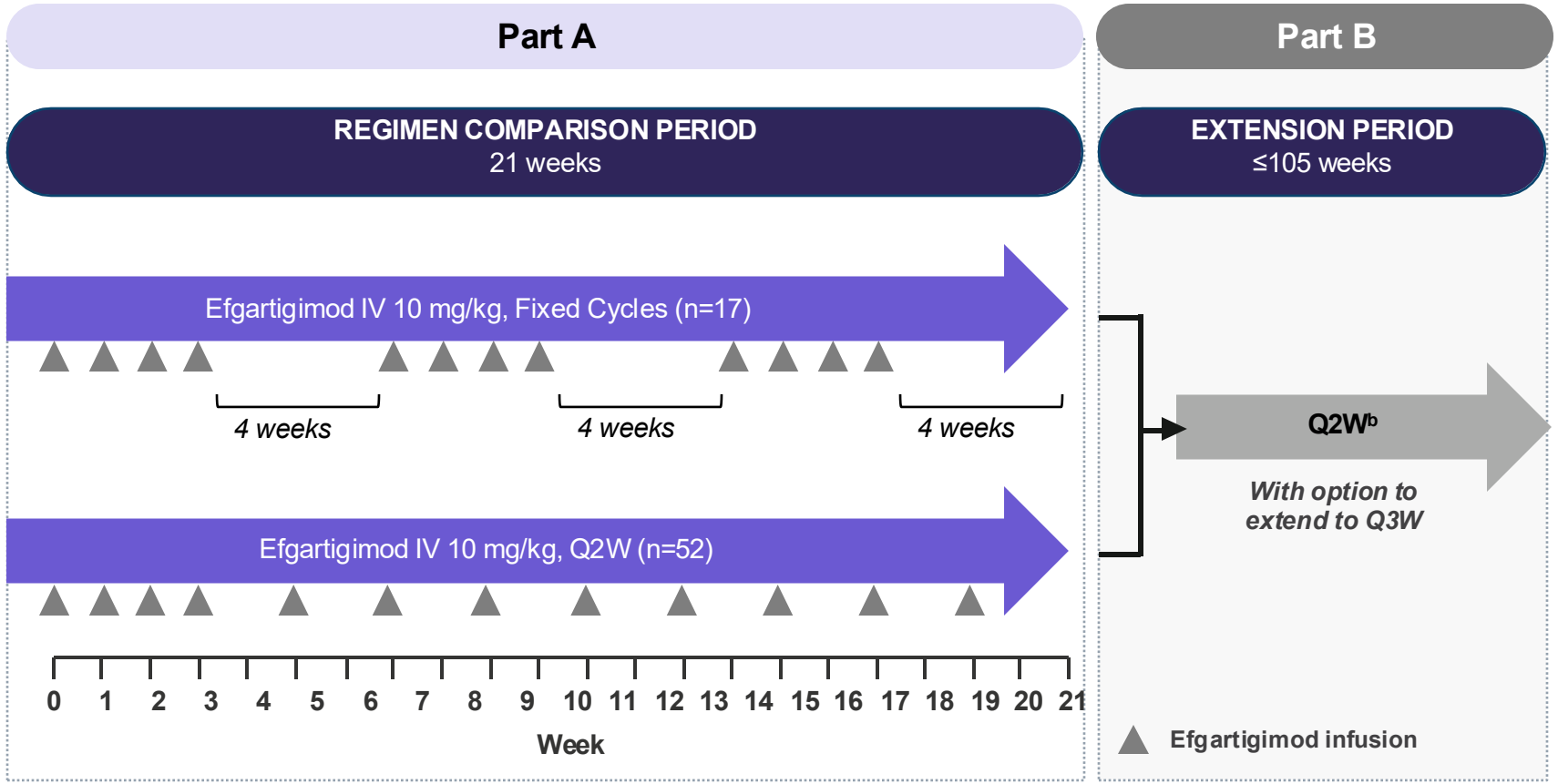
Ongoing, Phase IIIb, randomized, open-label, parallel-group study designed to evaluate two dosing regimens of efgartigimod IV in participants with AChR-Ab+ gMG

SCREENING
2 weeks

N=69 patients

3:1 Randomization

- Adults (≥18 years old) with AChR-Ab+ gMG
- MG-ADL score ≥5 (>50% nonocular)
- MGFA class II, III, or IV
- Concomitant gMG treatment permitted (NSISTs, corticosteroids, and/or AChEIs)[a]
- IgG ≥6 g/L

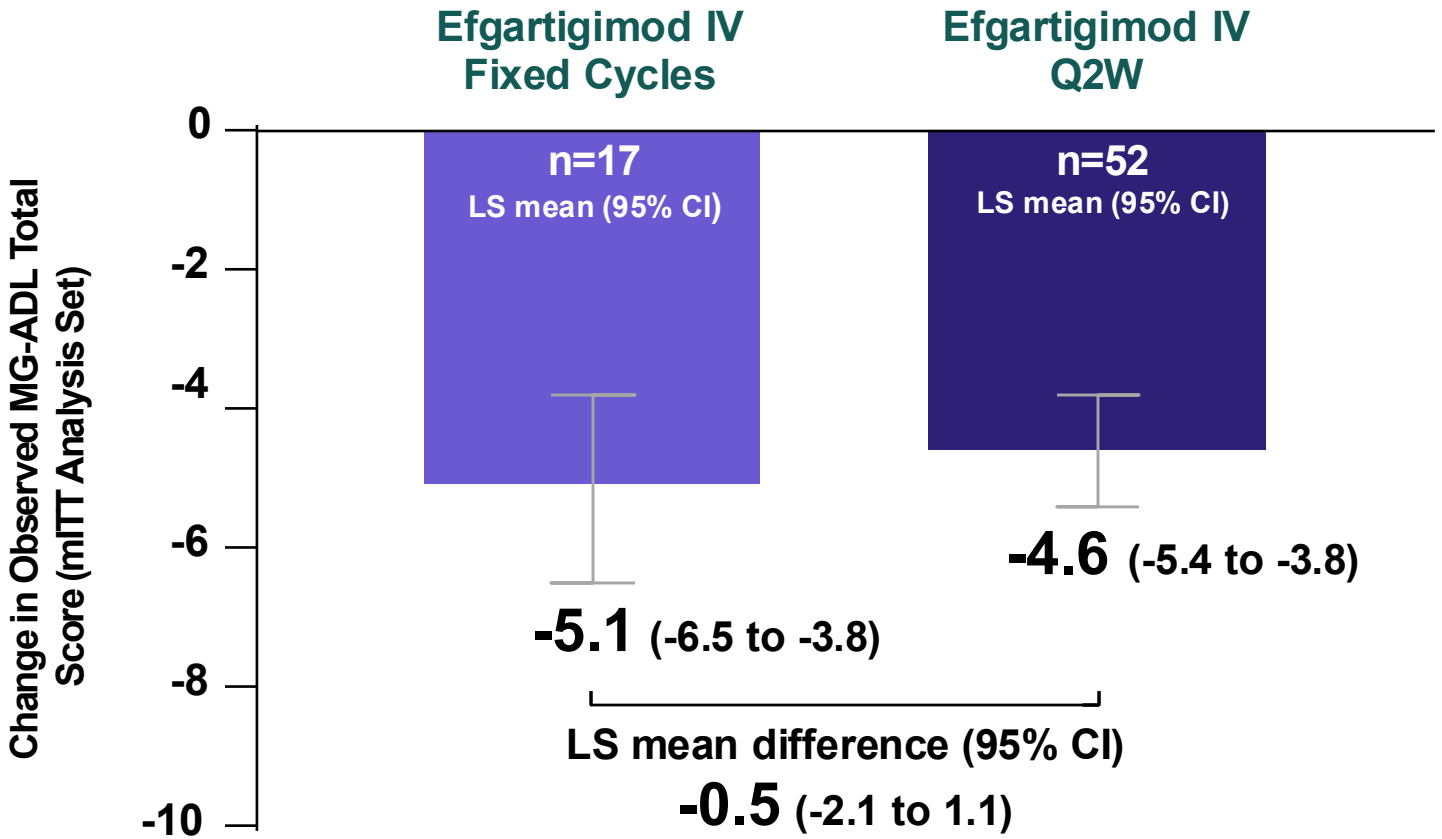


alf receiving corticosteroids and/or NSISTS, must be on a stable dose for ≥1 month before screening. bAll participants entering Part B will be transitioned to Q2W with the option to extend to Q3W dosing; patients in the Fixed Cycle arm will receive another cycle before transitioning to Q2W dosing.2

1. Study ARGX-113-2003 (ADAPT NXT) Clinical Trial Protocol v1.0, 06 July 2021. 2. Cortés-Vicente E, et al. Poster presented at: European Academy of Neurology Annual Meeting; June 29-July 2, 2024; Helsinki, Finland.

ADAPT NXT Part A Results: Mean Change in MG-ADL Total Score From Baseline (Week 1-21)

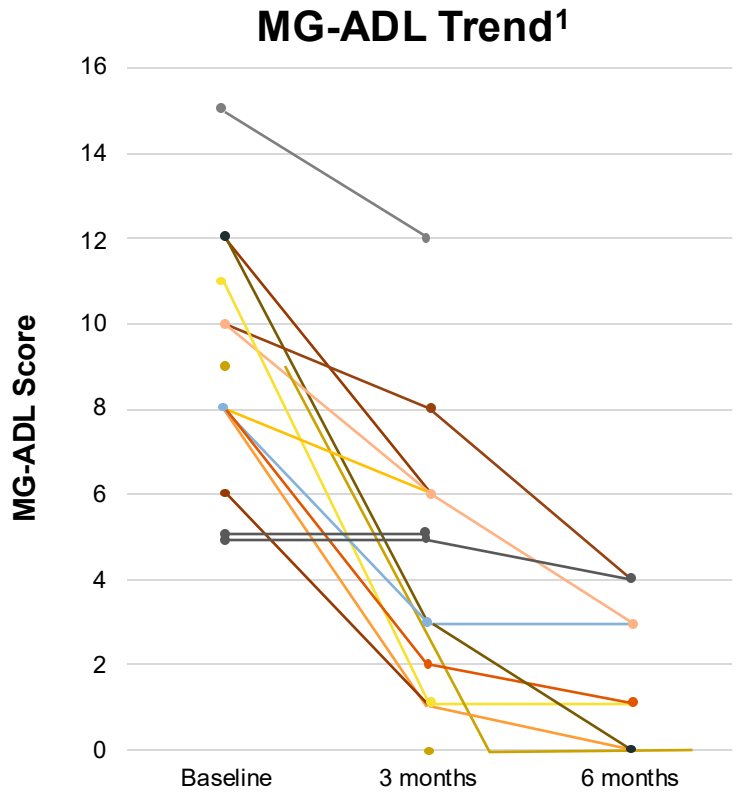
Primary Endpoint



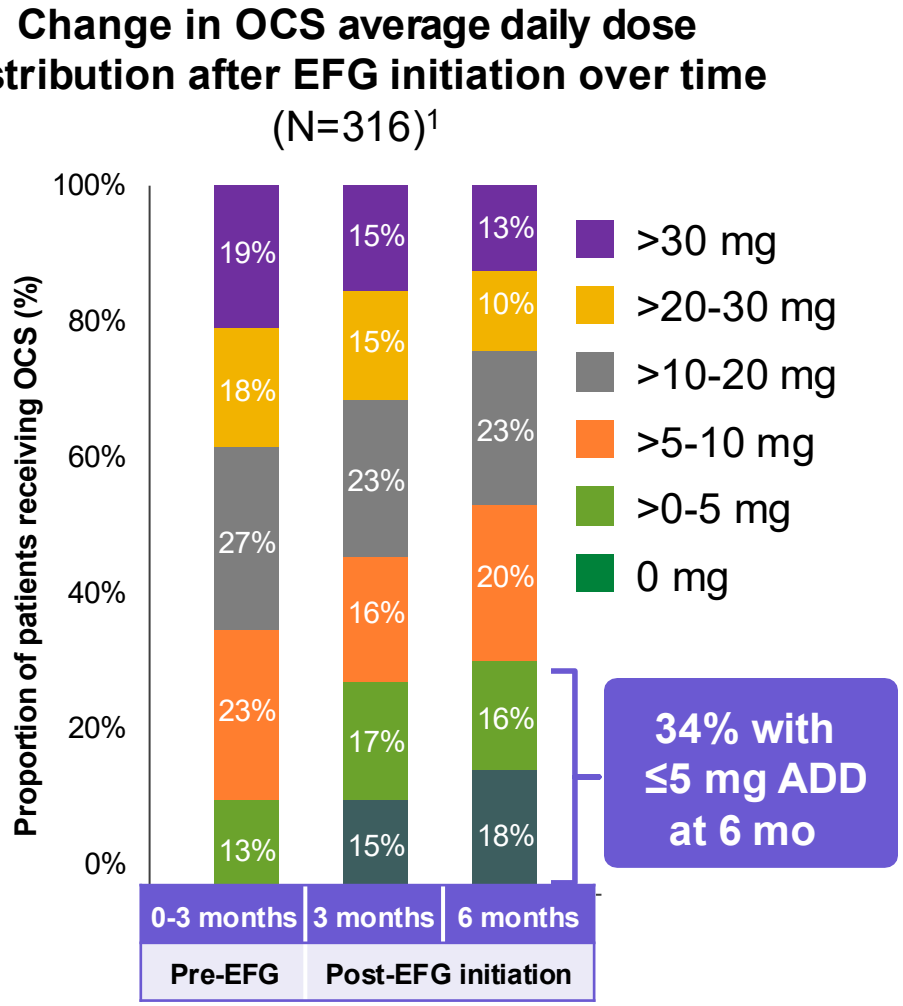
[a]The ANCOVA model used for statistical analysis included treatment arm as a factor and baseline MG-ADL total score as a covariate to account for any differences in baseline MG-ADL scores. ANCOVA, analysis of covariance; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living; LS, least squares; Q2W, every 2 weeks; Q3W, every 3 weeks

1. Habib AA, et al. Ann Clin Transl Neurol. Published online April 14, 2025.
2. Bril V, et al. Poster presented at: American Academy of Neurology (AAN) Annual Meeting; April 13-18, 2024; Denver, CO.

Improvement in ADL Scores and Steroid-Sparing Effects



- Efgartigimod group: improved by an average of 5.5 points at 3 months (*p*<0.001) and 7.1 points by 6 months (*p*<0.001).
- 40% of patients achieved MSE.



Efgartigimod alfa is approved for adult patients with anti-AChR antibody positive gMG; efficacy and safety in other indications have not been established.

1. Singer et al. Muscle & Nerve. 2024;69(1):87-92. 2. Frangiamore R, et al. Eur J Neurol. 2024;31:e16189.
2. Goyal et al. Oral Presentation at the American Academy of Neurology (AAN) Annual Meeting; April 13-18, 2024; Denver, CO, USA.

Ocular Myasthenia Gravis

Oculus

A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Parallel-Group Design Study Evaluating the Efficacy and Safety of Efgartigimod PH20 SC Administered by Prefilled Syringe in Adult Participants with Ocular Myasthenia Gravis

Program: Efgartigimod

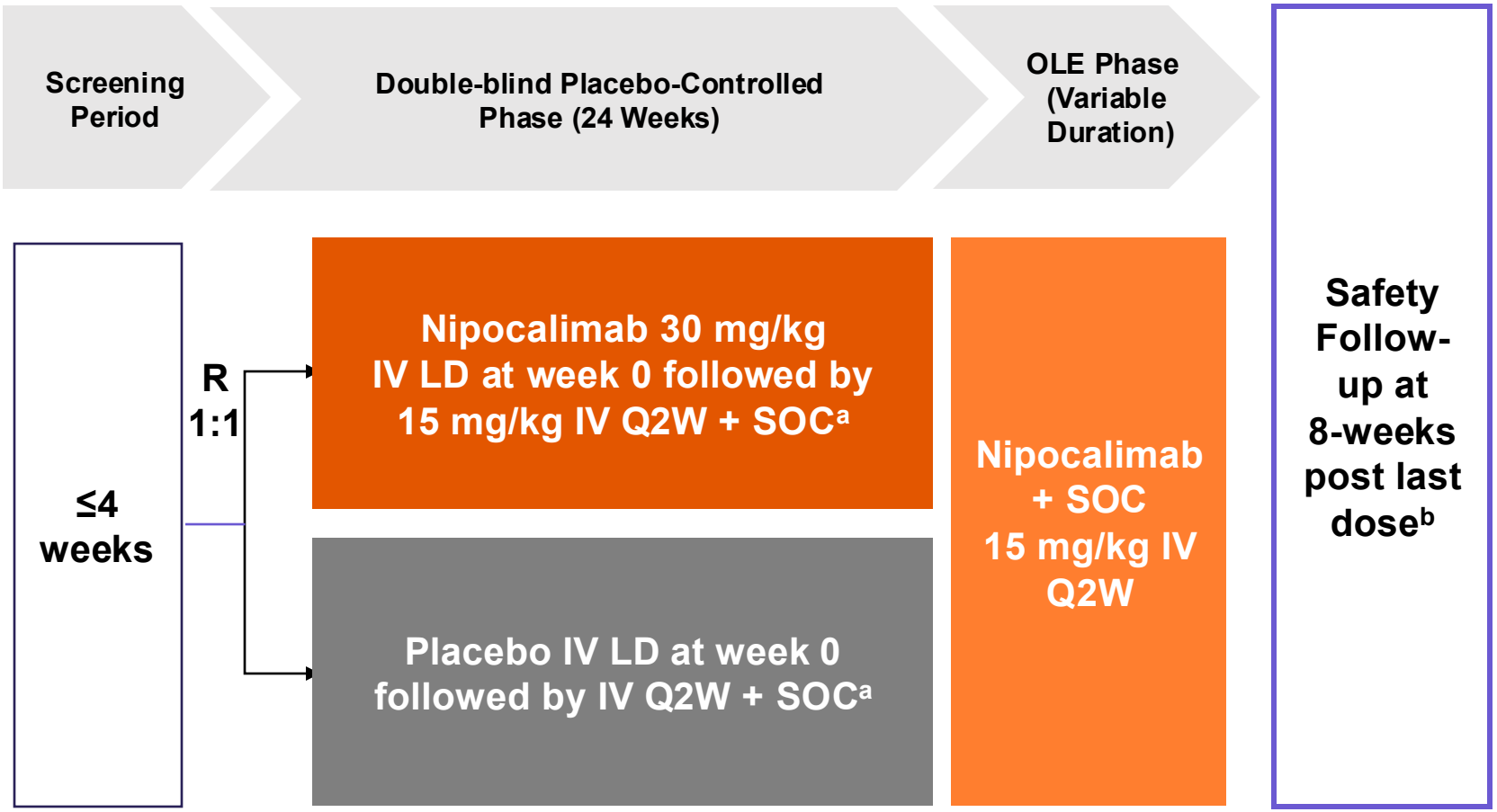
Seronegative gMG

ADAPT SERON

Phase 3 trial of IV efgartigimod for the treatment of AChR-Generalized Myasthenia Gravis (gMG).

Program: Efgartigimod

Nipocalimab: Phase 3 Vivacity-MG3



Primary endpoint:
change from baseline in MG-ADL score over weeks 22, 23, and 24

Primary efficacy cohort: all antibody-positive patients

Select Inclusion Criteria

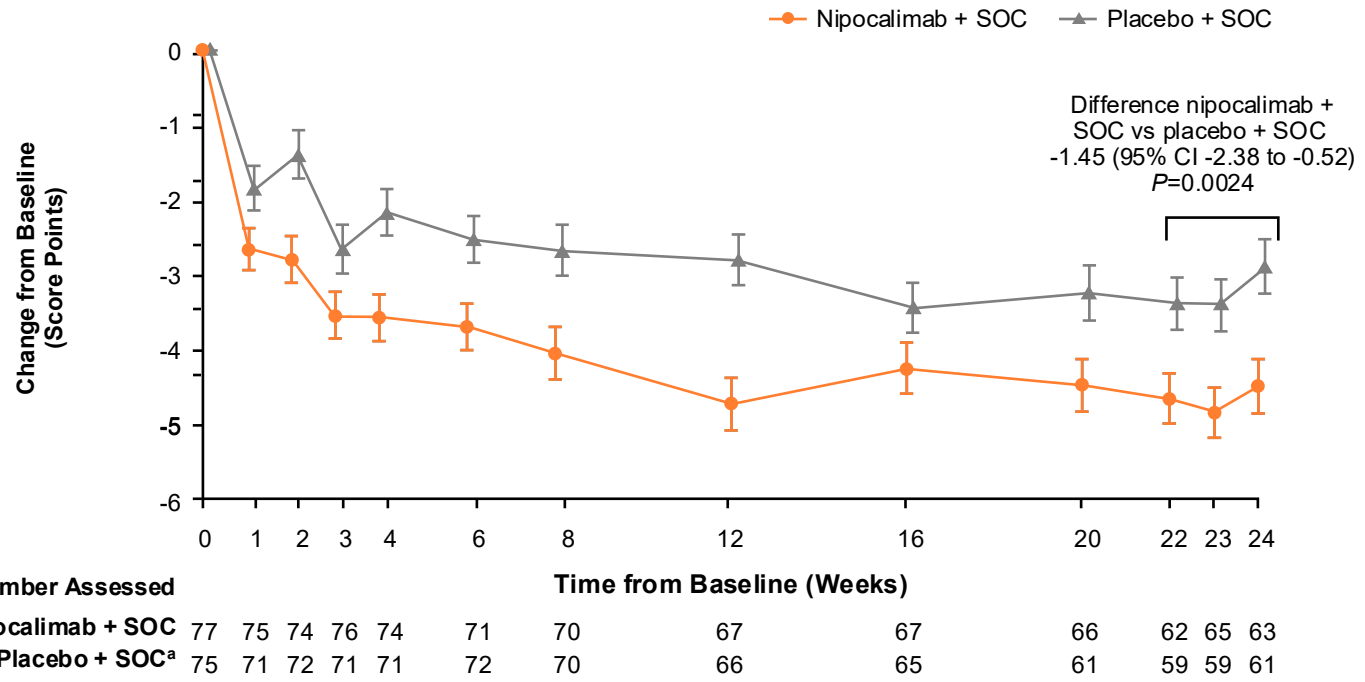
- Age ≥18 years with gMG MGFA Class IIa/b, III a/b or IV a/b
- Patients (except in France) who were antibody-positive (AChR+, MuSK+, or LRP4+) or triple-antibody-negative[a,b]
- MG-ADL score of ≥6 at screening and baseline
- Suboptimal reponse to current stable therapy for gMG or discontinued corticosteroids and/or immunosuppressants/ immunomodulators ≥4 weeks prior to screening due to intolerance or lack of efficacy

[a]Patients continued their background, stable SOC myasthenia gravis therapies, with no changes permitted during the double-blind phase
[b]Patients whot withdraw or discontinue after receiving any amount of study invervention will be required to complete a safety follow-up visit 8 weeks after the last infusion.

Vivacity-MG3: Significant Improvement in MG-ADL and QMG With Nipocalimab

Nipocalimab led to sustained improvements from baseline in MG-ADL and QMG in a broad antibody-positive population

CFB in MG-ADL Over 24 Weeks

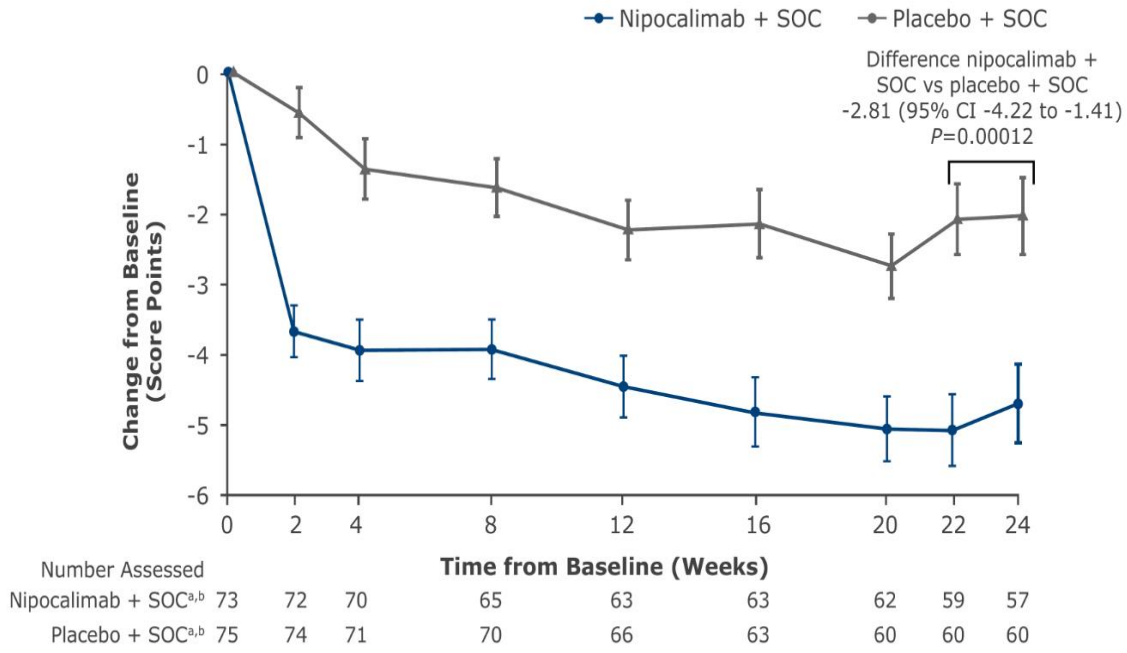


Average CFB in MG-ADL by Antibody Status

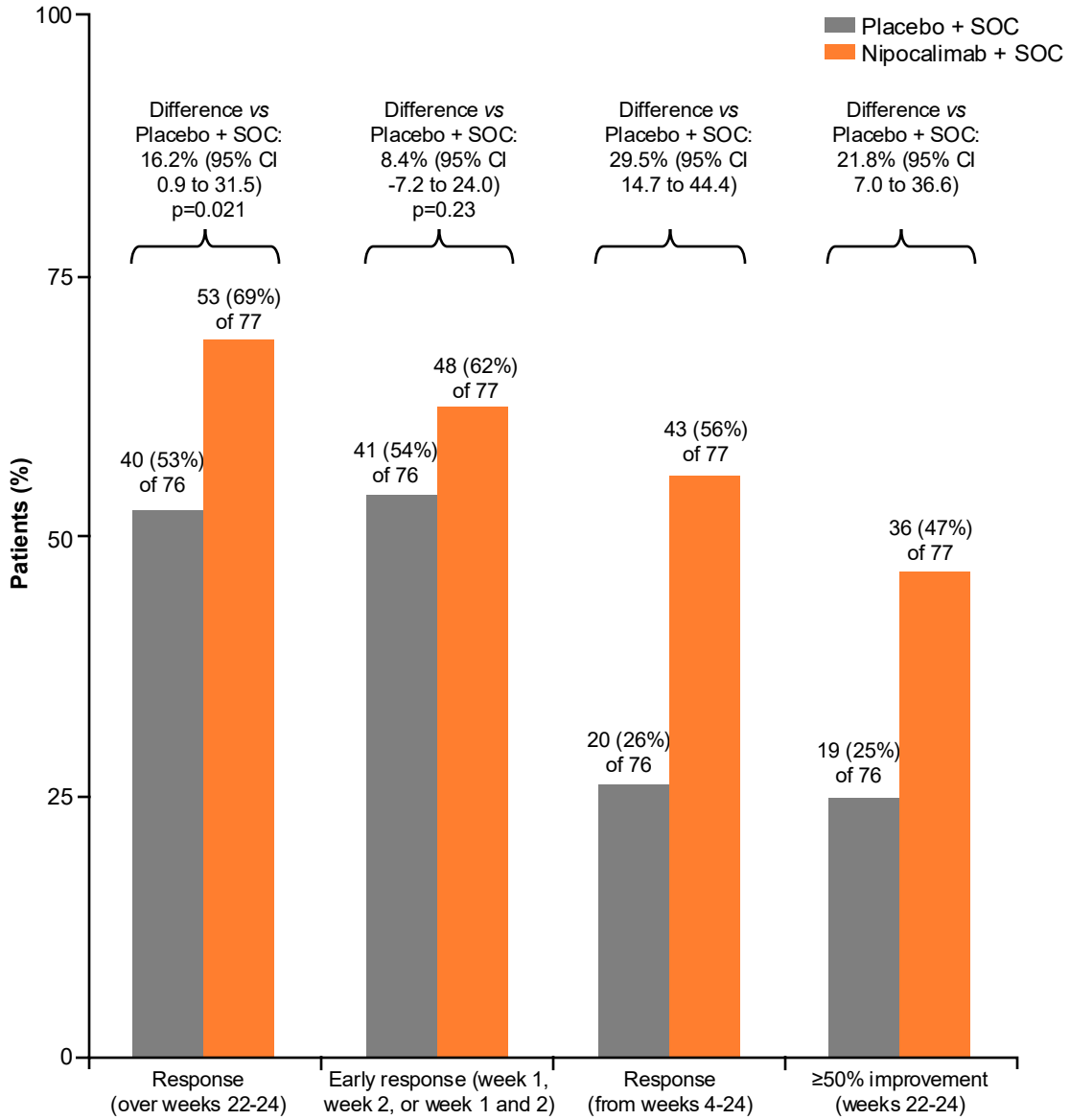
Subgroup	N	Nipocalimab + SOC LS Mean (95% CI)	N	Placebo + SOC LS Mean (95% CI)	Between-Group Difference (95% CI)
Anti-AChR+	63	-5.06 (-5.78 to -4.33)	70	-3.44 (-4.13 to -2.74)	-1.62 (-2.62 to -0.62)
Anti-MuSK+	12	-3.79 (-5.47 to -2.10)	4	-0.25 (-3.02 to 2.53)	-3.54 (-6.78 to -0.30)
Antibody-negative	20	-3.30 (-4.62 to -1.99)	22	-3.23 (-4.46 to -1.99)	-0.08 (-1.87 to 1.71)

Vivacity-MG3: Key Secondary Endpoints

Change in QMG Over 24 weeks



Responder Assessment



Phase 3 Vivacity, MG-ADL Total Score by Subgroups

MG-ADL Total Score: Analysis of Average Change From Baseline Over Weeks 22, 23, and 24 by Antibody Status*[1]

	Nipocalimab + SOC		Placebo + SOC		Between-Group Difference
Subgroup†	**n**	**LS Mean† (95% CI)**	**n**	**LS Mean† (95% CI)**	**Between-Group Difference‡ (95% CI)**
Anti-AChR+	63	-5.06 (-5.78, -4.33)	70	-3.44 (-4.13, -2.74)	-1.62 (-2.62, -0.62)
Anti-MuSK+	12	-3.79 (-5.47, -2.10)	4	-0.25 (-3.02, 2.53)	-3.54 (-6.78, -0.30)
Antibody-negative	20	-3.30 (-4.62, -1.99)	22	-3.23 (-4.46, -1.99)	-0.08 (-1.87 ,1.71)

- The primary endpoint population was participants with antibody-positive gMG including anti-AChR, anti-MuSK, and anti-LRP4[2]
- Subgroup analysis showed consistent efficacy results in AChR antibody-positive and MuSK antibody-positive populations‡, while no statistically significant difference was seen in the antibody-negative population[2]

*AChR, antibody positive, MuSK antibody positive, or antibody negative. †LS mean estimates and between-group differences are estimated from an MMRM, with factors for treatment group, autoantibody (anti-AChR+, anti-MuSK+, anti-LRP4+, antibody-negative), region, visit, treatment-by-visit interaction, treatment-by-autoantibody interaction, and treatment-by-autoantibody-by-visit interaction and baseline MG-ADL as a covariate. ‡Results for the anti-LRP4+ subgroup are not displayed because there were <4 anti-LPR4+ participants in both treatment groups.

AChR, acetylcholine receptor; CI, confidence interval; gMG, generalized myasthenia gravis; LRP4, low-density lipoprotein receptor 4; LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; MMRM, mixed-model repeated measures; MuSK, muscle-specific tyrosine kinase; n, number indicating a subset of the total population; SOC, standard-of-care.

1. Antozzi C, et al. *Lancet Neurol*. 2025;24(suppl 10):S1-S163. 2. Antozzi C, et al. *Lancet Neurol*. 2025;24(2):105-116.

Vivacity Efficacy Conclusions

- ☑ Vivacity-MG shows sustained efficacy through 6 months of dosing

- ☑ Broad autoantibody-positive (anti-AChR+, anti-MuSK+, and anti-LRP4+) gMG participant population, statistically significant and clinically meaningful improvement in:
  - MG-ADL and QMGS mean change from baseline
  - Greater responder rate (MG-ADL >2 points improvement)

- ☑ More participants treated with nipocalimab achieved sustained response from week 4-24 and had ≥50% improvement in MG-ADL compared to placebo

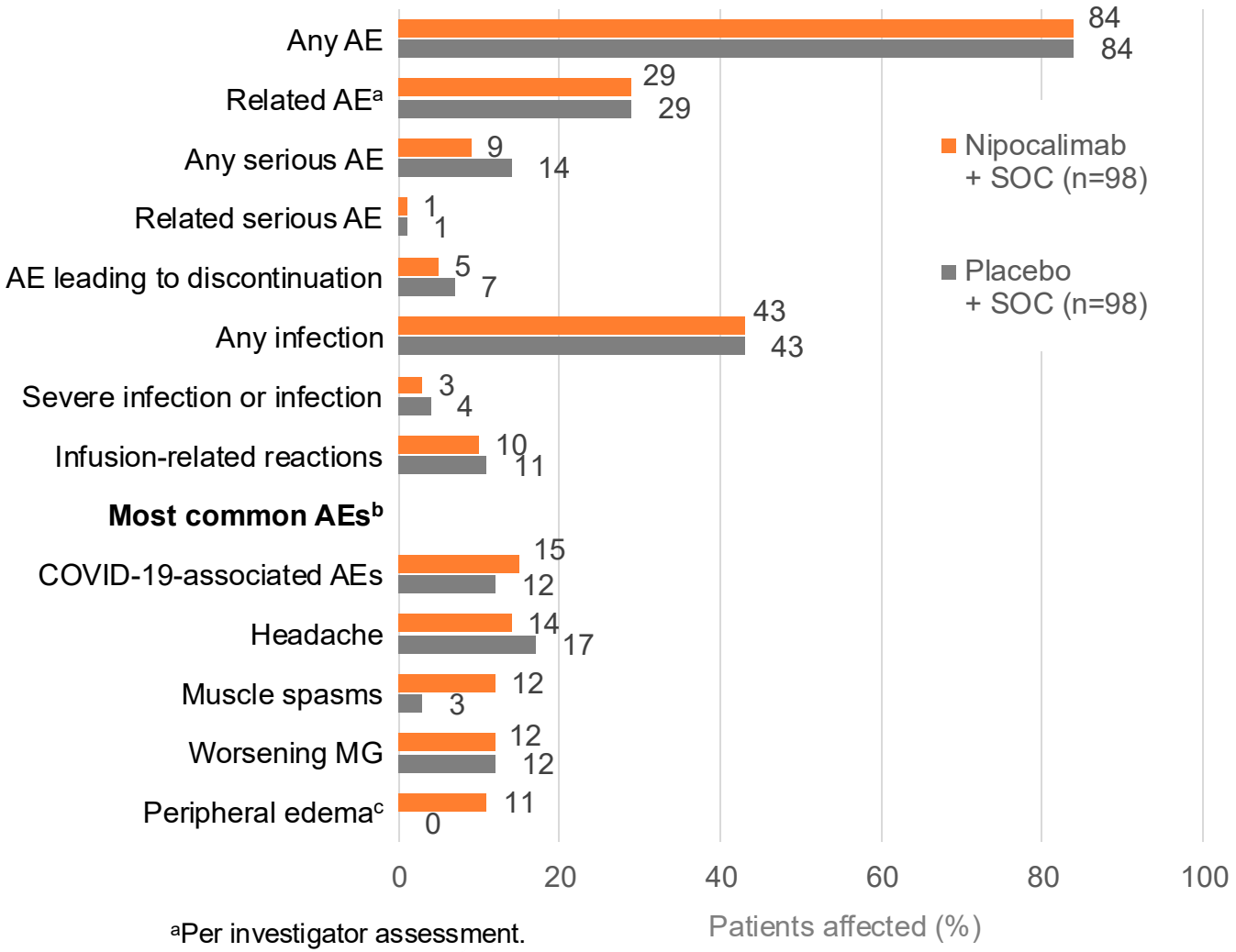
Vivacity Safety Summary

Safety analysis population: all patients (antibody-positive and antibody-negative) who received ≥1 dose of either study drug

Nipocalimab generally well tolerated in gMG participants

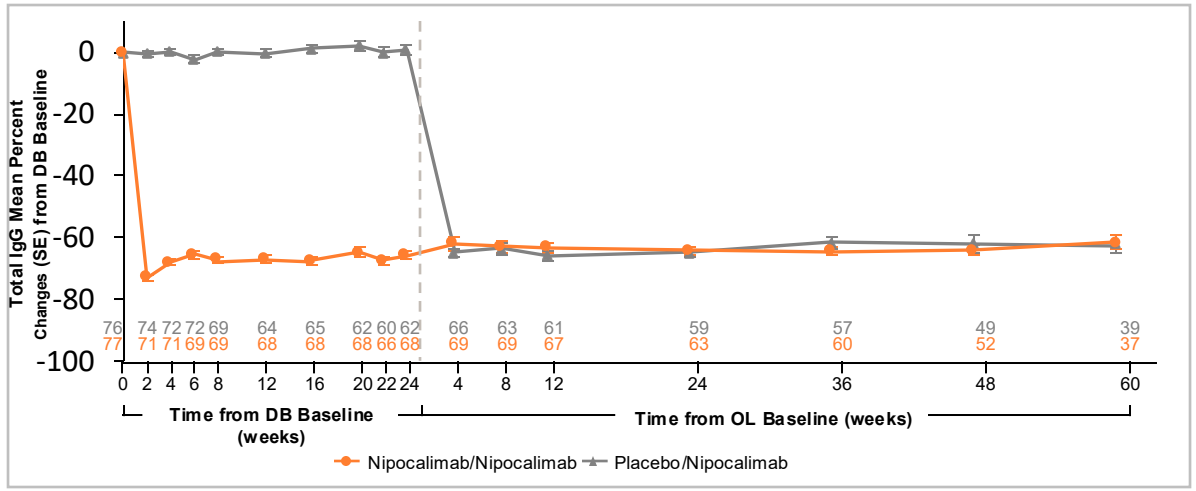
- Urinary tract infection was reported in 5% (5/98) of patients receiving nipocalimab compared to 2% (2/98) of patients receiving placebo.[4]
- One patient receiving nipocalimab experienced myasthenic crisis compared to 2 patients receiving placebo, and 5 and 7 patients received treatment with rescue medications, respectively.[4]

Treatment-Emergent AEs in the Double-blind Phase



[a]Per investigator assessment.
[b]≥10% in nipocalimab group
[c]All patients at the time of edema had albumin levels within normal limits (33-49, 33-46, and 30-46 g/L for patients aged 18-69, 70-80 and >80 years, respectively

OLE, Change from Baseline in MG-ADL and IgG Levels, reduction of steroids



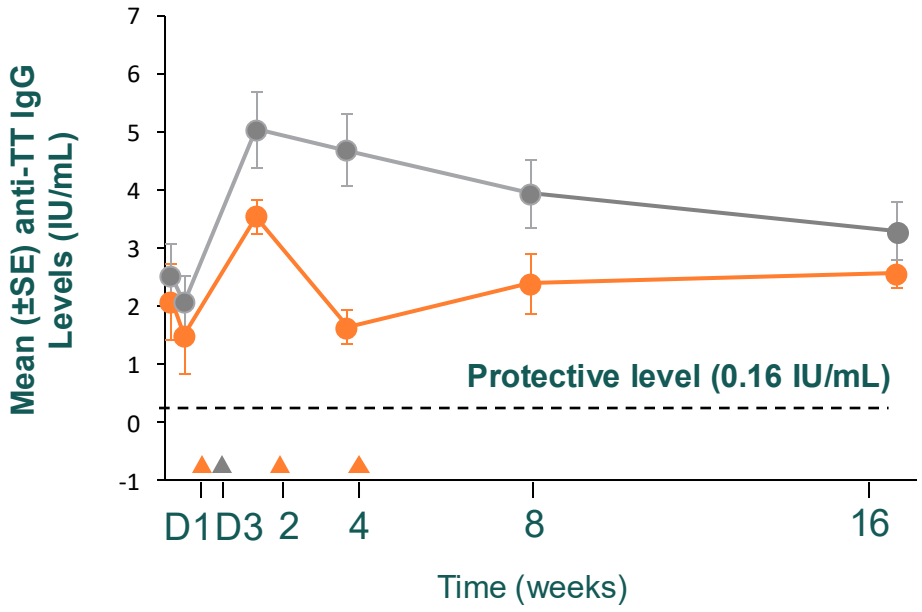
- 45% (40/89) of participants receiving steroids at open-label baseline were able to decrease or discontinue steroids at data cutoff*
  - Among these patients the mean dose of prednisone (mg eq per day) decreased from 23 to 10†
- Efficacy was maintained in participants who decreased/discontinued steroids

Note: p-value for comparison of MG-ADL total score change from baseline significantly different from zero using a one-sample t-test. *p<0.001.
DB, double-blind; MG-ADL, Myasthenia Gravis - Activities of Daily Living; OL, open-label; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; SE, standard error; SOC, standard-of- care; W, week.
Antozzi C, et al. AAN 2025. Poster #022.

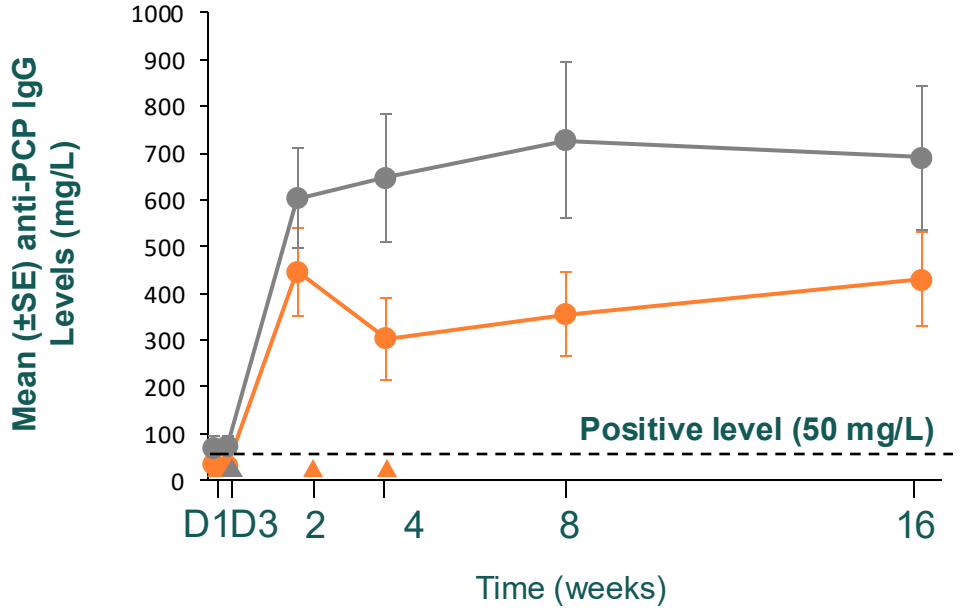
Poll #6: Which of the following is TRUE regarding vaccination and FcRn inhibitor therapy in MG?

Nipocalimab Anti-Vaccine Antibody Responses

Response to T-Cell-Dependent (Tdap) Vaccine (Completers Analysis Set)



Response to T-Cell-Independent (PPSV®23) Vaccine (Completers Analysis Set)



Active arm (Nipocalimab + Tdap + PPSV®23)

Control arm (Tdap + PPSV®23)

Nipocalimab administration

Tdap and PPSV®23 administration

*Except 1 participant in the active arm at week 4.

D, day; IgG. Immunoglobulin G; IQR, interquartile range; PCP, pneumococcal; PPSV®23, 23-polysaccharide pneumococcal vaccine; SE, standard error; Tdap, tetanus toxoid, diphtheria, and acellular pertussis vaccine; TT, tetanus toxoid.

Cossu M, et al. Presented at American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Annual Meeting. October 15-18, 2024.

Vaccination Considerations for Fc Receptor Inhibitors

Administer vaccines according to national immunization guidelines at least 4 weeks before initiating treatment with any FcRn inhibitor.

Consider checking vaccine serologic titers when clinically indicated, especially for high-risk patients or those undergoing prolonged treatment.

Vaccination with live or live attenuated vaccines is not recommended during active treatment with FcRn inhibitors.

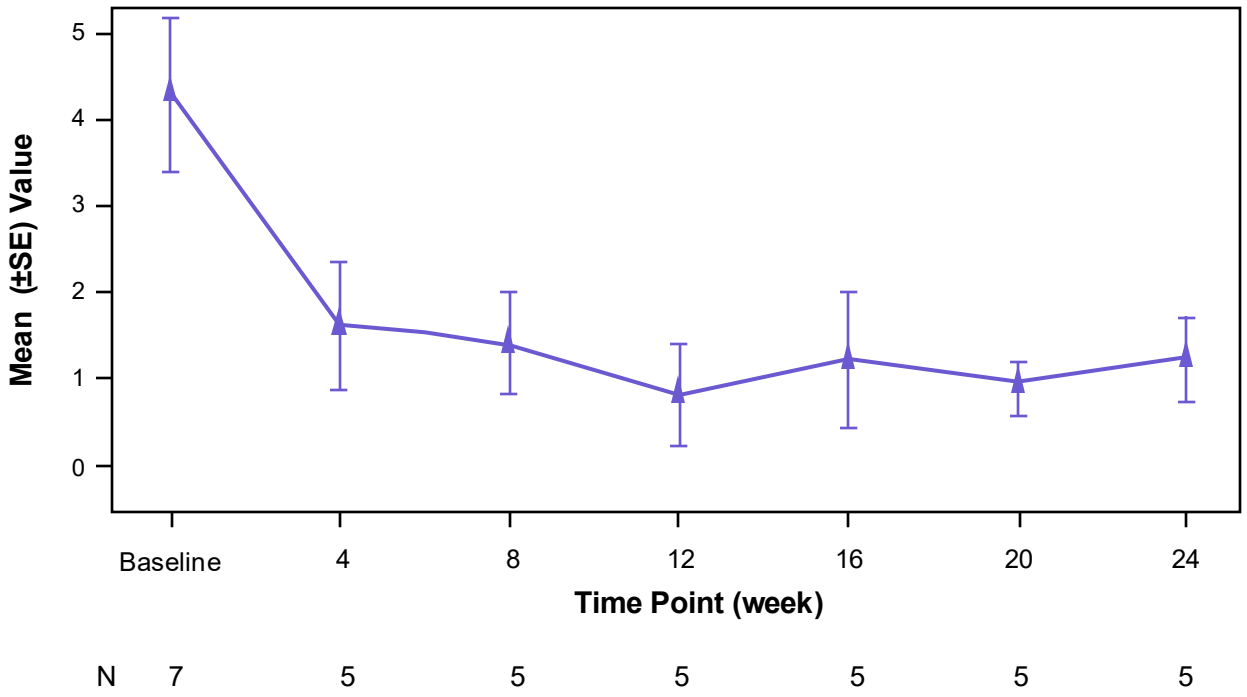
In patients received cyclic therapy, inactivated or subunit vaccines should ideally be administered at least 2 weeks after the last dose in a treatment cycle and 4 weeks before starting the next cycle

Phase 2/3 Vibrance-MG Study

A global, multicenter, open-label, phase 2/3 study of nipocalimab + SOC in children and adolescents with gMG

- Phase 2/3 open-label multicenter trial in children aged 2 to <18 years with gMG
  - Dosing: 30 mg/kg IV loading dose at day 1, then 15 mg/kg Q2W or 30 mg/kg Q4W
  - - IgG reduction at week 24: −69% (SE 7.6), primary endpoint met
- MG-ADL and QMG scores showed sustained improvement through week 24
  - 80% of participants achieved minimal symptom expression (MG-ADL = 0/1)
- No SAEs or treatment discontinuations reported

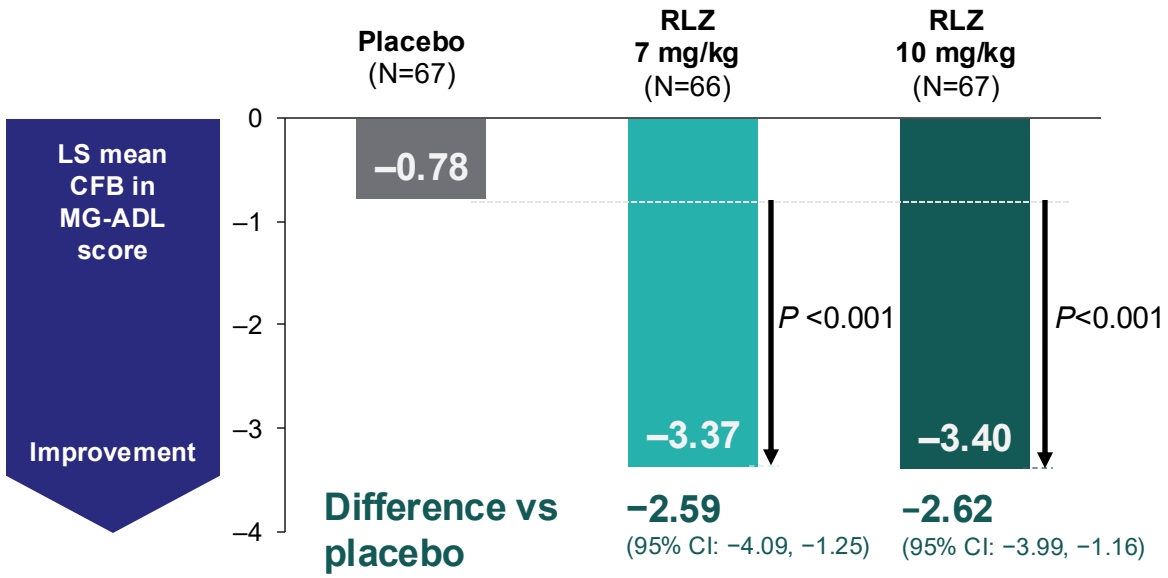
Mean MG-ADL Total Score Over Time



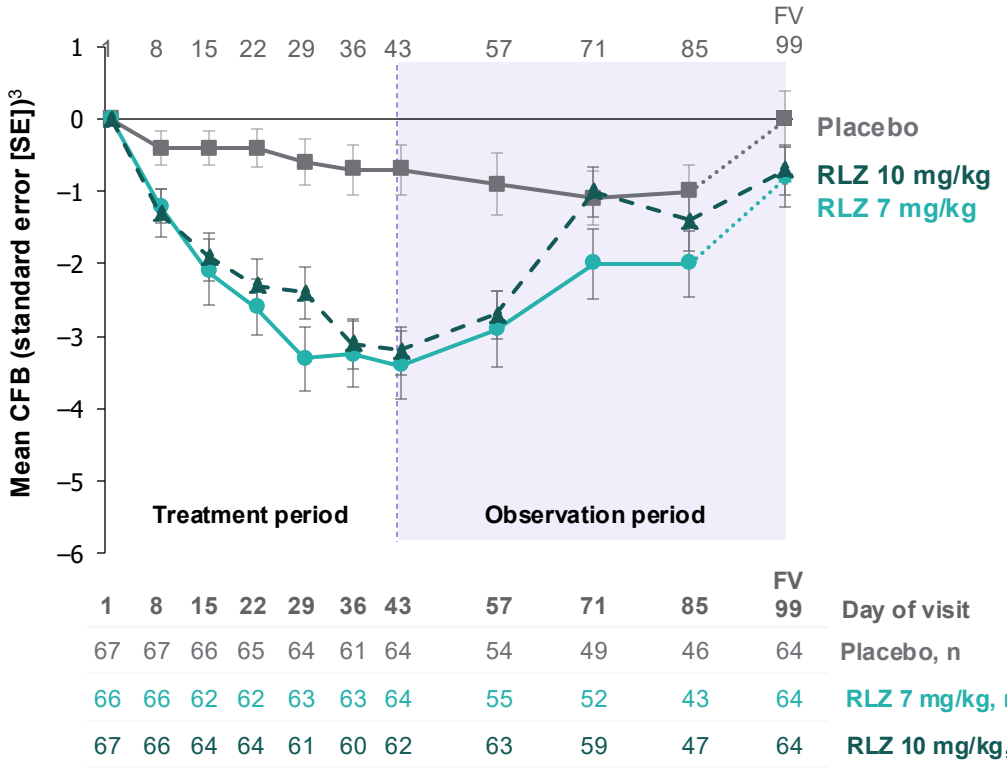
Rozanolixizumab (RLZ): Phase 3 MycarinG Study

Clinically meaningful and statistically significant improvements from baseline with RLZ 7 mg/kg and 10 mg/kg sc compared with placebo in the overall population.

Change from baseline (CFB) in MG-ADL at Day 43



MG-ADL over time



Day of visit	1	8	15	22	29	36	43	57	71	85	FV 99
Placebo, n	67	67	66	65	64	61	64	54	49	46	64
RLZ 7 mg/kg, n	66	66	62	62	63	63	64	55	52	43	64
RLZ 10 mg/kg, n	67	66	64	64	61	60	62	63	59	47	64

Key inclusion criteria

- Aged ≥18 years
- AChR Ab+ or MuSK Ab+ gMG*
- MGFA Class II to IVa
- MG-ADL score ≥3 (≥3 points from non-ocular symptoms) and QMG score ≥11
- Considered for additional treatment (eg, IVIg or PLEX)

All participants receiving RLZ mean MG-ADL baseline value (standard deviation [SD]) 8.3 (3.4)

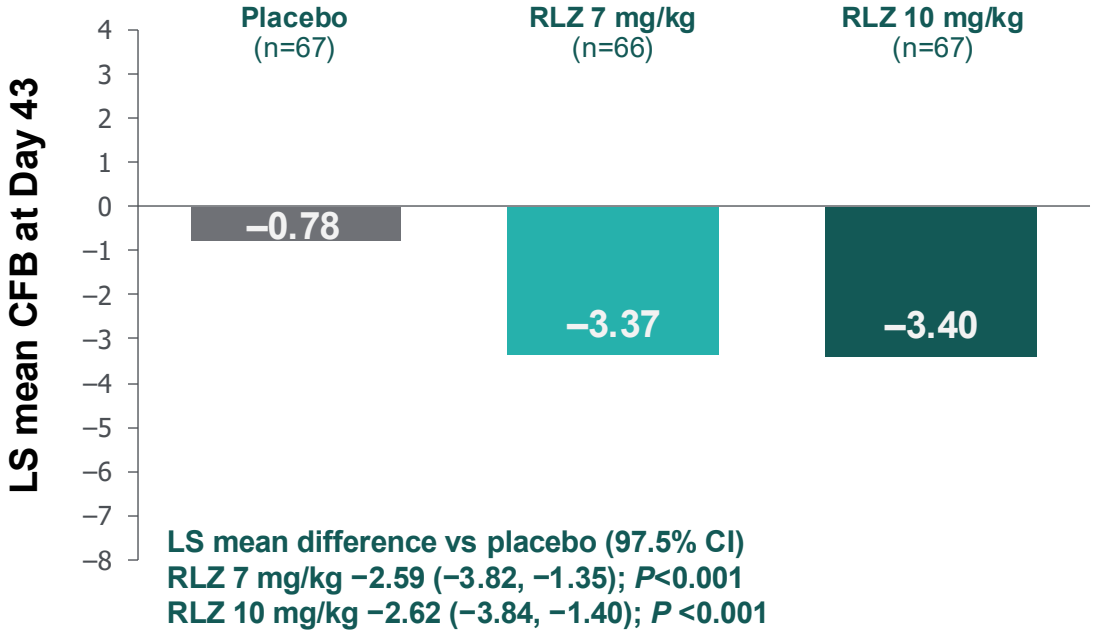
Adapted from: Bril V, et al. *Lancet Neurol*. 2023;22:383-394; Habib A, et al. Presented at: Presented at: MGFA Scientific Session 2022; September 21, 2022; Nashville, TN. Poster 16; Bril V, et al. Presented at: MGFA Scientific Session 2022; September 21, 2022; Nashville, TN. Poster 25; Vissing J, et al. Presented at: European Academy of Neurology (EAN) 2022; June 25-28, 2022.

MycarinG: MG-ADL Improvements in MuSK Ab+ Patients

Change from baseline to Day 43 in MG-ADL was higher with both RLZ dose groups vs placebo in patients with MuSK Ab+ gMG, as well as patients with AChR Ab+ gMG

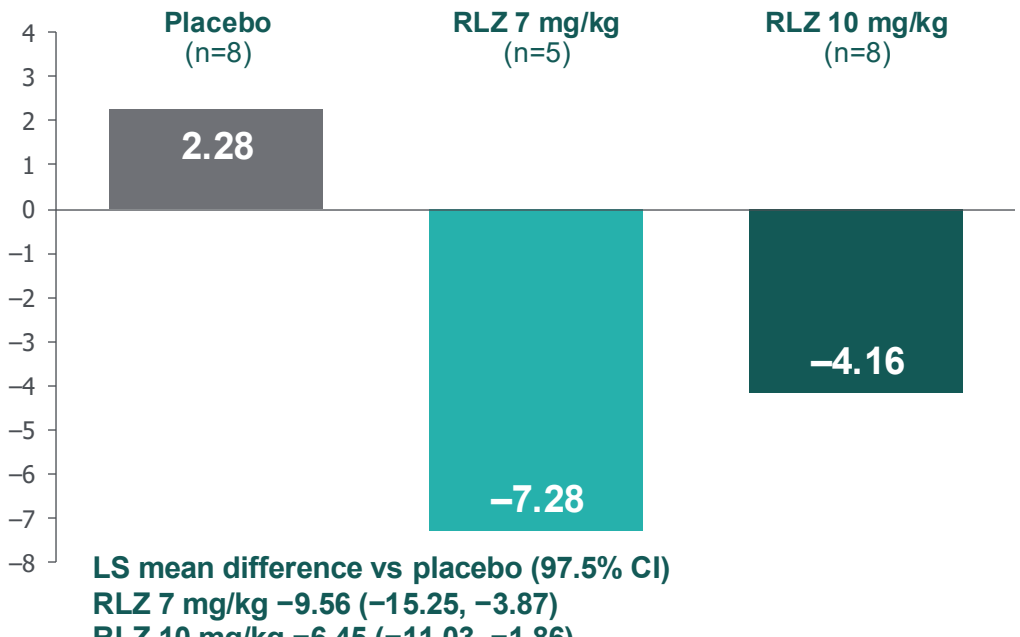
AChR Ab+ gMG: Change from baseline to Day 43 in MG-ADL → RLZ 7 mg/kg: –3.03, RLZ 10 mg/kg: –3.36, placebo: –1.10

Overall population



LS mean difference vs placebo (97.5% CI)
RLZ 7 mg/kg −2.59 (−3.82, −1.35); *P*<0.001
RLZ 10 mg/kg −2.62 (−3.84, −1.40); *P* <0.001

MuSK Ab+



LS mean difference vs placebo (97.5% CI)
RLZ 7 mg/kg −9.56 (−15.25, −3.87)
RLZ 10 mg/kg −6.45 (−11.03, −1.86)

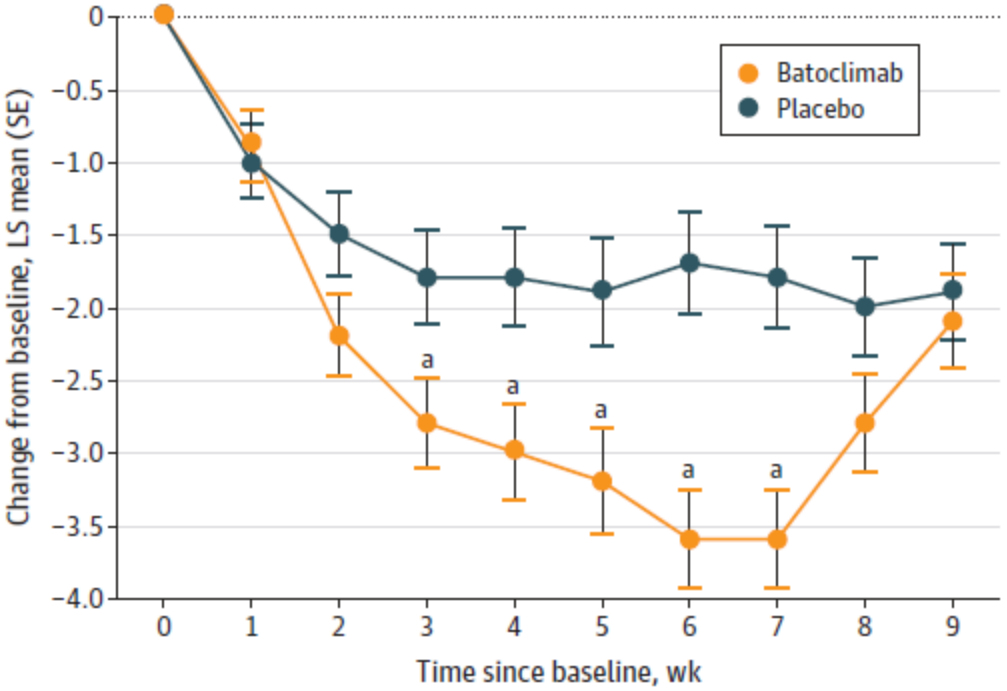
Overview of TEAEs in the Overall and MuSK Ab+ Populations
Most TEAEs were mild to moderate in severity.

Adapted from: Bril V, et al. *Lancet Neurol*. 2023;22:383-394; Habib A, et al. Presented at: Presented at: MGFA Scientific Session 2022; September 21, 2022; Nashville, TN. Poster 16.

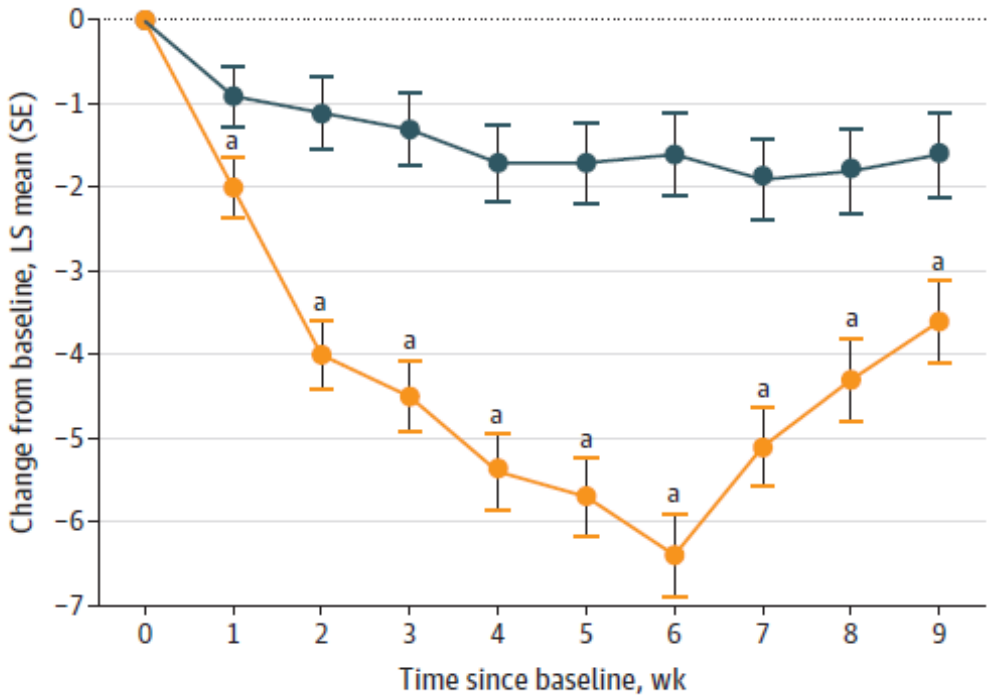
Batoclimab: Improvement in MG-ADL and QMG Versus Placebo (Cycle 1)

Multicenter phase 3 clinical trial conducted at 27 centers in China, enrolling 131 patients 18 years or older with generalized MG who were antibody positive

Change in MG-ADL Through Cycle 1



Change in QMG Through Cycle 1



Global phase 3 FLEX trial of batoclimab as induction and maintenance therapy in gMG is ongoing

Enrolling ~180 AChR Ab+ and ~60 AChR Ab- patients

Conclusions

- **Mechanism of Action:** FcRn inhibitors block IgG recycling, lowering pathogenic autoantibodies and improving neuromuscular transmission.
- **Efficacy:** Phase 3 trials of efgartigimod, rozanolixizumab, nipocalimab demonstrated significant improvements in MG-ADL and QMG scores.
- **Steroid-Sparing & MSE Achievement:** Up to 40% of patients achieve minimal symptom expression; many reduce or discontinue corticosteroids.
- **Pediatric & Special Populations:** Vibrance-MG (nipocalimab) shows promising efficacy and safety in children with gMG.
- **Vaccination Guidance:** Inactivated vaccines are safe; live vaccines should be avoided during therapy. Protective IgG responses are largely preserved

Advances
in Myasthenia Gravis

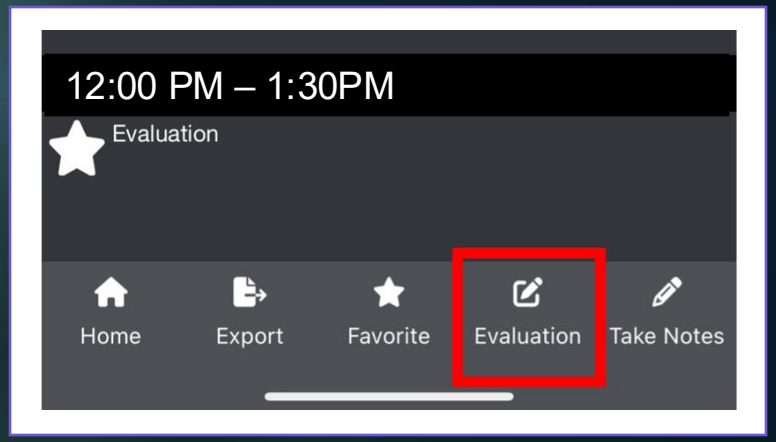
Emerging Biological Therapies and
Clinical Frontiers

Q&A Session

Audience Q&A

EVALUATION

1. Open the CNSF Congress App on your phone
2. Find this event under Browse Schedule
3. Click the Evaluation icon at the bottom




Thank you!