CME

Myasthenia Gravis Research Highlights: AAN 2023

Vera Bril, MD

University Hospital Network, Toronto, ON

Disclosures

Dr. Bril discloses the following:

- Advisory Board/Consultant: Grifols, CSL, UCB, Argenx, Takeda, Alnylam, Octapharma, Pfizer, Akcea, Ionis Immunovant, Sanofi, Momenta (J&J), Roche, Janssen, AstraZeneca-Alexion, Novo Nordisk, Japan Tobacco
- Grant/Research Support: AstraZeneca-Alexion, Grifols, CSL, UCB, Argenx, Takeda, Octapharma, Akcea, Momenta (J&J), Immunovant, Ionis

Planners have no relevant relationships with ineligible companies to disclose.

What Is Myasthenia Gravis?

Group of rare autoimmune diseases

Trademark: fluctuating but intense weakness in specific muscle groups – such as bulbar weakness, limb weakness, and ocular weakness

Often due to the presence of antibodies against acetylcholine (AChR-Ab+).

Ocular weakness - most common initial presentation of MG

Four drugs approved by the FDA:

- Eculizumab
- Efgartigimod
- Ravulizumab
- Rozanolixizumab

Therapy options in development include:

- Zilucoplan

AAN 2023

- **American Academy of Neurology**
- Held April 22-27, 2023, in Boston, Massachusetts with virtual component
- Abstracts published in the journal, *Neurology*

Treatments Approved

Efgartigimod

- Neonatal FcRn antagonist approved for treatment of AChR-Ab+ generalized myasthenia gravis (gMG)

ADAPT+

- ADAPT: 26-week, randomized, controlled, phase 3 trial evaluating efgartigimod in pts with gMG
  - 90% of pts (151/167) from ADAPT entered ADAPT+ extension study
- Aim of analysis: evaluate long-term safety and efficacy of efgartigimod.
- Results suggest long-term efgartigimod treatment is well-tolerated and results in consistent and repeatable reductions in IgG Ab levels and improves clinical outcomes in pts with gMG.

	MG Pts Received ≥ 1 cycle (N=145)		Notes
Antibody status	111 AChR-Ab+	34 AChR-Ab-	
Common adverse events	Headache (25%) Concomitant COVID-19 infection (15%) Nasopharyngitis (14%) Diarrhea (10%) UTI (9%)		Mostly mild-moderate; did not increase in frequency w/ subsequent cycles.
≥ 1 year of follow up across ADAPT/ADAPT+	n=95		
Median cycles per year	5.0		
MD-ADL: mean change from baseline to end of Cycle 1	-5.0		Up to 14 cycles
QMG: mean change from baseline to end of Cycle 1	-4.7		Up to 7 cycles
Mean reduction in total IgG	-55.9%		Up to 7 cycles
Mean reduction in AChR-Abs	-56.1%		Up to 7 cycles

Pasnoor M, et al. Long-Term Safety, Tolerability, And Efficacy of Efgartigimod in Patients with Generalized Myasthenia Gravis: Concluding Analyses from the ADAPT+ Study . Presented at AAN 2023. Boston, MA.

Treatment in Pts with Shorter Disease Duration

	Pts with <3 years disease duration (n=31)		Pts with ≥ 6 years disease duration (n=69)		Notes
	Efgartigimod (n=14)	Placebo (n=17)	Efgartigimod (n=37)	Placebo (n=32)	
MG-ADL responders	78.6% (n=11)	23.5% (n=4)	56.8% (n=21)	21.9% (n=7)	Similar results were observed in proportion of QMG responders between efgartigimod- and placebo-treated pts among <3 and ≥6-year subgroups.
Achieved MSE	42.9% (n=6)	12.5% (n=2)	40.5% (n=15)	9.4% (n=3)	

- Aim: assess efficacy of efgartigimod in AChR-Ab+ pts with gMG.
- Evaluated responder status and minimal symptom expression (MSE; MG-ADL 0 or 1) in subgroups of AChR-Ab+ pts with <3 years and ≥6 years disease duration.
- A greater percentage of pts early in their disease course treated with efgartigimod were responders and achieved MSE compared with placebo.

Bril V, et al. Efgartigimod Demonstrates Consistent Improvements in Generalized Myasthenia Gravis Patients of Shorter Disease Duration. Presented at AAN 2023. Boston, MA.

Two Cases of Pembrolizumab-Induced MG Treated with Efgartigimod

68-year-old female with metastatic gallbladder cancer

- Developed ptosis, ophthalmoparesis, and weakness 1 month after receiving pembrolizumab.
- Has acetylcholine receptor and striated muscle antibodies without thymoma.
- Ptosis improved with prednisone 20mg daily.
  - Developed dysphagia, hoarseness, and gait instability which resolved with increased prednisone 60mg.
  - Prednisone was tapered; proximal limb weakness and ptosis returned at 30mg.
- **Efgartigimod improved symptoms after second infusion.**
- 3 weeks after cycle 1 while alternating prednisone 25mg-20mg, pt developed exertional dyspnea, hoarseness, and worsening ptosis.
- Increased prednisone to 25mg. Pt symptoms persisted.
- Five weeks after cycle one**, the second cycle of efgartigimod started – symptoms nearly resolved**, with intermittent ptosis.
- Now stable on prednisone 25mg with slow taper.

Campbell M, et al. Efgartigimod for Pembrolizumab-induced Myasthenia Gravis Refractory to Standard Therapy . Presented at AAN 2023. Boston, MA.

Two Cases of Pembrolizumab-Induced MG Treated with Efgartigimod

78-year-old female with metastatic urothelial carcinoma

- Presented with dyspnea, leg weakness, and myalgias. Pt developed ptosis, ophthalmoparesis, and dysphagia after 2 doses of pembrolizumab.
  - Acetylcholine receptor and MuSK antibodies were negative.
- Intravenous immunoglobulin was ineffective to prevent worsening.
  - After the second dose, pt developed respiratory failure requiring intubation.
- Prednisone 40mg BID and plasmapheresis (PLEX) initiated.
- Pt strength improved enough for extubation; subsequently aspirated and required reintubation.
- Rituximab was infused for long-term immunosuppression while another PLEX cycle was started.
- Developed thrombocytopenia and gastrointestinal bleeding; PLEX was discontinued after 3 doses.
- **Efgartigimod initiation two days after the final PLEX infusion led to improved strength, ophthalmoparesis, and thrombocytopenia within one week.**
- Pt died from urosepsis two days after the second dose.

Campbell M, et al. Efgartigimod for Pembrolizumab-induced Myasthenia Gravis Refractory to Standard Therapy . Presented at AAN 2023. Boston, MA.

Eculizumab

- Monoclonal antibody; targets complement protein C5
- Approved for pts with AChR-Ab+ gMG

Eculizumab Leads to Discontinuation of Concomitant Therapies

- Aim: assess use of concomitant therapies at/after eculizumab initiation in pts with gMG.
- Use of azathioprine, mycophenolate mofetil, intravenous immunoglobulin (IVIg)/plasma exchange (PLEX), and oral corticosteroids at initiation of, and during eculizumab treatment analyzed.
- Approximately 25% of pts with gMG treated with eculizumab were able to discontinue one or more concomitant therapy.

At eculizumab initiation (N=94)	
Pts receiving…	
Zero concomitant therapies	25 (27%)
One concomitant therapy	40 (43%)
Two concomitant therapies	25 (27%)
Three concomitant therapies	3 (4%)
Pts on concomitant treatment	
Azathioprine	9 (10%)
Mycophenolate mofetil	26 (28%)
IVIg/PLEX	19 (20%)
Oral corticosteroids	48 (50%)

After eculizumab initiation (N=94)	
Number of concomitant therapies	
No change	57 (61%)
Reduced	26 (28%)
Increased	13 (14%)
Pts who discontinued…	
Azathioprine	2/9 (22%)
Mycophenolate mofetil	8/26 (31%)
IVIg/PLEX	5/19 (26%)
Oral corticosteroids	11/47 (23%)

Pulley M, et al. Change in Concomitant Therapies for Generalized Myasthenia Gravis in Patients Receiving Eculizumab: a Retrospective Analysis of Registry Data. Presented at AAN 2023. Boston, MA.

Ravulizumab

- Long-acting terminal complement C5 inhibitor
- Approved for pts with AChR-Ab+ gMG
- CHAMPION MG:
  - 26-week, phase 3, randomized, double-blind, placebo-controlled study; demonstrated the efficacy and safety of ravulizumab in pts with AChR Ab+ gMG.
  - Pts who completed randomized controlled period (RCP) could receive ravulizumab in an OLE; blinding to original treatment was maintained.

Ravulizumab Leads to Improvement Despite Minimal Manifestation Status

- Aim: determine whether ravulizumab treatment enables pts with AChR-Ab+ gMG to achieve the Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) of “improved”, with or without achieving minimal manifestation status (MMS).

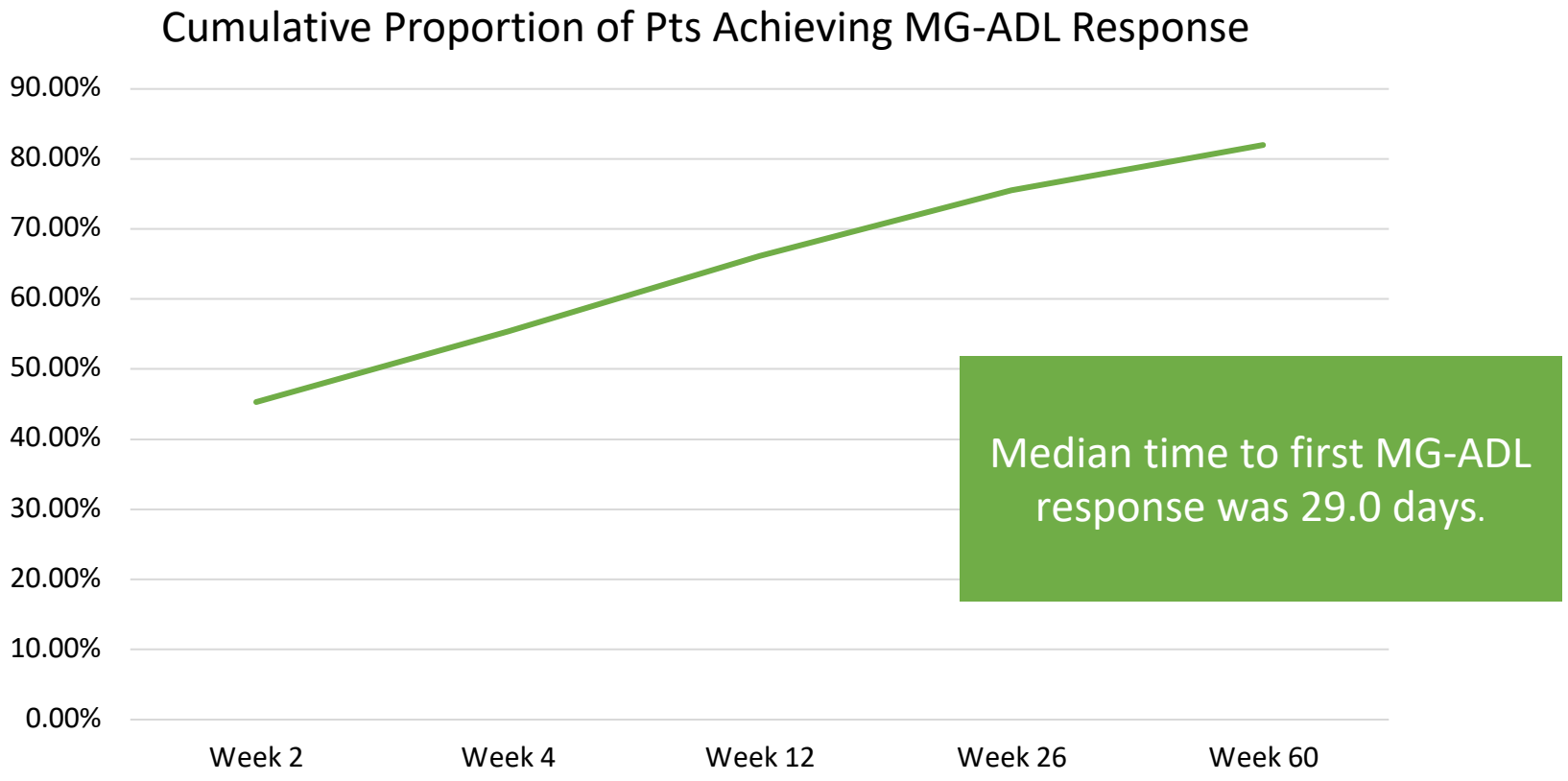
	Week 26				Week 60			
	Ravulizumab		Placebo		Continued ravulizumab		Placebo to ravulizumab	
	With MMS	Without MMS	With MMS	Without MMS	With MMS	Without MMS	With MMS	Without MMS
Achieved “improved” status	20/78 (25.6%)	17/78 (21.8%)	8/81 (9.9%)	18/81 (22.2%)	19/56 (33.9%)	18/56 (32.1%)	18/57 (31.6%)	24/57 (42.1%)

- Ravulizumab-treated pts more likely than those receiving placebo to achieve MGFA-PIS of improved, with or without MMS.
- The increase in the proportion of pts achieving MGFA-PIS of improved with continued treatment suggests longer-term treatment may be needed for some pts

Muppidi S, et al. Achievement of Improved Post-Intervention Status in Patients with Generalized Myasthenia Gravis Treated with Ravulizumab during the CHAMPION MG Study . Presented at AAN 2023. Boston, MA.

Timing of First Response to Ravulizumab

- Aim: assess timing of first response to ravulizumab in pts with gMG in CHAMPION MG study.
- Cumulative response rates indicate first response was achieved by almost half of pts after one ravulizumab infusion and by two-thirds of pts by Week 12



Habib A, et al. Ravulizumab for the Treatment of Generalized Myasthenia Gravis: Timing of Response. Presented at AAN 2023. Boston, MA.

Rozanolixizumab

- IgG4 monoclonal antibody; inhibits FcRn, reducing IgG and pathogenic IgG autoantibody levels.
- Approved for pts with AChR-Ab+ or MUSK-Ab+ gMG

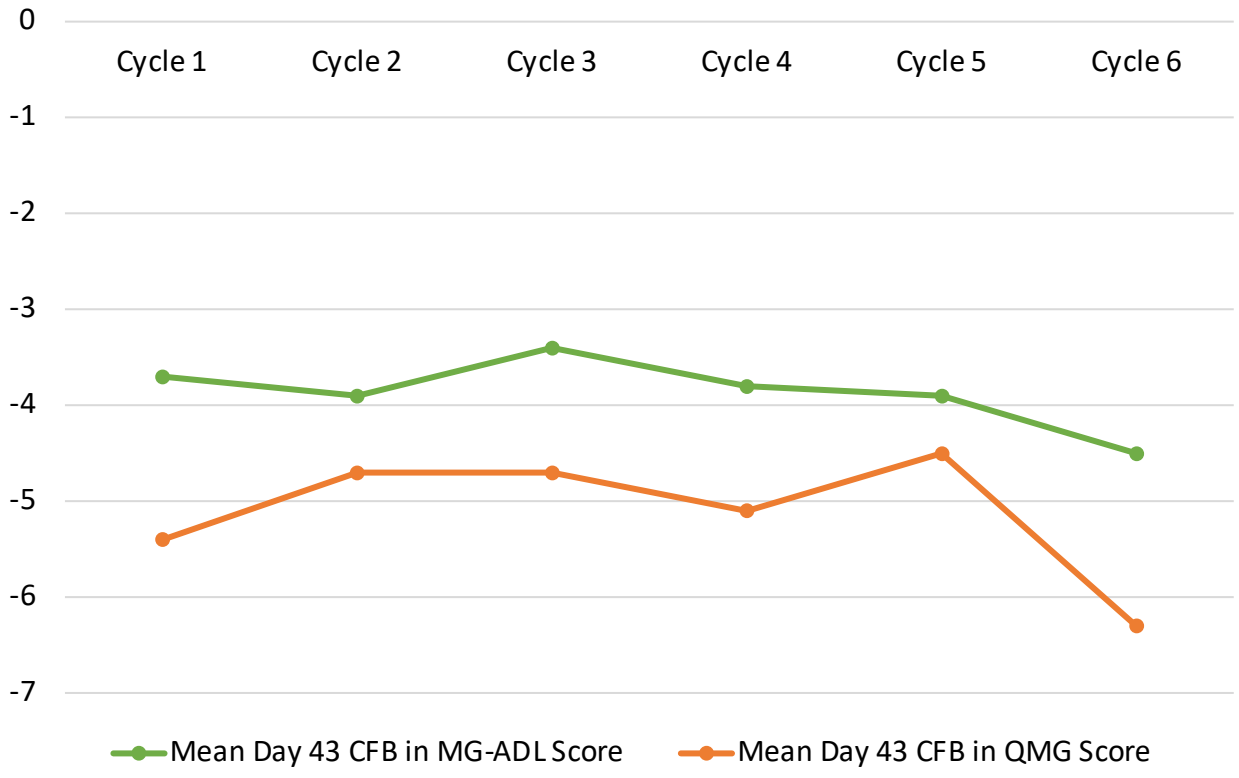
Efficacy of Rozanolixizumab

- Rozanolixizumab is a humanized IgG4 monoclonal antibody; inhibits FcRn, reducing IgG and pathogenic IgG autoantibody levels.
- Aim of analysis: establish efficacy of rozanolixizumab in pts with gMG across subgroups of prior therapy and disease severity/duration.
- Rozanolixizumab treatment demonstrated greater reductions in MG-ADL score than placebo in a broad range of pts with gMG.

	Rozanolixizumab 7mg/kg (n=66)	Rozanolixizumab 10mg/kg (n=67)	Placebo (n=67)
LS mean change from baseline at Day 43 in MG-ADL	-3.4	-3.4	-0.8
Mean observed change in MG-ADL from baseline			
≥ 1 prior therapy (n=163)	-3.2	-3.3	-1.0
≥ 2 prior therapies (n=84)	-2.5	-3.0	-0.8
Baseline QMG ≤15 (n=110)	-3.7	-2.6	-0.6
Baseline QMG >15 (n=90)	-3.0	-4.0	-0.7
Baseline disease duration <4 years (n=78)	-2.9	-3.1	-0.6
Baseline disease duration ≥4 years (n=122)	-3.8	-3.3	-0.7
Number of pts experienced TEAEs	52 (81.3%)	57 (82.6%)	45 (67.2%)

Vu T, et al. Efficacy of Rozanolixizumab in Generalized Myasthenia Gravis: Subgroup Analyses from the Randomized Phase 3 MycarinG Study. Presented at AAN 2023. Boston, MA.

Efficacy of Rozanolixizumab Continued



- Aim of analysis: assess efficacy of cyclic rozanolixizumab treatment for gMG.
- Pooled data reported across MycarinG and OLEs, MG0004 (first 6 weeks) and MG0007 (interim analysis), for pts with ≥2 symptom-driven cycles (≤6 cycles) and with ≥1 cycle.
- 169/188 (89.9%) pts receiving ≥1 cycle of rozanolixizumab reported ≥1 TEAE
- Rozanolixizumab efficacy maintained up to six 6-week treatment cycles across multiple MG-specific outcomes, with an acceptable safety profile following repeated cyclic treatment.

Bril V, et al. Long-term Efficacy and Safety of Symptom-driven Cyclic Rozanolixizumab Treatment in Patients with Generalized Myasthenia Gravis: A Pooled Analysis of a Phase 3 Study and Two Open-label Extension Studies. Presented at AAN 2023. Boston, MA.

Previous IVIg Use Does Not Affect Ravulizumab Response

	No previous IVIg use (n=79)		Acute IVIg use (n=50)		Chronic IVIg use (n=46)	
	RAV	Placebo	RAV	Placebo	RAV	Placebo
	41	38	29	21	22	24
LS mean change from baseline at Week 26 in MG-ADL total score	-2.1		-1.3		-1.1	
LS mean change from baseline at Week 26 in QMG total score	-2.4		-1.6		-2.3	

- Aim: assess differences in response to ravulizumab in pts with AChR-Ab+ gMG based on previous intravenous immunoglobulin (IVIg) treatment.
- While IVIg treatment was only allowed as rescue therapy during the CHAMPION MG study, many pts had a history of IVIg use prior to entering the study.
- There were no differences in response to ravulizumab re: improvements in functional ability and muscle strength in pts with AChR Ab+ gMG according to previous IVIg treatment.

Bril V, et al. Ravulizumab in Adults with Generalized Myasthenia Gravis: A Sub-Analysis of the Phase 3 CHAMPION MG Study According to Chronic IVIg Use at Study Entry. Presented at AAN 2023. Boston, MA.

Treatments in Development

Zilucoplan

- Zilucoplan is a macrocyclic peptide C5 inhibitor; resulted in statistically significant and clinically meaningful improvement in MG-related efficacy endpoints in pts with AChR Ab+ gMG.
- Aim of investigation: evaluate efficacy of zilucoplan in pts with AChR Ab+ gMG, stratified to specific disease characteristics.
- Overall, 174 participants were randomized to zilucoplan (n=86) or placebo (n=88).
- At Week 12, the mean CFB in MG-ADL for zilucoplan vs placebo was consistently improved in each subgroup, and showed a favorable safety profile.
- Daily subcutaneous zilucoplan demonstrated consistent improvements in MG-specific efficacy outcomes regardless of disease severity or duration.

	Change from Baseline in MG-ADL
Baseline MG-ADL: ≤9	
Zilucoplan	-3.88
Placebo	-2.48
Baseline MG-ADL: ≥10	
Zilucoplan	-5.24
Placebo	-3.08
Baseline QMG: ≤17	
Zilucoplan	-4.19
Placebo	-2.81
Baseline QMG: ≥18	
Zilucoplan	-5.11
Placebo	-2.88
Duration of disease: <5 yrs	
Zilucoplan	-3.92
Placebo	-3.04
Duration of disease: ≥5 yrs	
Zilucoplan	-5.38
Placebo	-2.62

Weiss MD, et al. Subgroup outcomes from RAISE: A randomized, Phase 3 trial of zilucoplan in generalized myasthenia gravis. Presented at AAN 2023. Boston, MA.

Additional Research

Incidence and Prevalence of Myasthenia Gravis in the United States: A Claims-Based Analysis

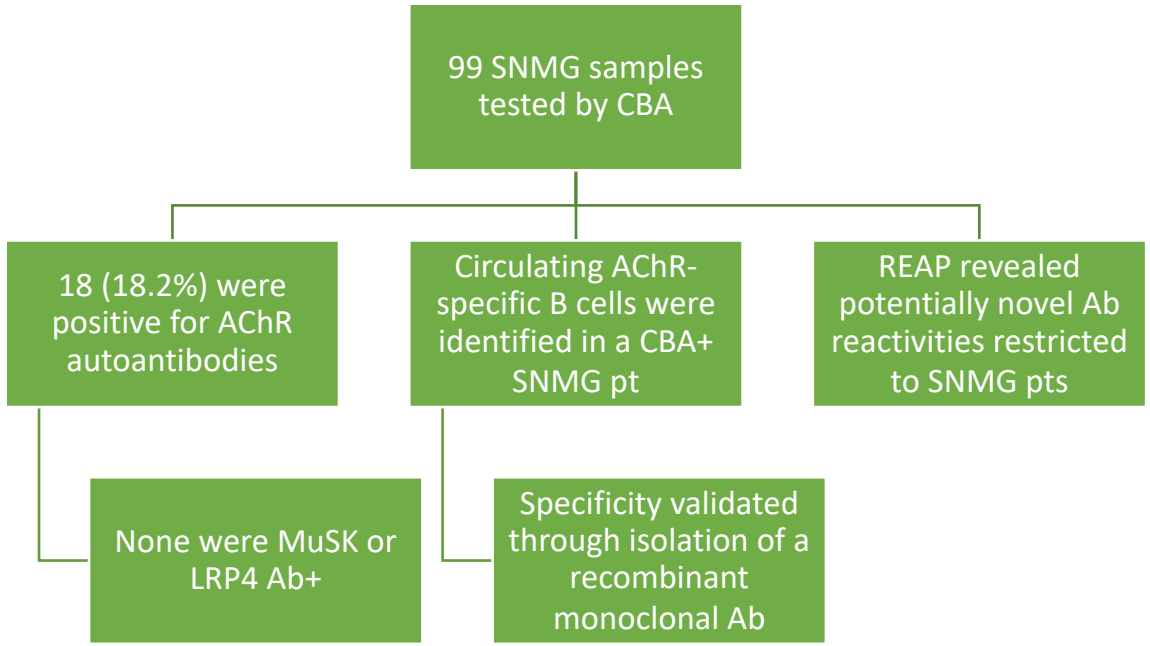
- Estimates of the incidence and prevalence of MG in the US are higher than older reported estimates.
- Updated prevalence estimates allow for more accurate quantification of the burden of disease associated with MG.

Age	Incidence (per 100,000)	Prevalence (per 100,000)
<2 years	0.3	0.4
2-5 years	0.5	2.1
6-11 years	0.2	3.7
12-17 years	0.4	5.6
18-49 years	1.5	18.3
50-64 years	4.0	47.9
65+ years	10.2	116.8
Overall	3.2	37.0

Rodrigues E, et al. Incidence and Prevalence of Myasthenia Gravis in the United States: A Claims-Based Analysis. Presented at AAN 2023. Boston, MA.

Investigating Autoantibody Profiles in SNMG

- Aim: refine serological characterization of pts with seronegative myasthenia gravis (SNMG) and explore novel disease-specific autoantibody reactivities.
- About 10% of MG pts are seronegative, lacking detectable autoantibodies. This delays diagnosis and restricts eligibility for clinical trials and reimbursement for therapy.
- In some SNMG pts, autoantibodies can be detected by cell-based assays (CBA).
  - However, data on CBA positivity rates in the U.S. are lacking.
- Findings from large SNMG cohort support clinical need to implement clustered AChR CBA testing in evaluation of SNMG pts.



Masi G, et al. Investigating Autoantibody Profiles in Seronegative Myasthenia Gravis . Presented at AAN 2023. Boston, MA.

Pregnancy in MG pts

	AChR Ab-	vs	AChR Ab+	MUSK+	P value
Risk of ICU admission	23%		16%	12%	0.058
Intubation	50%		4%	17%	0.007
C section	92%		23%	42%	0.001
Neonatal MG rates	67%		8%	0%	0.001
Unplanned pregnancy	75%		21%	50%	0.004

- Aim: assess impact of MG serological status on pregnancy-related and neonatal outcomes.
- Unknown if serological status impacts pregnancy and neonatal outcomes.
- AChR Ab- pts reported a greater risk of ICU admission, intubation, C-section, neonatal MG rates, and unplanned pregnancy than AChR Ab+ and MUSK+ pts
- First known study of association between negative serological status and poor pregnancy outcomes; may influence future preconception counselling and pregnancy monitoring.

Al Hussona M, et al. The impact of Myasthenia Gravis antibody status on pregnancy and neonatal outcomes. Presented at AAN 2023. Boston, MA.

Launch of International Electronic Database for MG

- Aim: develop and implement the first international observational database for pts with MG
- Background:
  - Developed from highly successful Multiple Sclerosis registry
  - >80,000 MG pts
  - In collaboration with MSBase Foundation
  - Leverages existing IT infrastructure, data security, privacy compliance and governance structures of MSBase registry.
- MGBase launched December 2021.

Demographics:			
Mean age of 59 yrs	67% male	Mean disease duration: 9.7 yrs	Disease type: ○ AChR +: n = 29 ○ MuSK: n =3 ○ SNMG: n = 14 ○ Unknown: n =3

Reddel S, et al. MGBase: The launch of an international electronic database for patients with Myasthenia Gravis. Presented at AAN 2023. Boston, MA.

Clinical Pearls

Clinical Pearls

- Long-term efgartigimod treatment is well-tolerated and early treatment leads to greater response
- Approximately 25% of pts with gMG treated with eculizumab were able to discontinue one or more concomitant therapy.
- Ravulizumab-treated pts more likely than those receiving placebo to achieve “improved” status, with or without MMS
- First response to ravulizumab achieved by almost half of pts after one infusion and by two-thirds of pts by Week 12
- Previous IVIg treatment does not affect response to ravulizumab
- Rozanolixizumab treatment demonstrated greater reductions in MG-ADL score than placebo in broad range of pts with gMG and efficacy was maintained over up to six 6-week treatment cycles.
- Daily zilucoplan demonstrated consistent improvements in MG-specific efficacy outcomes regardless of disease severity or duration.
- Incidence and prevalence of MG in the US are higher than previous estimates have shown.
- There is a clinical need to implement clustered AChR CBA testing in evaluation of SNMG pts.
- MGBase, an international electronic database for MG launched in December 2021.