CME Symposium at the South Carolina Neurological Society 2023 Annual Conference

Clinical Update for Individualized Treatment Plans for Patients with Generalized Myasthenia Gravis

Saturday, September 16, 2023 | 3:30 pm – 4:30 pm ET

James F. Howard Jr., MD

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Dr. Howard is Professor of Neurology, Medicine and Allied Health in the Department of Neurology at The University of North Carolina at Chapel Hill, School of Medicine. He is the former *James F Howard Distinguished Professor of Neuromuscular Disease* and the prior Chief of the Neuromuscular Disorders Section at UNC. He received his medical degree from the Larner School of Medicine at the University of Vermont and his neurological training at the University of Virginia in Charlottesville. Dr. Howard is a practicing neurologist for over 44 years with a focus on myasthenia gravis and EMG. He currently directs the Myasthenia Gravis Clinical Trials and Translational Research Unit at UNC.

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Clinical Update for Individualized Treatment Plans for Patients with Generalized Myasthenia Gravis

James F. Howard, Jr., MD
Professor of Neurology, Medicine & Allied Health
Department of Neurology
The University of North Carolina at Chapel Hill

Professor of Clinical Sciences (Neurology)
Department of Clinical Sciences (Neurology)
North Carolina State College of Veterinary Medicine
howardj@neurology.unc.edu

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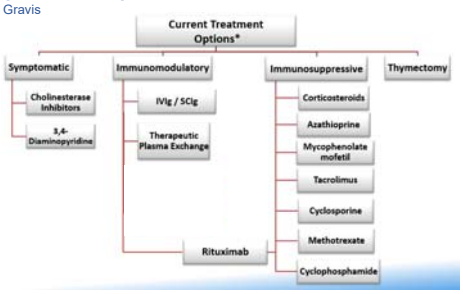
Therapeutic Options

Myasthenia Gravis



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Myasthenia Gravis

Why Are New Treatments Needed?


Neurology
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October 05, 2021; 97 (14) EDITORIAL
People With Myasthenia Are Getting Better, but Are They Doing Well?
Chloé Atkins, Carolina Barnett
First published August 10, 2021, DOI: https://doi.org/10.1212/WNL.0000000000012617

Atkins C and Barnett C. *Neurology*. 2021; 97(14): 663-664; DOI: 10.1212/WNL.0000000000012617.

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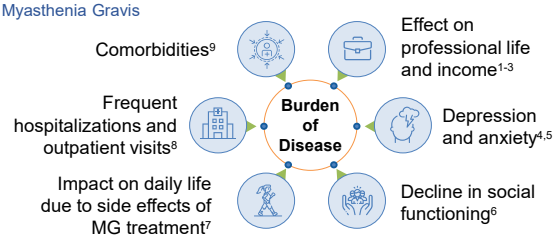
Disease Burden

Myasthenia Gravis



1. Guastafierro E, et al. *Neuroepidemiology*. 2020;54(4):304-312. **2.** Nagane Y, et al. *BMJ Open*. 2017;7(2):e013278. **3.** Frost A, et al. *BMC Neurology*. 2016;16:224. **4.** Jeong A, et al. *PLoS One*. 2018;13(11):e0206754. **5.** Law C, et al. *Cureus*. 2020;12(7):e9184. **6.** Garzón-Orjuela N, et al. *Intractable Rare Dis Res*. 2019;8(4):231-238. **7.** Bacci ED, et al. *BMC Neurol*. 2019;19:335. **8.** Guptill JT, et al. *Muscle Nerve*. 2012;45(3):363-366. **9.** Laakso SM, et al. *J Neurol Sci*. 2021;427:117549. doi:10.1016/j.jns.2021.117549.

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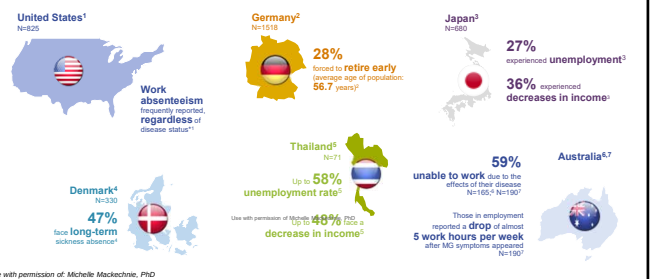
Myasthenia Gravis

Impact of Disease and Treatment Burdens on Employment



Use with permission of: Michelle Mackechnie, PhD

Results from surveys[1–6,7] and an observational study[6] of patients with MG. *Ranging from 1–3 days to over 1 month within the last 6 months in a survey of patients with gMG (N=825).
[g]MG, [generalized] myasthenia gravis. 1. Harris L, *et al. Muscle Nerve* 2019;60:700–706; 2. Twork S, *et al. Health Qual Life Outcomes* 2010;8:129; 3. Nagane Y, *et al. BMJ Open* 2017;7:e013278; 4. Frost A, *et al. BMC Neurol* 2016;16:224; 5. Kulkantrakorn K, *et al. Neurol Sci* 2010;31:571–73; 6. Blum S, *et al. J Clin Neurosci* 2015;22:1194–99; 7. Centre for International Economics. The cost to patients and the community of myasthenia gravis. Available at: https://www.touchneurology.com/wp-content/uploads/sk/2019/06/www.thecie.com_.au_wp-content_uploads_2014_06_Final-report_Economic-Impact-of-Myasthenia-Gravis-08112013.pdf

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Myasthenia Gravis

Treatment Burden

Based on surveys of Myasthenia Gravis Patient Registry participants; n=372[1] and n=298[2].
[a]Includes only those survey respondents who had ever taken prednisone; [b]For all types of MG treatments except PLEX; [c]Includes patients treated with rituximab, IVIg, PLEX, and/or current complement inhibitors.
AE, adverse event; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange.

1. Mindspot Research. *Myasthenia Gravis Patient Needs Exploration*. 2018. **2.** Lee I, et al. *Neurol Neuroimmunol Neuroinflamm*. 2018; 5(6):e507.

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Mechanisms of Disease

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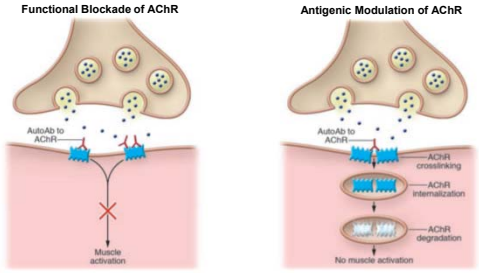
Myasthenia Gravis

Mechanisms of Synaptic Block



Conti-Fine, BM et al. *The Journal of Clinical Investigation*. 2006; 116(11): 2843-54. doi:10.1172/JCI29894.

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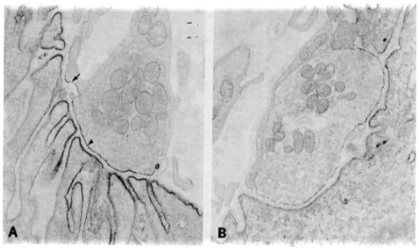
Myasthenia Gravis

NMJ Alterations



Normal **Myasthenia Gravis**

Engel AG, et al. *Neurology*. 1977; 27:307-315.

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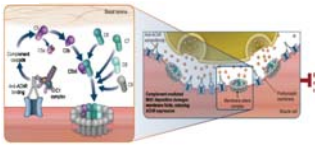
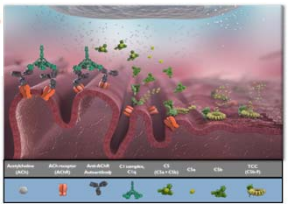
Complement Activation

Myasthenia Gravis





- Anti-AChR antibodies bind to the AChR and initiate the complement cascade via activation of the C1 complex
- The product of the complement cascade is the membrane attack complex (MAC / TCC)

Howard JF., et al. *Exp Opinion Invest Drugs*. 2021; v30 p483.

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Complement Inhibition

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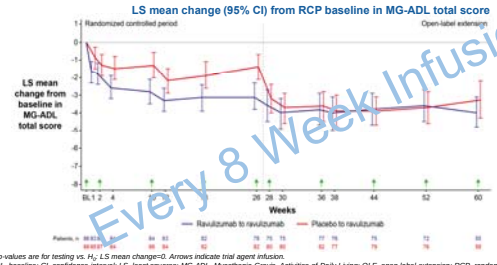
Ravulizumab

Complement Inhibition



Every 8 Week Infusion

150 patients continuing in the OLE at data cut-off

- Ravulizumab → ravulizumab: 71
- Placebo → ravulizumab: 79

*p-values are for testing vs. H_0: LS mean change=0. Arrows indicate trial agent infusion.
BL, baseline; CI, confidence interval; LS, least squares; MG-ADL, Myasthenia Gravis–Activities of Daily Living; OLE, open-label extension; RCP, randomized controlled period; SD, standard deviation

Vu T, et al: Presented at: AAN 2022. April, 2022. Seattle, WA.; Howard JF Jr, et al: Presented at: AAN 2022. April, 2022. Seattle, WA.; Vu T, et al. *NEJM Evidence*. 2022; 1(5).

ClinicalTrials.gov Identifier: NCT03920293.

18

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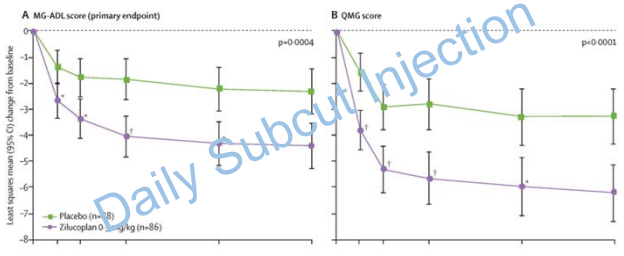
Zilucoplan Phase 3 – MG-ADL & QMG

Complement Inhibition



Daily Subcut Injection

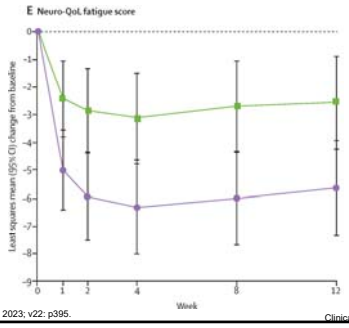
Howard JF Jr, et al. *Lancet Neurology*. 2023; v22: p395.

ClinicalTrials.gov Identifier: NCT04115293.

19

Zilucoplan Phase 3 OLE - Fatigue

Complement Inhibition



Howard JF Jr, et al. *Lancet Neurology*. 2023; v22: p395.

ClinicalTrials.gov Identifier: NCT04115293.

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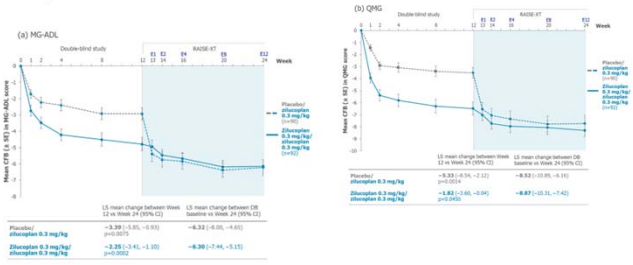
Zilucoplan Phase 3 OLE

Complement Inhibition



Friemer M, et al. Presented at: AAN 2023. April, 2023. Denver, CO.

ClinicalTrials.gov Identifier: NCT04115293.
ClinicalTrials.gov Identifier: NCT04225871.

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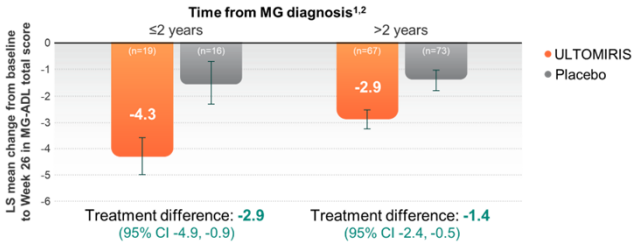
Ravulizumab Response Time

Complement Inhibition



Howard JF Jr, et al. Presented at: AAN 2023. April, 2023. Denver, CO.

ClinicalTrials.gov Identifier: NCT03920293.

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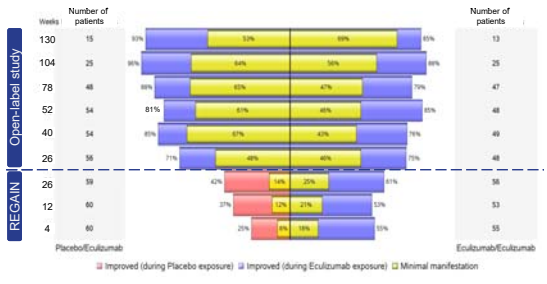
REGAIN and Extension Trial

Minimal Manifestations - ? Role of Remodeling



Vissing J, Jacob S, Fujita KP, O'Brien F, Howard JF Jr. *Journal of Neurology*. 2020; 267(7): 1991-2001.

ClinicalTrials.gov Identifier: NCT01997229.
ClinicalTrials.gov Identifier: NCT02301624.

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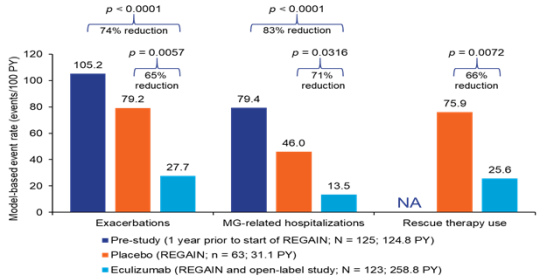
REGAIN and Extension Trial

Exacerbations and Rescue Therapy



Jacob S, Guptill JT, Meisel A, Fujita KP, Patra, K, Howard JF Jr. Presented at: the 2018 Annual Meeting of the AANEM. October, 2018. Washington, D.C.

ClinicalTrials.gov Identifier: NCT01997229.
ClinicalTrials.gov Identifier: NCT02301624.

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REGAIN and Extension Trial

Safety from Extension Study

Outcome	REGAIN placebo (n = 61, 30.9 PY[a])		REGAIN eculizumab (n = 56, 28.2 PY[a])		REGAIN and OLE eculizumab (N = 117, 305.1 PY[a])	
	Patients with event, n (%)	Event rate, events/100 PY[a]	Patients with event, n (%)	Event rate, events/100 PY[a]	Patients with event, n (%)	Event rate, events/100 PY[a]
Exacerbation	13 (21.3)	77.7	4 (7.1)	35.5	34 (29.1)	23.9
Rescue therapy use	10 (16.4)	68.0	4 (7.1)	35.5	30 (25.6)	22.0
Most common AEs[b,c] (> 15% of all patients)						
Headache	12 (19.7)	90.6	10 (17.9)	88.7	52 (44.4)	32.8
Nasopharyngitis	10 (16.4)	42.1	9 (16.1)	46.1	45 (38.5)	32.1
Diarrhea	8 (13.1)	29.1	8 (14.3)	35.5	33 (28.2)	17.4
Upper respiratory tract infection	12 (19.7)	45.3	9 (16.1)	46.1	31 (26.5)	25.2
Nausea	9 (14.8)	84.1	7 (12.5)	35.5	27 (23.1)	12.1
Myasthenia gravis[d]	9 (14.8)	58.3	4 (7.1)	14.2	30 (25.6)	17.4
Arthralgia	5 (8.2)	29.1	1 (1.8)	3.5	24 (20.5)	10.5
Pain in extremity	2 (3.3)	6.5	4 (7.1)	14.2	20 (17.1)	8.5
Urinary tract infection	5 (8.2)	22.7	3 (5.4)	14.2	20 (17.1)	12.5

Mantegazza R, et al. *Neurology*. 2021;96:e610-e618. ClinicalTrials.gov Identifier: NCT02301624.

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Neonatal Fc Receptor Inhibition

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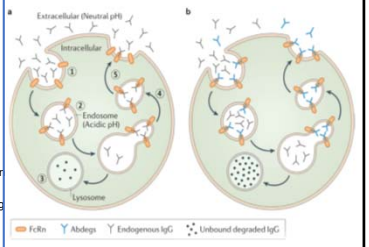
FcRn Mechanism of Action

A.

- IgG molecules enter cells by pinocytosis (step 1)
- Held within neonatal Fc receptor (FcRn) containing acidic endosomes (step 2)
- FcRn binds tightly to the Fc portion of IgG
- IgG that does not bind to FcRn is targeted for lysosomal degradation (step 3)
- Bound IgG molecules are recycled and released by exocytosis (steps 4, 5), as the FcRn releases IgG at neutral pH

B.

- Antibodies that enhance IgG degradation (Abdegs), e.g. efgartigimod, bind to FcRn with greater affinity than endogenous IgGs at both near-neutral and acidic pH
- Thus, compete with endogenous IgGs for FcRn binding
- As a result, more endogenous IgG molecules are targeted for lysosomal degradation



Lünemann JD. *Nat Rev Neurol*. 2021; 17(10): 597-598.

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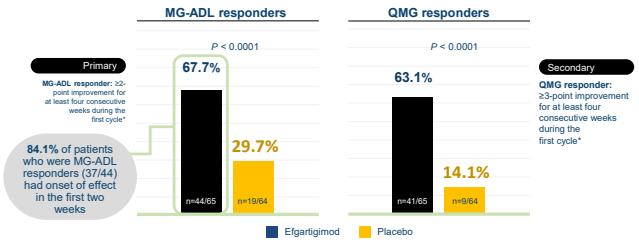
ADAPT

Clinical Response (AChR-Ab+ patients, Cycle 1)



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

Howard JF Jr, et al. *Lancet Neurol*. 2021; 20(7): 526-536. ClinicalTrials.gov Identifier: NCT03669588.

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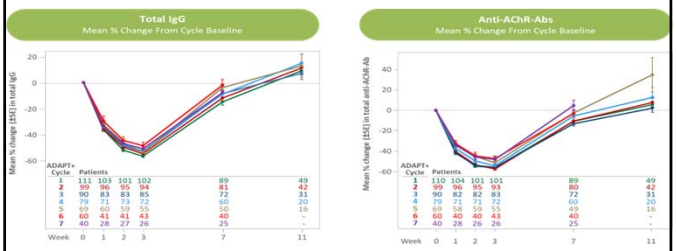
Efgartigimod (ADAPT+)

FcRn Inhibition



AChR-Ab, acetylcholine receptor autoantibody; IgG, immunoglobulin G.
[a]*Samples for pharmacodynamic biomarkers, including total IgG levels, were collected only during part A (year 1) of ADAPT+.*

Pasnoor M, et al. Presented at: AAN 2023. April, 2023. Denver, CO. ClinicalTrials.gov Identifier: NCT03770403.

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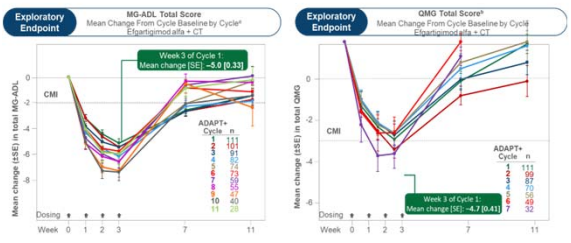
Efgartigimod (ADAPT+)

FcRn Inhibition



AChR-Ab, acetylcholine receptor autoantibody; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis; TX, treatment. [a] *Only cycles with data out to week 11 are depicted*

Pasnoor M, et al. Presented at: AAN 2023. April, 2023. Denver, CO. ClinicalTrials.gov Identifier: NCT03770403.

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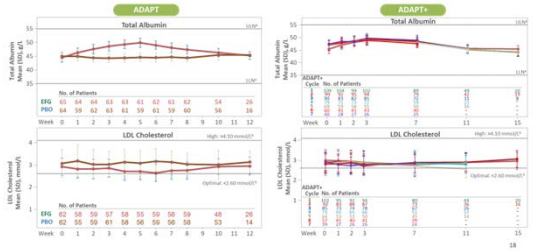
Efgartigimod (ADAPT+)

FcRn Inhibition



*AChR-Ab, acetylcholine receptor autoantibody; LDL, low-density lipoprotein; LLN, lower limit of normal; ULN, upper limit of normal. *Reference values are based on Kratz A, et al.[1]*Reference values are based on mayoclinic.org.[2] 1. Kratz A, et al. N Engl J Med. 2004;351(15):1548-1563. 2. Cholesterol test. Mayo Clinic Staff. Mayo Clinic. February 24, 2023. Accessed March 6, 2023. https://www.mayoclinic.org/tests-procedures/cholesterol-test/about/pac-20384601*

Pasnoor M, et al. Presented at: AAN 2023. April, 2023. Denver, CO.

ClinicalTrials.gov Identifier: NCT03770403.

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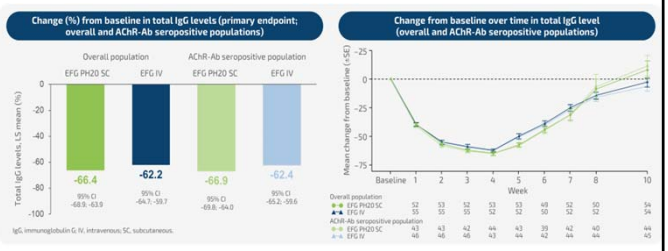
Non-Inferiority Response in IgG Level (AChR-Ab+, Cycle 1)

Efgartigimod (ADAPTsc)



Mantegazza R, et.al. Presented at: the 7th International Myology Congress. September 12th–15th, 2022. Nice, France.

ClinicalTrials.gov Identifier: NCT04818671.

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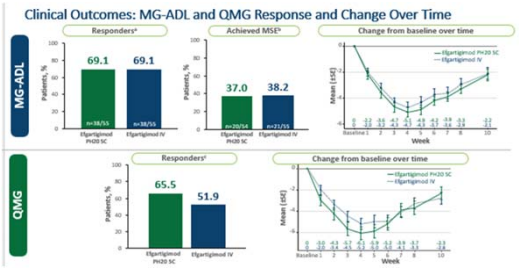
Pharmacodynamic Noninferiority Study

Efgartigimod (ADAPTsc)



Presented at: MGFA Scientific Sessions. September, 2022. Nashville, TN.

ClinicalTrials.gov Identifier: NCT04818671.

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ADL Change in gMG

Rozanolixizumab-noli

https://www.rystiggohcp.com/clinical-trial

ClinicalTrials.gov Identifier: NCT04650854.

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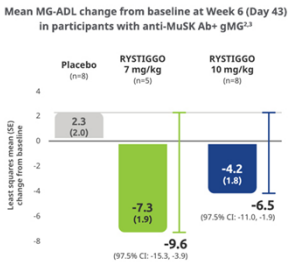
ADL Change in Musk MG

Rozanolixizumab-noli



https://www.rystiggohcp.com/clinical-trial

ClinicalTrials.gov Identifier: NCT04650854.

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Safety

Efgartigimod (ADAPT, ADAPT+)

	ADAPT				ADAPT+	
	Placebo (n=83) [34.51 PY]		Efgartigimod (n=84) [34.86 PY]		Efgartigimod (n=139) [138.14 PY]	
	IR/PY	% (n)	IR/PY	% (n)	IR/PY	% (n)
AEs	**7.83**	84 (70)	**7.23**	77 (65)	**4.06**	81 (112)
SAEs	**0.29**	8 (7)	**0.11**	5 (4)	**0.25**	15 (21)
≥1 Infusion-related reaction event	**0.26**	10 (8)	**0.09**	4 (3)	**0.09**	7 (10)
Infection AEs	**1.22**	37 (31)	**1.61**	46 (39)	**0.84**	47 (65)
Discontinued study treatment due to AEs	**0.09**	4 (3)	**0.20**	4 (3)	**0.07**	6 (8)
Severe AEs (grade ≥3)	**0.35**	10 (8)	**0.29**	11 (9)	**0.41**	19 (26)
Death	**0**	0 (0)	**0**	0 (0)	**0.04**	4 (5)
Most frequent AEs						
Nasopharyngitis	**0.49**	18 (15)	**0.34**	12 (10)	**0.14**	11 (15)
Upper respiratory tract infection	**0.15**	5 (4)	**0.32**	11 (9)	**0.04**	4 (5)
Urinary tract infection	**0.12**	5 (4)	**0.26**	10 (8)	**0.09**	7 (10)
Headache	**1.13**	28 (23)	**1.15**	29 (24)	**0.49**	22 (31)
Nausea	**0.43**	11 (9)	**0.20**	8 (7)	**0.07**	5 (7)
Diarrhea	**0.41**	11 (9)	**0.17**	7 (6)	**0.11**	9 (12)

Howard JF Jr, et al. Presented at: AAN 2023. April, 2023. Denver, CO.

ClinicalTrials.gov Identifier: NCT03669588.
ClinicalTrials.gov Identifier: NCT03770403.

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B-Cell Depletion

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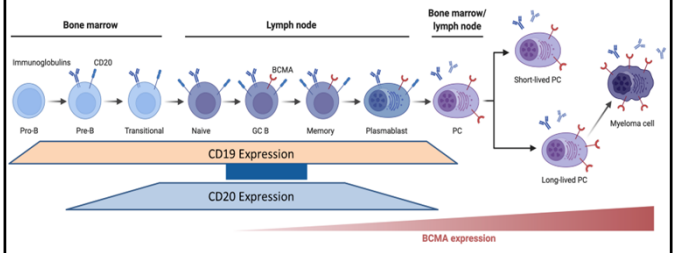
B-cell Depletion Therapies

Myasthenia Gravis



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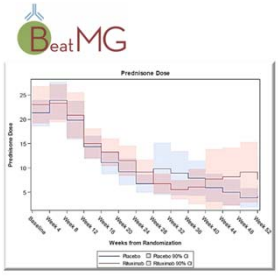
Rituximab

B-Cell Depletion



OBSERVED MGC SCORE CHANGE FROM BASELINE TO WEEK 52		
TREATMENT GROUP	Change in MGC (SD) (Min, Max)	Model Adjusted Difference (90% CI)
Rituximab	-5.7 (7.26) (-24 , +9)	-0.11 (-2.24 , 2.02)
Placebo	-4.0 (4.10) (-11 , +5)	
OBSERVED QMG SCORE CHANGE FROM BASELINE TO WEEK 52		
TREATMENT GROUP	Change in QMG (SD) (Min, Max)	Model Adjusted Difference (90% CI)
Rituximab	-3.95 (5.43) (-15 , +6)	-1.09 (-3.22 , 1.03)
Placebo	-1.70 (3.91) (-10 , +5)	

No significant difference observed for change in MGC score or QMG score across the groups (p=0.93 and p=0.39, respectively).

Nowak RJ, et al. *Neurology.* 2021; v98: p376.

ClinicalTrials.gov Identifier: NCT02110706.

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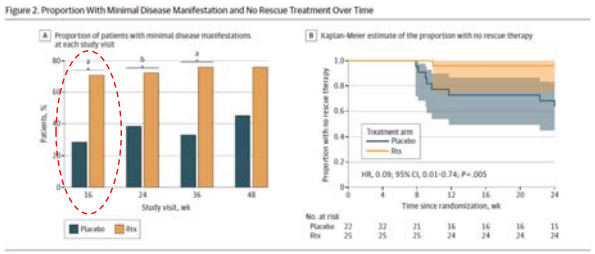
RINOMAX Trial Results

B-Cell Depletion in Early Onset MG (<1 year)



Piehl F, et al. *JAMA Neurology.* 2023; v79: p1105.

ClinicalTrials.gov Identifier: NCT02950155.

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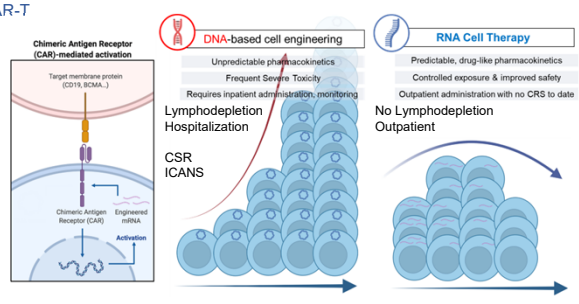
Targeting B-Cell Precursors

CAR-T



Courtesy of Volkan Granit, MD

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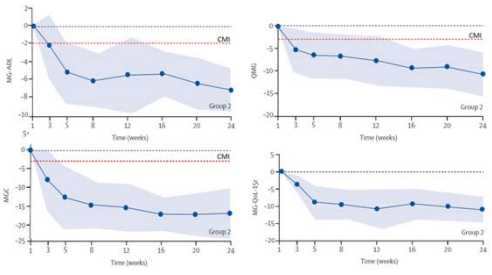
Descartes-08 Trial (rCAR-T, Phase 1b, Open Label)

Myasthenia Gravis



- PLEX to harvest lymphocytes
- Engineer cells (~4 weeks)
- Reinfuse cells (outpatient) weekly x 6
- Duration of Effect
  - 8 – 16+ months
- Retreatment when needed
  - 1 subject at year 1

Granit V, et al. *Lancet Neurology.* 2023; v22: p578.

ClinicalTrials.gov Identifier: NCT02950155.

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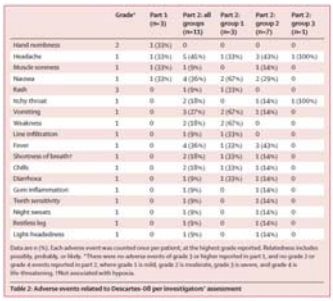
Descartes-08 Trial (rCAR-T, Phase 1b)

Myasthenia Gravis



Granit V, et al. *Lancet Neurology*. 2023; v22: p578.

Descartes-08
- CSR – 0%
- ICANS – 0%

In contrast, DNA CART
- CSR – 25% – 90%*
- ICANS – 20% – 67%

**disease dependent*

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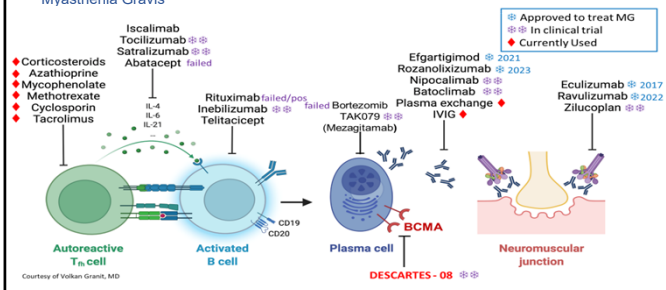
Landscape of Therapeutic Targets

Myasthenia Gravis



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Traditional Immunosuppressive Therapy
Slow onset of action / Not suited for fluctuating disease

Treatments	Onset of action	Maximum efficacy
Tacrolimus	4-8 weeks	3 months
Cyclosporine	2-3 months	3-6 months
Cyclophosphamide	2-4 weeks	3-6 months
Methotrexate	1-3 months	3-6 months
Mycophenolate mofetil	4-12 months	6-18 months
Azathoiprine	6-12 months	12-36 months
Complement Inhibitors	<1-2 weeks	2-3 months
FcRn Inhibitors	<1-2 weeks	4-5 weeks

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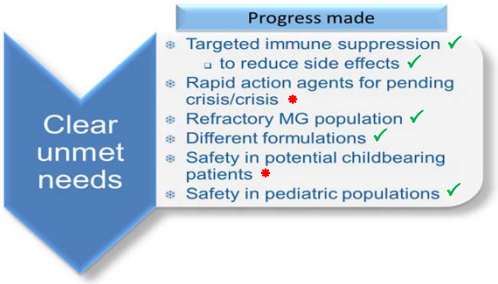
Final Thoughts

Myasthenia Gravis 2023



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Question and Answer Segment

James F. Howard, Jr., MD
Professor of Neurology, Medicine & Allied Health
Department of Neurology
The University of North Carolina at Chapel Hill

Professor of Clinical Sciences (Neurology)
Department of Clinical Sciences (Neurology)
North Carolina State College of Veterinary Medicine
howardj@neurology.unc.edu

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