Activities of daily living as monitoring tool in myasthenia gravis

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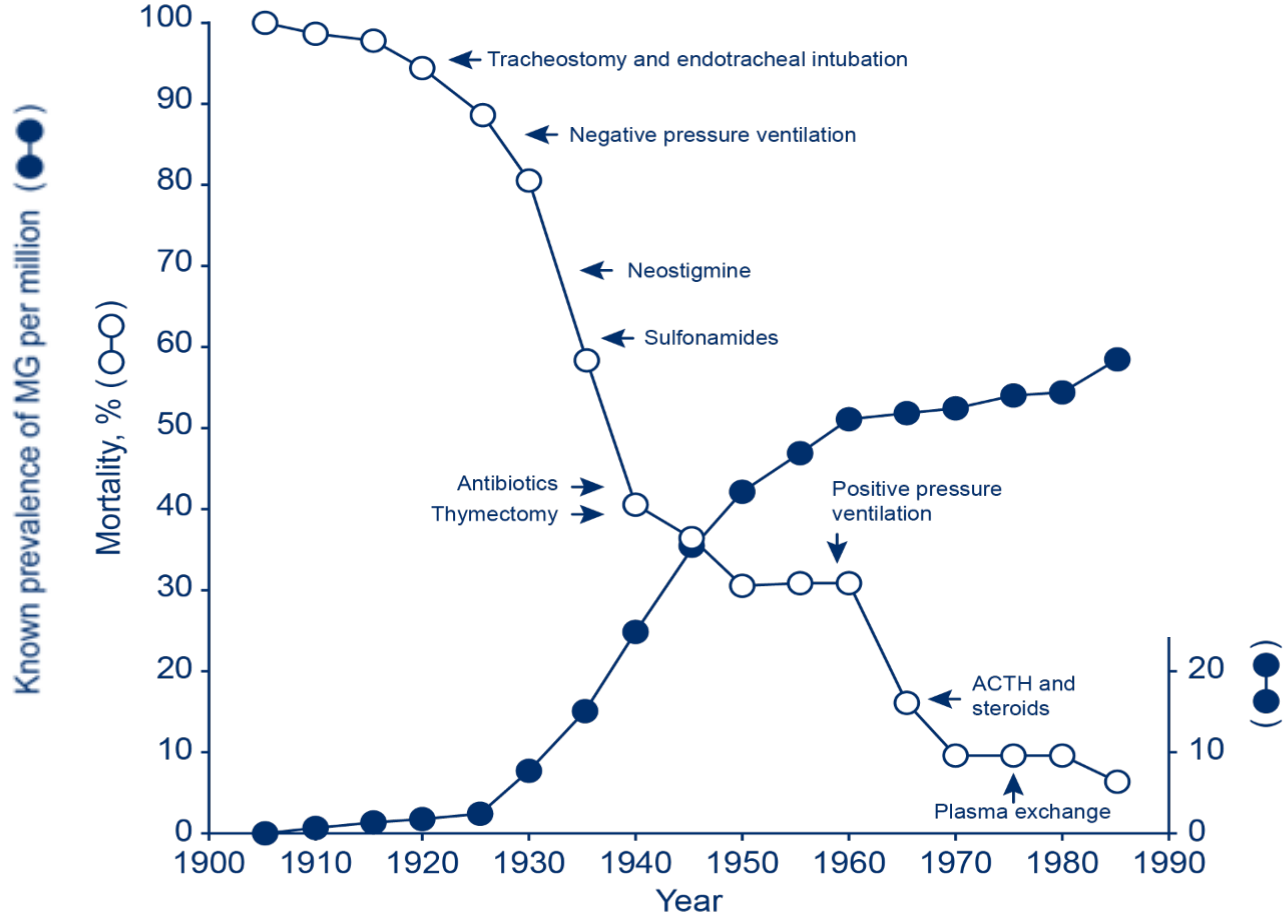
Disclosures John Vissing

- **Consultant on advisory boards** for Sanofi Genzyme, Sarepta Therapeutics, Novartis Pharma AG, Fulcrum Therapeutics, Stealth Biotherapeutics, Biogen, Lupin, Amicus, Zogenix, Regeneron, UCB Biopharma SPRL, Arvinas, ML Biopharma, and Horizon Therapeutics

- **Research, travel support, and/or speaker honoraria** from Sanofi Genzyme, Alexion Pharmaceuticals, Stealth Biotherapeutics, Edgewise Therapeutics, Fulcrum Therapeutics, and UCB Biopharma SPRL

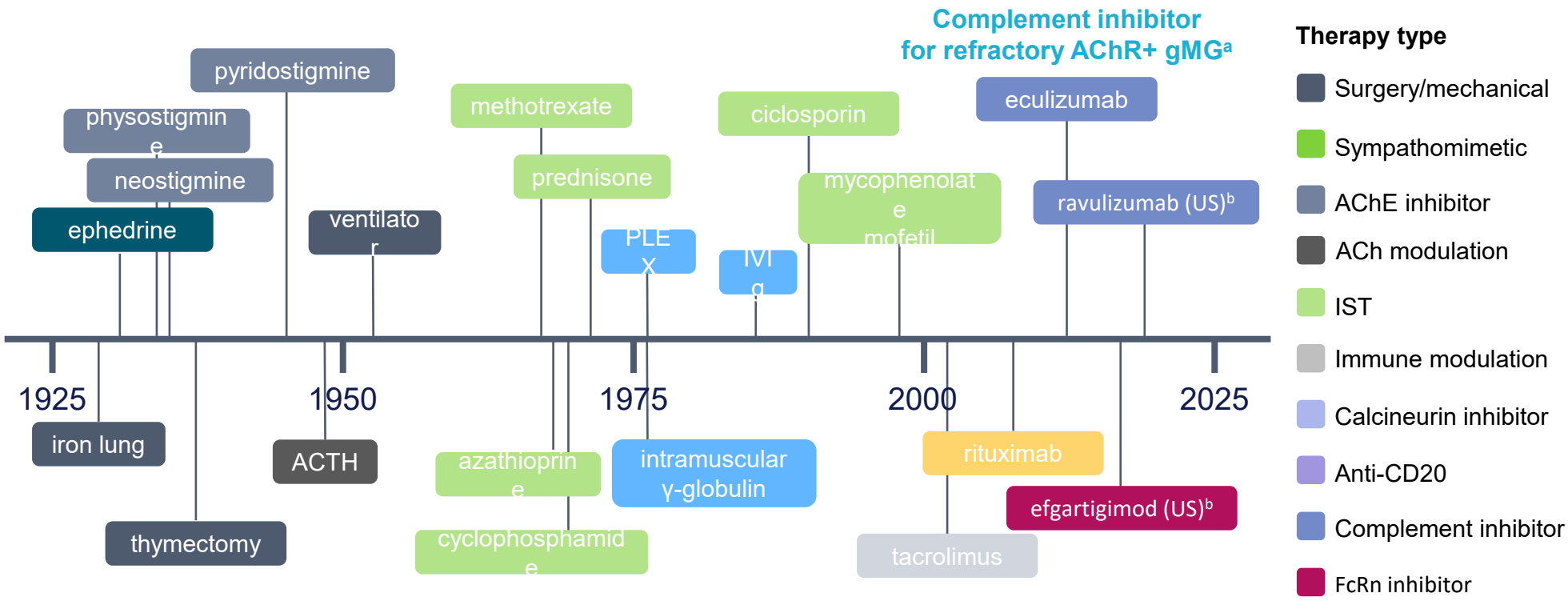
- **Principal investigator in clinical trials** for Sanofi Genzyme, Roche, Horizon Therapeutics, Argenx BVBA, Novartis Pharma AG, Alexion Pharmaceuticals, Stealth Biotherapeutics, UCB Biopharma SPRL, Genethon, ML Biopharma, Reneo Pharma, Pharnext, Janssen Pharmaceutical, Khondrion, Regeneron, and Dynacure SAS

Development in mortality and treatment of myasthenia gravis



All treatments should be used in accordance with their product label indications. Please refer to the product label before administering treatment.
ACTH, adrenocorticotropic hormone; MG, myasthenia gravis.
Adapted from: Grob D et al. Muscle Nerve. 2008;37(2):141–9.

The evolution of AChR+ gMG treatment[1–7]



Graphic includes unapproved, off-label treatments; dates refer to the first use of each treatment in patients, including in clinical trials

[a]Approved in 2017 by the FDA for use in AChR+ gMG and by the EMA for use in refractory AChR+ gMG[1]

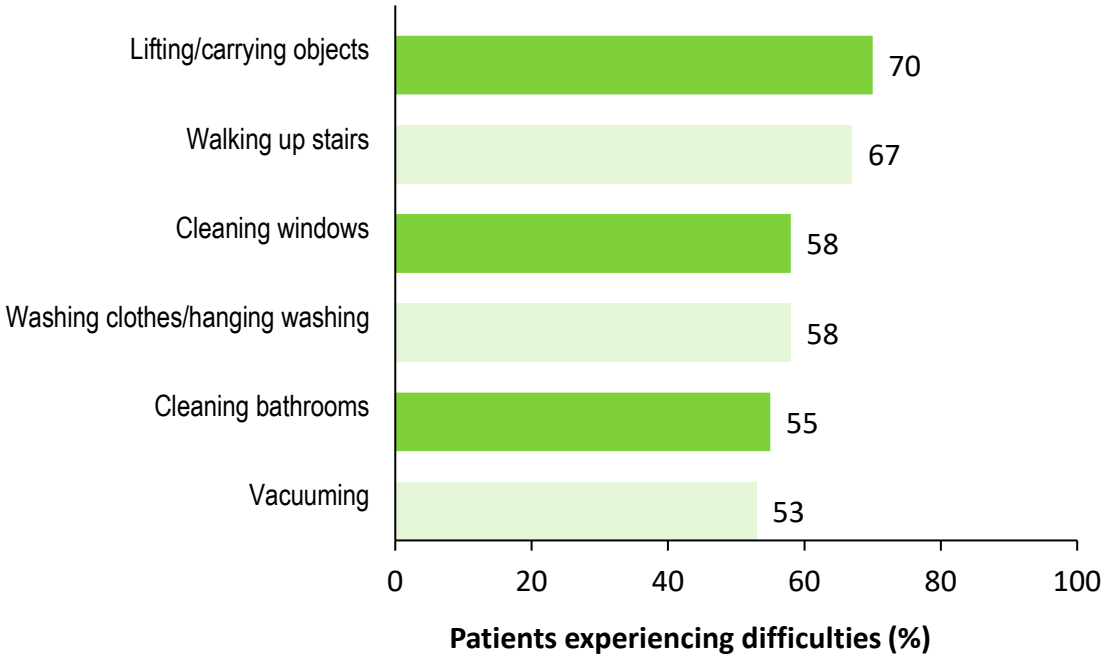
[b]These are investigational products that have been approved by the FDA only.[8,9] Information regarding these products should under no circumstances be regarded as a recommendation for their use or their safety or efficacy

ACh, acetylcholine; AChE, acetylcholine esterase; AChR+, anti-acetylcholine receptor antibody-positive; ACTH, adrenocorticotropic hormone; EMA, European Medicines Agency; FcRn, neonatal fragment crystallizable receptor; FDA, US Food and Drug Administration; gMG, generalized myasthenia gravis; IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; PLEX, plasma exchange

1. Alexion Europe SAS. Summary of product characteristics, Soliris (eculizumab). EMA, 2020; Available from: https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf. (Accessed June 2022); 2. Keesey JC. *Semin Neurol* 2004;24:5–16; 3. Evoli A *et al. Muscle Nerve* 2002;25:111–4; 4. Hain B *et al. Muscle Nerve* 2006;33:575–80; 5. Howard JF *et al. Muscle Nerve* 2013;48:76-84; 6. Howard JF *et al. Neurology* 2019;92:e2661–73; 7. ClinicalTrials.gov NCT03920293. Available https://clinicaltrials.gov/ct2/show/NCT03920293 Accessed June 2022); 8. Alexion US. Product Information, Ultomiris (ravulizumab). Available from: https://alexion.com/Documents/Ultomiris_USPI.pdf (Accessed June 2022); 9. Argenx. Product Information, Vyvgart (efgartigimod). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761108s020lbl.pdf (Accessed June 2022)

Debilitating and fluctuating symptoms can occur at any time for many people with generalized MG and can impact daily activities[1,2]

Difficulties with daily activity[3]



(g)MG, (generalised) myasthenia gravis.

1. Khadilkar SV, *et al. Neurol India* 2014;62:492–97; 2. Twork S, *et al. Health Qual Life Outcomes* 2010;8:129; 3. Centre for International Economics. The cost to patients and the community of myasthenia gravis. Available at: https://www.touchneurology.com/wp-content/uploads/sites/3/2018/06/www.thecie.com_.au_wp-content_uploads_2014_06_Final-report_Economic-Impact-of-Myasthenia-Gravis-08112013.pdf (Accessed April 2021).

Quantitative, validated measures of myasthenia gravis status

- MG-ADL (patient-reported outcomes)
- MG-QoL15 (patient-reported outcomes)
- MG Composite (patient-/physician-reported outcomes)
- MGFA classification (physician-reported outcomes)
- QMG (physician-reported outcomes)

MG, myasthenia gravis; MG-ADL, myasthenia gravis – activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15, myasthenia gravis – quality of life 15; QMG, quantitative motor assessment.

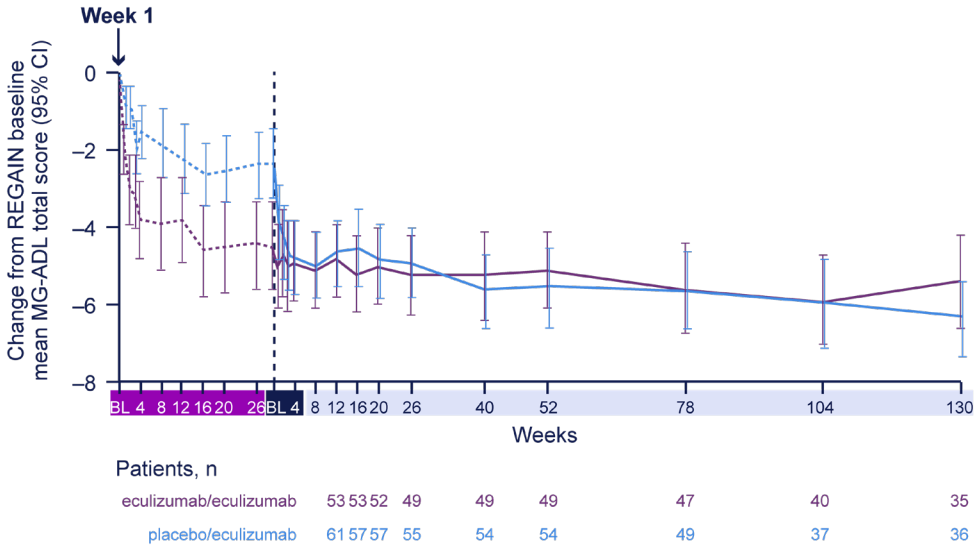
MG-ADL: patient-reported outcomes

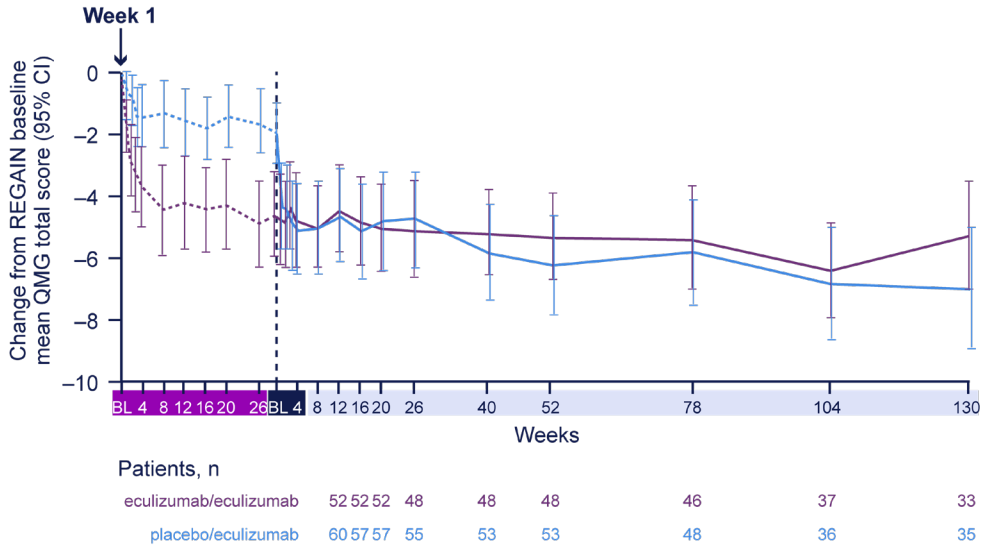
Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating change in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
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	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score: _____

MG-ADL, myasthenia gravis – activities of daily living.
Wolfe GI et al. Neurology. 1999;52(7):1487–9.

REGAIN trial and its OLE; eculizumab led to improvements in MG-ADL and QMG scores[a,1]





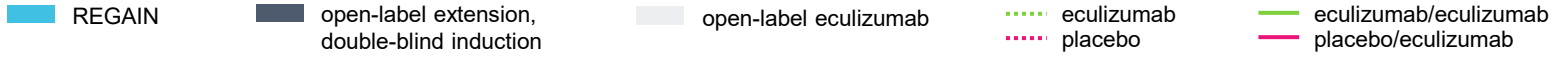


Figure adapted from Mantegazza R *et al*. *Ann Clin Transl Neurol* 2020;7:1327–39

[a]The primary endpoint of REGAIN was not met: the mean-ranked difference in change in MG-ADL score from baseline to week 26 between eculizumab and placebo was not statistically significant, as measured by the worst-rank analysis[2]

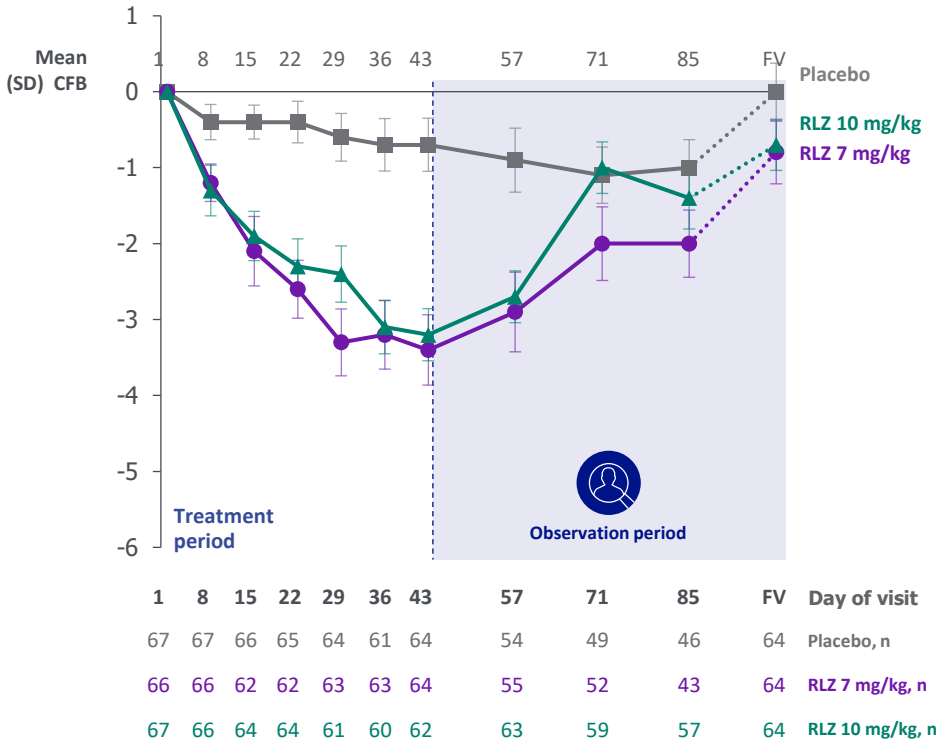
BL, baseline; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis scale

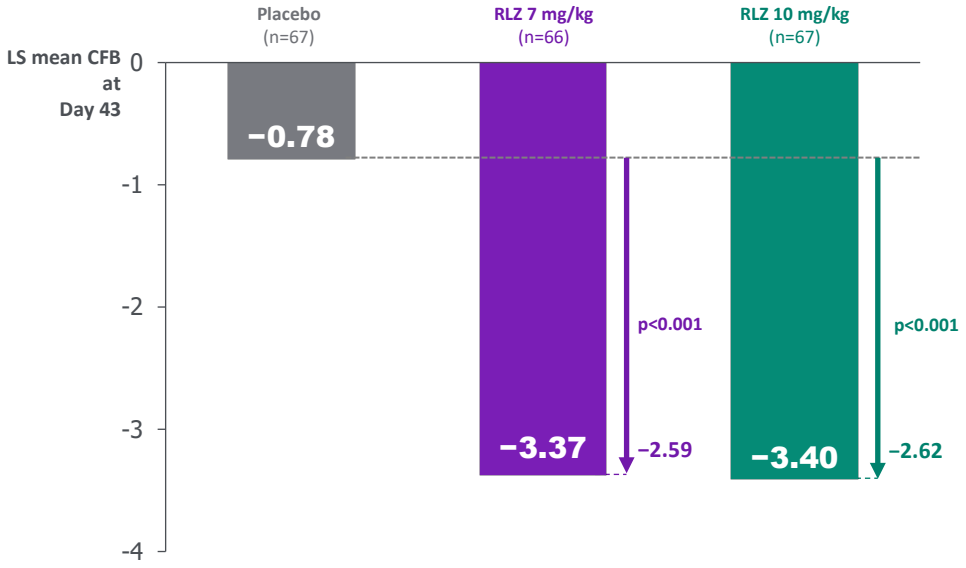
1. Mantegazza R *et al*. *Ann Clin Transl Neurol* 2020;7:1327–39; 2. Howard JF Jr *et al*. *Lancet Neurol* 2017;16:976–86

Mean change from baseline in and LS mean MG-ADL change from baseline at Day 43

PRIMARY ENDPOINT

Improvements from baseline with rozanolixizumab 7 mg/kg and 10 mg/kg were both clinically meaningfully and highly statistically significantly different compared with placebo (p<0.001 for both doses).

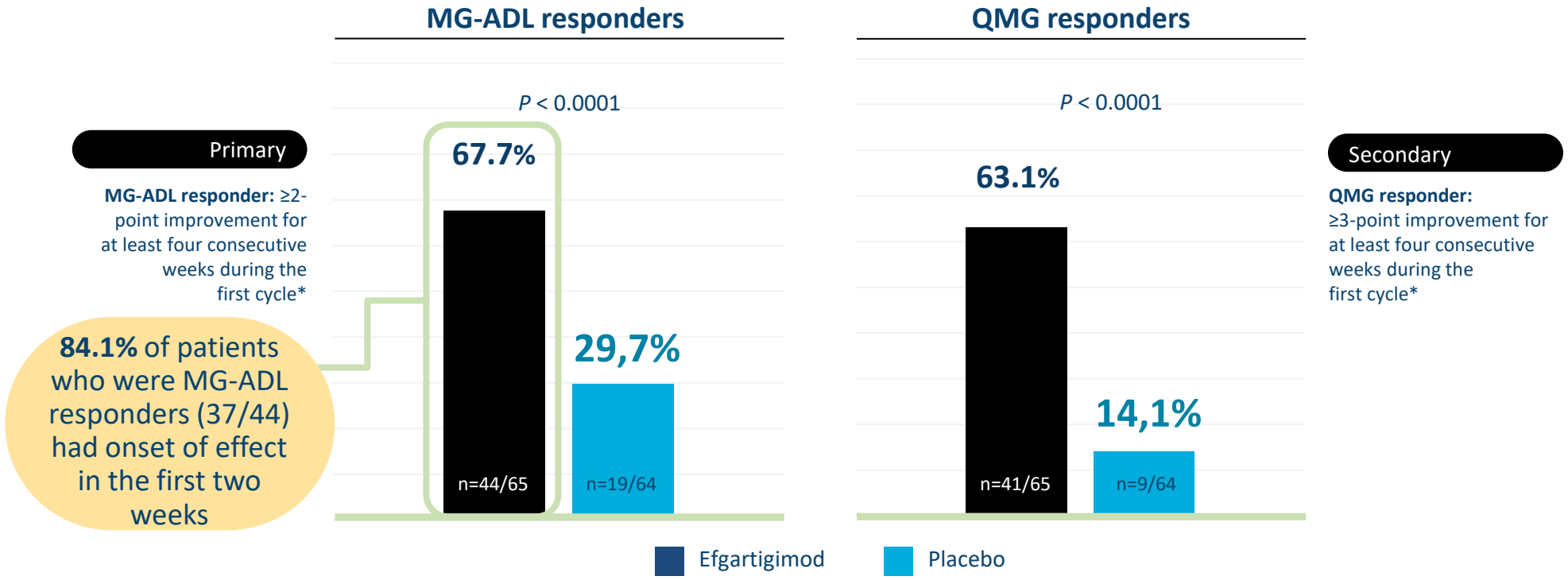




LS mean difference vs placebo (95% CI)	
RLZ 7 mg/kg	**−2.59** (−4.09, −1.25)
RLZ 10 mg/kg	**−2.62** (−3.99, −1.16)

CI, confidence interval; FV, final visit (could occur up to Day 99); LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; RLZ, rozanolixizumab; SD, standard deviation; SEM, standard error of the mean.
Rozanolixizumab is an investigational new product and has not been approved by any authority.

ADAPT
Clinical Response (AChR-Ab+ Patients, Cycle 1)



Primary

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

84.1% of patients who were MG-ADL responders (37/44) had onset of effect in the first two weeks

Secondary

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

Significantly more efgartigimod treated patients had clinically meaningful improvement in function and strength

* The first reduction had to occur no later than 1 week after the last infusion

MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis Score

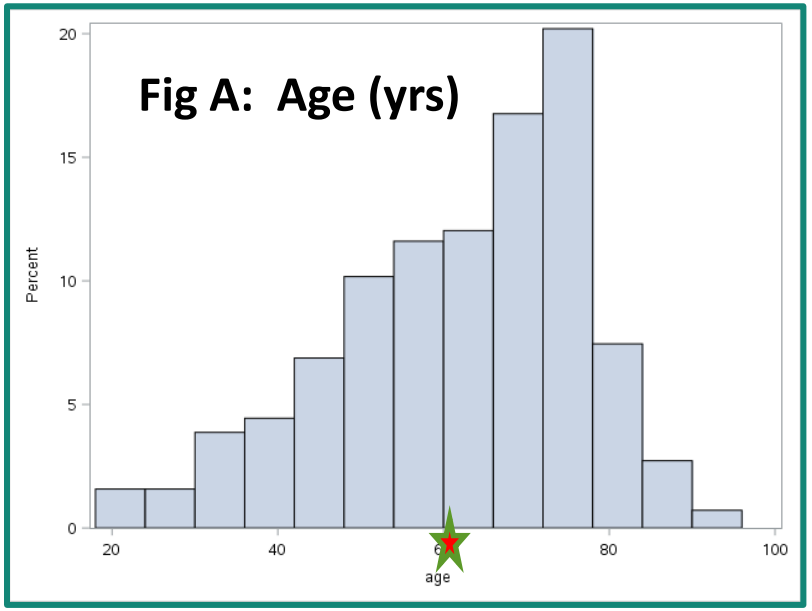
Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526-536.

Use of MG scales to guide decisions on whether patients are ‘difficult-to-treat’ and whether they are eligible for clinical trials

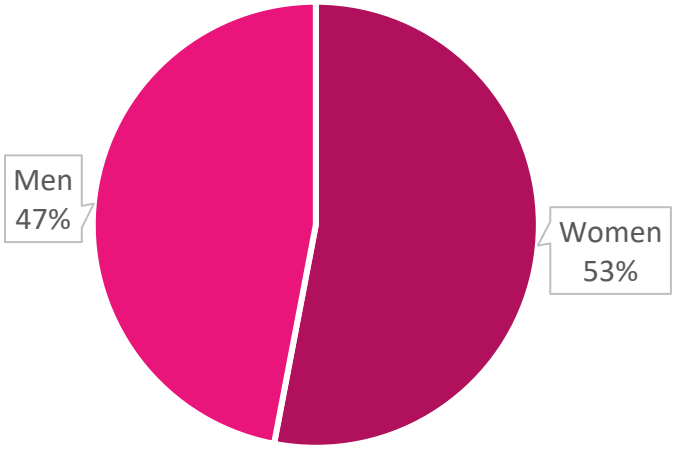
- MG-ADL > 5
- MG-QoL15 > 10
- MG Composite > 15–20
- MGFA classification > IIb
- QMG > 10

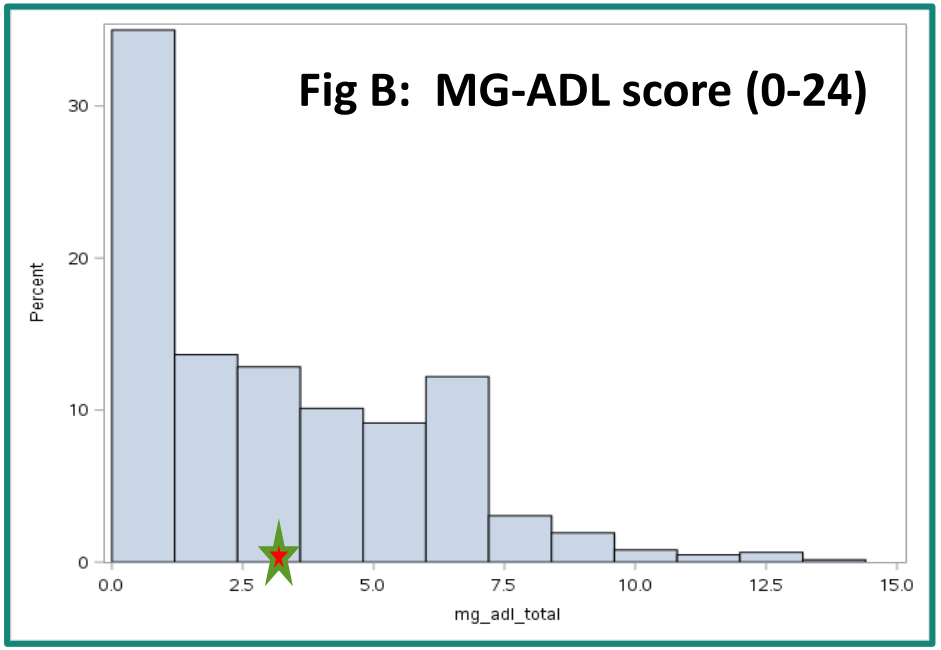
MG, myasthenia gravis; MG-ADL, myasthenia gravis – activities of daily living; MGFA, Myasthenia Gravis Foundation of America; MG-QoL15, myasthenia gravis – quality of life 15; QMG, quantitative motor assessment.

Survey cohort (n=779)



Mean: 60.8 (15,5)



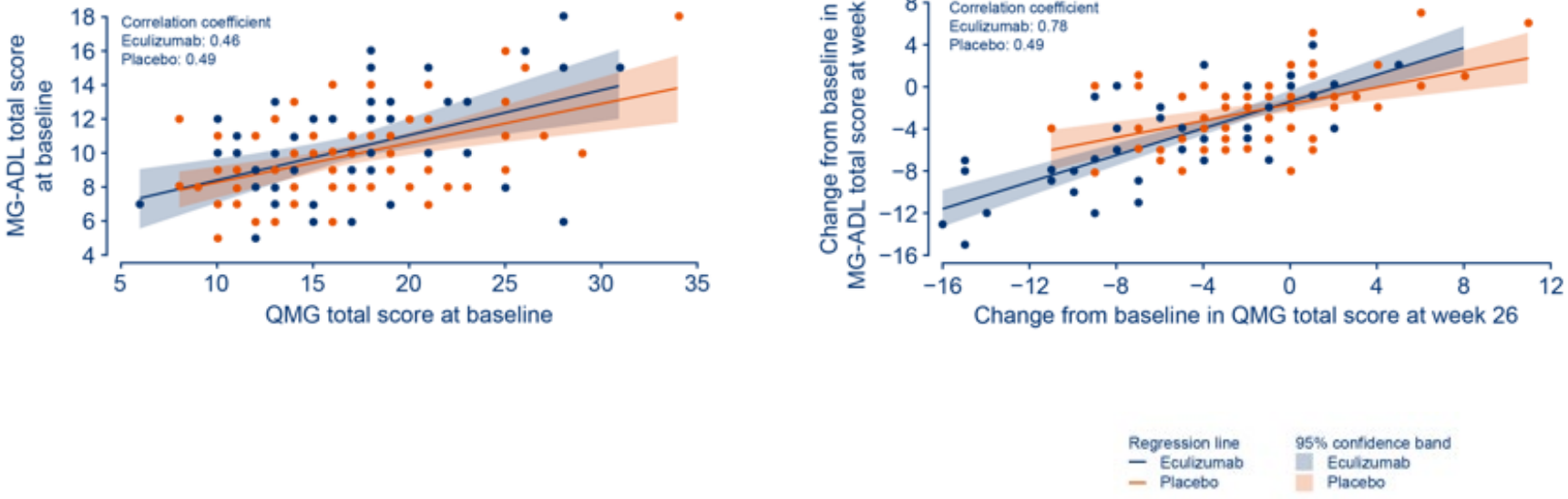


Median: 3 (1-5)

MG patient populations

Generalized AChR antibody positive
Ocular
MUSK positive
LRP4, agrin antibodies
Seronegative
Thymoma
Treatment resistent
Young women/pregnancies
Elderly

Patient- and physician-reported myasthenia gravis outcomes correlate; but not perfectly so



MG-ADL, myasthenia gravis – activities of daily living; QMG, quantitative motor assessment.
Vissing J et al. Muscle Nerve. 2018;58(2):E21–2.

Journal of Neurology
https://doi.org/10.1007/s00415-021-10902-1

ORIGINAL COMMUNICATION

Causes of symptom dissatisfaction in patients with generalized myasthenia gravis

Linda Kahr Andersen[1,2] · Anna Sofie Jakobsson[1] · Karoline Lolk Revsbech[1,2] · John Vissing[1,2]

Received: 6 August 2021 / Revised: 8 November 2021 / Accepted: 10 November 2021

PASS

The Patient Acceptable Symptom State

"Considering all the ways you are affected by Myasthenia gravis, if you had to stay in your current state for the next months, would you say that you are satisfied with your current disease state"?

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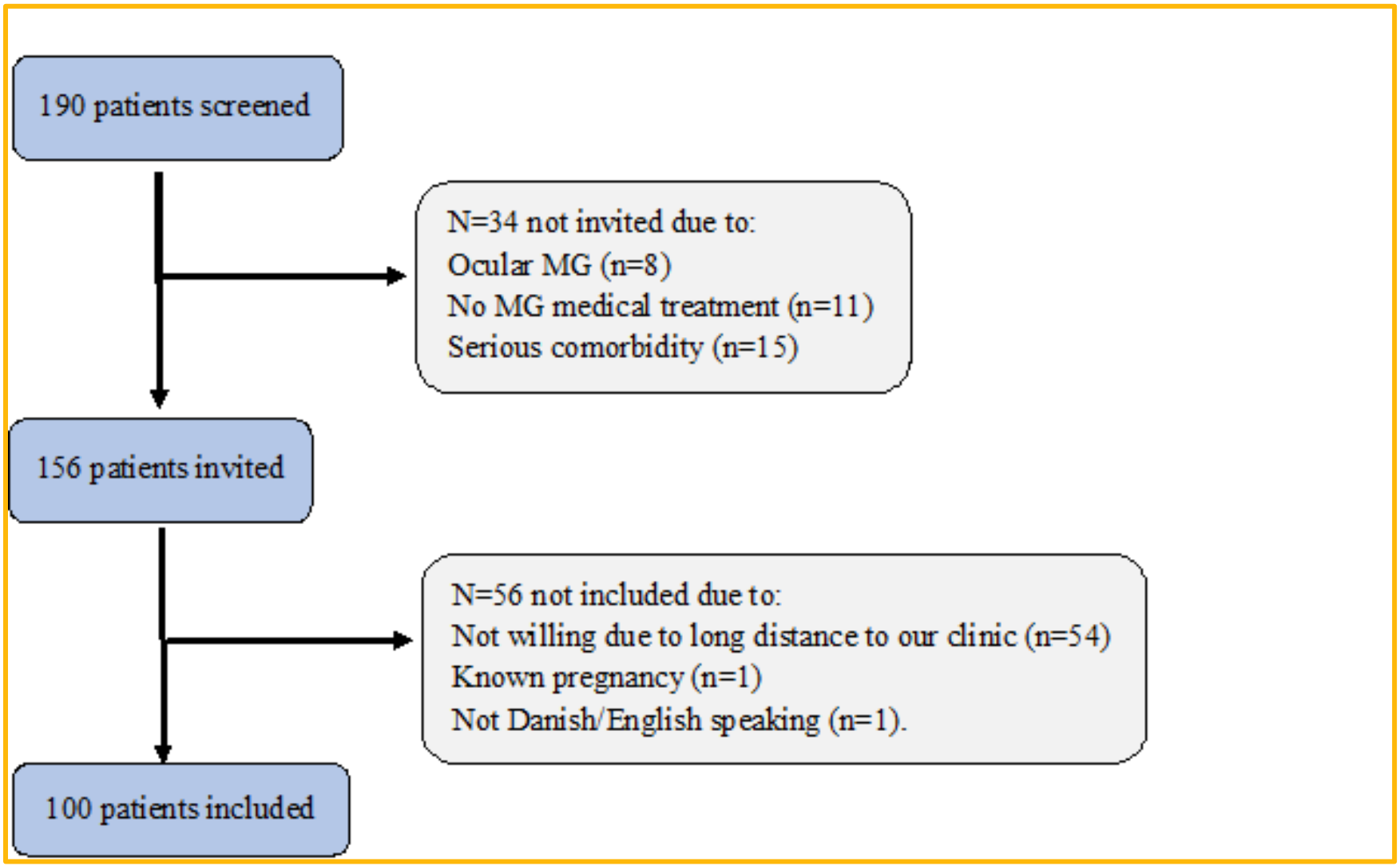
Study enrollment



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Questionnaires

- The Quantitative MG score (QMG)
- The MG Composite scale (MGC)
- The MG Activities of Daily Living profile (MG-ADL)
- The MG specific quality of life instrument (MG-QoL15)

- The Multidimensional Fatigue Inventory (MFI-20)
- The Major Depression Inventory (MDI)
- The Charlson Comorbidity Index (CCI)
- The EQ-5D-3L

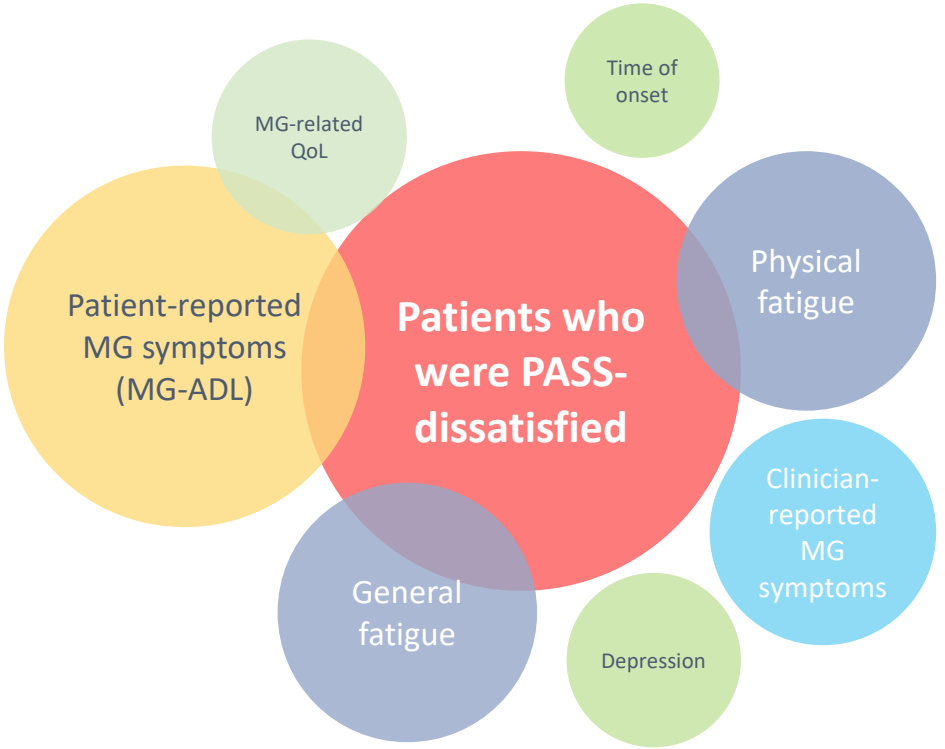
- Satisfaction with adverse effects of MG medical treatment

Age, years	60.2 ± 15.4
Sex, women	57
MG duration, years	6 (3-13)
Antibody status, n	
AChR positive	94
AChR negative	5
MUSK positive	1
Thymectomy, n	
Yes	41
MG Treatment	
Pyridostigmine only	20
Pyridostigmine + Prednisolone	11
Pyridostigmine + Immunosuppressant	26
Immunosuppressant only	30
Immunosuppressant + Prednisolone	4
Pyridostigmine + prednisolone + immunosuppressant	9
MG-ADL	3 (0-5)
QMG	9 (5-11)
MGC	5 (3-10)
MG-QoL15	8 (3-21)

	PASS negative (n=33)	PASS positive (n=67)	*p*-value
Age, years	58.3 ± 14.0	61.1 ± 16.1	.409
Sex, Women	18 (55%)	39 (58%)	.831
BMI, kg/m^2	28.9 ± 6.8	27.7 ± 5.7	.372
MG length, years	3 (1-6)	8 (4-15)	.001
Job status, n			
Working full- or part-time	12 (37%)	26 (39%)	
Unemployed/sick leave	7 (21%)	3 (5%)	
Retired due to sickness	3 (9%)	2 (3%)	.033
Retired due to age	11 (33%)	32 (48%)	
Student	0	3 (5%)	
Antibody status, n			.135
Thymectomy, n			1.00
MG Treatment [a]			0.28
MG-ADL	5 (4-7)	1 (0-3)	<.0001
QMG	11 (9-13)	8 (5-10)	.0001
MGC	9 (4-13)	5 (2-8)	.001
MG-QoL15	25 (12-32)	6 (1-12)	<.0001
MFI-20, general fatigue	17 (12-18)	10 (7-14)	<.0001
MFI-20, physical fatigue	17 (14-18)	11 (9-14)	<.0001
MFI-20, reduced activity	13 (12-16)	9 (6-12)	<.0001
MFI-20, reduced motivation	9 (7-13)	7 (5-10)	.001
MFI-20, mental fatigue	11 (7-13)	8 (5-11)	.003
MDI	17 (12-25)	8 (3-14)	<.0001
EQ-5D-3L	0.71 (0.66-0.78)	0.83 (0.78-1.00)	<.0001
EQ-5D-VAS	60 (50-75)	80 (70-85)	<.0001
CCI	3 (1-5)	3 (2-5)	.767

There are many potential factors that contribute to patients' dissatisfaction with their symptom status.

- The size of the circles and the degree of overlap reflect the association with symptom dissatisfaction



PASS considers the perspective of the patient and should be used in clinical practice to determine a patient's burden of disease

MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; PASS, patient-acceptable symptom state; QoL, quality of life.
Personal communication from Jhn Vissing, 09 April 2021.

Follow-up of the ”PASS-study” to map disease burden in MG

- Prospective assessments similar to the the PASS study in appr. 400 MG patients in our clinic (supported by UCB)
- Cross-sectional granular phenotyping with the plan to continue with longitudinal measures
- Data capture in RedCap

Physical examination/assessments:

- QMG
- MG Composite scale
- MGII
- Trunk strength

Questionnaires:

- MG symptoms satisfaction
- MG symptoms PRO
- MG-QOL15r
- Eq5d5l
- PGI-S
- MGII
- PASS – with why not options
- MDI
- Stress questionnaire
- International physical activity questionnaire
- Care questionnaire
- Satisfaction survey – the clinic
- MG-ADL

Data capture of MG patients in the clinic using the RealWorld MG App developed by Argenx

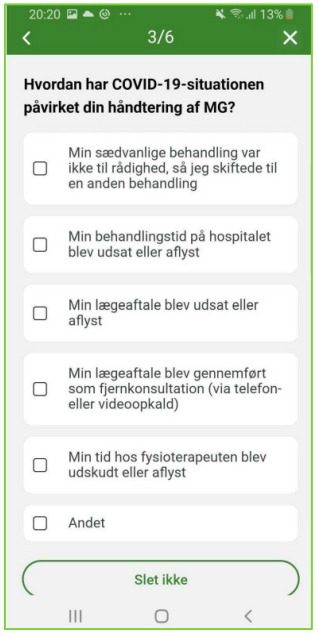
MYREALWORLD™ MG-APPEN

Patientprofil

Udfyldes én gang

Regelmæssige spørgeundersøgelser

Meddelelserne i appen underretter deltageren om, at en ny spørgeundersøgelse er klar til at blive udfyldt



Disease burden in MG

- We are moving from physician to patient-reported outcomes
- Many common symptoms and signs characterize MG patients but disease burden is perceived very different from person to person
- Follow-up of MG should be more reliant on PROMs

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Thank you for your attention

www.neuromuscular.dk

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