

Acetylcholine Receptor-Autoantibody Detection and Therapeutic Assessment of Nipocalimab in Seronegative Patients With Myasthenia Gravis in Vivacity-MG3

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Introduction

- Generalized myasthenia gravis (gMG) is an autoimmune neuromuscular disorder driven by pathogenic immunoglobulin G (IgG) autoantibodies and characterized by chronic muscle weakness and fatigue^{1,2}
- Nipocalimab is the first FcRn blocker approved for the treatment of gMG in anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) antibody-positive adult and adolescent (≥12 years of age) patients^{3,4}
- Although most patients are positive for anti-AChR or anti-MuSK antibodies by conventional radioimmunoprecipitation assay (RIPA), approximately 5% to 15% remain seronegative^{5,6}
 - These seronegative patients may experience delayed diagnosis, substantial disease burden and limited access to targeted therapies⁶
- Emerging evidence suggests that live cell-based assays (CBA) can identify low-affinity or conformation-dependent anti-AChR autoantibodies not detected by RIPA⁷
- In the 24-week double-blind phase of the Vivacity-MG3 study, nipocalimab+SOC (vs placebo+SOC) has demonstrated rapid and sustained efficacy in seropositive patients with gMG; although seronegative patients were enrolled, they were not included in the primary efficacy endpoint analysis^{8,9}

Objective

To evaluate the efficacy and safety of nipocalimab+SOC versus placebo+SOC in a subgroup of conventional seronegative patients with gMG who were anti-AChR autoantibody-positive based on a CBA

Methods

Study Design and Assessment

- The present post hoc analysis used data from the phase 3, randomized, double-blind, placebo-controlled Vivacity-MG3 study⁸
- Samples from adults with gMG who were RIPA-seronegative for anti-AChR autoantibodies at baseline were retrospectively tested using a live anti-AChR CBA
- Anti-AChR autoantibodies were assessed using a live HEK293T CBA expressing clustered adult AChR; samples were independently reviewed by 3 assessors, with scores ≥1 considered positive
- Patients received nipocalimab+SOC or placebo+SOC during the 24-week double-blind treatment period

Outcomes

- Mean change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) total scores at week 24
- Proportion of patients achieving a meaningful within-patient change, defined as a ≥2-point improvement (meaningful clinical improvement [MCI]) in MG-ADL total scores and a ≥3-point improvement in QMG total scores at week 24
- Safety assessments: Incidence of treatment-emergent adverse events (TEAEs) during the double-blind period

Statistical Analysis

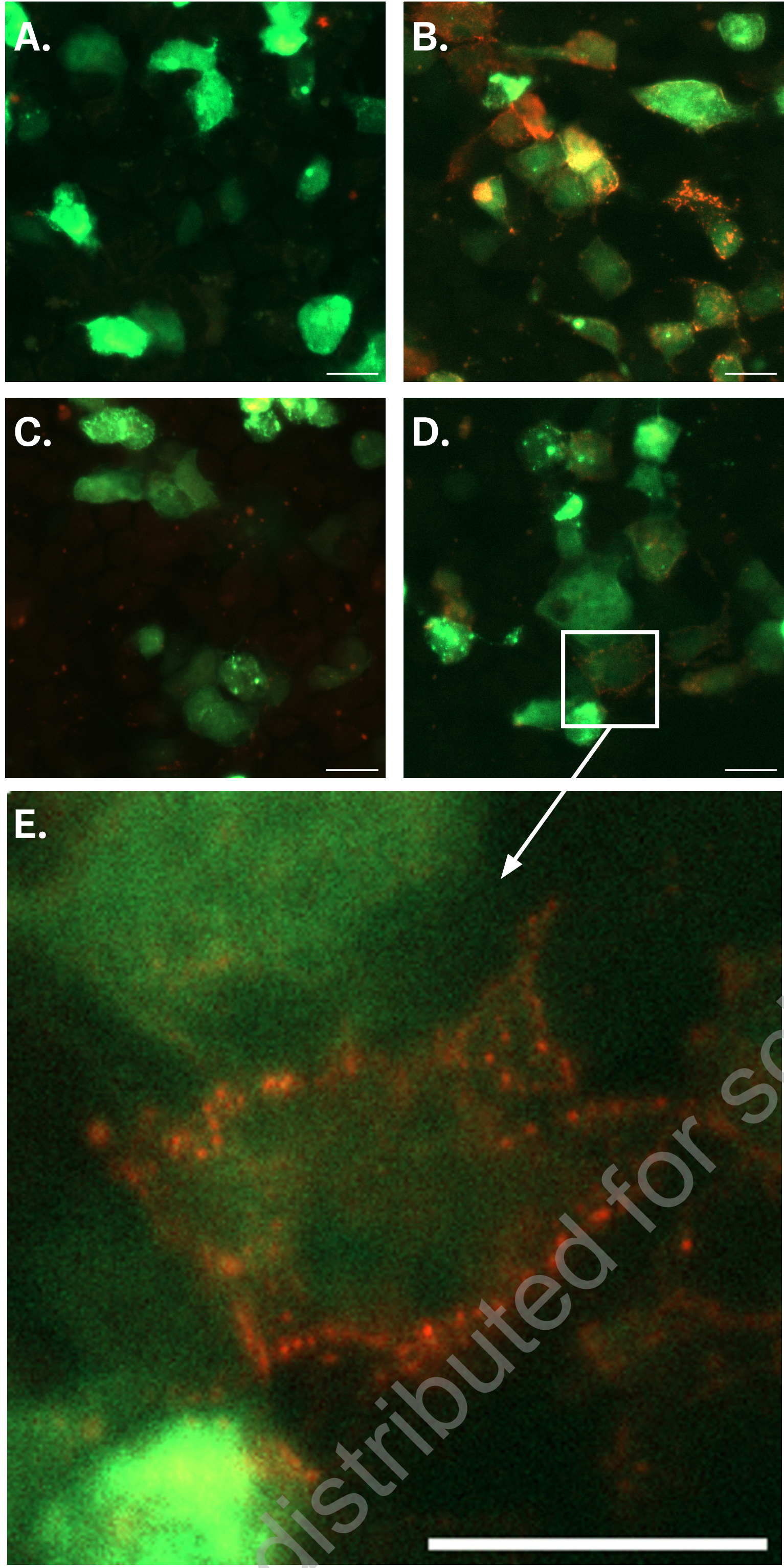
- Mean changes from baseline in MG-ADL and QMG scores were analyzed using Mixed Models for Repeated Measures
- The percentage of patients achieving MCI at week 24 compared to baseline was analyzed by the Cochran-Mantel-Haenszel test

Results

Baseline demographics and characteristics

- A total of 43 RIPA-seronegative patients were tested using live CBA (Figure 1)
- 7/43 patients (16.3%) were identified as anti-AChR positive: Nipocalimab+SOC: n=5; placebo+SOC: n=2 (Table 1)

Figure 1. Visualization of Anti-AChR autoantibody positivity using CBA



Representative fluorescent microscope images of CBA stained with rhapsyn (green) and patient serum (1:20 dilution, red): A, healthy control. B, RIPA-AChR-positive patient. C, RIPA and CBA-seronegative patient. D, RIPA seronegative and CBA seropositive patient. E, Zoomed-in image of the region outlined by the white box in D showing punctate staining of AChR clusters lining the cell. Scale bar, 20 μm. AChR=anti-acetylcholine receptor, CBA=cell-based assays, RIPA=radioimmunoprecipitation assay.

Table 1. Patient demographics and baseline characteristics (Seropositive efficacy analysis set; AChR+ by CBA)

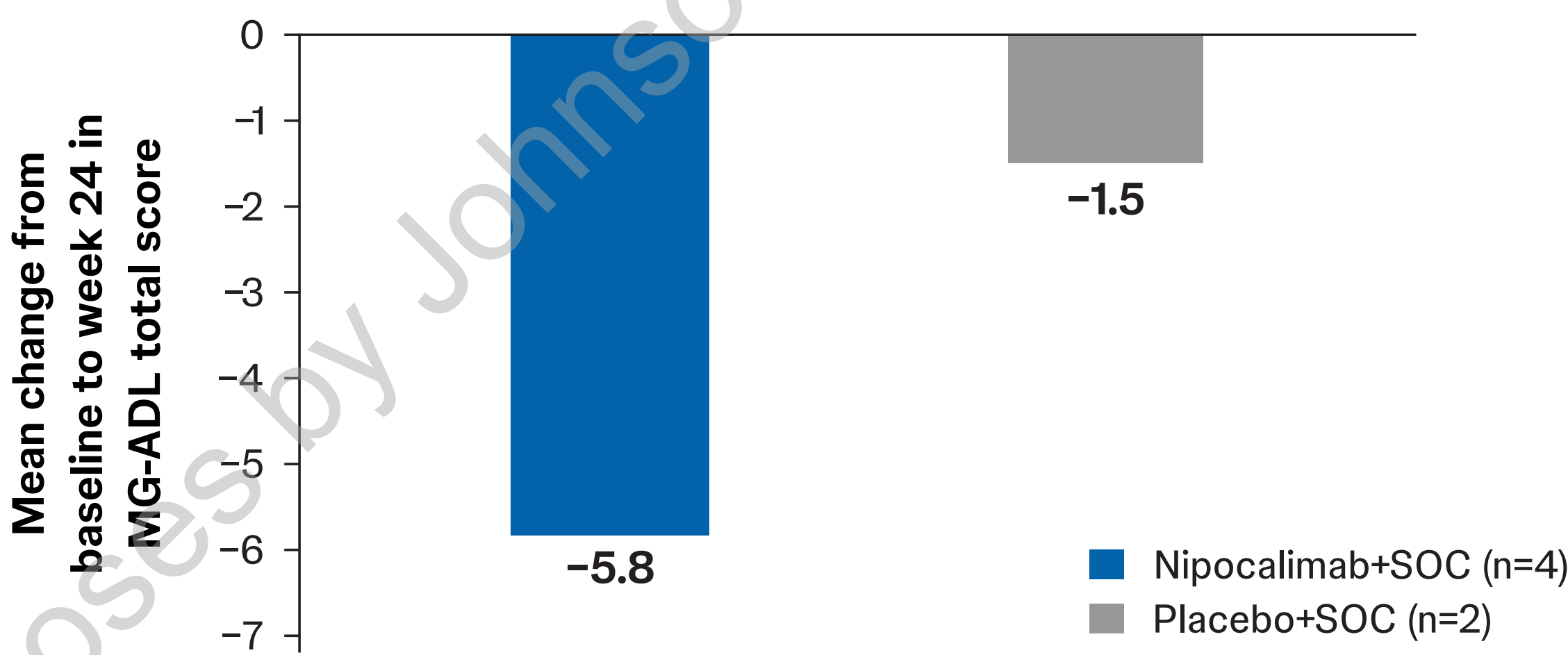
	Nipocalimab+SOC (n=5)	Placebo+SOC (n=2)
Age, median (range), years	51.0 (37–65)	64.5 (51–78)
Female, n (%)	4 (80.0)	1 (50.0)
Duration of MG, mean (SD), years	8.0 (7.57)	4.5 (2.12)
Age at onset, median (range), years	43.5 (34–58)	60.0 (45–75)
Baseline MG-ADL total score, mean (SD)	8.5 (2.72)	11.5 (2.12)
Baseline QMG total score, mean (SD)	14.9 (2.90)	15.0 (4.24)
Antibody-positive at screening*, n (%)		
Seronegative	5 (100.0)	2 (100.0)

*By radioimmunoprecipitation assay (RIPA). AChR=anti-acetylcholine receptor, CBA=cell-based assays, MG=myasthenia gravis, MG-ADL=Myasthenia Gravis-Activities of Daily Living, QMG=Quantitative Myasthenia Gravis, RIPA=radioimmunoprecipitation assay, SD=standard deviation, SOC=standard-of-care.

MG-ADL: Mean change from baseline, MCI, and SCI

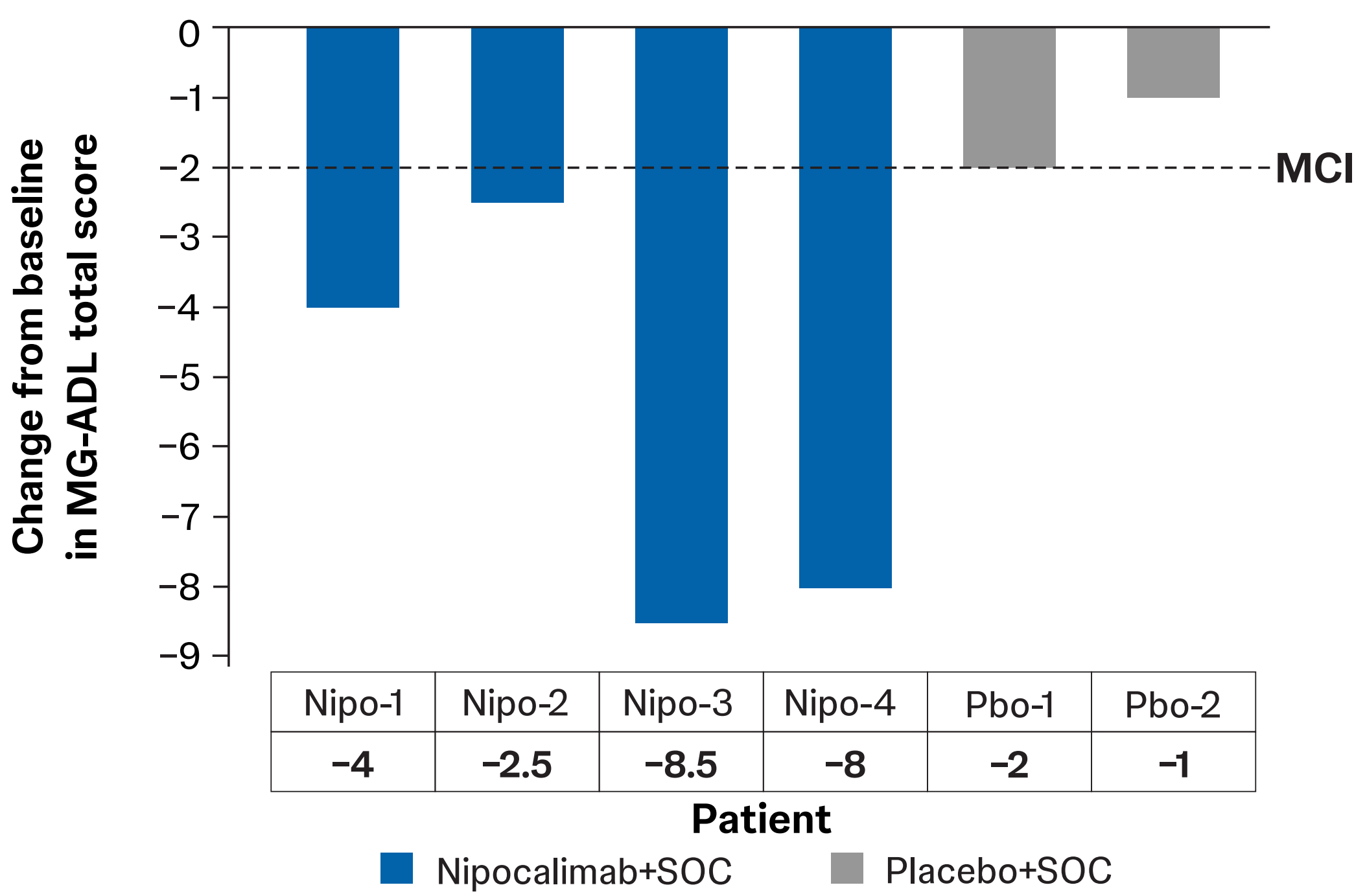
- At week 24, mean (SD) MG-ADL total scores were: nipocalimab+SOC: 3.8 (2.06), n=4; placebo+SOC: 10.0 (2.83), n=2
- At week 24, mean (SD) reductions in MG-ADL total scores were greater in the nipocalimab+SOC group vs placebo+SOC group (Figure 2)
 - Nipocalimab+SOC: -5.8 (2.96), n=4; placebo+SOC: -1.5 (0.71), n=2
- At week 24, all tested nipocalimab-treated patients achieved MCI (vs 1/2 [50%] placebo-treated patient) (Figure 3)

Figure 2. Mean change baseline to week 24 in MG-ADL total score



MG-ADL=Myasthenia Gravis Activities of Daily Living, SOC=standard-of-care.

Figure 3. Patient-level change from baseline in MG-ADL total score at week 24



Note: Value for 1 nipocalimab-treated patient was not available at week 24. MCI=meaningful clinical improvement, MG-ADL=Myasthenia Gravis Activities of Daily Living, SOC=standard-of-care.

Safety

- Safety findings in this subgroup were consistent with those in the overall Vivacity-MG3 population
- TEAEs were reported in 60% (3/5) of patients in the nipocalimab+SOC arm and 100% (2/2) of patients in the placebo+SOC arm (Table 2)
- No deaths or permanent treatment discontinuations due to TEAEs were reported in the nipocalimab group and no new safety signals were identified

Table 2. Safety Summary (Seropositive efficacy analysis set; AChR+ by CBA)

	Nipocalimab+SOC (n=5)	Placebo+SOC (n=2)
Any TEAE	3 (60.0)	2 (100.0)
Related TEAE*	1 (20.0)	0
TEAEs leading to death*	0	0
Any serious TEAEs	0	1 (50.0)
Related serious TEAEs	0	0
TEAE leading to temporary discontinuation of study drug*	0	1 (50.0)
TEAE leading to permanent discontinuation of study drug*	0	0
Any infection or infestation*	1 (20.0)	1 (50.0)

*A TEAE is assessed by the investigator as related to study agent; *TEAEs leading to death are based on TEAE outcome of fatal; *TEAEs leading to temporary discontinuation of study treatment is based on TEAE action taken of drug interrupted; *TEAEs leading to permanent discontinuation of study treatment is based on TEAE action taken of drug withdrawn; *Infections and infestations are based on system organ class. AChR=anti-acetylcholine receptor, CBA=cell-based assays, SOC=standard-of-care, TEAE=treatment-emergent adverse event.

Key Takeaways

- In the Vivacity-MG3 study, a total of 7 RIPA-seronegative patients (5 nipocalimab, 2 placebo) were subsequently identified as anti-AChR positive using live-CBA
- Nipocalimab+SOC demonstrated meaningful clinical improvement in all 4 patients who had efficacy data
- These findings support the value of sensitive antibody detection methods to improve patient identification and access to targeted therapies for gMG
- Interpretation of these findings are limited by the small sample size of the CBA-positive subgroup of patients with gMG