FcRn and Myasthenia Gravis: Treatment Options

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Accredited Continuing Education

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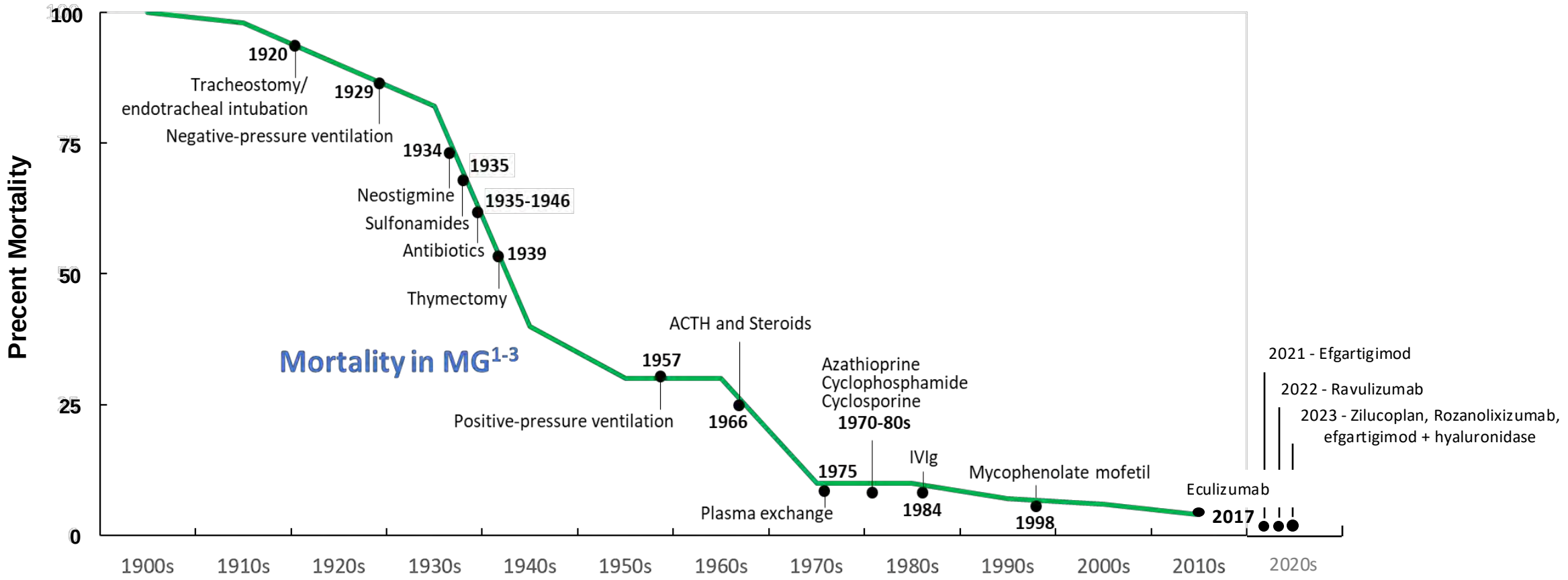
History of Treatment Options



1. Mantegazza R, Antozzi C. *Ther Adv Neurol Disord.* 2018;11:1756285617749134. 2. Grob D, et al. *Muscle Nerve.* 2008;37:141-149. 3. Keesey JC. *Semin Neurol*. 2004;24(1):5-16.

FDA Approved Treatments

Neonatal Fc receptor (FcRn)

Efgartigimod
FcRn antagonist

Efgartigimod + hyaluronidase
FcRn antagonist + endoglycosidase

Rozanolixizumab
Monoclonal antibody targeting FcRn

Complement system

Eculizumab
Monoclonal antibody targeting C5

Ravulizumab
Long-acting monoclonal antibody targeting C5

Zilucoplan
Peptide inhibitor of C5

Treatments in Late-stage Development

Neonatal Fc receptor (FcRn)

Nipocalimab

Monoclonal antibody targeting FcRn

Phase 3 study complete. Under review with FDA at the time of this program

Batoclimab

Monoclonal antibody targeting FcRn

Phase 3 RCT underway: NCT0503541

≥

Other

Gefurulimab (ALXN1720)

Monoclonal antibody targeting C5

Phase 3 RCT underway in MG: NCT05556096

Inebilizumab

Monoclonal antibody targeting CD19

Currently approved for NMOSD

Phase 3 RCT underway in MG: NCT04524273

Telitacicept

Binds to B-lymphocyte stimulator

Phase 3 RCT underway in MG: NCT06456580

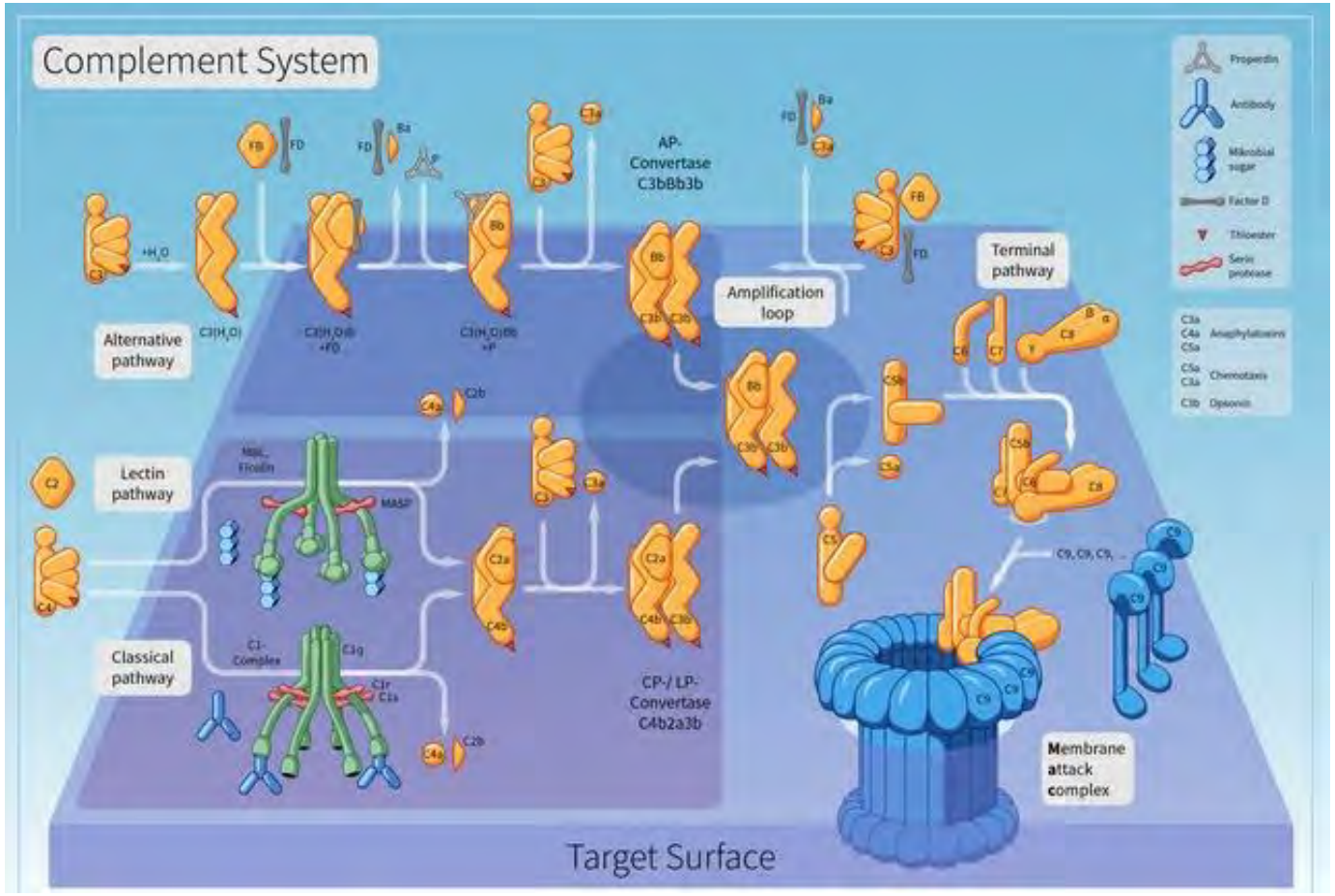
Satralizumab

Monoclonal antibody targeting IL-6 receptor

Currently approved for NMOSD

Phase 3 RCT underway in MG: NCT04963270

Complement Inhibitors



Eculizumab

FDA approval: 2017.

Indication: To treat adults with generalized myasthenia gravis.

MOA: A terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity.

Dosage: 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

Route of Administration: Intravenous infusion (35 minutes).

Boxed Warning: Meningococcal infections.

Ravulizumab

FDA approval: 2022.

Indication: To treat adults with AChR antibody-positive generalized myasthenia gravis.

MOA: A recombinant humanized monoclonal IgG antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement.

Dosage: Loading dose of 2,400 – 3,000 mg, and maintenance dose of 3,000 – 3,600 mg, depending on weight**.**

Route of Administration: Intravenous infusion once every 8 weeks.

Boxed Warning: Meningococcal infections.

Zilucoplan

FDA approval: 2023.

Indication: To treat adults with AChR antibody-positive generalized myasthenia gravis.

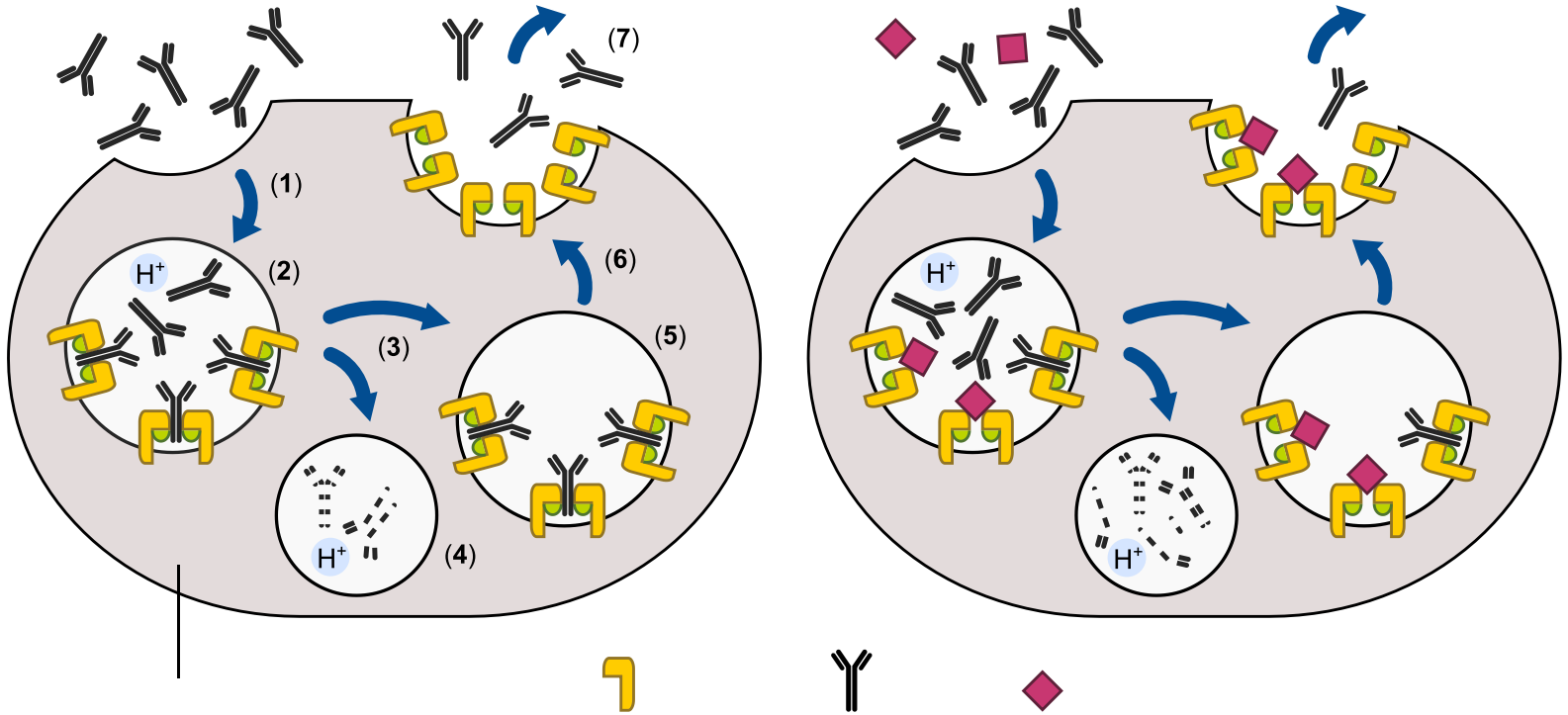
MOA: Peptide inhibitor of complement C5.

Dosage: 0.3 mg/kg once daily.

Route of Administration: Subcutaneous.

Boxed Warning: None.

FcRn Inhibitors



Efgartigimod

FDA approval: 2021.

Indication: To treat adults with generalized myasthenia gravis who are AChR antibody positive.

MOA: FcRn blocker.

Dosage: 10 mg/kg administered weekly for the first 4 weeks. Subsequent treatment cycles based on clinical evaluation. In persons weighing 120 Kg or more, recommended dose is 1200 mg.

Route of Administration: Intravenous infusion (60 minutes).

Boxed Warning: None.

Efgartigimod: ADAPT and ADAPT+ Study

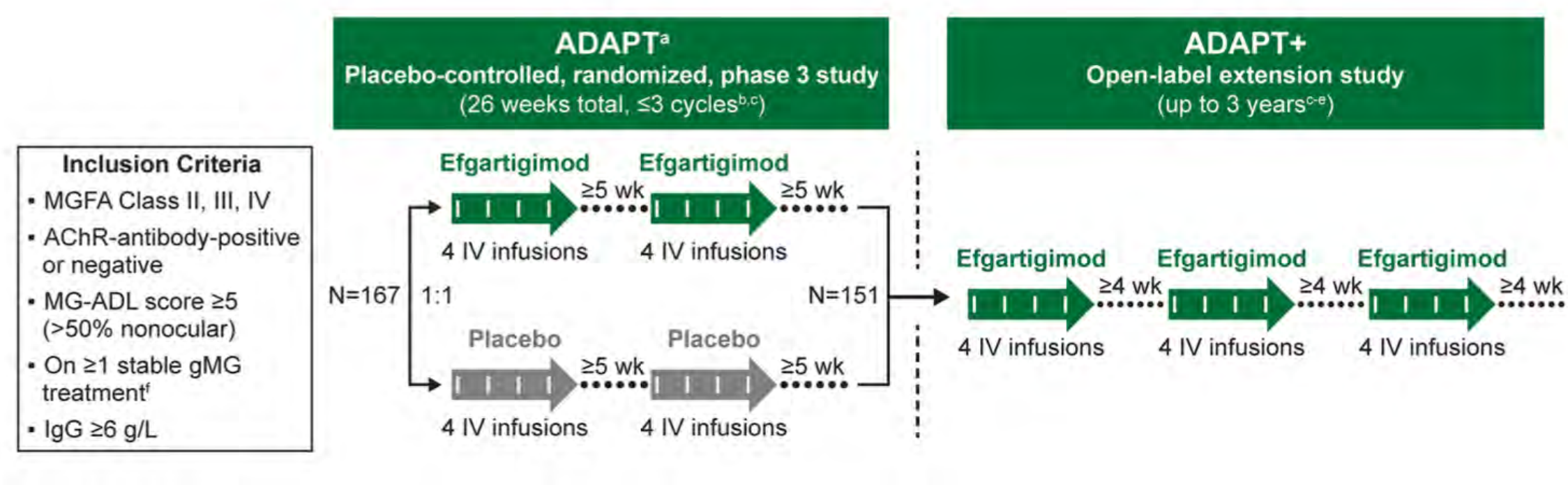
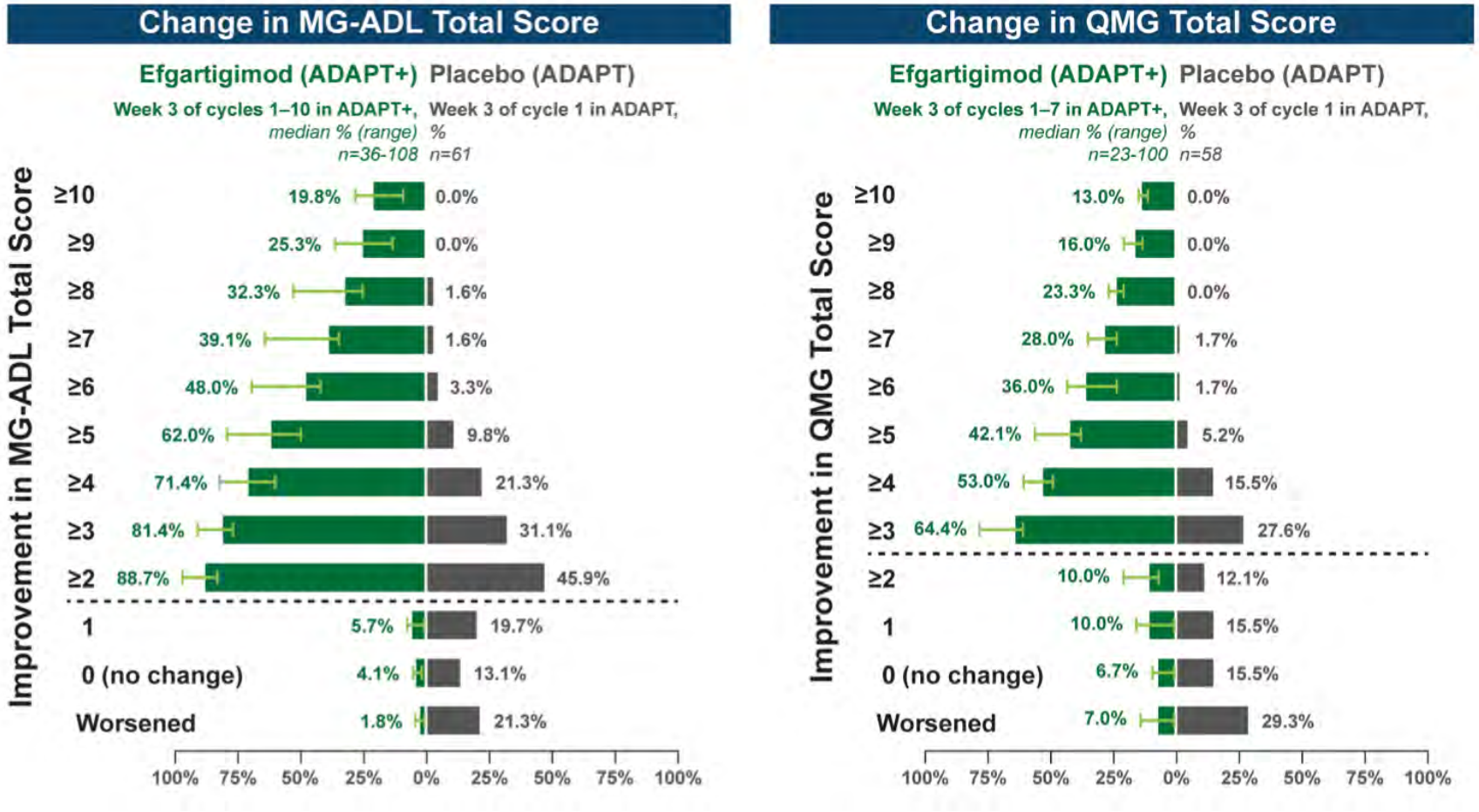


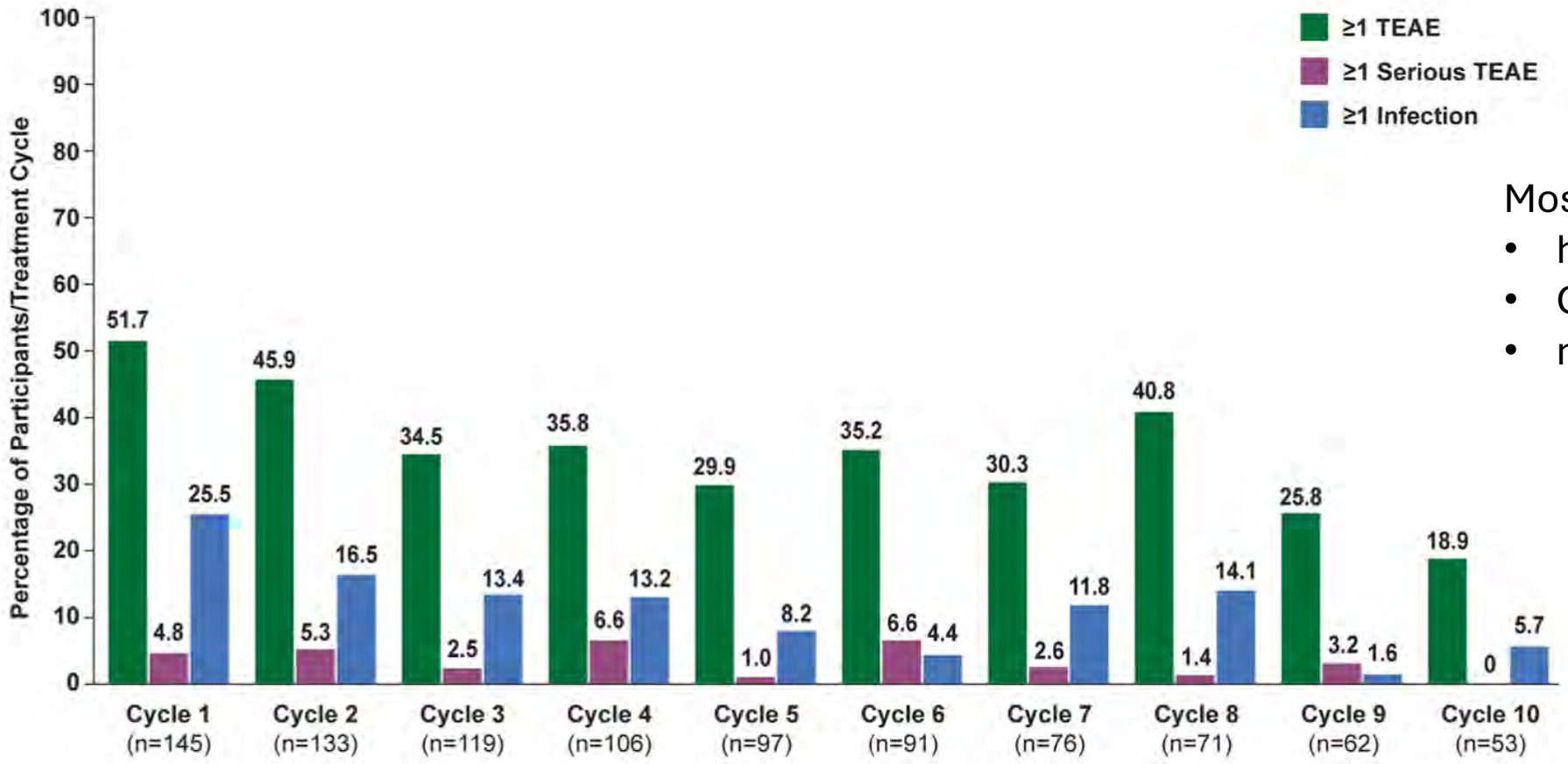
Figure from Howard et al. *Front Neurol.* 2024;14:1284444. [creative commons].
Howard JF et al. *Lancet Neurol.* 2021; 20:526-536.

Efficacy: MG-Activities of Daily Living (MG-ADL) and Quantitative MG (GMG) Scores



Figures from Howard et al. *Front Neurol.* 2024;14:1284444. [creative commons]

Safety: Treatment-emergent Adverse Events (TEAEs)



Most common TEAEs

- headache (24%)
- Covid-19 (15.2%)
- nasopharyngitis (13.8%)

Figures from Howard et al. *Front Neurol.* 2024;14:1284444. [creative commons]

Efgartigimod + hyaluronidase

FDA approval: 2023.

Indication: To treat adults with generalized myasthenia gravis who are AChR antibody positive. Also approved to treat patients with chronic inflammatory demyelinating polyneuropathy.

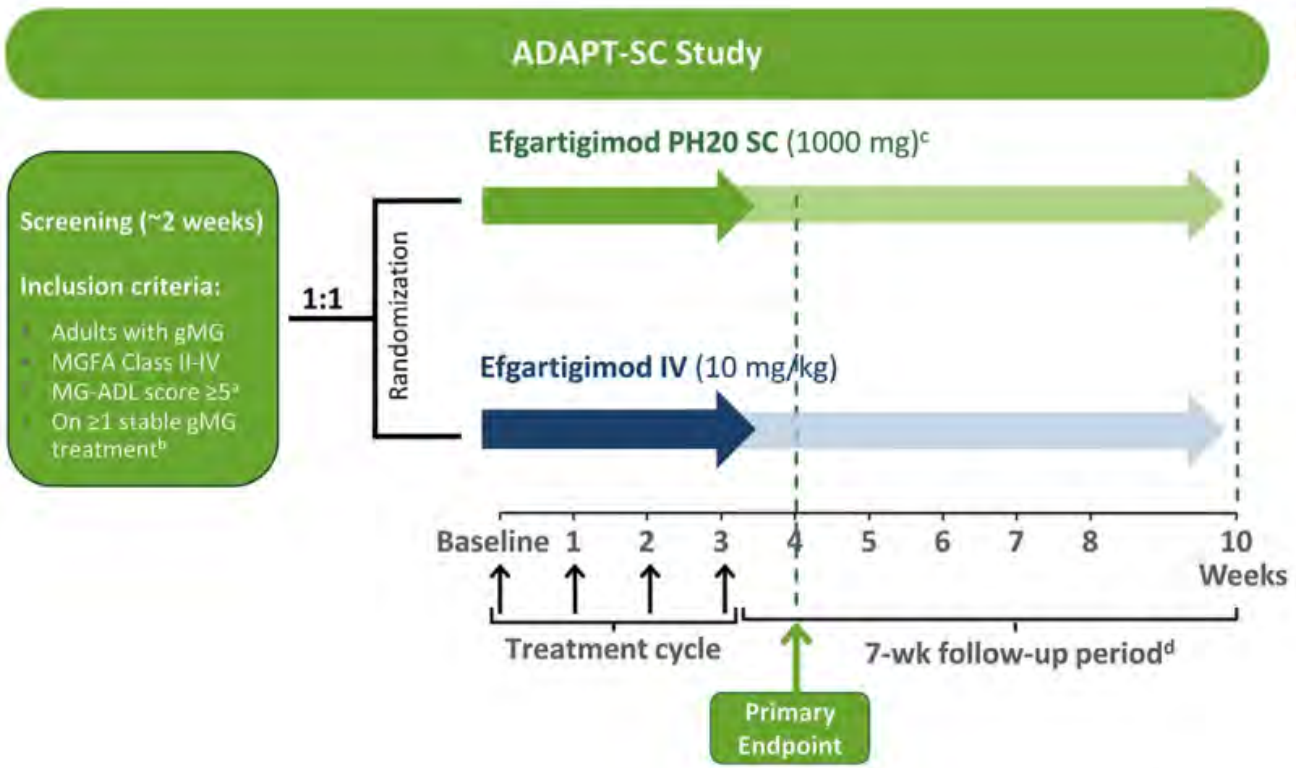
MOA: FcRn blocker plus an endoglycosidase.

Dosage: 1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) in cycles of once weekly injections for 4 weeks. Subsequent treatment cycles based on clinical evaluation.

Route of Administration: subcutaneous injections (30 to 90 sec by a healthcare professional).

Boxed Warning: None.

ADAPT SC Study



- Participants from ADAPT-SC rolled over to ADAPT-SC+ and received efgartigimod PH20 SC
- Participants received 4 weekly injections of PH20 SC 1000 mg over a 3-week period
- Number of treatment cycles received was based on clinical evaluation
- ADAPT-SC+ is ongoing; study duration is up to 3 years

Figure from Howard et al. *Neurotherapeutics 2024. online ahead of print [creative commons]*

Efficacy

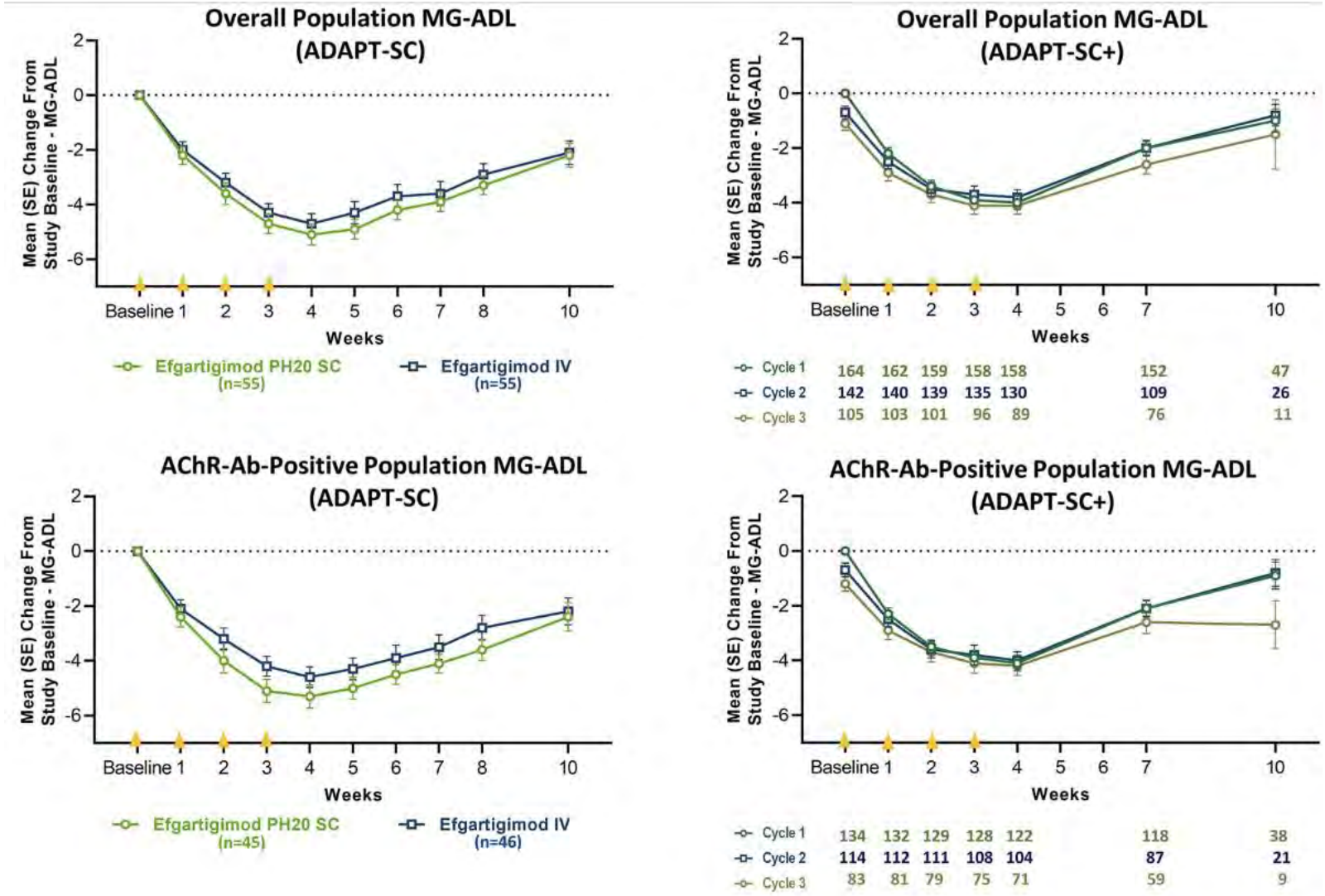


Figure from Howard et al. *Neurotherapeutics 2024. online ahead of print [creative commons]*

Safety

	ADAPT-SC				ADAPT-SC+	
	EFG PH20 SC (n=55)		EFG IV (n=55)		EFG PH20 SC (n=164)	
	n (%)	No. events	n (%)	No. events	n (%)	No. events
AEs	37 (67.3)	133	28 (50.9)	80	125 (76.2)	790
Severe AEs (grade ≥ 3)	9 (16.4)	11	4 (7.3)	5	19 (11.6)	41
Treatment discontinued due to AEs	2 (3.6)	2	0 (0.0)	0	3 (1.8)	4
Death	0 (0.0)	0	0 (0.0)	0	2 (1.2)	3
Most frequent AES						
Injection site reactions	21 (38.2)	39	1 (1.8)	0	69 (42.1)	307
Headache	7 (12.7)	10	7 (12.7)	11	25 (15.2)	58
COVID-19	2 (3.6)	2	0 (0.0)	0	19 (11.6)	20
Myasthenia gravis	6 (10.9)	8	1 (1.8)	2	7 (4.3)	10

Figure from Howard et al. *Neurotherapeutics 2024. online ahead of print [creative commons]*

Rozanolixizumab

FDA approval: 2023.

Indication: To treat adults with generalized myasthenia gravis who are AChR or MuSK antibody positive.

MOA: Monoclonal antibody targeting FcRn.

Dosage: 420 – 840 mg (based on body weight) infusions every week for six weeks. Subsequent treatment cycles based on clinical evaluation.

Route of Administration: subcutaneous infusions using an infusion pump.

Boxed Warning: None.

MycarinG Study

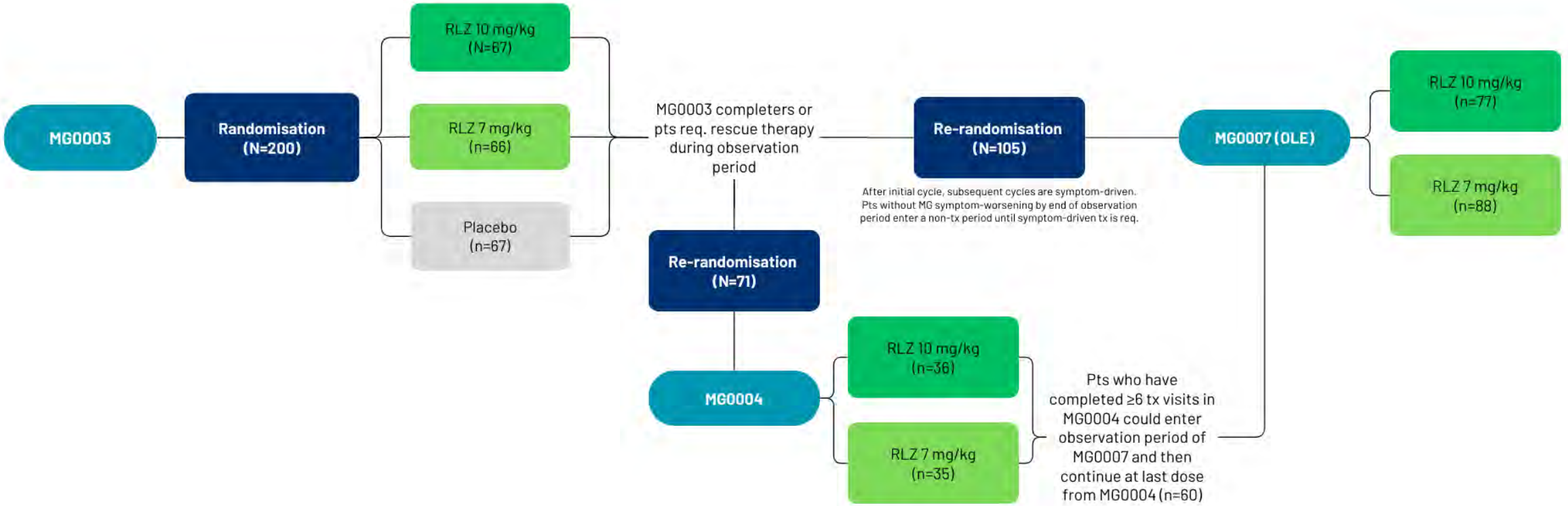


Figure adapted from Bril V et al. *Lancet Neurol. 2023; 22: 383-394.*

Efficacy: MG-ADL Scores

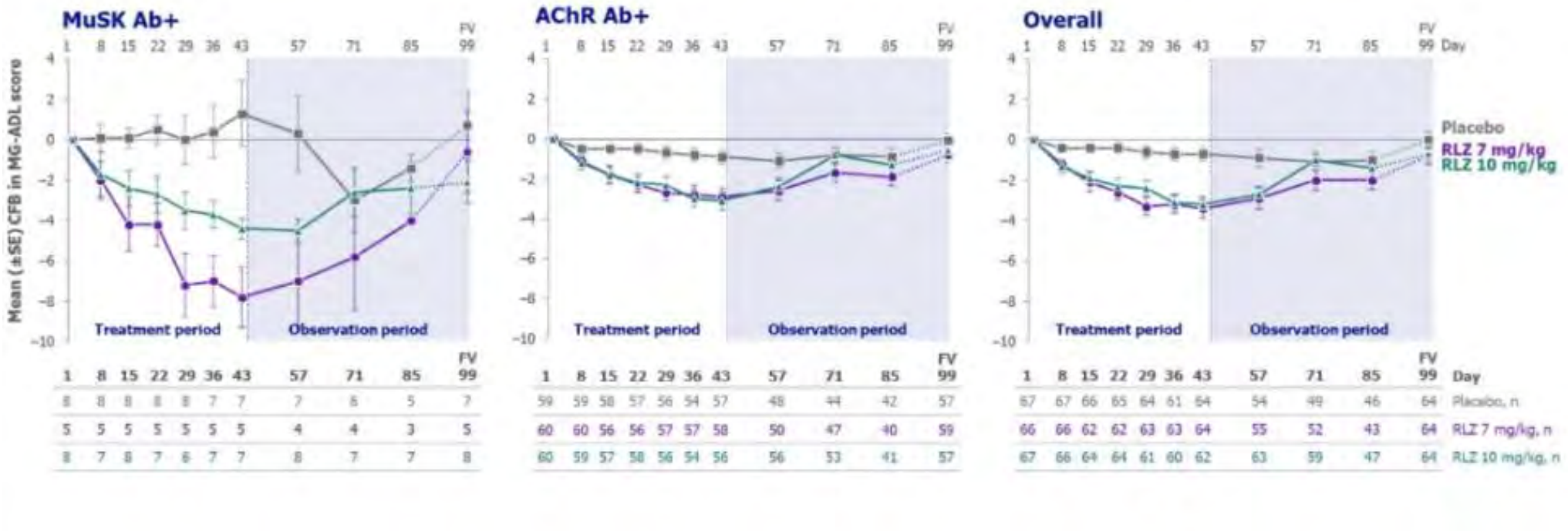


Figure from Habib AA et al. *Ther Adv Neurol Dis. 2024; 17: 17562864241273036.*

Efficacy

	MuSK Ab+ population			AChR Ab+ population			Overall population		
	Placebo (n=7)	RLZ 7 mg/kg (n=5)	RLZ 10 mg/kg (n=7)	Placebo (n=57)	RLZ 7 mg/kg (n=58)	RLZ 10 mg/kg (n=56)	Placebo (n=64)	RLZ 7 mg/kg (n=64)	RLZ 10 mg/kg (n=62)
Responders, n (%)									
MG-ADL	1 (14.3)	5 (100)	7 (100)	19 (33.3)	40 (69.0)	37 (66.1)	20 (31.3)	46 (71.9)	43 (69.4)
MGC	0	5 (100)	7 (100)	25 (43.9)	33 (56.9)	40 (71.4)	26 (40.6)	39 (60.9)	46 (74.2)
QMG	2 (28.6)	5 (100)	6 (85.7)	23 (40.4)	30 (51.7)	40 (71.4)	25 (39.1)	35 (54.7)	45 (72.6)

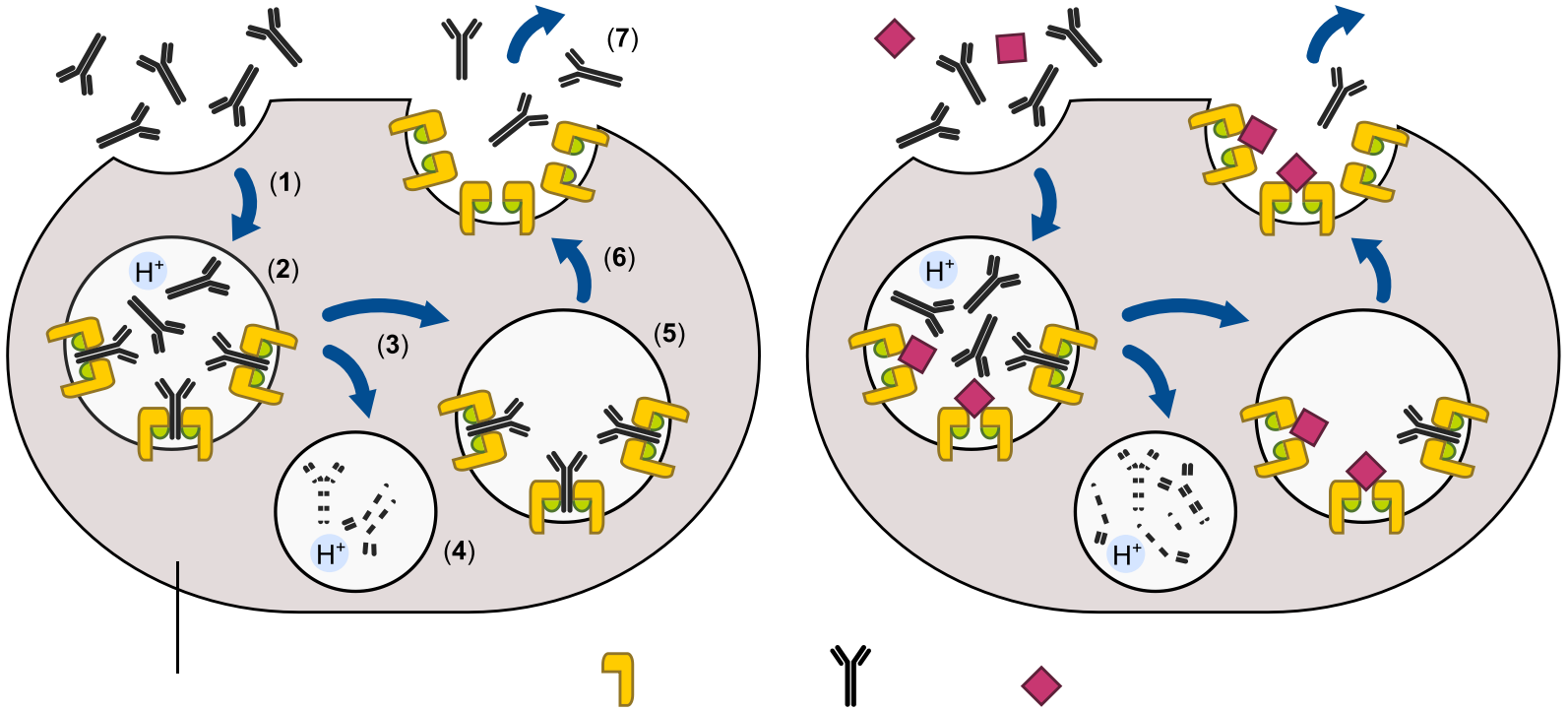
Figure adapted from Habib AA et al. *Ther Adv Neurol Dis. 2024; 17: 17562864241273036.*

Safety

Category, n (%)	MuSK Ab+ population			AChR Ab+ population			Overall population		
	Placebo (n=8)	RLZ 7 mg/kg (n=5)	RLZ 10 mg/kg (n=8)	Placebo (n=59)	RLZ 7 mg/kg (n=58)	RLZ 10 mg/kg (n=62)	Placebo (n=67)	RLZ 7 mg/kg (n=64)	RLZ 10 mg/kg (n=69)
Any TEAE Headache Diarrhea Pyrexia Nausea Arthralgia Nasopharyngitis UTI Myalgia Vomiting Hypertension	3 (37.5)	4 (80.0)	5 (62.5)	41 (69.5)	47 (81.0)	52 (83.9)	45 (67.2)	52 (81.3)	57 (82.6)
Any serious TEAE	0	0	0	6 (10.2)	5 (8.6)	7 (11.3)	6 (9.0)	5 (7.8)	7 (10.1)
Study discontinuation due to TEAE	0	0	1 (12.5)	2 (3.4)	2 (3.4)	4 (6.5)	2 (3.0)	2 (3.1)	5 (7.2)
Treatment discontinuation due to TEAE	0	0	1 (12.5)	2 (3.4)	2 (3.4)	3 (4.8)	2 (3.0)	2 (3.1)	4 (5.8)
Treatment-related TEAEs	1 (12.5)	2 (40.0)	4 (50.0)	21 (35.6)	30 (51.7)	35 (56.5)	22 (32.8)	32 (50.0)	39 (56.5)
Severe TEAEs	0	0	0	3 (5.1)	3 (5.2)	13 (21.0)	3 (4.5)	3 (4.7)	13 (18.8)

Figure adapted from Habib AA et al. *Ther Adv Neurol Dis. 2024; 17: 17562864241273036.*

FcRn Inhibitors in Late-stage Development



Nipocalimab

FDA approval: Under review.

Indication: TBD.

MOA: Monoclonal antibody targeting FcRn.

Dosage: TBD.

Route of Administration: Intravenous.

Boxed Warning: TBD.

Phase 2 study

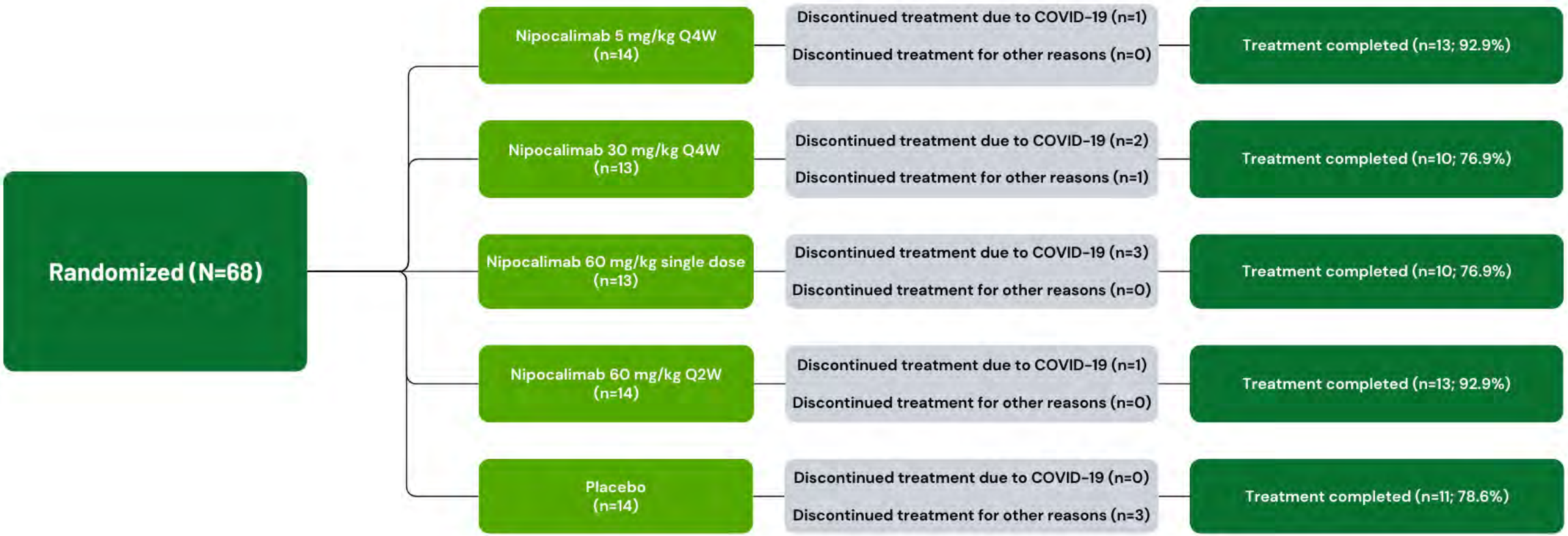
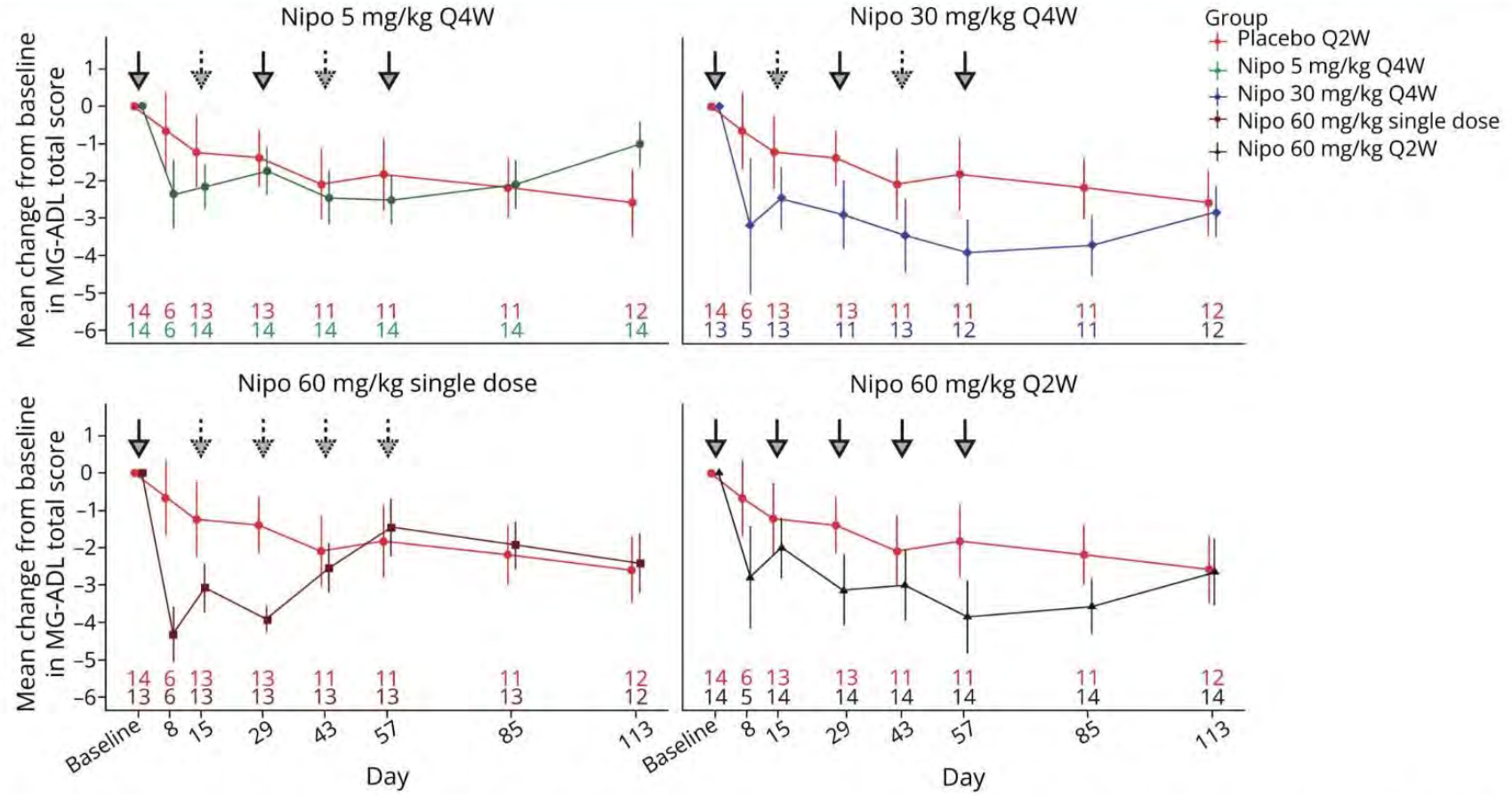


Figure adapted from Antozzi C et al. *Neurol*. 2024;102: e2077937. [creative commons]

Efficacy



ITT = intent-to-treat; Nipo = nipocalimab; MG-ADL = Myasthenia Gravis-Activities of Daily Living; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error. Bold downward arrows denote the doses of nipocalimab administered at different time points. Dotted downward arrows denote placebo administered.

Figure from Antozzi C et al. *Neurol*. 2024;102: e2077937. [creative commons]

Safety

	Placebo	Nipocalimab				
	Q2W (n=14)	5 mg/kg Q4W (n=14)	30 mg/kg Q4W (n=13)	60 mg/kg single dose (n=13)	60 mg/kg Q2W (n=14)	Combined (n=54)
Any TEAEs	11 (78.6)	12 (85.7)	9 (69.2)	12 (92.3)	12 (85.7)	45 (83.3)
Related to study agent	1 (7.1)	5 (35.7)	3 (23.1)	6 (46.2)	7 (50.0)	21 (38.9)
Leading to tx discontinuation	2 (14.3)	0	0	0	0	0
Serious TEAEs	2 (14.3)	0	1 (7.7)	0	0	1 (1.9)
Most common TEAEs:						
Diarrhea						
Headache						
Nasopharyngitis						
Rash						
Back pain						
Dizziness						
Hypertension						
Musculoskeletal pain						
Edema peripheral						

Figure adapted from Antozzi C et al. *Neurol*. 2024;102: e2077937. [creative commons]

Batoclimab

FDA approval: N/A.

Indication: TBD.

MOA: Monoclonal antibody targeting FcRn.

Dosage: TBD.

Route of Administration: Intravenous.

Boxed Warning: TBD.

Phase 2 Study

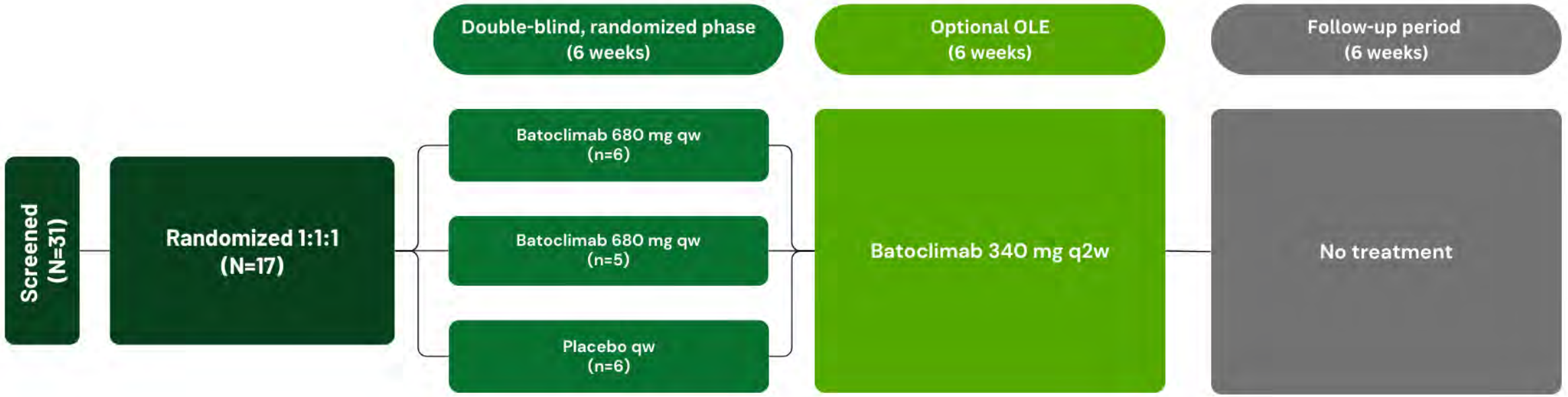


Figure adapted from Nowak RJ et al. *Ann Clin Transl Neurol*. 2024; 11: 194-206. [creative commons]

Phase 2 Study: Efficacy

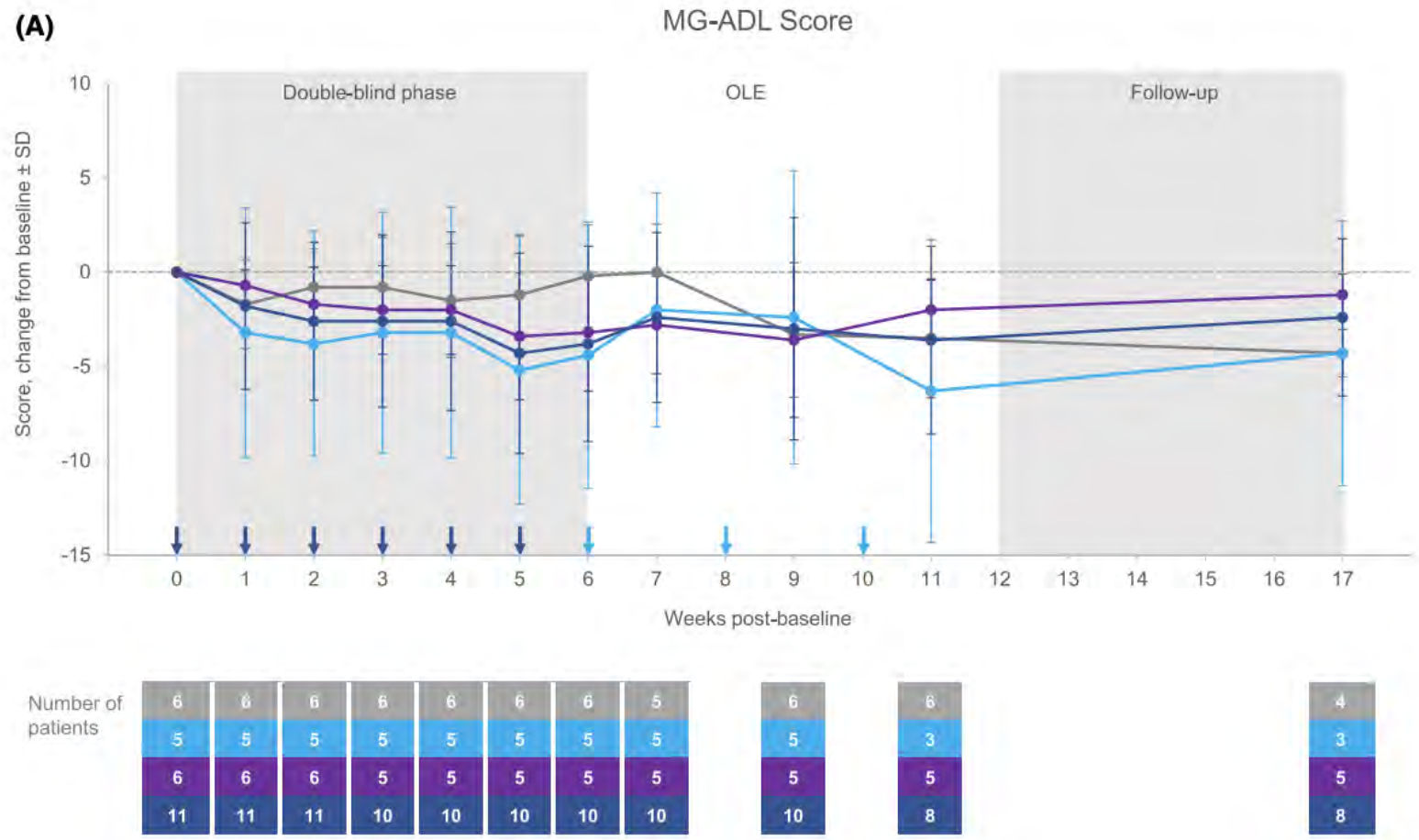


Figure from Nowak RJ et al. *Ann Clin Transl Neurol*. 2024; 11: 194-206. [creative commons]

Phase 2 Study: Safety

Patients, n (%)	Double-blind phase			OLE	Follow-up
	Batoclimab 680 mg qw (n=6)	Batoclimab 340 mg qw (n=5)	Placebo qw (n=6)	Batoclimab 340 mg q2w (n=15)	No treatment (n=13)
Any AE	5 (83.3)	4 (80.0)	5 (83.3)	7 (46.7)	6 (46.2)
Any TRAE (All Grade 1-2)	2 (33.3)	3 (60.0)	3 (50.0)	3 (20.0)	-
SAEs	1 (16.7)	0	0	0	1 (7.7)
AEs leading to tx discontinuation	1 (16.7)	0	0	0	0
Tx-related injection site reactions	1 (16.7)	2 (40.0)	1 (16.7)	3 (20.0)	-
Most common TRAEs:	• Decreased appetite • Viral URTI	• Increased RBC count • Muscle spasms • UTI • Pyuria	• Headache • Constipation • Decreased complement activity • Diarrhea	-	-

Figure adapted from Nowak RJ et al. *Ann Clin Transl Neurol*. 2024; 11: 194-206. [creative commons]

Phase 3 FLEX study

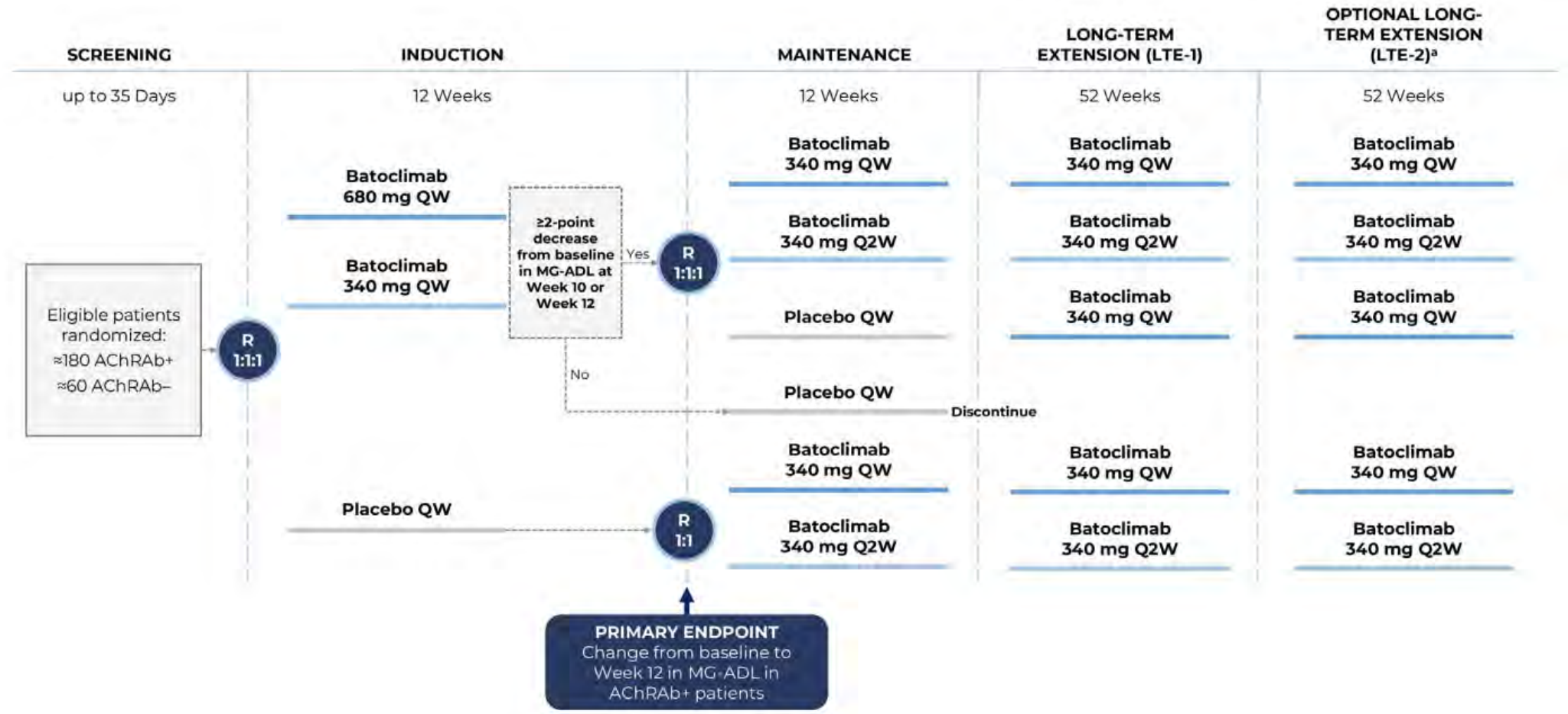


Figure from Benatar M et al. *BMJ Neurol Open*. 2024; 6: e000536.

Batoclimab: China-based Study

- Multicenter randomized study conducted from September 15, 2021, to June 29, 2022, in China.
- Adult pts ≥18 years w/ generalized MG were screened; those who were antibody positive were enrolled
- Eligible pts received batoclimab or matching placebo in addition to SOC.
- Each treatment cycle consisted of 6 weekly subcutaneous injections of batoclimab (680 mg), or matching placebo, followed by 4 weeks of observation.
- Second treatment cycle was conducted in pts who required continuing treatment

Figure adapted from Yan C et al. *JAMA Neurol*. 2024; 81: 336-345.

Batoclimab: Efficacy and Safety

	Placebo, n (%)	Batoclimab, n (%)	p-value
MG-ADL improvement	20/64 (31.3)	39/67 (58.2)	p = 0.001
TRAEs	24/65 (36.9)	47/67 (70.1)	-
S-TEAEs	5/65 (7.7)	2/67 (3.0)	-

Figure adapted from Yan C et al. *JAMA Neurol*. 2024; 81: 336-345.

Summary Table

	FDA approval	Route of administration	Clinical trial link
Efgartigimod	Adults with gMG, AchR-Ab+	IV, weekly	
Efgartigimod SC	Adults with gMG, AchR-Ab+	SC, weekly	
Rozanolixizumab	Adults with gMG, AchR-Ab+ or MuSH Ab+	SC, weekly	
Nipocalimab	N/A	IV, every two weeks	Adults with gMG (phase 3) https://clinicaltrials.gov/study/NCT04951622 Children with gMG (phase 2/3) https://clinicaltrials.gov/study/NCT05265273
Batoclimab	N/A	SC, weekly	Adults with gmG, AchR Ab+ (phase 3) https://clinicaltrials.gov/study/NCT05403541

Clinical Pearls

- Numerous therapies are approved and in development that attack FcRn to reduce pathologic levels of IgG associated with MG.
- Three medications that alter FcRn activity are currently approved to treat MG and two are in last stage development to treat MG.
- FcRn blockers, along with medications that interfere with the complement system, provide clinicians with more options to tailor therapy best suited for the patient.