Efficacy and Safety of Nipocalimab in Patients with Generalized Myasthenia Gravis - Top Line Results from the Double-Blind, Placebo-Controlled, Randomized Phase 3 Vivacity-MG3 Study

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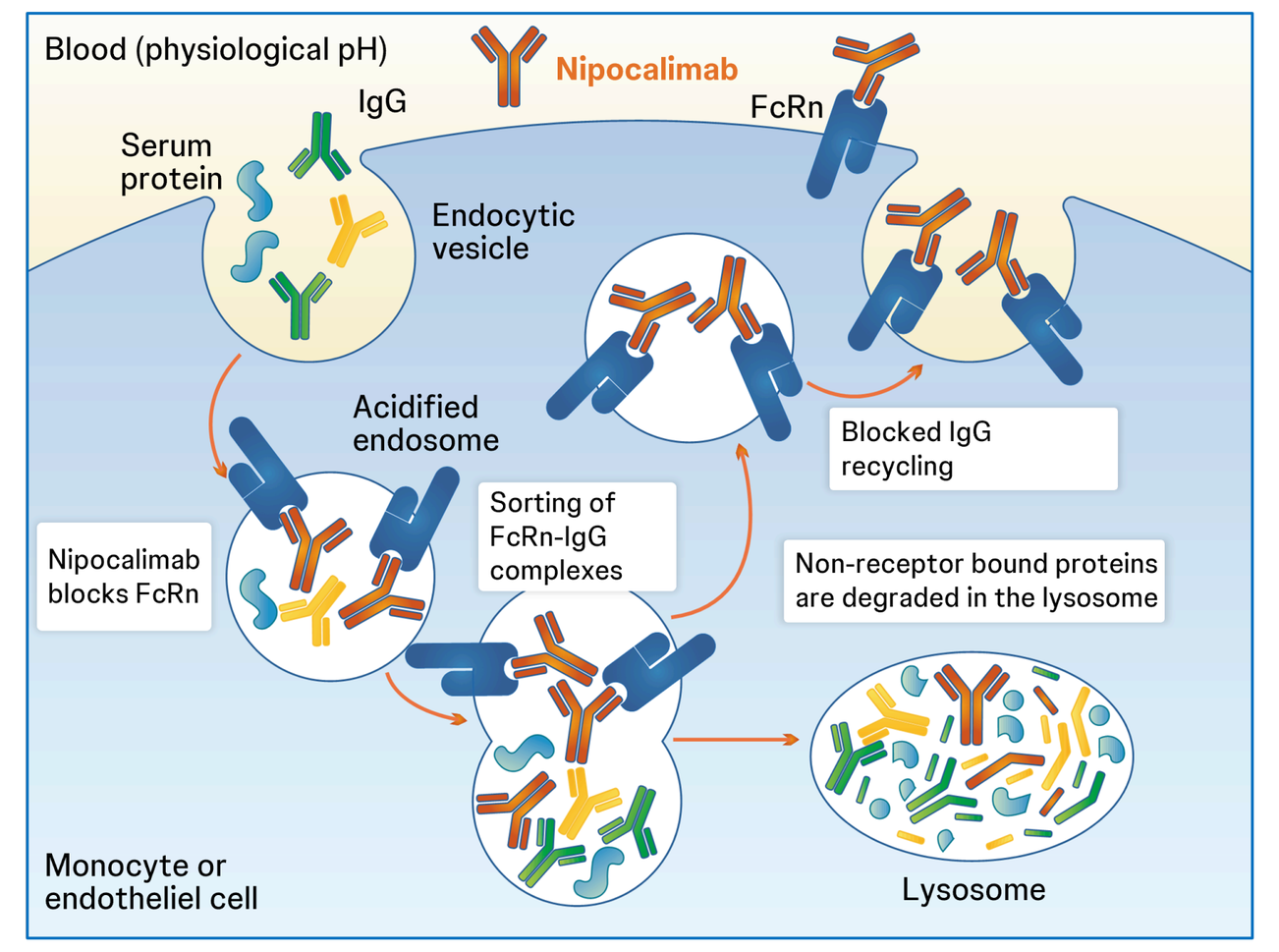
Introduction

- Nipocalimab is an investigational monoclonal antibody, designed to bind with high affinity and selectively block anti-neonatal Fc receptor(FcRn) to reduce levels of circulating immunoglobulin G (IgG) antibodies, while preserving immune function without causing broad immunosuppression[1,2]
- Nipocalimab may ameliorate generalized myasthenia gravis (gMG) disease manifestations by selectively targeting FcRn IgG recycling and lowering IgG, including pathogenic auoantibodies in gMG[3]


Blood (physiological pH)
Nipocalimab
IgG
FcRn
Serum protein
Endocytic vesicle
Acidified endosome
Sorting of FcRn-IgG complexes
Blocked IgG recycling
Nipocalimab blocks FcRn
Non-receptor bound proteins are degraded in the lysosome
Monocyte or endothelial cell
Lysosome

FcRn=Anti-neonatal Fc receptor; gMG=Generalized myasthenia gravis; IgG=Immunoglobulin G.

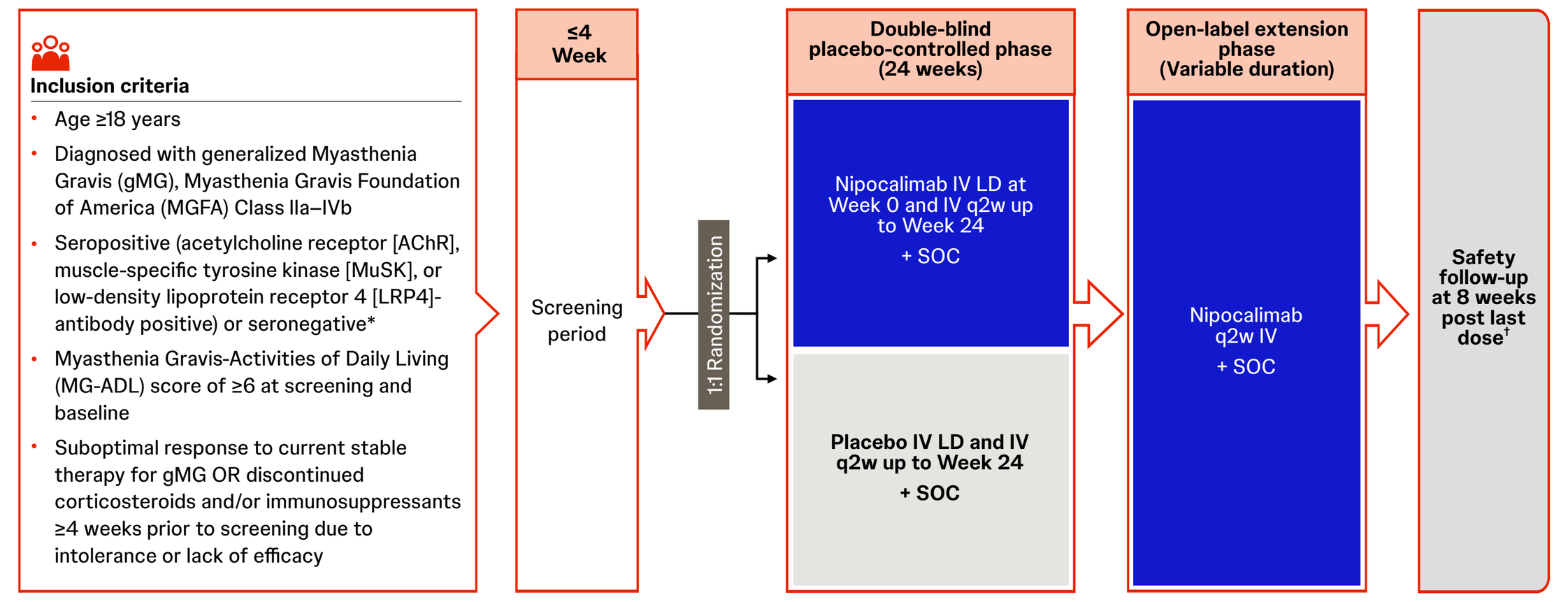
Objective

To assess the efficacy and safety of nipocalimab in patients with gMG in the Phase 3 Vivacity-MG3

Methods

Phase 3 Vivacity-MG3 (NCT04951622): Study Design

- Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of nipocalimab in adults with gMG[4,5]


Inclusion criteria
Age ≥18 years
Diagnosed with generalized Myasthenia Gravis (gMG), Myasthenia Gravis Foundation of America (MGFA) Class IIa–IVb
Seropositive (acetylcholine receptor [AChR], muscle-specific tyrosine kinase [MuSK], or low-density lipoprotein receptor 4 [LRP4]-antibody positive) or seronegative*
Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of ≥6 at screening and baseline
Suboptimal response to current stable therapy for gMG OR discontinued corticosteroids and/or immunosuppressants ≥4 weeks prior to screening due to intolerance or lack of efficacy
≤4 Week
Screening period
1:1 Randomization
Double-blind placebo-controlled phase (24 weeks)
Nipocalimab IV LD at Week 0 and IV q2w up to Week 24 + SOC
Placebo IV LD and IV q2w up to Week 24 + SOC
Open-label extension phase (Variable duration)
Nipocalimab q2w IV + SOC
Safety follow-up at 8 weeks post last dose†

Please visit ClinicalTrials.gov for a complete list of eligibility criteria. *In all countries seronegative except France. †Patients who withdrew or discontinued after receiving any amount of study intervention were required to complete a safety follow-up visit 8 weeks after the last infusion. AChR=Acetylcholine receptor; gMG=Generalized myasthenia gravis; IV=Intravenous; LD=Loading dose; Q2W=Every 2 weeks.

- Safety analysis population: All randomized patients who received ≥1 dose (partial or complete) of any study intervention in the double-blind phase
- Efficacy analysis population: All patients from the safety analysis dataset who were antibody positive for a gMG-related pathogenic antibody (anti-AChR, anti-MuSK, or anti-LRP4)

Results

Table 1: Treatment Disposition

	Nipocalimab + SOC 30 mg/kg LD + 15 mg/kg q2w n (%)	Placebo + SOC n (%)
Analysis set: full	98	98
Completed study intervention	87 (88.8)	82 (83.7)
Discontinued study intervention	11 (11.2)	16 (16.3)
Reason for discontinuation		
Adverse event	4 (4.1)	7 (7.1)
Adverse event: COVID-19 related	0	1 (1.0)
Protocol deviation	2 (2.0)	2 (2.0)
Death†	1 (1.0)	2 (2.0)
Disease relapse	1 (1.0)	0
Progressive disease	1 (1.0)	1 (1.0)
Withdrawal by patient	1 (1.0)	0
Lack of efficacy	0	2 (2.0)
Randomized by mistake to study treatment	0	1 (1.0)
Patient refused further study treatment	0	1 (1.0)
Other‡	1 (1.0)	0

†Number and cause of death in nipocalimab + SOC arm: 1 (Myasthenia Gravis); placebo + SOC arm: 2 (myocardial infarction; cardiac arrest). All deaths in both arms were assessed by PI as not related to study drug. ‡Other: Participant withdrew for personal reason: participant felt they had improved on treatment and did not need to be in the study anymore. COVID-19=Coronavirus disease 2019; LD=Loading dose; q2w=Every 2 weeks; SOC=Standard of care.

Table 2: Baseline Disease Characteristics

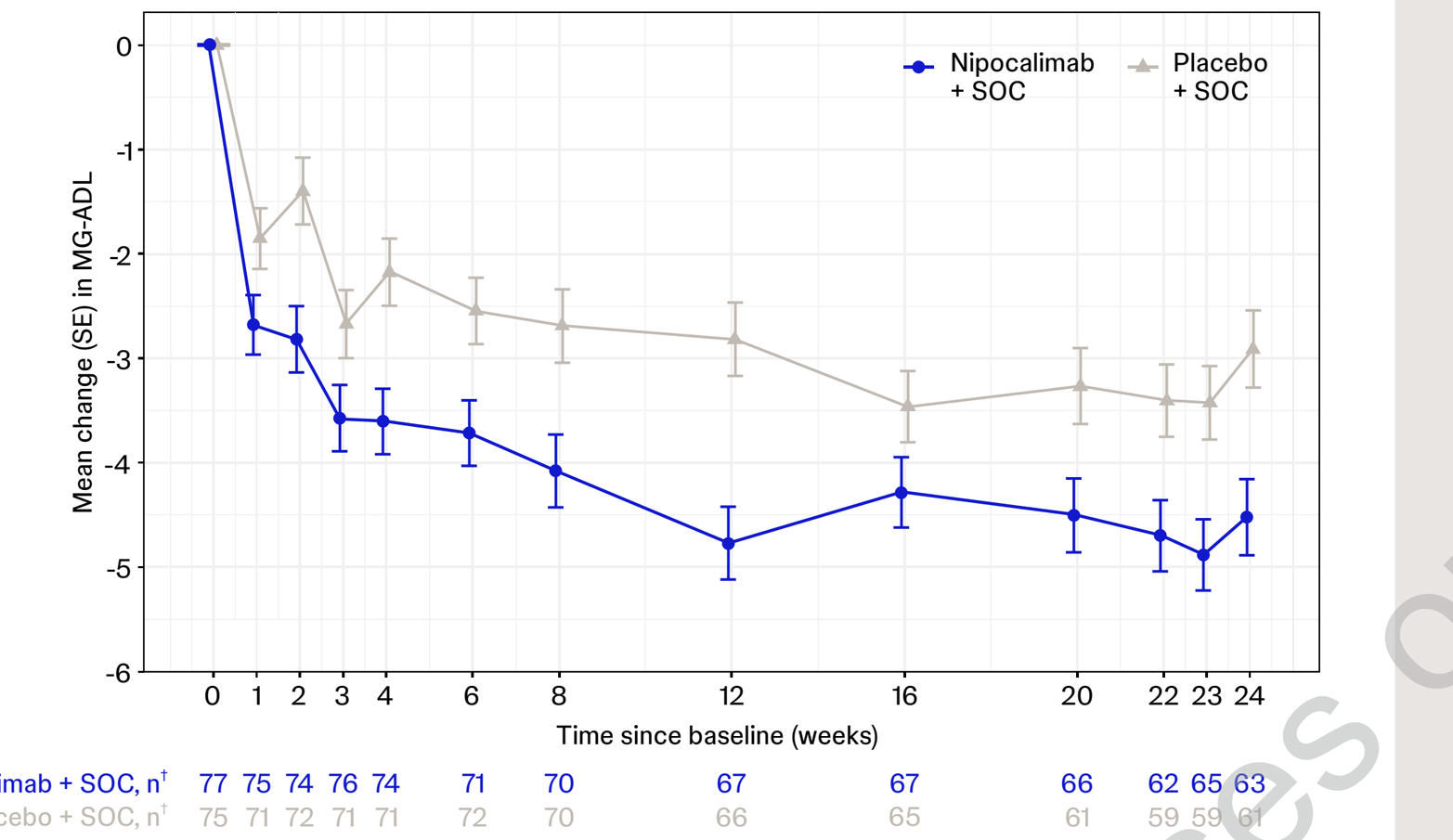
	Nipocalimab + SOC 30 mg/kg LD + 15 mg/kg q2w	Placebo + SOC	Total
Analysis set: primary efficacy*	77	76	153
Demographics			
Age, years, mean (SD)	52.5 (15.7)	52.3 (16.4)	52.4 (16.0)
Race, n (%)			
White	49 (63.6)	47 (61.8)	96 (62.7)
Asian	24 (31.2)	25 (32.9)	49 (32.0)
Sex, Female, n (%)	50 (64.9)	42 (55.3)	92 (60.1)
MG-ADL total score, mean (SD)	9.4 (2.7)	9.0 (2.0)	9.2 (2.4)
QMG total score, mean (SD)	15.1 (4.8)	15.7 (4.9)	15.4 (4.9)
Duration of gMG, years, mean (SD)	6.9 (7.4)	8.9 (8.1)	7.9 (7.8)
Age at onset of gMG, years, mean (SD)	45.1 (17.3)	42.6 (18.7)	43.8 (18.0)
Autoantibody status at screening			
Seropositive	77 (100.0)	76 (100.0)	153 (100.0)
Anti-AChR+, n (%)	63 (81.8)	71 (93.4)	134 (87.6)
Anti-MuSK+, n (%)	12 (15.6)	4 (5.3)	16 (10.5)
Anti-LRP4+, n (%)	2 (2.6)	1 (1.3)	3 (2.0)

*Primary efficacy analysis dataset included patients from the safety analysis dataset who were antibody positive for a generalised Myasthenia Gravis-related pathogenic antibody (anti-AChR, anti-MuSK, or anti-LRP4). AChR=Acetylcholine receptor; LD=Loading dose; LRP4=Low-density lipoprotein receptor 4; MuSK=Muscle-specific tyrosine kinase; q2w=Every 2 weeks; SOC=Standard of care.

Primary Efficacy Endpoint: Myasthenia Gravis Activities of Daily Living (MG-ADL)

- Primary endpoint was the mean change in MG-ADL (LS mean) from baseline to the average over weeks 22, 23, and 24 in seropositive (anti-AChR+, anti-MuSK+, anti-LRP4+) patients with gMG
- Nipocalimab + SOC demonstrated a statistically significant MG-ADL improvement compared to placebo + SOC: –4.7 (SE, 0.329) vs –3.25 (SE, 0.335); difference in LS mean: –1.45 (SE, 0.470), p=0.002 **(Figure 1)**

Figure 1: Mean change in MG-ADL (SE) from baseline

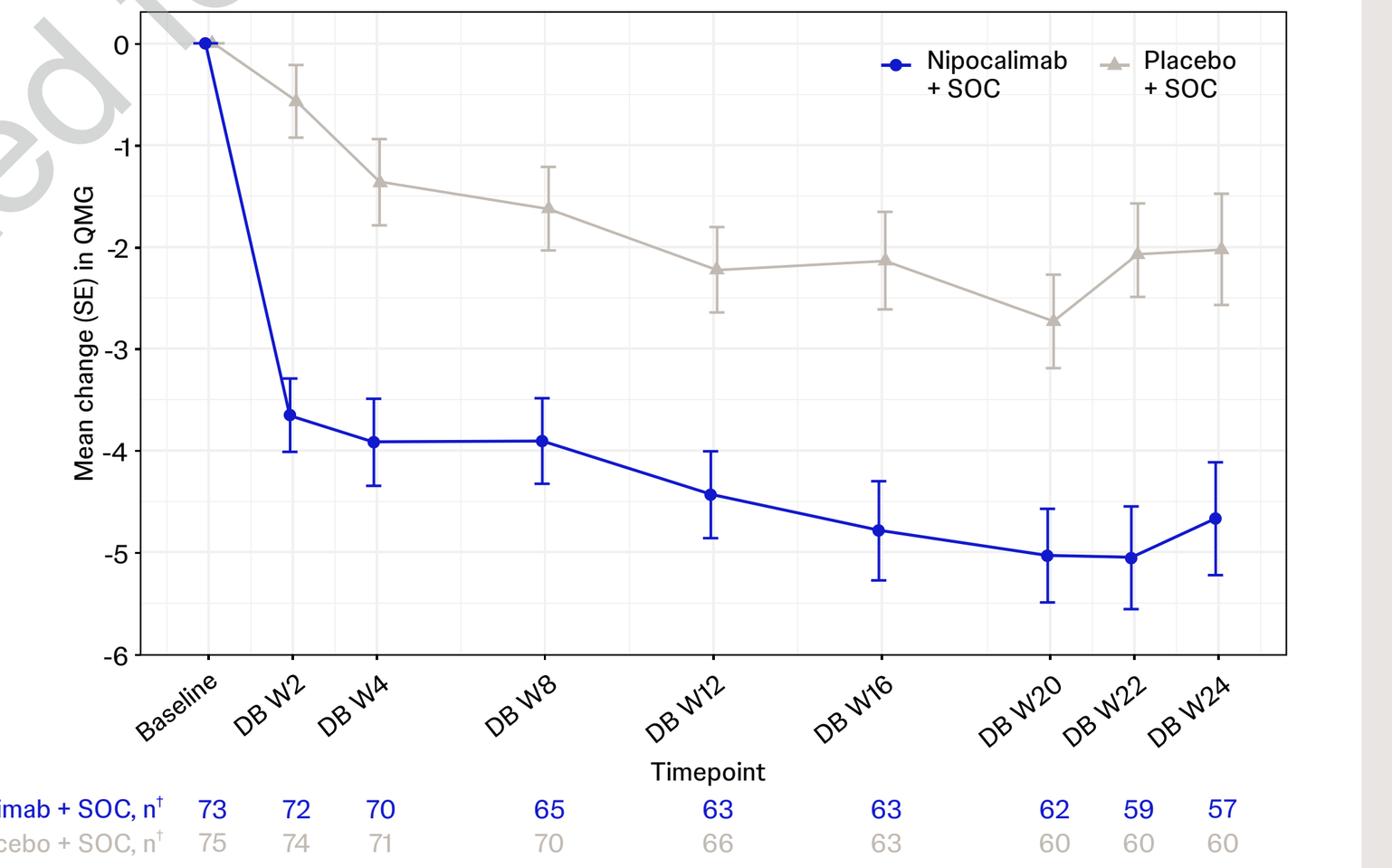


†Note: Number of placebo patients 75 and not 76, as one participant who was randomized and treated but had only a baseline assessment and no post-baseline assessment. Therefore, the subject had no non-missing change and is not counted in summaries of change, like this figure. AChR=Acetylcholine receptor; ADA=Anti-drug antibodies; gMG=Generalized myasthenia gravis; LRP4=Low-density lipoprotein receptor 4; LS=Least squares; MG-ADL=MG Activities of Daily Living; PK=Pharmacokinetics; SE=Standard error; SOC=Standard of care.

Key Secondary Endpoint: Quantitative Myasthenia Gravis (QMG)

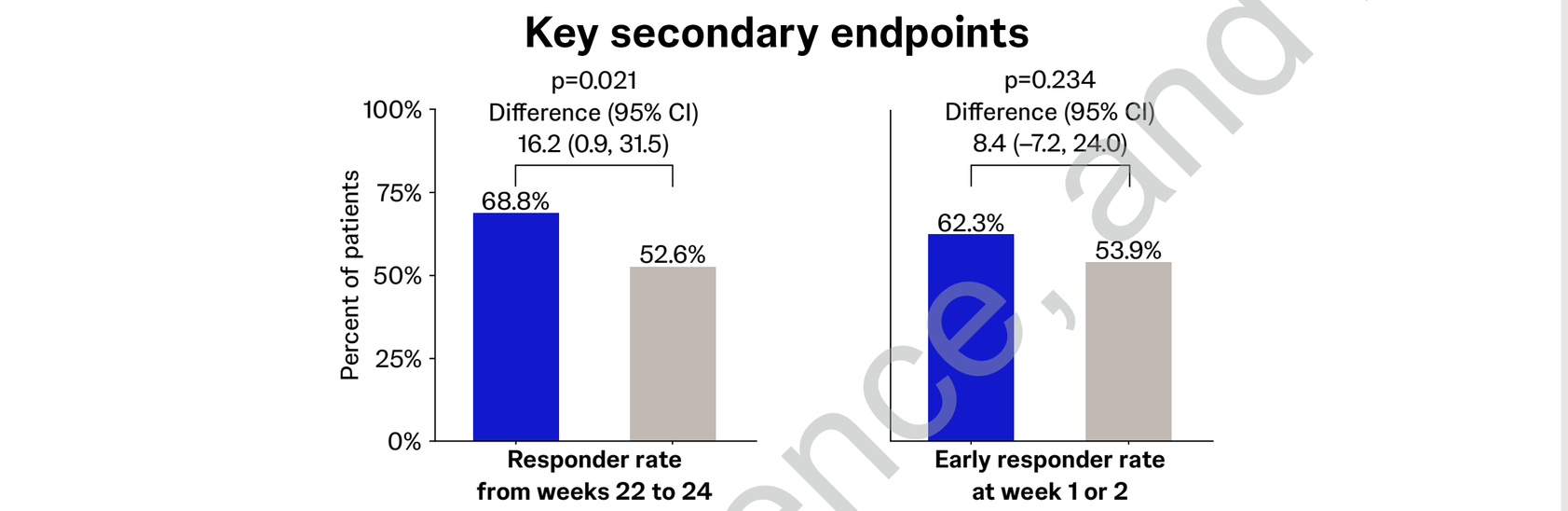
- Key secondary endpoint was the mean change in QMG (LS mean) from baseline to the average over weeks 22, 23, and 24 in seropositive (anti-AChR+, anti-MuSK+, anti-LRP4+) patients with gMG
- Nipocalimab + SOC demonstrated a statistically significant QMG improvement compared to placebo + SOC: –4.86 (SE, 0.504) vs –2.05 (0.499); difference in LS mean: –2.81 (SE, 0.710), p<0.001 **(Figure 2)**

Figure 2: Mean change (SE) in QMG from baseline

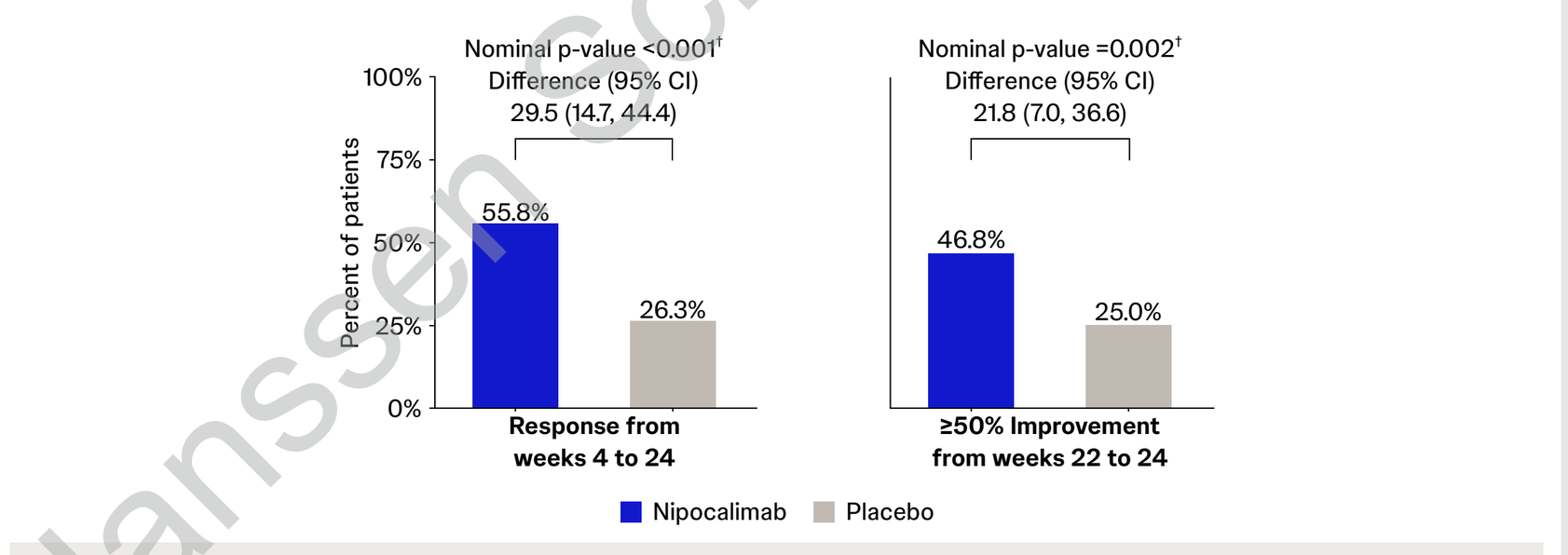


†Note: Number of nipocalimab and placebo patients on x-axis reflect numbers who were randomized and had a post-baseline assessment, to include in summaries of change, like this figure. AChR=Acetylcholine receptor; ADA=Anti-drug antibodies; DB=Double blind; gMG=Generalized myasthenia gravis; LRP4=Low-density lipoprotein receptor 4; LS=Least squares; PK=Pharmacokinetics; QMG=Quantitative Myasthenia Gravis; SE=Standard error; SOC=Standard of care; W=Week.

MG-ADL Responder Endpoints



Responder rate: % of patients with ≥2-point improvement on average change of MG-ADL over weeks 22, 23 and 24. Early responder rate: % of patients with ≥2-point improvement on MG-ADL at Week 1 or Week 2. P-values from CMH test controlling for baseline MG-ADL total score (<9, ≥9), autoantibody status, and region.



†Based on the predefined statistical testing hierarchy to control for multiplicity, this endpoint cannot be formally tested since a preceding comparison was not statistically significant at 2-sided alpha=0.05. Nominal p-value is shown

Response from Weeks 4 through 24: At least 2-point improvement from Week 4 to Week 24 with no more than 2 non-consecutive excursions from Week 6 to Week 23. 50% symptom improvement: % of patients with ≥50% improvement on average change of MG-ADL over weeks 22, 23 and 24. P-values from CMH test controlling for baseline MG-ADL total score (<9, ≥9), autoantibody status, and region. NA: Test not performed because a preceding comparison was not statistically significant at 2-sided alpha=0.05. P values for endpoints that were not multiplicity controlled are nominal. CMH=Cochran-Mantel-Haenszel; DB=Double blind; MG-ADL=MG Activities of Daily Living; NA=Not applicable; PBO=Placebo; SOC=Standard of care.

- Approximately one-third (31.2%, 24/77) of patients on nipocalimab + SOC achieved minimal symptom expression (MG-ADL total score of 0 or 1, pre-specified endpoint) versus 13.2% (10/76) on placebo + SOC at any time during the DB phase; 10.4% of nipocalimab + SOC treated patients achieved minimal symptom expression at ≥75% of all time points during the DB phase, versus 1.3% of placebo + SOC treated patients

Subgroup Analysis

- The primary endpoint population was patients with seropositive gMG including anti-AChR+, anti-MuSK+, and anti-LRP4+
- Subgroup analysis showed consistent efficacy results in anti-AChR+ and anti-MuSK+ populations, while no statistically significant difference was seen in the seronegative population **(Table 3)**

Table 3: MG-ADL Total Score: Analysis of Average Change From Baseline Over Weeks 22, 23, and 24 by Seropositive Subgroups*, and Seronegative

	Nipocalimab + SOC		Placebo + SOC		
Subgroup	N	LS Mean (95% CI)	N	LS Mean (95% CI)	Between-group difference (95% CI)
Anti-AChR+	63	–5.06 (–5.78, –4.33)	70	–3.44 (–4.13, –2.74)	–1.62 (–2.62, –0.62)
Anti-MuSK+	12	–3.79 (–5.47, –2.10)	4	–0.25 (–3.02, 2.53)	–3.54 (–6.78, –0.30)
Seronegative	20	–3.3 (–4.62, –1.99)	22	–3.23 (–4.46, –1.99)	–0.08 (–1.87, 1.71)

*Seropositive gMG: anti-AChR+, anti-MuSK+, anti-LRP4+. Note: Results for the anti-LRP4+ subgroup are not displayed because there were <4 anti-LPR4+ subjects in both treatment groups. LS Mean estimates and between-group differences are estimated from an MMRM with factors for treatment group, autoantibody (seropositive/seronegative), region, visit, treatment-by-visit interaction, treatment-by-autoantibody interaction, and treatment-by-visit-by-autoantibody and baseline MG-ADL as a covariate. AChR=Acetylcholine receptor; CI=Confidence interval; gMG=Generalized myasthenia gravis; LRP4=Low-density lipoprotein receptor 4; LS=Least squares; MG-ADL=MG Activities of Daily Living; MMRM=Mixed-model repeated measures; MuSK=Muscle-specific tyrosine kinase; SOC=Standard of care.

PD Biomarker: Total and Pathogenic IgG Reduction from Baseline

- The median pre-dose reduction from baseline in total serum IgG was 69% at Week 24 in the nipocalimab + SOC group
  - Similar to IgG, reductions were also observed in anti-AChR and anti-MuSK antibodies

Figure 3: Percent Change in Total IgG and Anti-AChR Antibodies from Baseline to Week 24

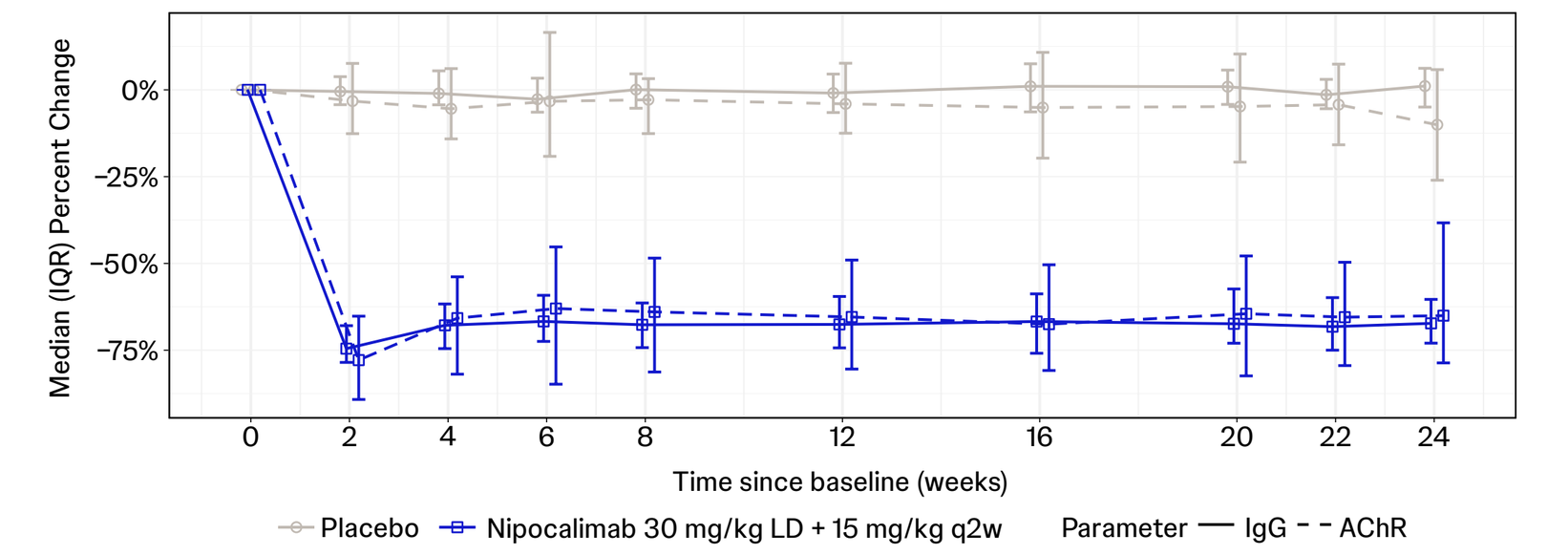


Table 4: Percent Change in Anti-AChR and Anti-MuSK from Baseline to Week 24

	Nipocalimab + SOC		Placebo + SOC	
Pathogenic IgG	N	Median (IQR)	N	Median (IQR)
Anti-AChR	46	–65.1% (–78.7, –38.4)	50	–10.1% (–26.0, +5.8)
Anti-MuSK	9	–38.8% (–49.4, +4.0)	5	–4.4% (–23.2, –3.9)

AChR=Acetylcholine receptor; IgG=Immunoglobulin G; IQR-Interquartile range; LD=Loading dose; MuSK=Muscle-specific tyrosine kinase. PD=Pharmacodynamics; q2w=Every 2 weeks; SOC=Standard of care.

- Median pre-dose reduction in antibody titers was ~7-fold greater with nipocalimab than with placebo (–65.1% vs –10.1%) for anti-AChR, and ~9-fold greater for anti-MuSK (–38.8% vs –4.4%)

Safety and Tolerability

Table 5: Overall Adverse Events

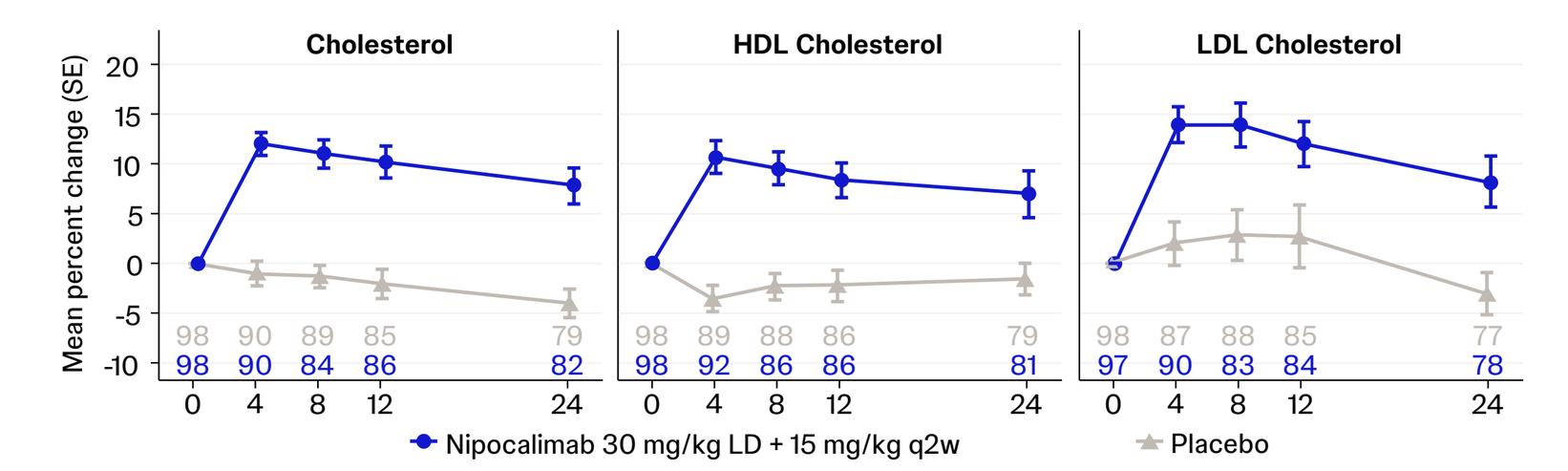
	Nipocalimab + SOC (n=98) n (%)	Placebo + SOC (n=98) n (%)
AE	82 (83.7)	82 (83.7)
Related AE	28 (28.6)	28 (28.6)
Serious AE	9 (9.2)	14 (14.3)
Related serious AE	1 (1.0)	1 (1.0)
AE leading to death*	1 (1.0)	2 (2.0)
Most common AEs (≥10% with nipocalimab)		
Headache	14 (14.3)	17 (17.3)
Muscle spasms	12 (12.2)	3 (3.1)
Myasthenia gravis worsening	12 (12.2)	12 (12.2)
COVID-19	15 (15.3)	10 (10.2)
Peripheral edema	11 (11.2)	0 (0.0)
AE of special or clinical interest		
Severe infection or infection requiring invasive treatment	3 (3.1)	4 (4.1)
Hypoalbuminemia (<2 g/dL)	0	0
Infusion-related reactions	10 (10.2)	11 (11.2)

Note: Top Line results may be updated as more safety data becomes available. Data are n (%). *AE leading to death: Nipocalimab + SOC: 1 (Myasthenia Gravis); Placebo + SOC: 2 (myocardial infarction; cardiac arrest); all deaths in both arms were assessed by PI as not related to study drug. Peripheral edema includes edema peripheral, edema, and peripheral swelling. AE=Adverse event; COVID-19=Coronavirus disease-19, PI=Principal investigator; SOC=Standard of care.

Lipids

- Mean LDL increase 8.3%, Mean HDL increase 7.0%; Cholesterol: HDL ratio <4 at Week 24

Figure 4: Mean Percent (SE) Change Over Time



HDL=High-density lipoprotein; LDL=Low-density lipoprotein; q2w=Every 2 weeks; SE=Standard error.

Conclusions

- Phase 3 Vivacity-MG3 is the first registrational study of an FcRn blocker to show sustained efficacy through 6 months fixed schedule dosing
- In a broad antibody-positive (anti-AChR+, anti-MuSK+, and anti-LRP4+) gMG patient population, nipocalimab demonstrated statistically significant and clinically meaningful improvement in:
  - MG-ADL mean change from baseline
  - QMG mean change from baseline
  - Percentage of responders (as measured by MG-ADL ≥2 points improvement)
- More patients achieved sustained response from Week 4 to Week 24 with nipocalimab compared to placebo
- More patients had ≥50% improvement in MG-ADL with nipocalimab compared to placebo
- Nipocalimab was generally well-tolerated in patients with gMG

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