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

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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.**

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-AChR or anti-MuSK antibody-positive adult and adolescent (≥12 years of age) patients.[3,4]
- Although most patients are positive for anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (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 therapies.[6]
- Emerging evidence suggests that live cell-based assays (CBA) can identify low-affinity or conformation-dependent anti-AChR autoantibodies not detected by RIPA.[7]
- 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 study.[8]
- 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

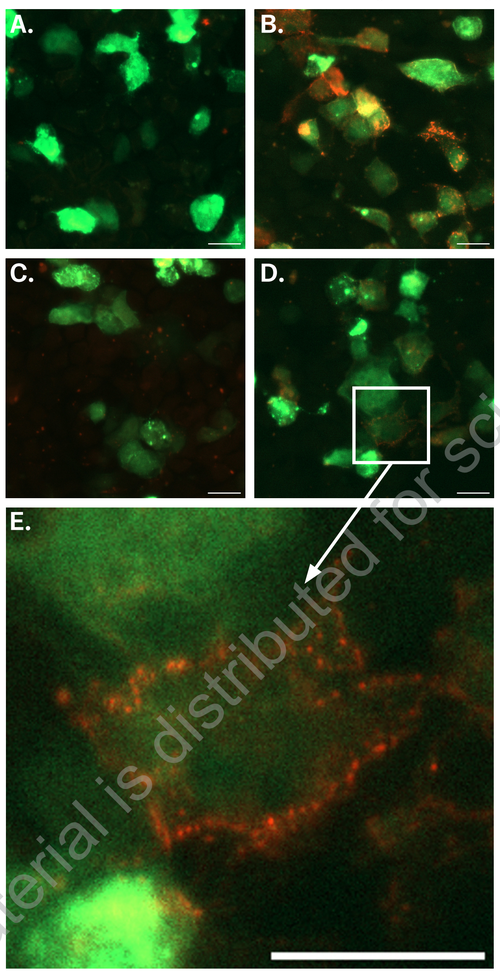
- Mean changes from baseline in MG-ADL and QMG scores were analyzed using Mixed Models for Repeated Measures.
- The percentage of patients achieving MCI at week 24 compared to baseline was analyzed by the Cochran-Mantel-Haenszel test.

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)

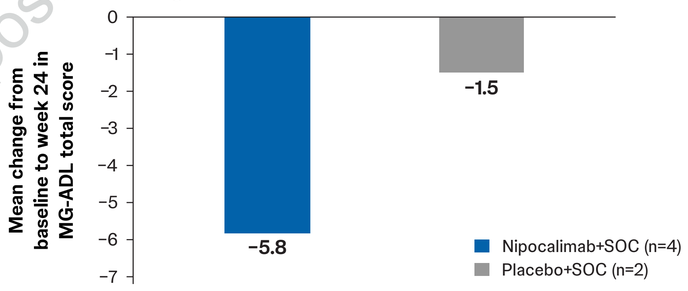
	Nipocalimab+SOC (n=5)	Placebo+SOC (n=2)
Age, median (range), years	51.0 (37–65)	64.5 (51–78)
Female, n (%)	4 (80.0)	1 (50.0)
Duration of MG, mean (SD), years	8.0 (7.57)	4.5 (2.12)
Age at onset, median (range), years	43.5 (34–58)	60.0 (45–75)
Baseline MG-ADL total score, mean (SD)	8.5 (2.72)	11.5 (2.12)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

[a]*By radioimmunoprecipitation assay (RIPA).* ***MG****=myasthenia gravis,* ***MG-ADL****=Myasthenia Gravis-Activities of Daily Living,* ***QMG****=Quantitative Myasthenia Gravis,* ***SD****=standard deviation,* ***SOC****=standard-of-care.*

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

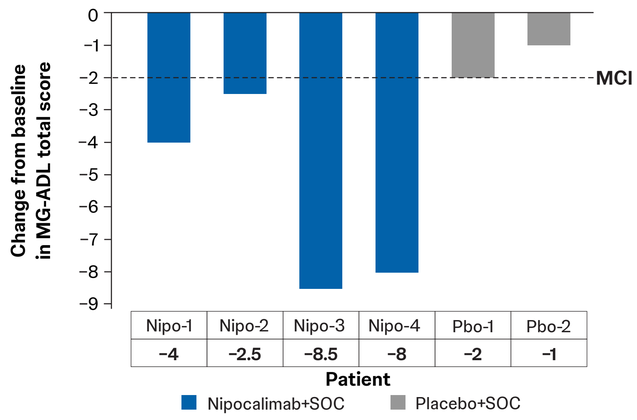
- At week 24, mean (SD) MG-ADL total scores were: nipocalimab+SOC: 3.8 (2.06), n=4; placebo+SOC: 10.0 (2.83), n=2
- At week 24, mean (SD) reductions in MG-ADL total scores were greater in the nipocalimab+SOC group vs placebo+SOC group (**Figure 2**)
  - Nipocalimab+SOC: −5.8 (2.96) , n=4; placebo+SOC: −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 in MG-ADL total score,* ***SOC****=standard-of-care.*

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

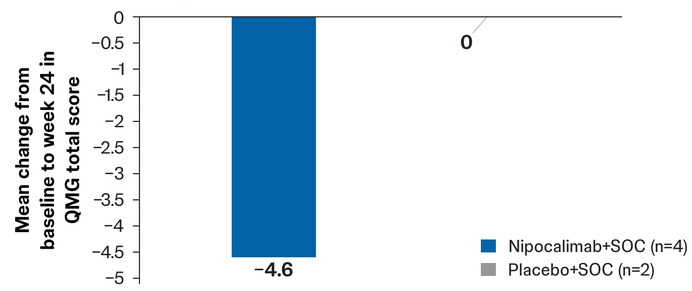


Note: Value for 1 nipocalimab-treated patient was not available at week 24.
MCI*=meaningful clinical improvement,* ***MG-ADL****=Myasthenia Gravis Activities of Daily Living,* ***SOC****=standard-of-care.*

QMG: Mean change from baseline, MCI, and SCI

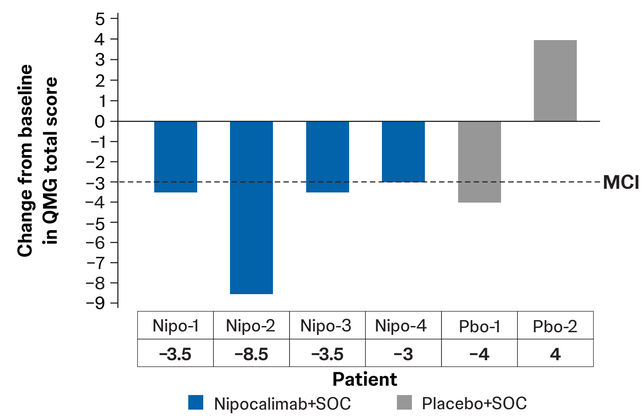
- At week 24, mean (SD) QMG total scores were: nipocalimab+SOC: 10.3 (5.19), n=4; placebo+SOC: 15.0 (9.90), n=2
- At week 24, mean (SD) reductions in QMG total scores were greater in the nipocalimab+SOC group vs placebo+SOC group (**Figure 4**)
  - Nipocalimab+SOC: −4.6 (2.59), n=4; placebo+SOC: 0.0 (5.66), n=2
- At week 24, all tested nipocalimab-treated patients achieved MCI (vs 1/2 [50%] placebo-treated patient) (**Figure 5**).

Figure 4. Mean change baseline to week 24 in QMG total score



QMG*=Quantitative Myasthenia Gravis,* ***SOC****=standard-of-care.*

Figure 5. Patient-level change from baseline in QMG total score at week 24



Note: Value for 1 nipocalimab-treated patient was not available at week 24.
MCI*=meaningful clinical improvement,* ***QMG****=Quantitative Myasthenia Gravis,* ***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[a]	1 (20.0)	0
TEAEs leading to death[b]	0	0
Any serious TEAEs	0	1 (50.0)
Related serious TEAEs	0	0
TEAE leading to temporary discontinuation of study drug[c]	0	1 (50.0)
TEAE leading to permanent discontinuation of study drug[d]	0	0
Any infection or infestation[e]	1 (20.0)	1 (50.0)

[a]*A TEAE is assessed by the investigator as related to study agent;* [b]*TEAEs leading to death are based on TEAE outcome of fatal;* [c]*TEAEs leading to temporary discontinuation of study treatment is based on TEAE action taken of drug interrupted;* [d]*TEAEs leading to permanent discontinuation of study treatment is based on TEAE action taken of drug withdrawn;* [e]*Infections and infestations are based on system organ class.* ***SOC****=standard-of-care,* ***TEAE****=treatment-emergent adverse event.*

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