Neuromuscular Updates: ALS, Idiopathic & Diabetic Neuropathy, Myasthenia Gravis and CIDP

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Professor and Chair of Neurology
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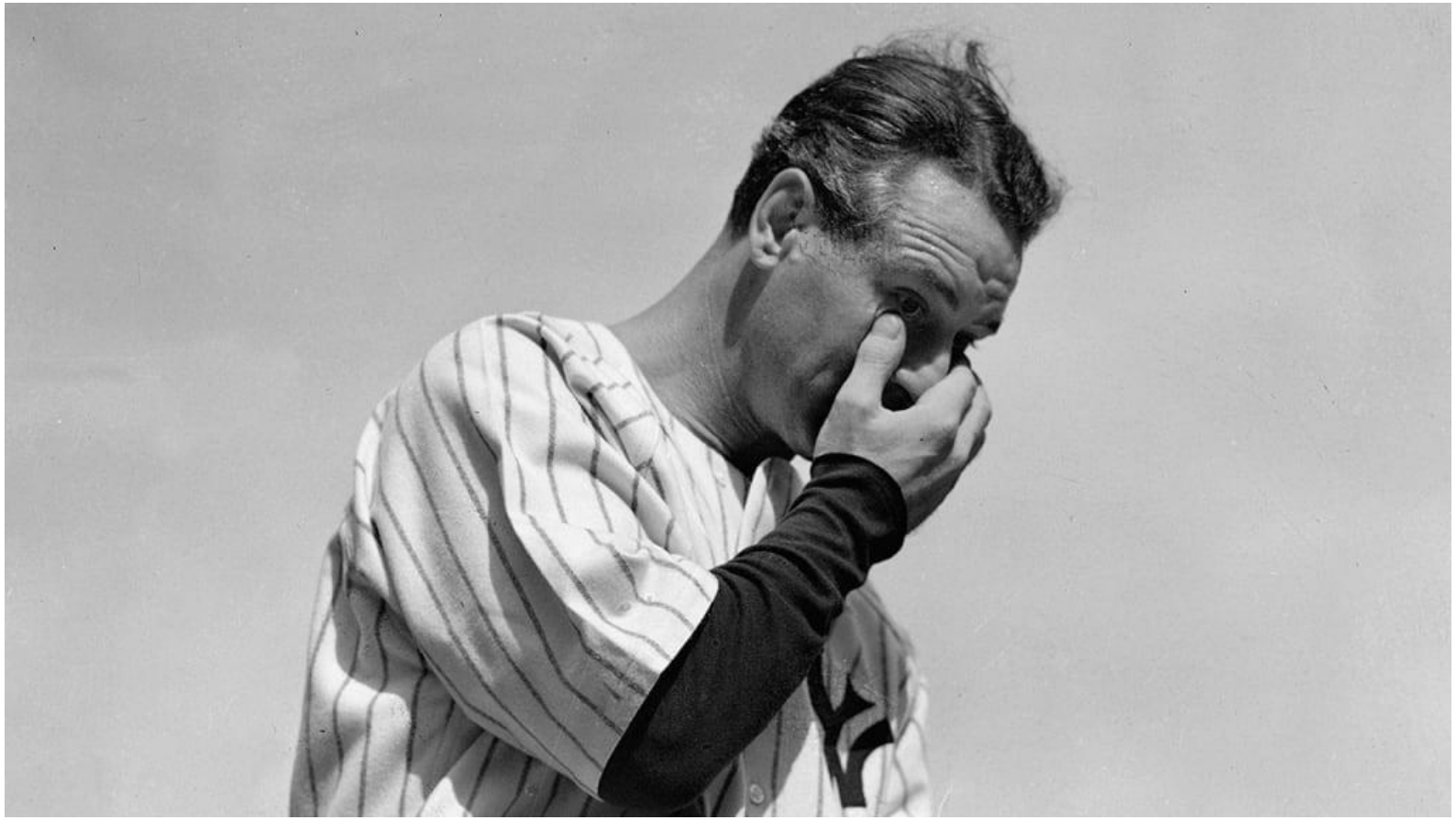
Financial Disclosure

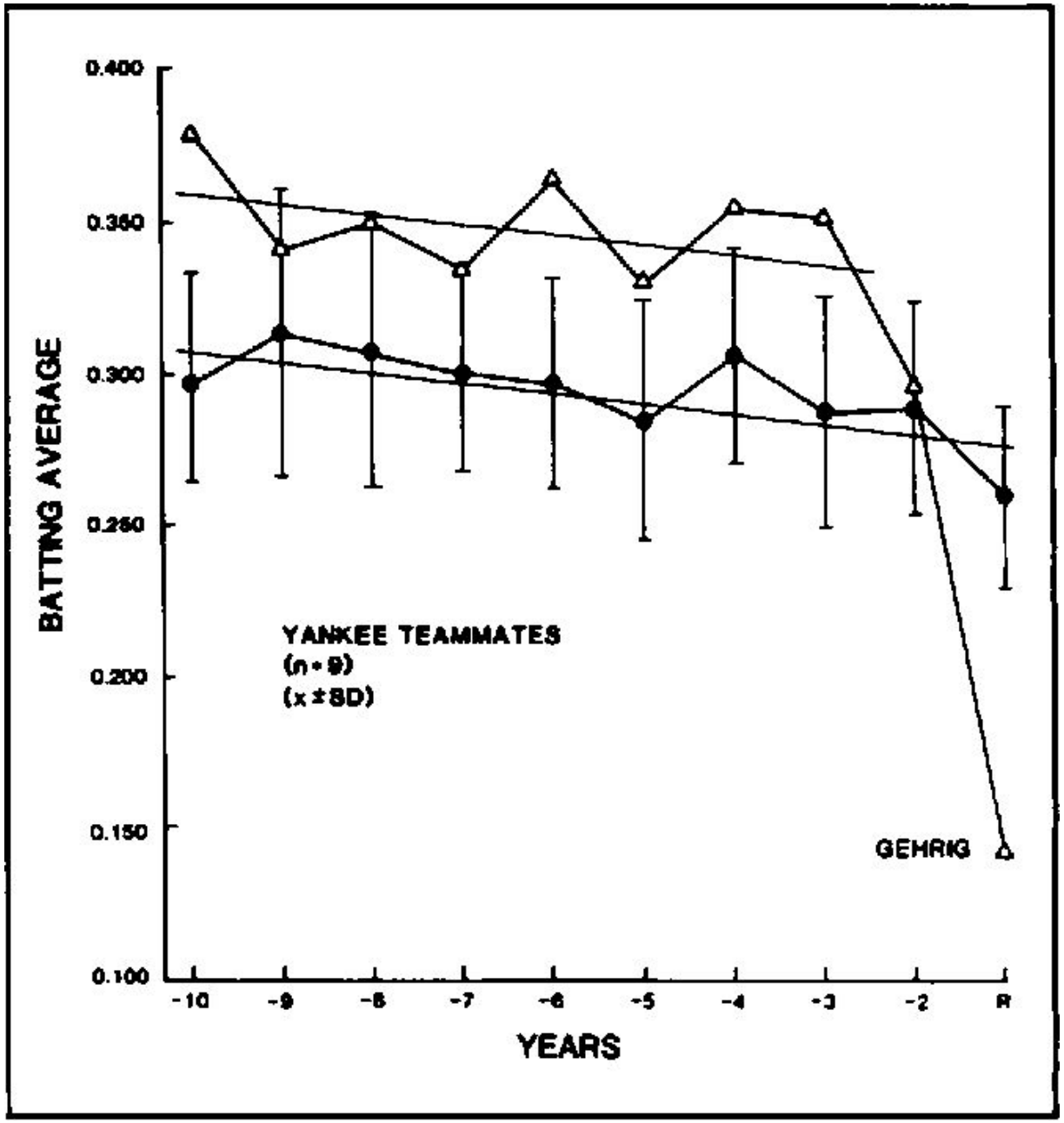
- **Consulting Fee (e.g., Advisory Board)**
  - Alexion, Argenx, Eidos, Lilly, UCB, Kriya, Sangano, Seismic, Lexicon
- **Contracted Research (Principal Investigators must provide information, even if received by the institution)**
  - Cour
- **Speakers' Bureau**
  - Alexion, UCB

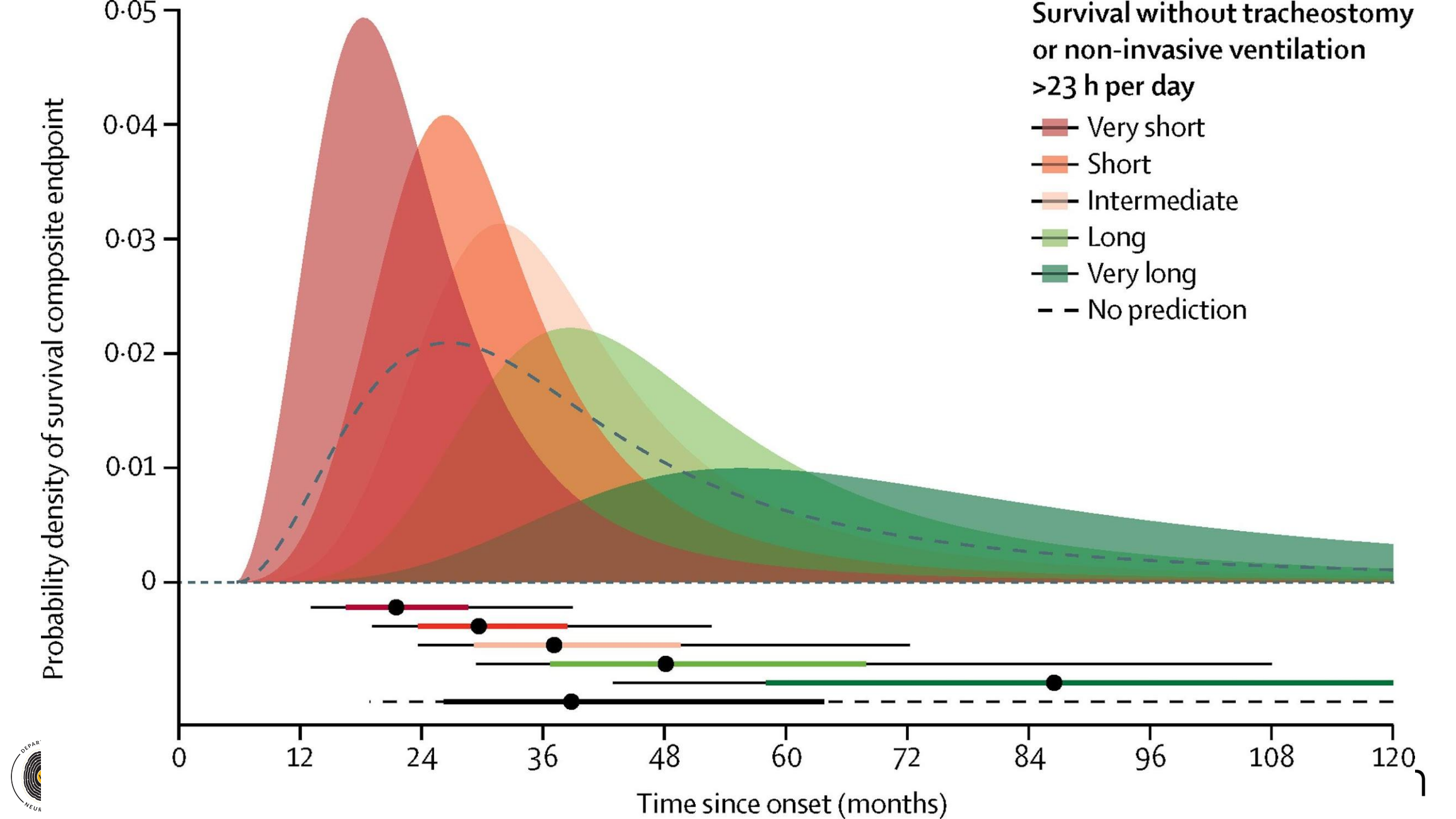
Learning Objectives

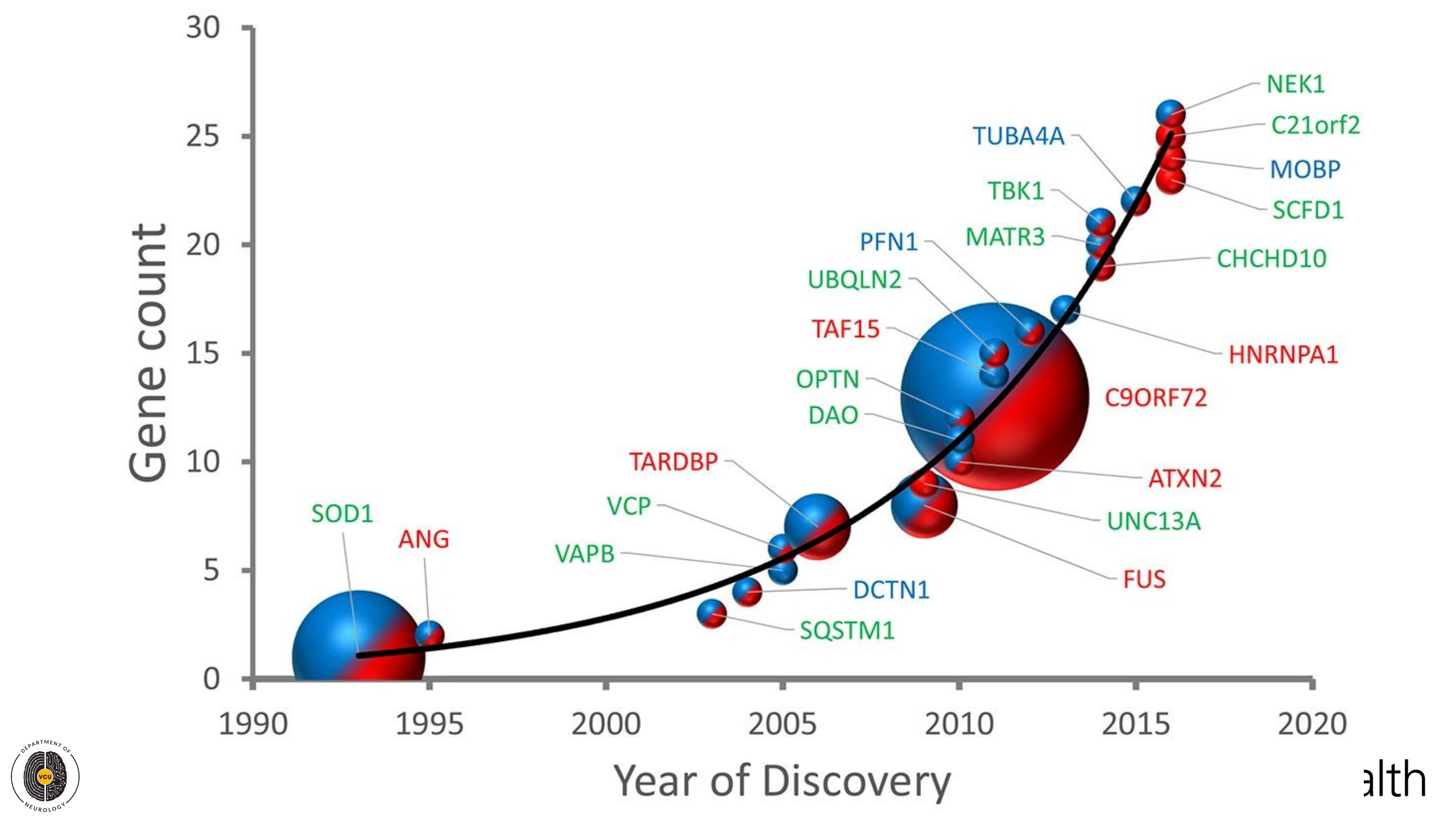
- Discuss past and present clinical trials and studies.

Amyotrophic Lateral Sclerosis is a Treatable Disease




0.400
0.350
0.300
0.250
0.200
0.150
0.100
BATTING AVERAGE
YANKEE TEAMMATES
(n = 9)
(x ± SD)
GEHRIG
-10
-9
-8
-7
-6
-5
-4
-3
-2
R
YEARS


Survival without tracheostomy or non-invasive ventilation >23 h per day
Very short
Short
Intermediate
Long
Very long
No prediction
Probability density of survival composite endpoint
0·05
0·04
0·03
0·02
0·01
0
0
12
24
36
48
60
72
84
96
108
120
Time since onset (months)

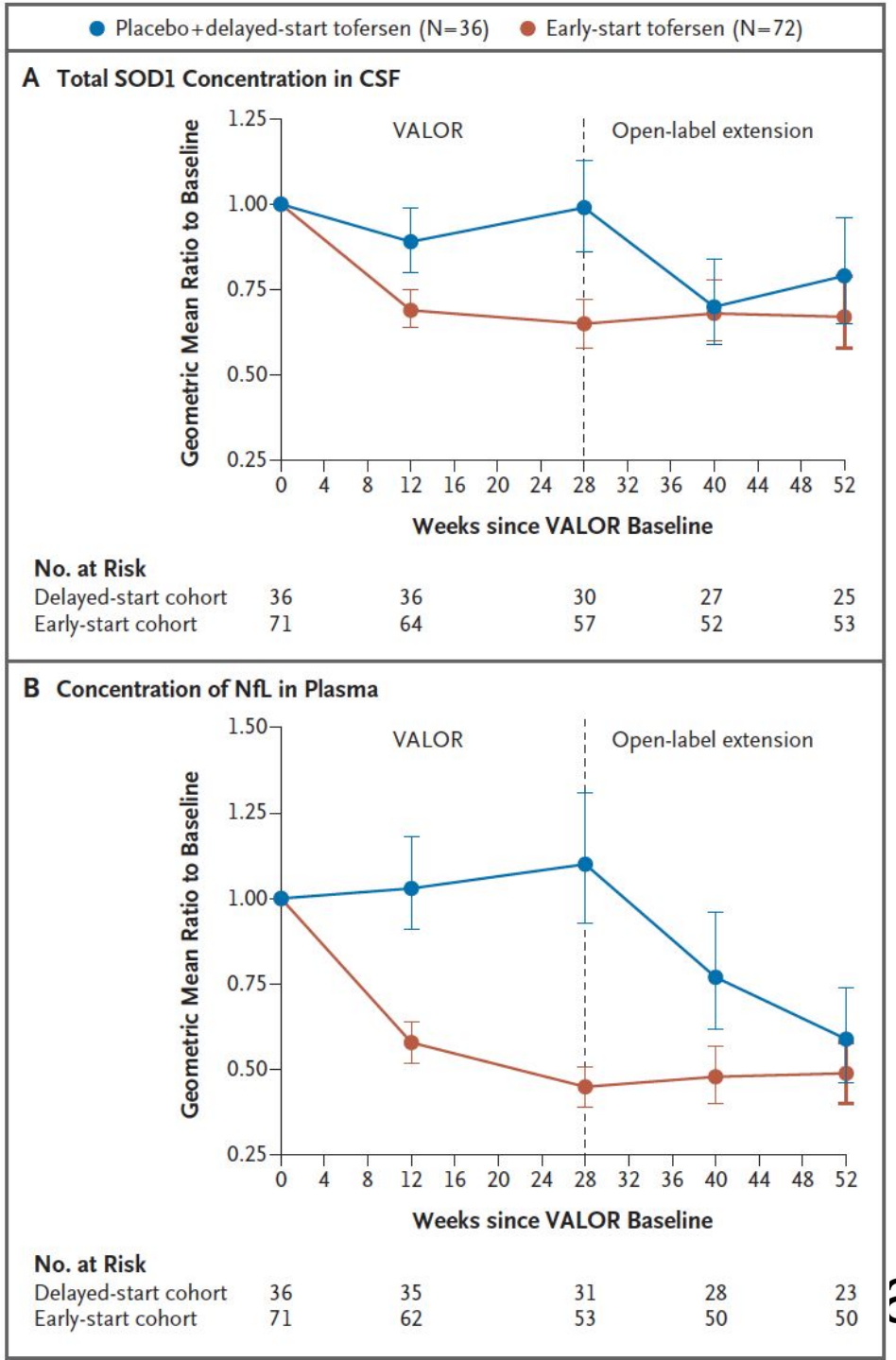

Gene count
30
25
20
15
10
5
0
1990
1995
2000
2005
2010
2015
2020
Year of Discovery
NEK1
C21orf2
MOBP
SCFD1
TUBA4A
TBK1
MATR3
PFN1
CHCHD10
UBQLN2
TAF15
HNRNPA1
OPTN
C9ORF72
DAO
TARDBP
ATXN2
VCP
UNC13A
SOD1
ANG
VAPB
FUS
DCTN1
SQSTM1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T.M. Miller, M.E. Cudkowicz, A. Genge, P.J. Shaw, G. Sobue, R.C. Bucelli, A. Chiò, P. Van Damme, A.C. Ludolph, J.D. Glass, J.A. Andrews, S. Babu, M. Benatar, C.J. McDermott, T. Cochrane, S. Chary, S. Chew, H. Zhu, F. Wu, I. Nestorov, D. Graham, P. Sun, M. McNeill, L. Fanning, T.A. Ferguson, and S. Fradette, for the VALOR and OLE Working Group*



Miller, T. M., et al. (2022). "Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS." N Engl J Med **387**(12): 1099-1110.

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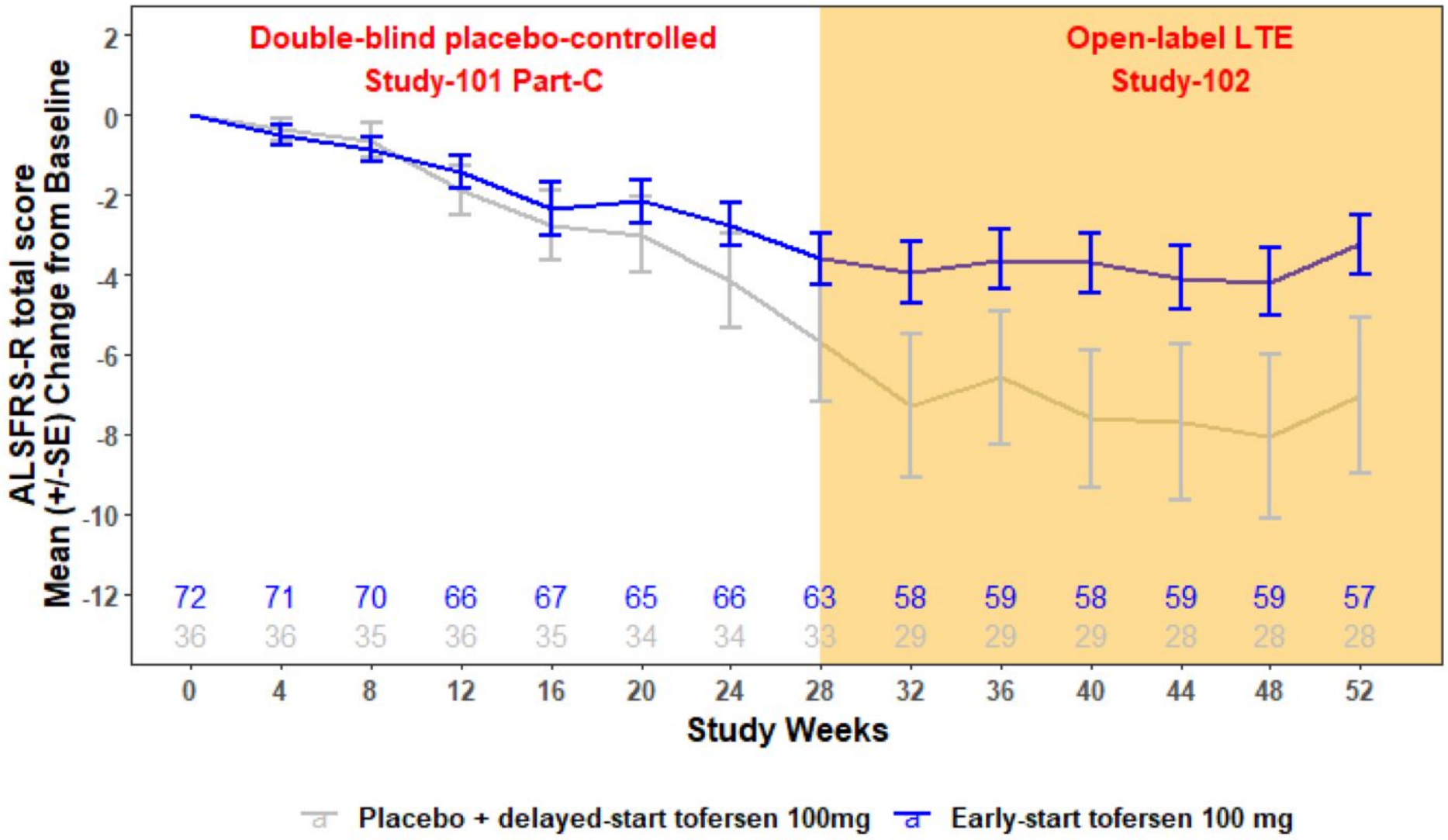


https://www.fda.gov/media/166392/download

Received: 19 January 2024 | Revised: 26 May 2024 | Accepted: 1 June 2024
DOI: 10.1002/mus.28182

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Clinical and patient-reported outcomes and neurofilament response during tofersen treatment in *SOD1*-related ALS—A multicenter observational study over 18 months

- 16 patients
- Mean of 11 months of treatment (6-18)
- 7 patients had improvement in ALSFRS-R

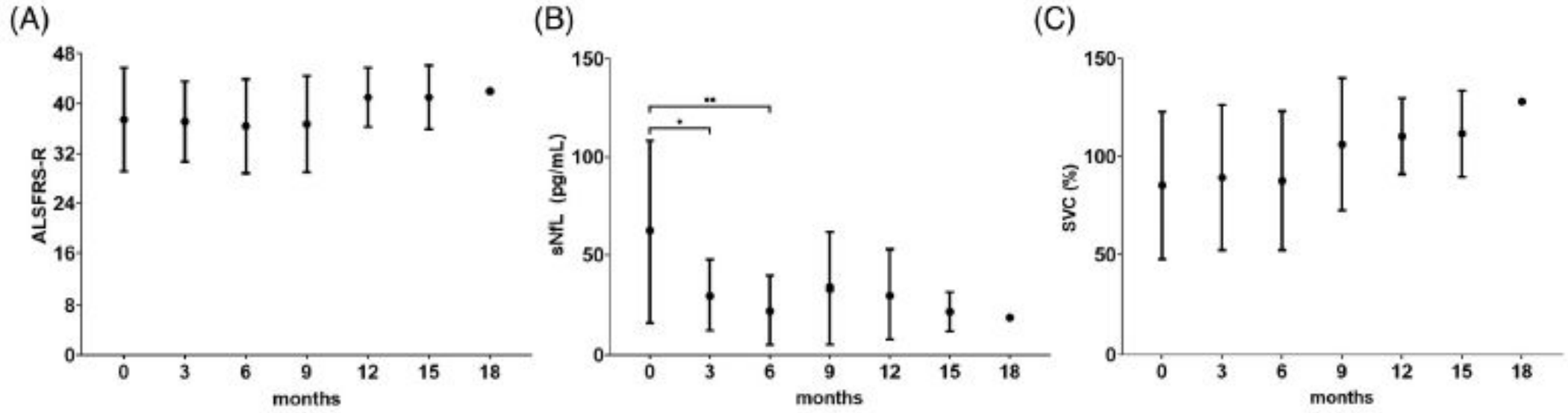


FIGURE 2 ALSFRS-R, sNfL and SVC during treatment with tofersen. (A) ALS functional rating scale—revised (ALSFRS-R), (B) serum neurofilament light chain (sNfL), and (C) slow vital capacity in percent of normal (SVC) during the treatment with tofersen. Tofersen (months), number of months of tofersen treatment. Bar, mean value; hinges, standard deviation. Significance levels: $^{*}p \leq .05$; $^{**}p \leq .01$.

The ATLAS Study

Proceed to Part C upon:
Emergence of clinically manifest ALS[b]

Proceed to Part B if:
- NfL ≥ 44 pg/mL and Δ from baseline ≥ 10 pg/mL[a]
- Still presymptomatic[b]

Randomization (1:1)

Part B: Placebo-controlled, n ~ 28
Tofersen 100 mg or placebo

Part C: Open-label
Tofersen 100 mg

Study screening and enrollment

Part A: Natural history run-in (with monthly NfL screen), n ~ 150
No intervention[c]

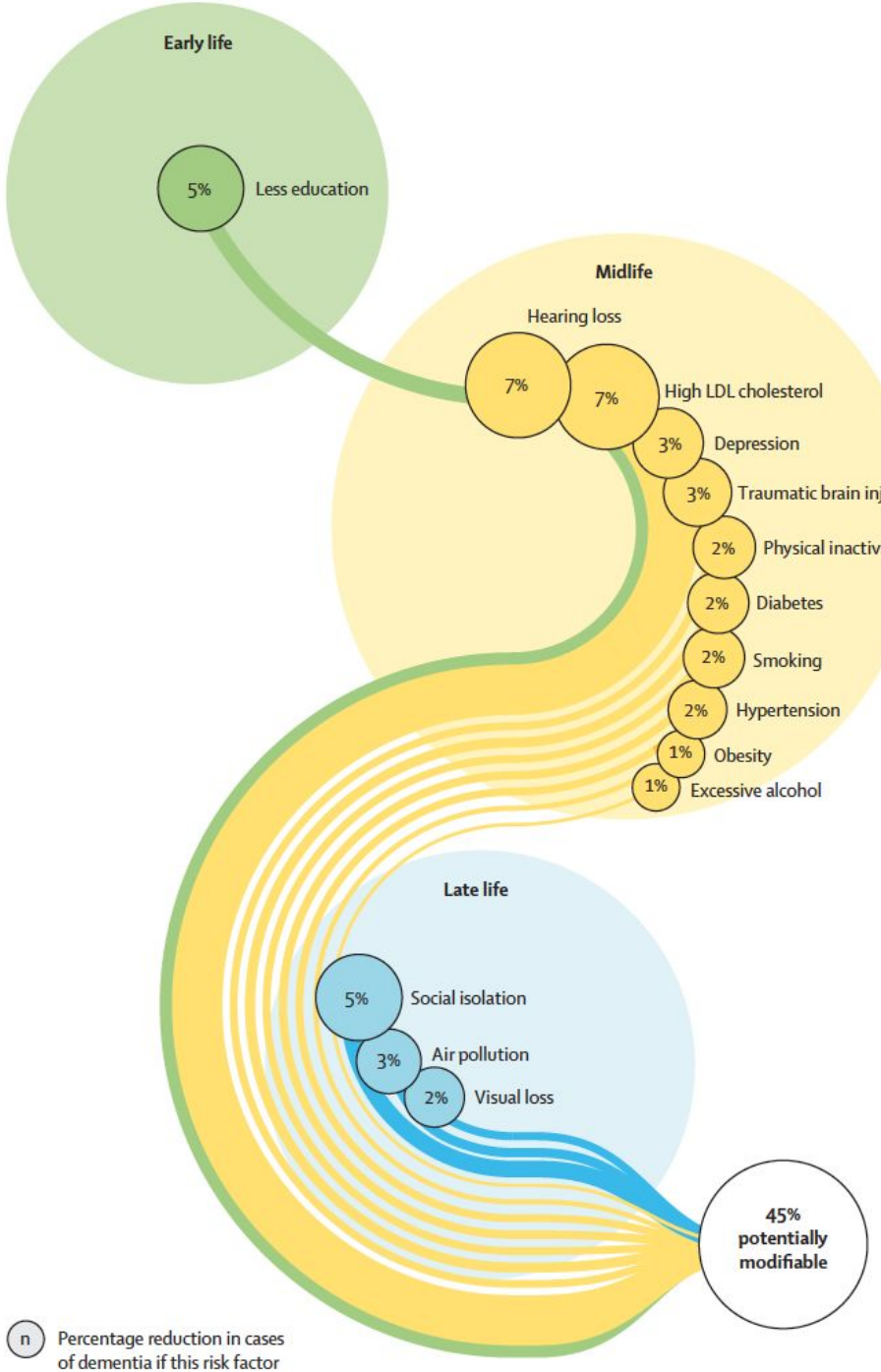
Proceed to Part D upon:
- Emergence of clinically manifest ALS (prior to detection of elevation in neurofilament)[b]

Part D: Open-label[d]
Tofersen 100 mg

Up to 2 years in duration

Benatar, M., et al. (2022). "Design of a Randomized, Placebo-Controlled, Phase 3 Trial of Tofersen Initiated in Clinically Presymptomatic SOD1 Variant Carriers: the ATLAS Study." Neurotherapeutics **19**(4): 1248-1258.

Metabolic Neuropathy (Idiopathic Neuropathy with Metabolic Syndrome & Type 2 Diabetes) may also be Treatable



Livingston, G., et al. (2024). "Dementia prevention, intervention, and care: 2024 report of the Lancet Standing Commission." Lancet **404**(10452): 572-628.

TopCSPN

NeuroNEXT

The NEXT Generation of Neurologic Treatments
NIH-Network for Excellence in Neuroscience Clinical Trials

Topiramate as a Disease Modifying Therapy for CSPN (TopCSPN – NN108)

Research

JAMA Neurology | Original Investigation

Safety and Efficacy of Topiramate in Individuals With Cryptogenic Sensory Peripheral Neuropathy With Metabolic Syndrome
The TopCSPN Randomized Clinical Trial

A. Gordon Smith, MD; J. Robinson Singleton, MD; Adrienne Aperghis, BS; Christopher S. Coffey, PhD; Peter Creigh, MD; Merit Cudkowicz, MD; Robin Conwit, MD; Dixie Ecklund, RN, MSN, MBA; Janel K. Fedler, PhD; Anna Gudjonsdottir, MS; Peter Hauer, BS; David N. Herrmann, MBBCh; Marianne Kearney, BA; John Kissel, MD; Elizabeth Klingner, MS; Adam Quick, MD; Cathy Revere, BS; Amro Stino, MD; for the NeuroNEXT NN108 TopCSPN Study Team

Department of Neurology VCU

NIH National Institute of Neurological Disorders and Stroke

The University of Iowa

MGH 1811 Massachusetts General Hospital

Virginia Commonwealth University MCV RPI 1838 VCU Health

University of Utah Health

Co-Primary Outcome Measures

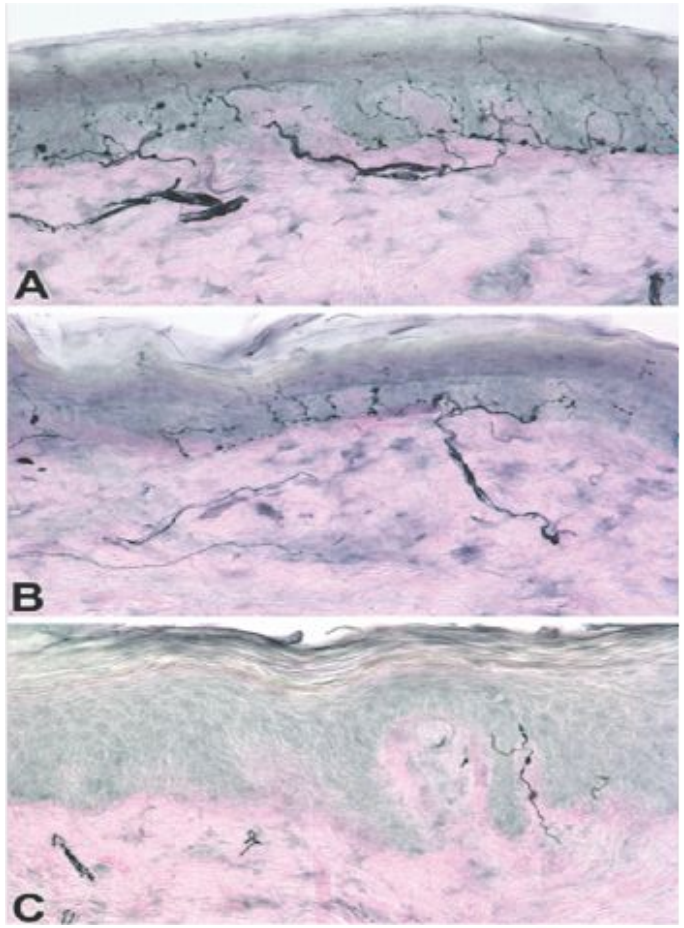
(1) NQOL-DN

Total Score: Range -4 to 136

6 Sub-scores:

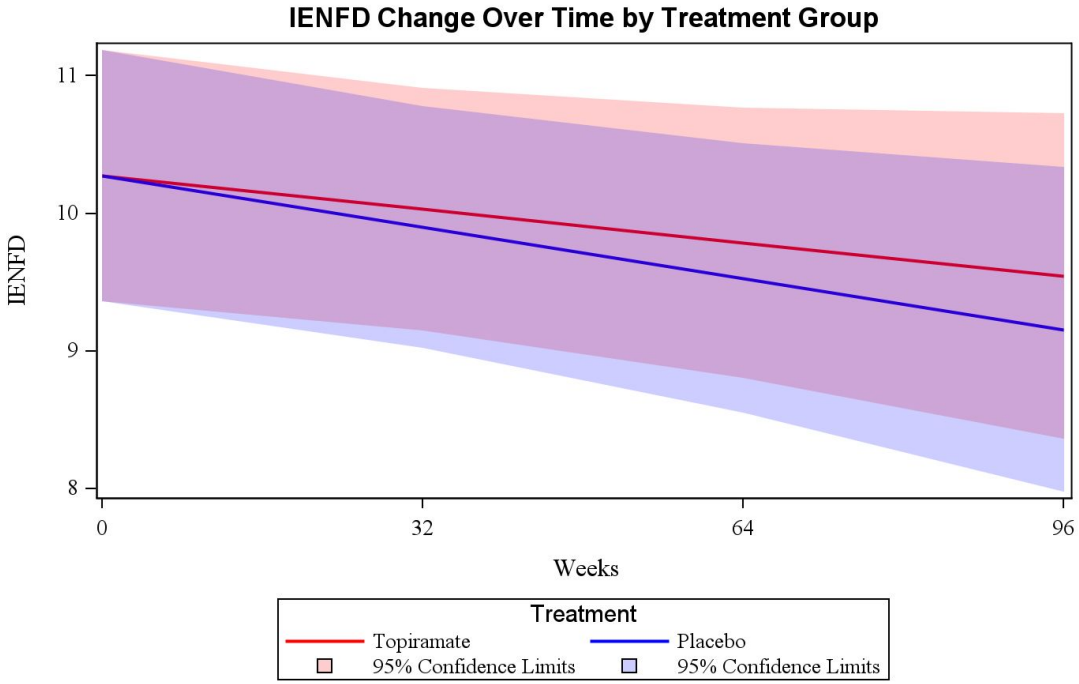
1. Symptoms
2. Physical functioning
3. Activity of daily living
4. Large fiber neuropathy
5. Small fiber neuropathy
6. Autonomic neuropathy

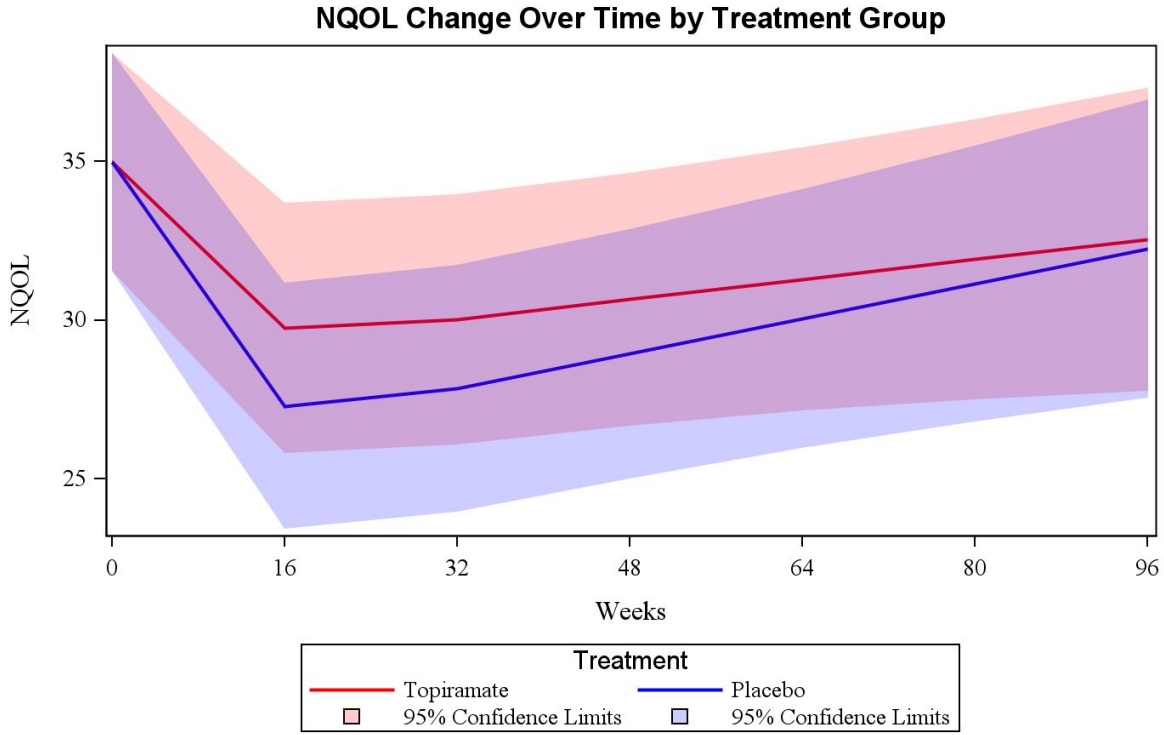
(2) IENFD at the Distal Thigh



Smith, A. G., et al. (2023). "Safety and Efficacy of Topiramate in Individuals With Cryptogenic Sensory Peripheral Neuropathy With Metabolic Syndrome: The TopCSPN Randomized Clinical Trial." JAMA Neurol.

Intent to Treat Analysis was Negative



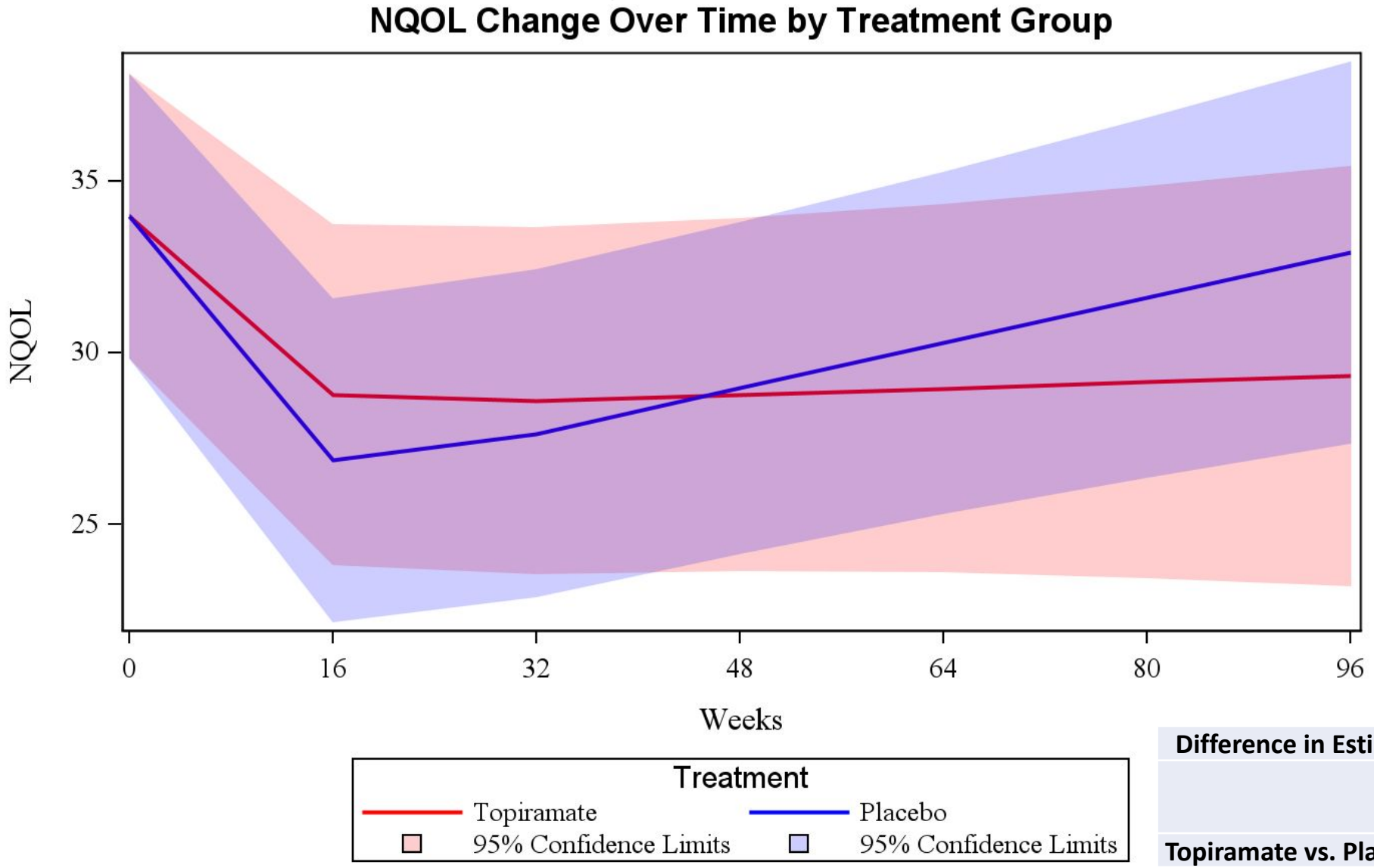


Difference in Estimated Annual Rate of IENFD Change	
	Estimate (One-Sided 95% CI)
Topiramate vs. Placebo	0.21 (-0.43, Inf)

Difference in Estimated Annual Rate of NQOL-DN Change	
	Estimate (One-Sided 95% CI)
Topiramate vs. Placebo	-1.52 (-Inf , 1.19)

Smith, A. G., et al. (2023). "Safety and Efficacy of Topiramate in Individuals With Cryptogenic Sensory Peripheral Neuropathy With Metabolic Syndrome: The TopCSPN Randomized Clinical Trial." JAMA Neurol.

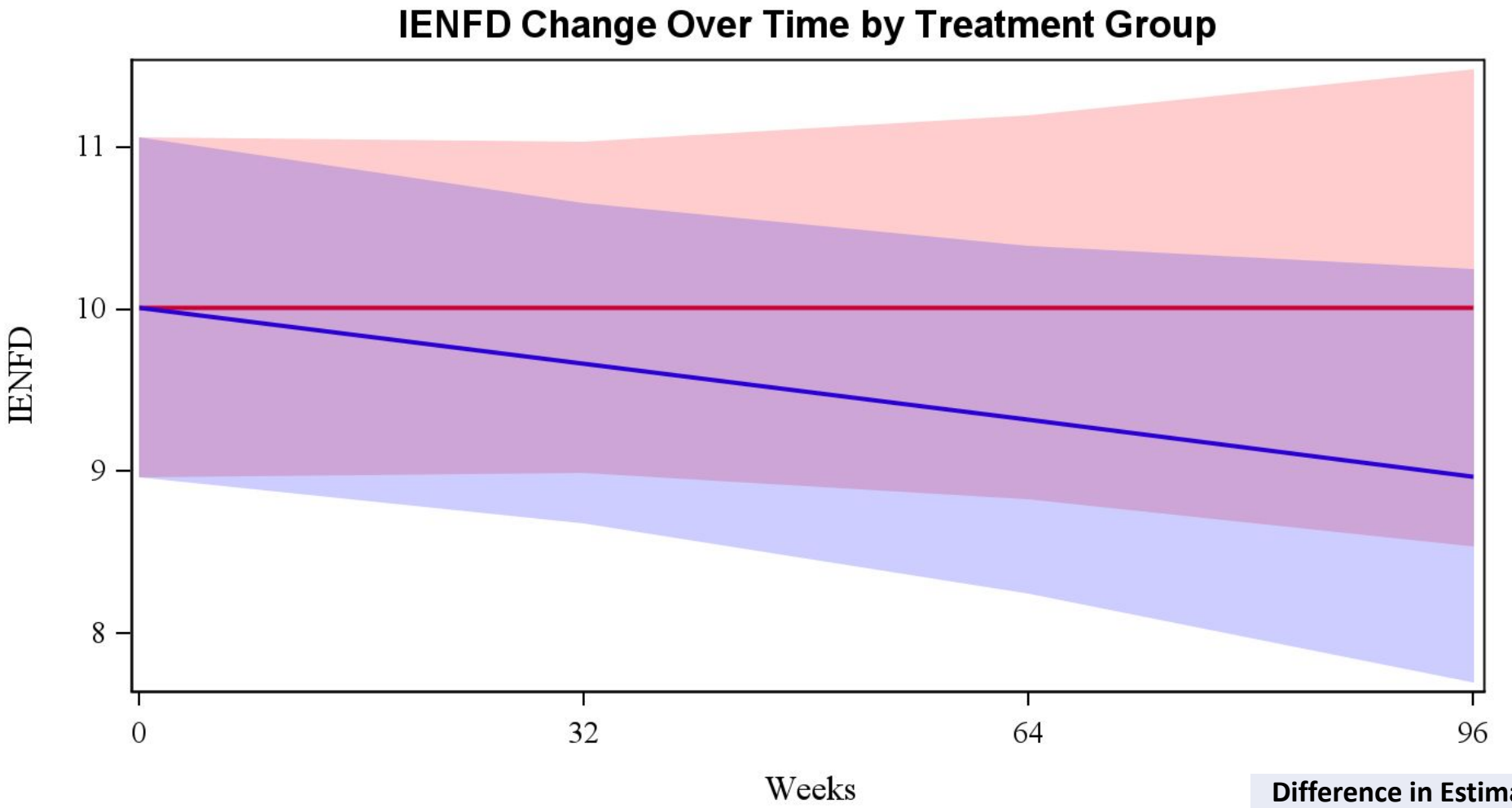
Per Protocol Analysis



Difference in Estimated Annual Rate of IENFD Change	
	Estimate (One-Sided 95% CI)
Topiramate vs. Placebo	-3.69 (-Inf, -0.73)

Smith, A. G., et al. (2023). "Safety and Efficacy of Topiramate in Individuals With Cryptogenic Sensory Peripheral Neuropathy With Metabolic Syndrome: The TopCSPN Randomized Clinical Trial." JAMA Neurol.

Per Protocol Analysis



Difference in Estimated Annual Rate of IENFD Change	
	Estimate (One-Sided 95% CI)
Topiramate vs. Placebo	0.56 (-0.21, Inf)

Smith, A. G., et al. (2023). "Safety and Efficacy of Topiramate in Individuals With Cryptogenic Sensory Peripheral Neuropathy With Metabolic Syndrome: The TopCSPN Randomized Clinical Trial." JAMA Neurol.

The Utah Diabetic Neuropathy Study (UDNS)

Exercise results in cutaneous reinnervation

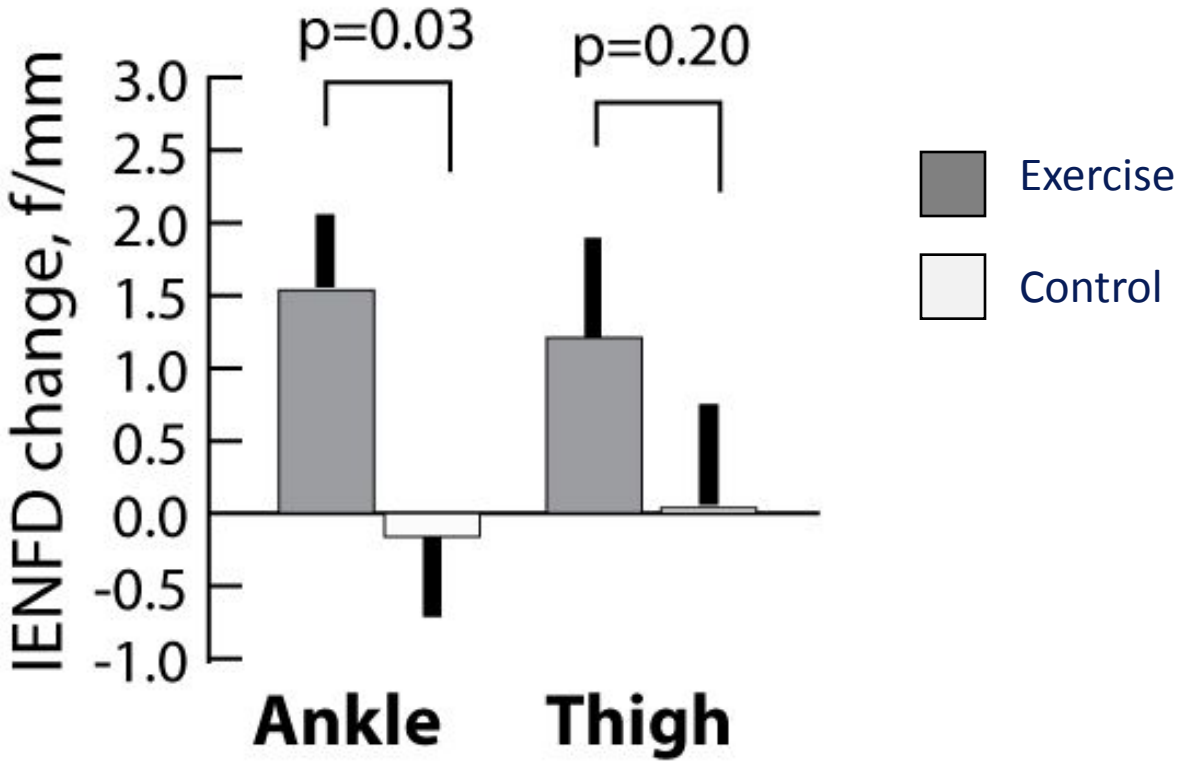


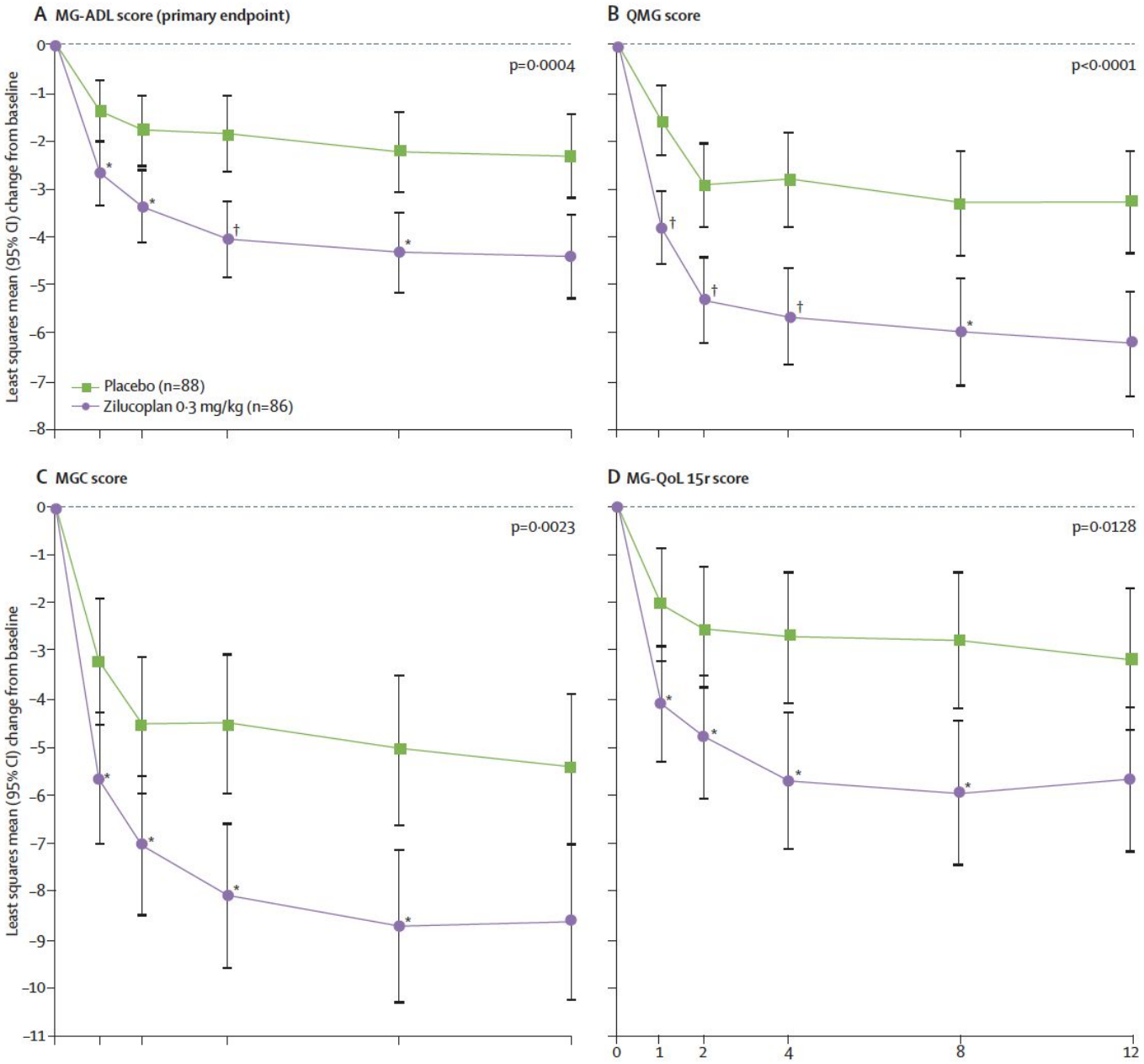
Figure 2. Supervised exercise over 12 months improves intraepidermal nerve fiber density (IENFD) in non-neuropathic patients with diabetes. Bars represent change in IENFD 0-12 months +/- SEM for exercise (filled bar) or control (unfilled) participants. Participants receiving standard-of-care counseling showed stasis or slow decline in fiber density.

Singleton, J. R., Marcus, R. L., Jackson, J. E., K Lessard, M., Graham, T. E., & Smith, A. G. (2014). Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Annals of Clinical and Translational Neurology, 1(10), 844–849. doi:10.1002/acn3.125

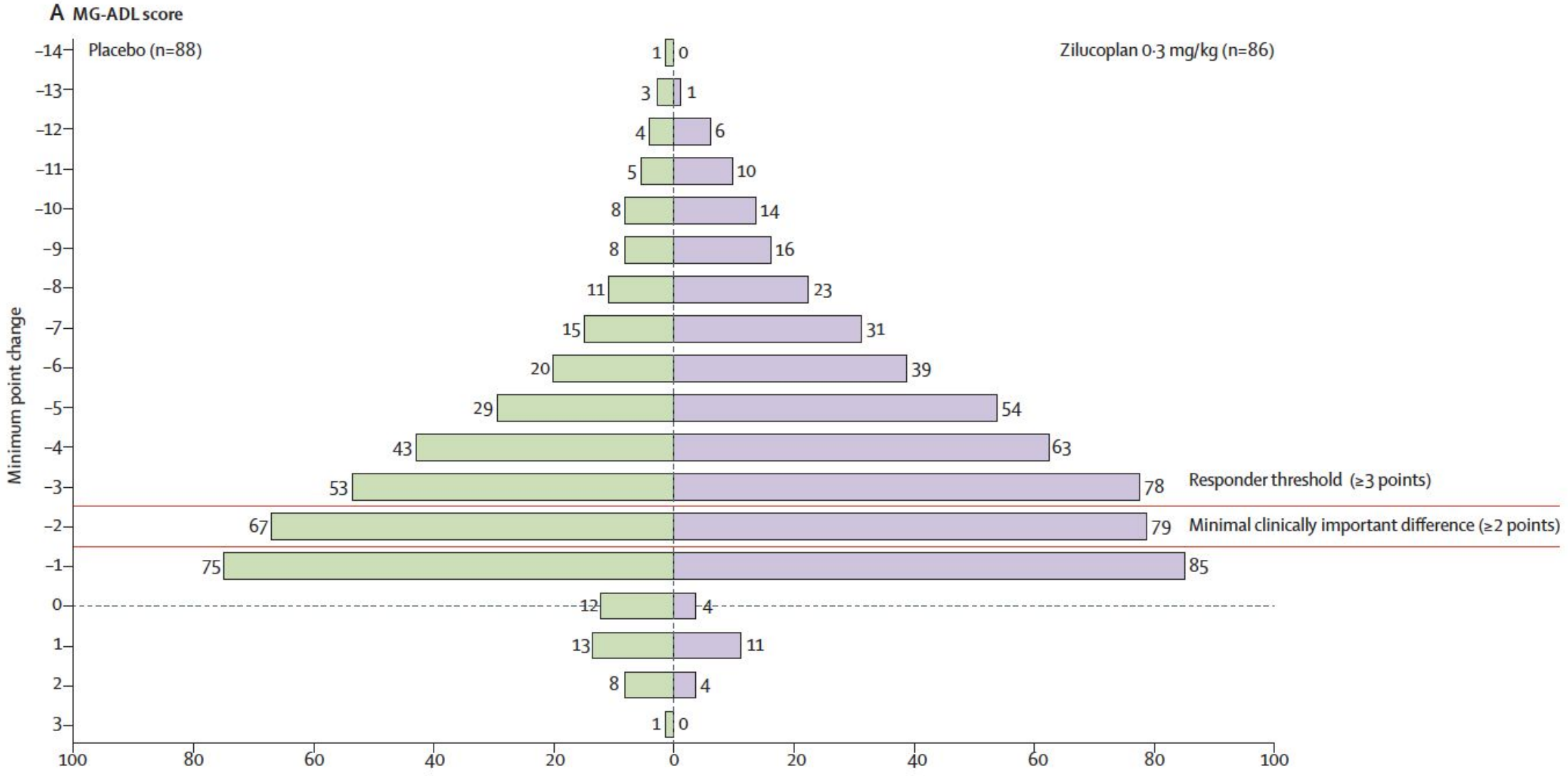
Treatment Updates in Myasthenia Gravis

Therapeutic Armamentarium

Therapeutic	Mechanism of Action
Corticosteroids	Lymphocytic (among others)
“Steroid-sparing” immunosuppressives	Reduced T-cells and B-cells (among others)
Plasma exchange (PLEX)	Reduced immunoglobulin levels
Intravenous Immunoglobulin (IVIg)	Multitude of mechanisms
Anti-CD20 (e.g. Rituximab)	Reduced production of auto-antibodies
Anti-CD19 (e.g. Inebelizumab)	Reduced production of auto-antibodies
Anti-CD38 (e.g. TAK-079)	Reduced plasmablasts, plasma cells, NK cells, activated T and B-cells
Proteosome inhibition (e.g. bortezomib)	Plasma cell depletion
Complement inhibition (e.g. Eculizumab)	Reduced effector function of anti-AChR antibodies
FcRN antagonism (e.g. Efgartigimod)	Reduced IgG levels
Thymectomy	Modulation of both B-cell and T-cell function
CAR T-cell therapy (anti-BCMA)	Reduction of auto-antibody producing plasma cells
Re-establish Self Tolerance (e.g. CN-106)	AChR fragment containing nanoparticles



Howard, J. F., Jr., et al. (2023). "Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study." Lancet Neurol **22**(5): 395-406.



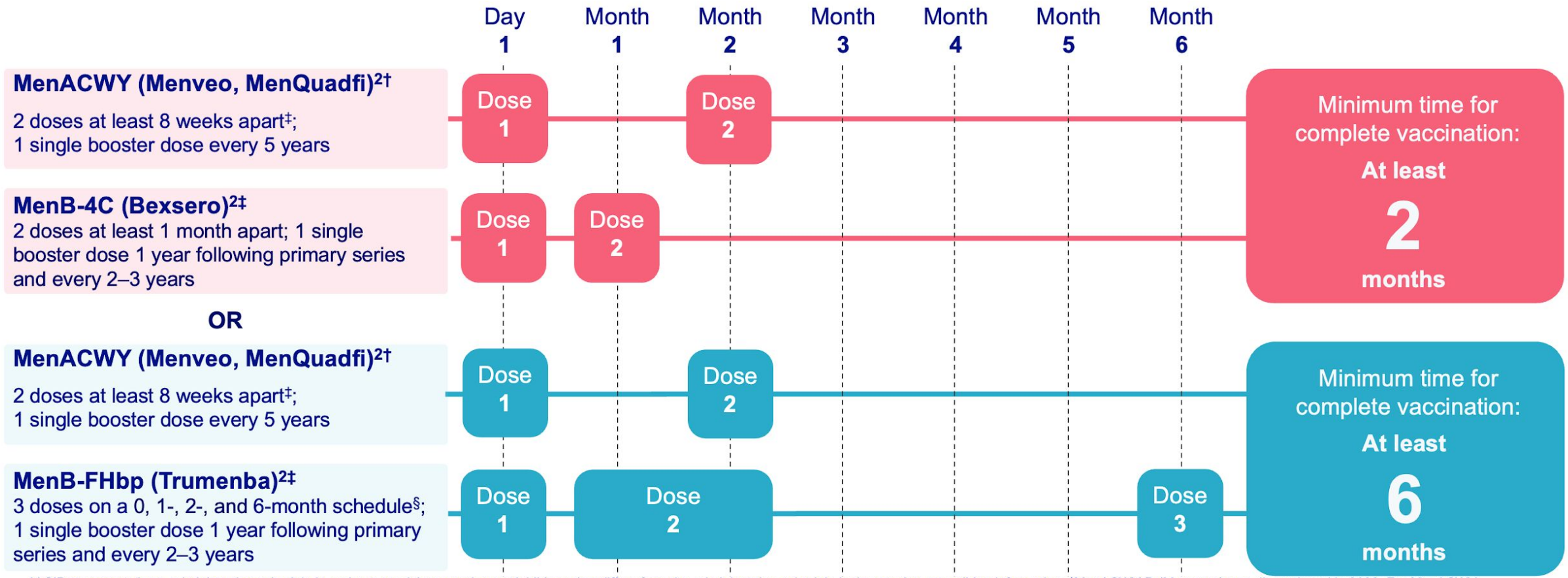
Howard, J. F., Jr., et al. (2023). "Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study." Lancet Neurol **22**(5): 395-406.

1. **Are you going to use conventional therapy?** — *Yes* → Corticosteroids, MMF/AZA etc.

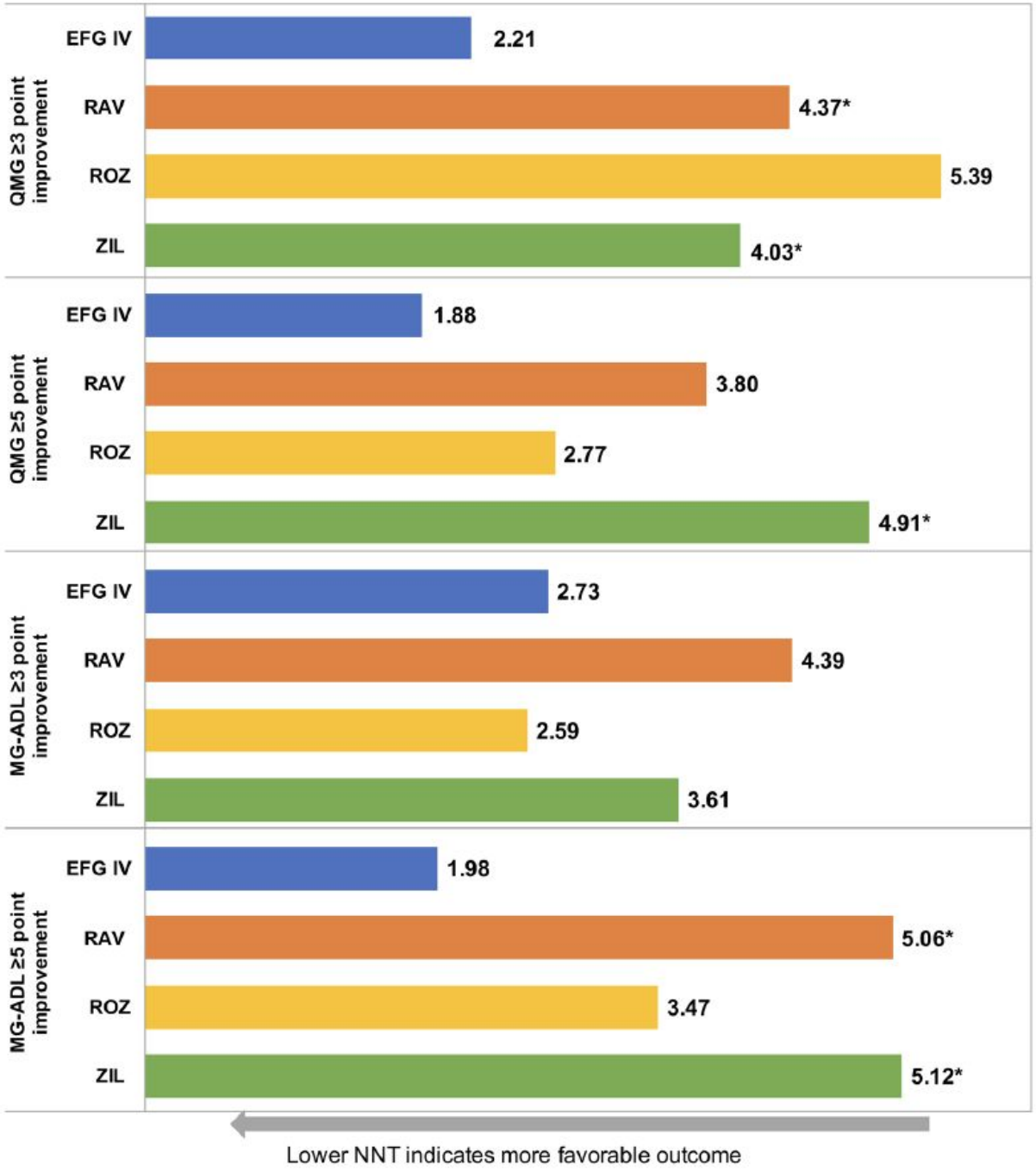
   No ↓

2. **Complement Inhibitor vs. FCRN?**
3. **IV or Subcutaneous**

Route of Administration	Complement Inhibitor (NM Vaccination)	FCRN Inhibitor (all Cyclical)
IV	• Eculizumab (Soliris) – q2 weeks • Ravulizumab (Ultomiris) – q 8 weeks	• Efgartigimod (Vyvgart)
Subcutaneous	• Zilucoplan (ZilbrysQ) - daily	• Rozanolixizumab (Rystiggo) • Efgartigimod alfa/hyaluronidase (Vyvgart Hytrulo)



*ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. †MenACWY-D (Menactra) was discontinued in 2022. For MenACWY vaccines, the same vaccine product is recommended, but not required, for all doses.[3,4] ‡MenB vaccines are not interchangeable; the same brand must be used for each dose of the primary series and all booster doses.[2] §If dose 2 was administered at least 6 months after dose 1, then dose 3 is not needed. If dose 3 is administered earlier than 4 months after dose 2, a fourth dose should be administered at least 4 months after dose 3.[2] ACIP, Advisory Committee on Immunization Practices; MenACWY, meningococcal serogroups A, C, W, and Y; MenB, meningococcal serogroup B. **1**. ZILBRYSQ® [prescribing information]. Smyrna, GA: UCB, Inc. **2**. https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Accessed April 2024. **3**. https://portal.ct.gov/immunization/-/media/Departments-and-Agencies/DPH/dph/infectious_diseases/immunization/CVP-2020/2022-CVP-Communications/update-menactra-discontinuation-2-24-22.pdf. Accessed April 2024. **4**. Mbaeyi SA, et al. MMWR Recomm Rep. 2020;69:1-41.



COST PER IMPROVED OUTCOME (≥ 3 POINT IMPROVEMENT IN MG-ADL)

1. EFG - $645,406
2. RAV - $2,551,316
3. ROZ - $1,839,110
4. ZIL - $1,936,905

Smith, A. G., et al. (2024). "Risk-Benefit Analysis of Novel Treatments for Patients with Generalized Myasthenia Gravis." Adv Ther **41**(12): 4628-4647.

What About B Cell Depletion for Myasthenia Gravis?

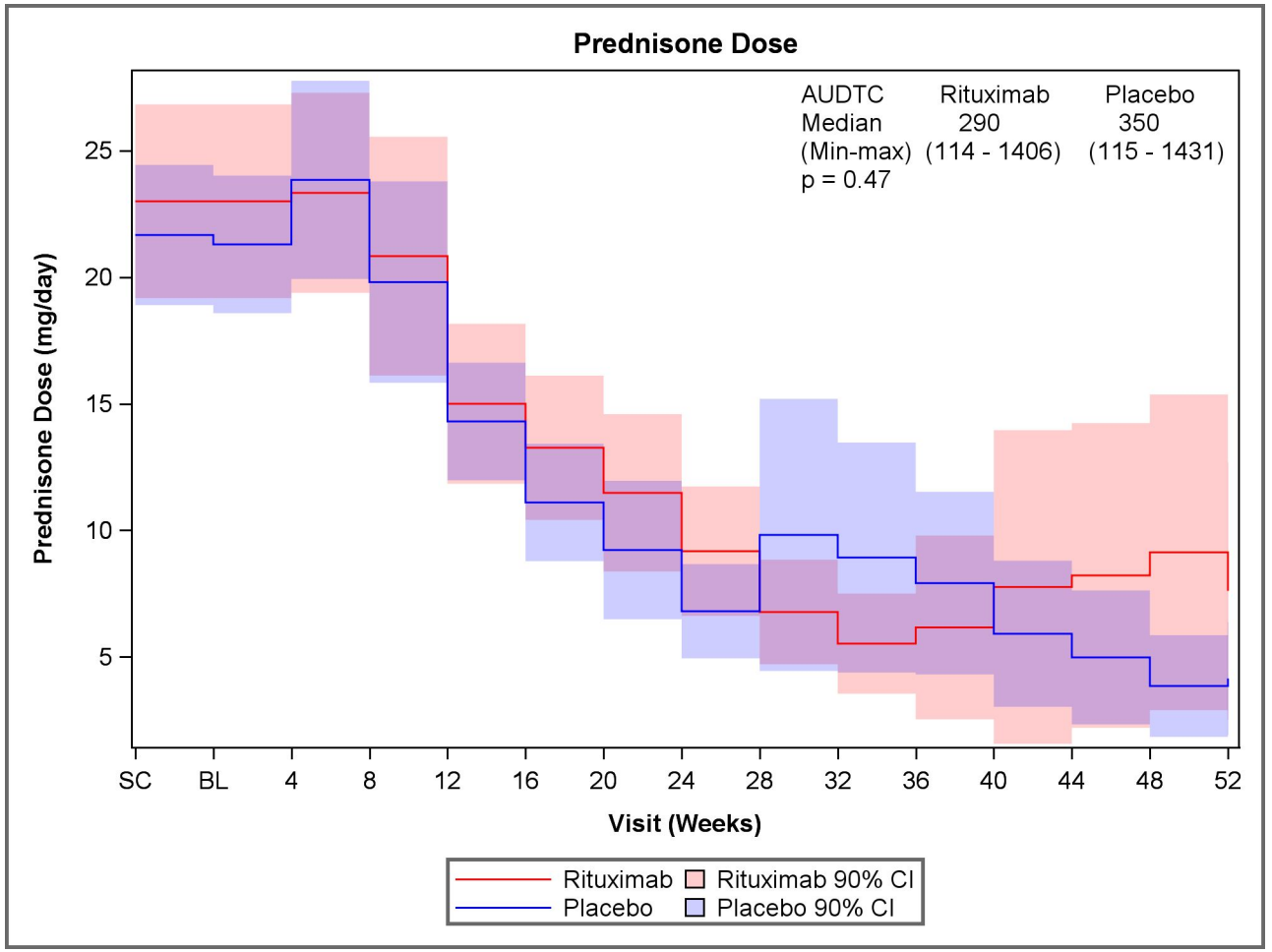
BeatMG

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

- Rituximab was safe, with similar adverse event profile to placebo.
- 60% of rituximab and 56% of placebo treated patients met the predefined outcome.

But…

- Patients had mild MG
- The very high placebo rate suggests that this patient population may have been on too much prednisone.
- It was a small study

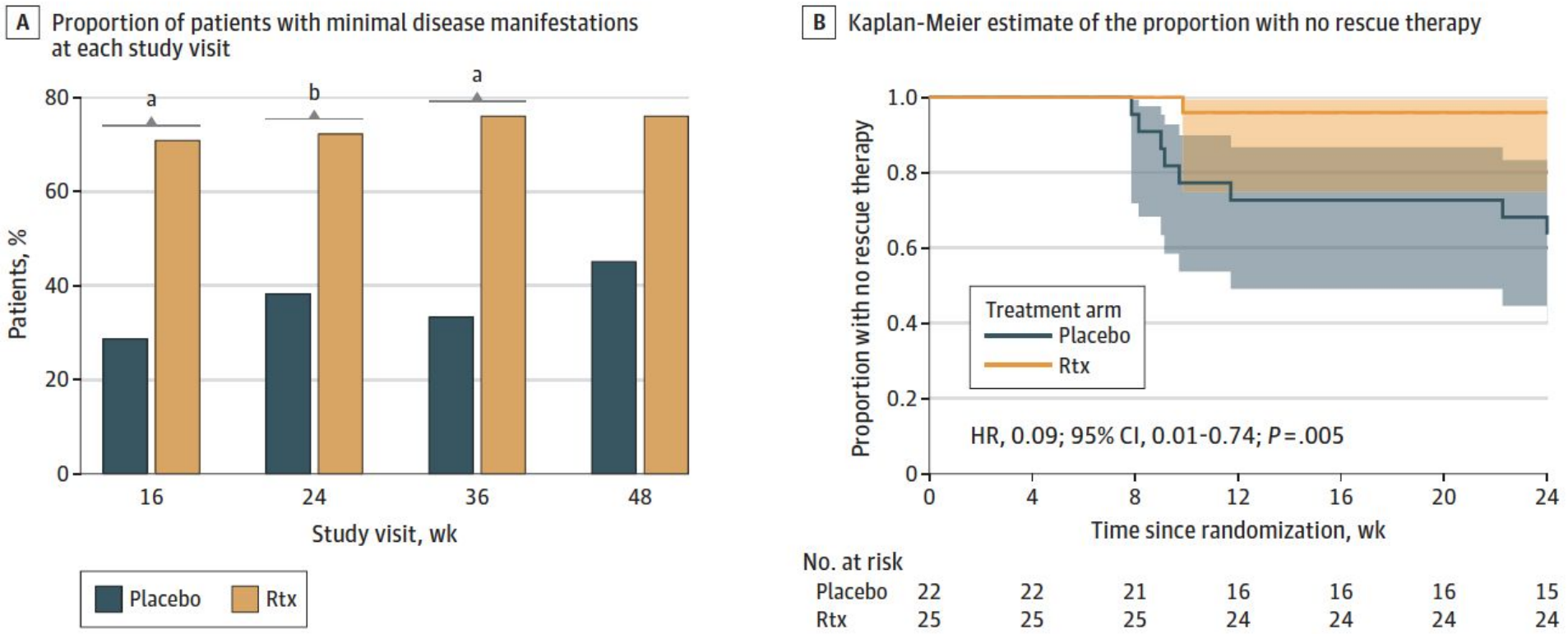


DEPARTMENT OF NEUROLOGY VCU

VCU Health

RINOMAX - ≤12 Months of gMG Symptoms

Figure 2. Proportion With Minimal Disease Manifestation and No Rescue Treatment Over Time



Piehl, F., et al. (2022). "Efficacy and Safety of Rituximab for New-Onset Generalized Myasthenia Gravis: The RINOMAX Randomized Clinical Trial." JAMA Neurol **79**(11): 1105-1112.

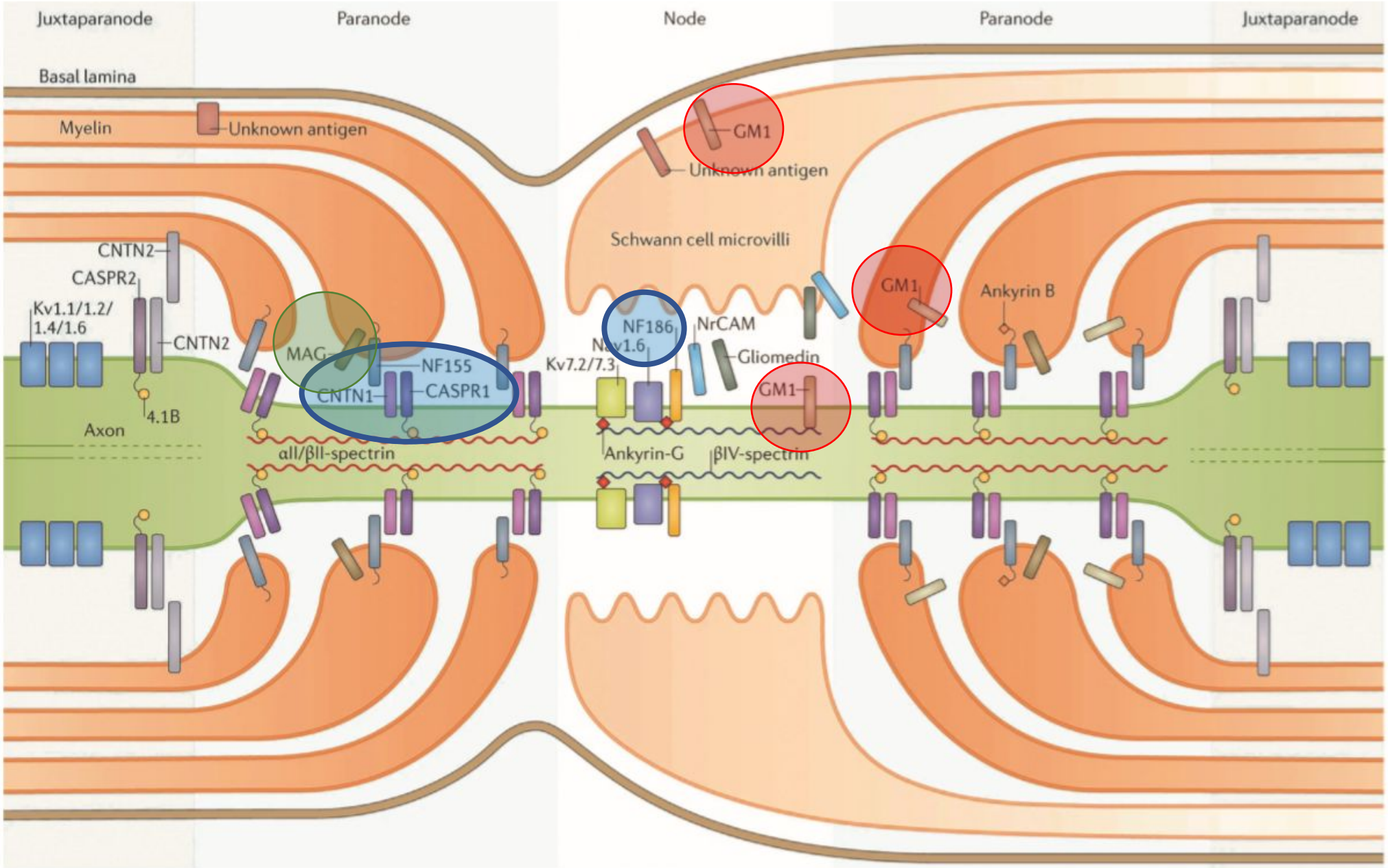
AMGEN PRESENTS POSITIVE PHASE 3 DATA FOR UPLIZNA® (INEBILIZUMAB-CDON) IN GENERALIZED MYASTHENIA GRAVIS (GMG) AT AANEM 2024

MINT Study Results Show Clinically Meaningful and Statistically Significant Efficacy in AChR+ and MuSK+ Patients

First and Only Phase 3 Placebo-Controlled gMG Trial for a Biologic That Tapered Corticosteroid Use

https://clinicaltrials.gov/study/NCT04524273?intr=Inebilizumab&rank=10

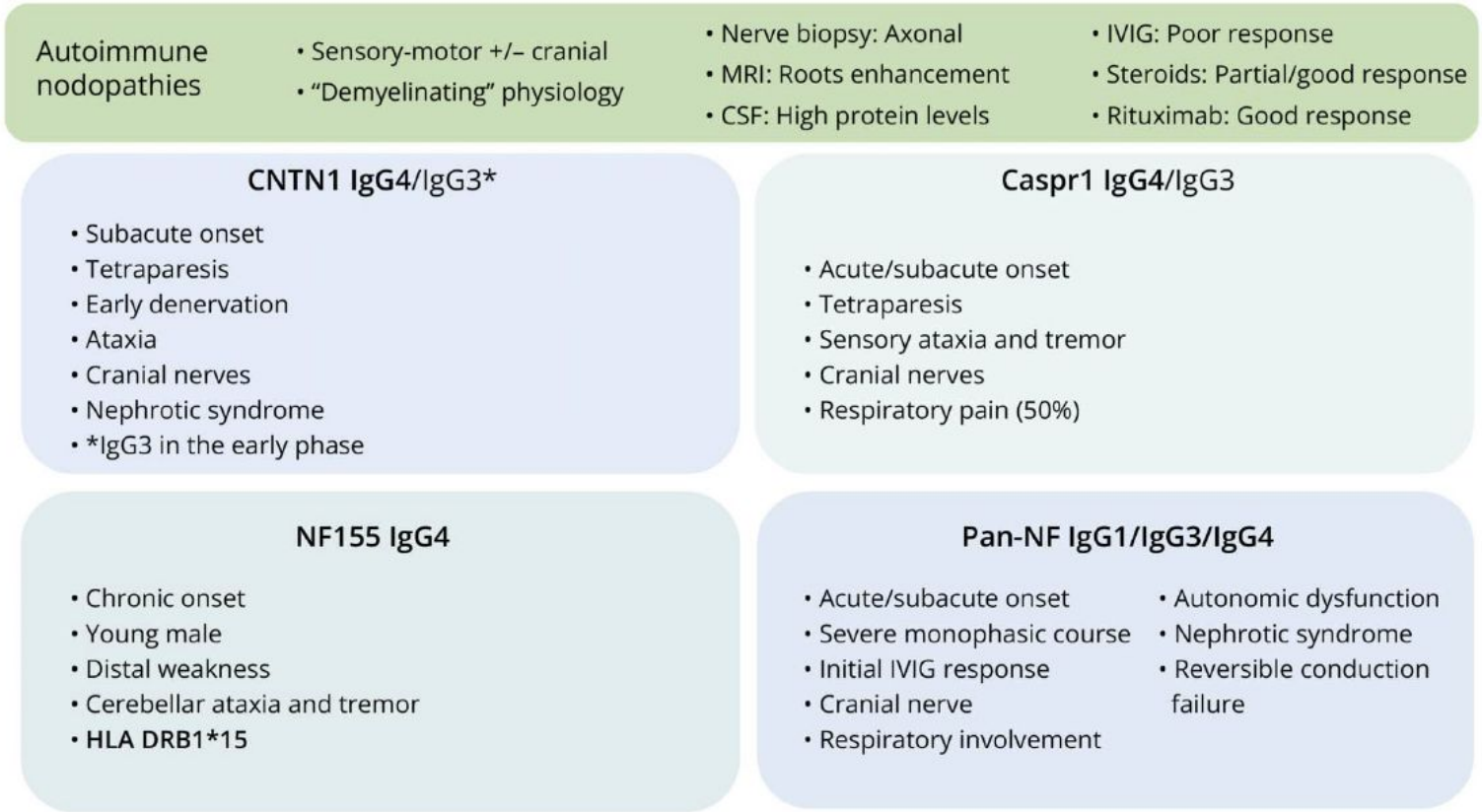
Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Updates



Vural A, Doppler K, Meinl E. Autoantibodies Against the Node of Ranvier in Seropositive Chronic Inflammatory Demyelinating Polyneuropathy: Diagnostic, Pathogenic, and Therapeutic Relevance. *Front Immunol*. 2018;9:1029. Published 2018 May 14.

5-10% of CIDP Patients have a Nodopathy/Paranodopathy

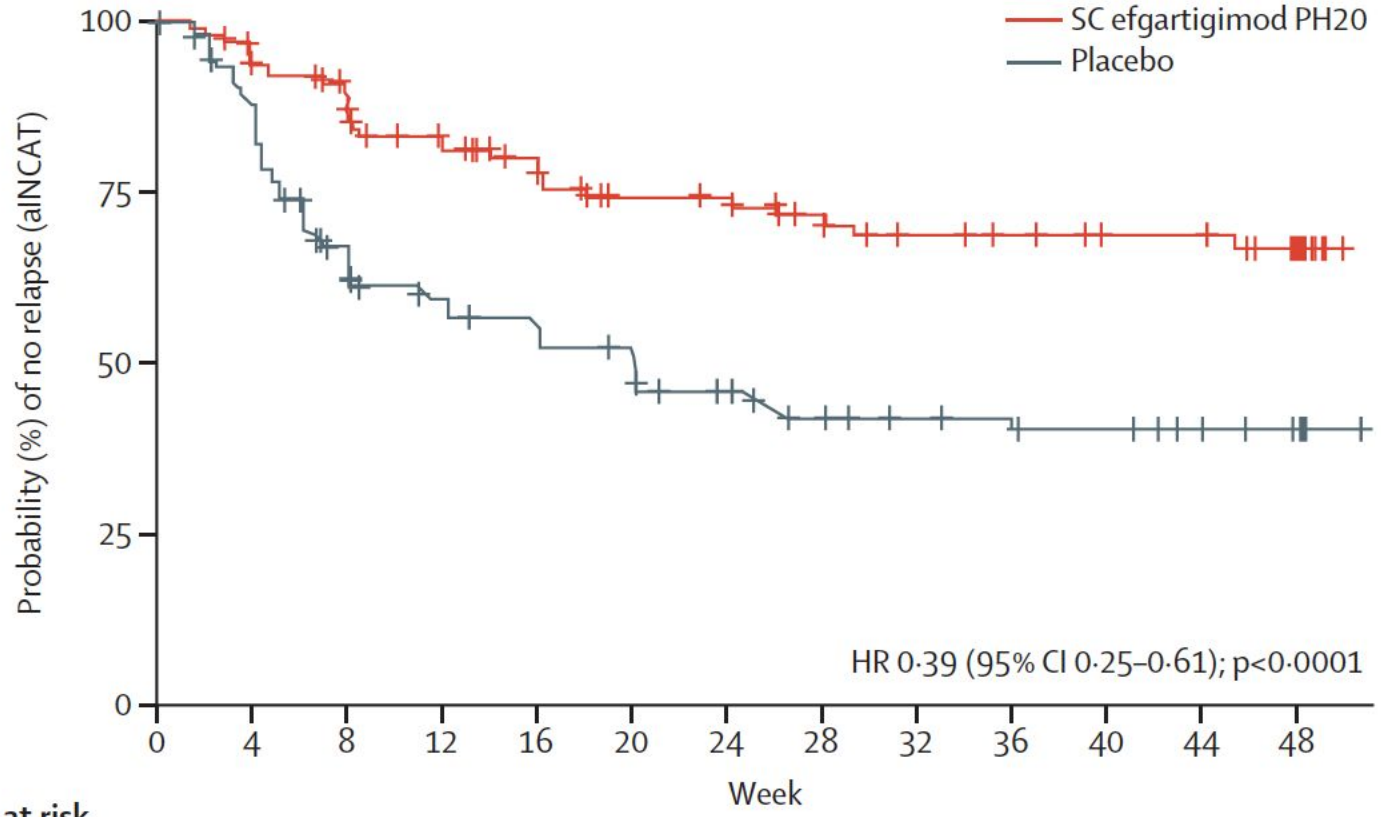
Figure 2 Autoimmune Nodopathies: Key Features That Should Prompt Testing for Nodal/Paranodal Antibodies



Caspr1 = contactin-associated protein 1; CNTN1 = contactin-1; IVIg = IV immunoglobulin; NF155 = neurofascin 155; PanNF = pan-neurofascin.

Pascual-Goñi, E., et al. (2024). "Antibodies in Autoimmune Neuropathies: What to Test, How to Test, Why to Test." Neurology **103**(4): e209725

Weekly SQ Efgartigimod for CIDP (ADHERE)



Number at risk (number censored)													
SC efgartigimod PH20	111	107	93	80	68	56	55	48	42	40	36	36	28
	(0)	(2)	(8)	(14)	(22)	(29)	(30)	(35)	(39)	(41)	(45)	(45)	(55)
Placebo	110	94	67	55	51	47	38	31	28	26	24	21	16
	(0)	(3)	(8)	(12)	(13)	(14)	(17)	(21)	(24)	(26)	(27)	(31)	(35)

Allen, J. A., et al. (2024). "Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial." Lancet Neurol **23**(10): 1013-1024.