Post-hoc Evaluation of the Clinical Effects of Nipocalimab, a New Neonatal Fragment Crystallizable Blocker, Over Time in the Vivacity-MG3 Study

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Introduction

- Generalized myasthenia gravis (gMG) is a rare autoimmune disease resulting from immunoglobulin G (IgG)-mediated disruption of cholinergic neuromuscular transmission.[1,2]
- gMG is marked by chronic weakness of the bulbar muscles, extremities, or axial muscles, resulting in debilitating symptoms such as fatigue and impaired mobility that significantly impact patients' daily activities and health-related quality of life.[3]
- While advanced therapies such as targeted immunotherapies are now available, there remains an unmet need for effective gMG treatment to maintain sustained control of disease activity and minimize symptoms.[4]
- The neonatal Fc receptor (FcRn) extends the half-life of serum IgG by preventing IgG clearance via lysosomal degradation; targeted inhibition of FcRn-IgG binding accelerates IgG clearance, potentially benefiting patients with gMG.[4,5]
- Nipocalimab, a fully human anti-FcRn monoclonal antibody that inhibits FcRn-IgG binding, demonstrated rapid, substantial, and sustained efficacy in the 24-week phase 3 Vivacity-MG3 (NCT04951622) study in participants with gMG[4,6,7]

Objective

- To evaluate disease control over time as measured using MG Activities of Daily Living (MG-ADL) in the Vivacity-MG3 study population

Methods

- In the Vivacity-MG3 study (NCT04951622), participants with a suboptimal response to standard-of-care (SOC)* treatment were randomly assigned (1:1) to receive either placebo or nipocalimab administered intravenously every two weeks for 24 weeks.
- The MG-ADL scale, a clinician-reported outcome measure, was used to assess participants' MG symptoms and functional activities. MG-ADL scores range from 0 to 24, with higher scores indicating greater disease severity.
- All analyses were conducted on the primary efficacy analysis set, which included all randomized, seropositive (positive for anti-AChR, anti-MuSK, and anti-LRP4 antibodies) participants who received at least one dose of the study intervention.
- Changes in MG-ADL scores from baseline over time were evaluated using a mixed-effects model for repeated measures (MMRM), with treatment group, randomization factors, week, and treatment-by-week interaction as factors.
  - The baseline MG-ADL score was included as a covariate.
- The proportion of participants achieving a meaningful within-patient change, defined as a ≥2-point improvement[8] (minimal clinically important [MCI] improvement) and a ≥3-point improvement (substantial improvement) in MG-ADL total scores at weeks 22, 23, and 24, were reported.
  - Differences between treatment groups in achieving MCI and clinically substantial improvements were assessed using unadjusted odds ratios (ORs) and 95% confidence intervals (CIs).
- Minimal symptom expression (MSE) was defined as an MG-ADL score of 0 or 1.
- Additionally, the proportion of participants achieving sustained MCI, sustained substantial improvement, and sustained MSE, were presented.
  - Differences between treatment groups were examined using ORs and 95% CIs.
- The median percentage of time in the study during which the participants maintained MCI, substantial improvement, and MSE were compared between groups using the Wilcoxon rank-sum test.

*Most participants were on concomitant stable gMG therapy with an anticholinesterase either alone (placebo 14.5%, nipocalimab 23.4%), an anticholinesterase in combination with a corticosteroid (placebo 26.2%, nipocalimab 20.8%), or a combination of an anticholinesterase, a corticosteroid, and 1 immunosuppressant (placebo 34.2%, nipocalimab 29.9%)

Results

- The baseline demographic and disease characteristics were generally balanced between the treatment groups.

Table 1 (A): Demographics

	Nipocalimab 30 mg/kg LD + 15 mg/kg q2w + SOC	Placebo + SOC	Total
Analysis set: primary efficacy*	77	76	153
Age, years			
Mean (SD)	52.5 (15.66)	52.3 (16.37)	52.4 (15.97)
Median (range)	53.0 (20–81)	51.5 (20–81)	52.0 (20–81)
Sex, n (%)			
Female	50 (64.9)	42 (55.3)	92 (60.1)
Male	27 (35.1)	34 (44.7)	61 (39.9)
Race, n (%)			
American Indian or Alaska Native	1 (1.3)	0	1 (0.7)
Asian	24 (31.2)	25 (32.9)	49 (32.0)
Black or African American	1 (1.3)	1 (1.3)	2 (1.3)
White	49 (63.6)	47 (61.8)	96 (62.7)
Not reported	2 (2.6)	3 (3.9)	5 (3.3)

*Primary efficacy analysis dataset included participants 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-related protein 4; MuSK=Muscle-specific kinase; q2w=Every 2 weeks; SD=Standard deviation; SOC=Standard-of-care

Table 1 (B): Baseline disease characteristics

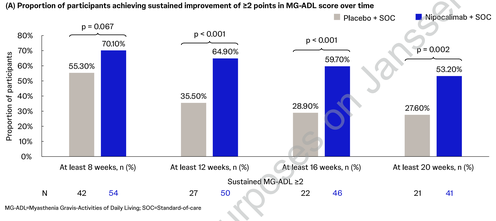
	Nipocalimab 30 mg/kg LD + 15 mg/kg q2w + SOC	Placebo + SOC	Total
MG-ADL total score			
Mean (SD)	9.4 (2.73)	9.0 (1.97)	9.2 (2.38)
Median (range)	8.5 (6–18)	9.0 (6–13)	8.5 (6–18)
≤9, n (%)	48 (62.3)	45 (59.2)	93 (60.8)
>9, n (%)	29 (37.7)	31 (40.8)	60 (39.2)
QMG total score			
Mean (SD)	15.1 (4.78)	15.7 (4.92)	15.4 (4.85)
Median (range)	14.5 (7; 28)	15.0 (5; 28)	15.0 (5; 28)
Duration of gMG (years)			
Mean (SD)	6.9 (7.44)	8.9 (8.13)	7.9 (7.83)
Median (range)	5.0 (0; 38)	7.0 (0–37)	6.0 (0–38)
Age at onset of gMG (years)			
Mean (SD)	45.1 (17.27)	42.6 (18.70)	43.8 (17.98)
Median	45.5 (4–78)	41.0 (7–80)	43.0 (4–80)
Autoantibody status at screening, n (%)			
Seropositive	77 (100.0)	76 (100.0)	153 (100.0)
Anti-AChR+	63 (81.8)	71 (93.4)	134 (87.6)
Anti-MuSK+	12 (15.6)	4 (5.3)	16 (10.5)
Anti-LRP4+	2 (2.6)	1 (1.3)	3 (2.0)
MGFA classes, n (%)			
I	1* (1.3)	0	1 (0.7)
IIa	7 (9.1)	10 (13.2)	17 (11.1)
IIb	11 (14.3)	10 (13.2)	21 (13.7)
IIIa	34 (44.2)	29 (38.2)	63 (41.2)
IIIb	17 (22.1)	15 (19.7)	32 (20.9)
IVa	3 (3.9)	10 (13.2)	13 (8.5)
IVb	4 (5.2)	2 (2.6)	6 (3.9)

*Patient with MGFA of I at baseline had MGFA of IIa at screening and MG-ADL of 8 at both screening and baseline.
AChR=Acetylcholine receptor; LD=Loading dose; LRP4=Low-density lipoprotein receptor-related protein 4; gMG=Generalized myasthenia gravis; MG-ADL=Myasthenia Gravis Activities of Daily Living scale; MGFA=Myasthenia Gravis Foundation of America; MuSK=Muscle-specific kinase; q2w=Every 2 weeks; QMG=Quantitative myasthenia gravis; SD=Standard deviation; SOC=Standard-of-care

- **Nipocalimab + SOC demonstrated statistically significant improvement in MG-ADL total score vs placebo + SOC over weeks 22, 23, and 24**
  - LS-mean change (SE): −4.7 (0.329) vs −3.25 (0.335); difference in LS-means (SE): −1.45 (0.470), p=0.002
- **The mean difference, in favor of nipocalimab + SOC, was significant as early as week 1**
  - LS-mean change (SE): −2.72 (2.979) vs −1.77 (2.426); difference in LS-means (SE): −0.82 (0.410), p=0.046
- Significantly greater proportion of participants treated with nipocalimab + SOC achieved sustained improvement over time in MG-ADL ≥2 versus placebo + SOC (**Figure 1**).
- The odds of achieving a ≥2-point improvement in MG-ADL at weeks 22, 23, and 24 were 2.49 times higher with nipocalimab + SOC compared to placebo + SOC (61.0% vs 38.7%; OR [95% CI]: 2.49 [1.29, 4.77]; p=0.009).
- Similarly, the median percentage of time in the study with ≥2-point improvement in MG-ADL total score was significantly higher for the nipocalimab + SOC group (84.5%) compared to the placebo + SOC group (39.9%), p-value=0.007.

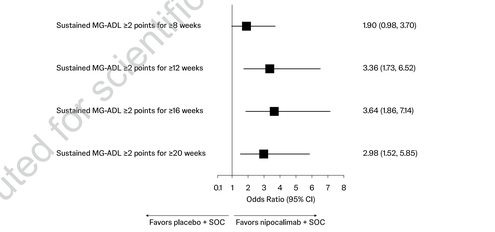
Figure 1: Participants achieving sustained improvement of ≥2 points in MG-ADL score over time

(A) Proportion of participants achieving sustained improvement of ≥2 points in MG-ADL score over time



MG-ADL=Myasthenia Gravis Activities of Daily Living; SOC=Standard-of-care

(B) Probability of achieving sustained improvement of ≥2 points in MG-ADL score

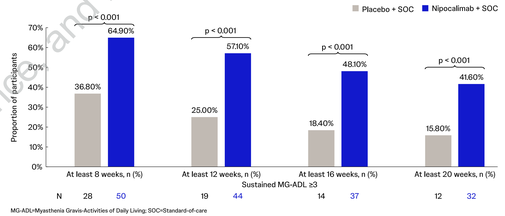


CI=Confidence interval; MG-ADL=Myasthenia Gravis Activities of Daily Living; SOC=Standard-of-care

- Significantly greater proportion of participants treated with nipocalimab + SOC achieved sustained improvement over time in MG-ADL ≥3 (substantial improvement) versus placebo + SOC (**Figure 2**).
- The odds of achieving a clinically substantial improvement in MG-ADL score, defined as a ≥3-point change at weeks 22, 23, and 24 were 2.93 times higher with nipocalimab + SOC compared to placebo + SOC (53.2% vs 28.1%; OR [95% CI]: 2.93 [1.492, 5.747]).
- Similarly, the median percentage of time with a ≥3-point improvement in MG-ADL total score was 69.6% for the nipocalimab + SOC group, compared to 20.2% for the placebo + SOC group, p-value <0.001.

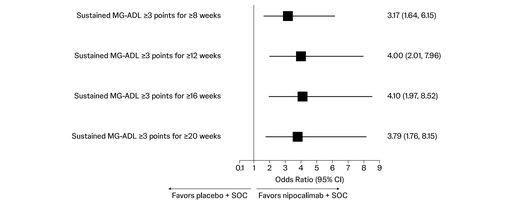
Figure 2: Participants achieving sustained substantial improvement of ≥3 points in MG-ADL total score over time

(A) Proportion of participants achieving sustained substantial improvement of ≥3 points in MG-ADL score over time



MG-ADL=Myasthenia Gravis Activities of Daily Living; SOC=Standard-of-care

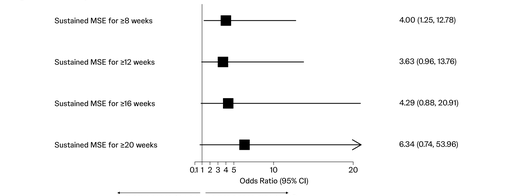
(B) Probability of achieving sustained substantial improvement of ≥3 points in MG-ADL score



CI=Confidence interval; MG-ADL=Myasthenia Gravis Activities of Daily Living; SOC=Standard-of-care

- Participants treated with nipocalimab + SOC were approximately three times more likely to achieve MSE at any point during the 24-week study compared to those receiving placebo + SOC, with an OR of 2.99 (95% CI: 1.314, 6.796) and a MSE rate of 31.2% vs 13.2%, respectively
- For the 25 participants (18 nipocalimab, 7 placebo) who reached MSE at any time during the double-blind phase, the median time with sustained MSE was approximately double for nipocalimab + SOC with 101.5 days (60.4%) vs 55 days (32.7%) for placebo + SOC

Figure 3: Participants with sustained MSE: treatment effect



CI=Confidence interval; MSE=Minimal symptom expression; SOC=Standard-of-care

Conclusions

Based on MG-ADL data from the 24-week Phase 3 Vivacity-MG3 study, the FcRn blocker nipocalimab demonstrated rapid, substantial and sustained symptom control in participants with gMG

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