Symptom Severity Assessment Using Quantitative Myasthenia Gravis Items and Domains in a 24-week, Phase 3 Study (Vivacity-MG3) of Nipocalimab in Generalized Myasthenia Gravis

Mazen M. Dimachkie,[1] Constantine Farmakidis,[1*] Kavita Gandhi,[2] Maria Ait-Tihyaty,[2¥] Ibrahim Turkoz,[3] Sheryl Pease,[2] Zia Choudhry,[4] Charlotte Gary,[5] Antoine C. El Khoury,[2] Sindhu Ramchandren[3]

[1]University of Kansas Medical Center, Kansas City, KS, USA; [2]Johnson & Johnson, Raritan, NJ, USA; [3]Johnson & Johnson, Titusville, NJ, USA; [4]Johnson & Johnson, Horsham, PA, USA; [5]Johnson & Johnson, Issy-les-Moulineaux, France

*Presenting author
¥Affiliation at the time of study

Key Takeaways

- **QMG total score changes at 24-weeks from baseline were driven by improvements in most QMG items and domains.**
- **The changes in item/domain scores generally favored nipocalimab + SOC versus PBO + SOC.**
- **The likelihood of achieving meaningful within-person improvement thresholds on QMG items and domains generally favored nipocalimab + SOC versus PBO + SOC over 24 weeks.**

Background

- Generalized myasthenia gravis (gMG) is an autoimmune neuromuscular disease characterized by fluctuating and fatigable muscle weakness that gets worse with activity and may improve with rest.[1]
- Quantitative Myasthenia Gravis (QMG) is a physician-assessed tool quantifying MG disease severity, with higher scores indicating worse disease severity.[2]
- Nipocalimab binds to neonatal Fc receptor (FcRn) and reduces the circulating levels of immunoglobulin G (IgG), including pathogenic IgG antibodies.[3]
- Nipocalimab demonstrated sustained disease control in patients with gMG, as assessed by Myasthenia Gravis-Activities of Daily Living (MG-ADL).[4]
- In the VIVACITY-MG3 study (NCT04951622), nipocalimab + standard-of-care (SOC) demonstrated statistically significant improvements in QMG total score versus placebo (PBO) + SOC over Weeks (W) 22 to 24 (between-group difference in least square [LS]-mean= −2.81; 95% confidence interval [CI]= −4.22 to −1.41; p <0.001).[4]

Objective

- **To evaluate changes in QMG total score for nipocalimab + SOC versus PBO + SOC driven by individual items, domains, or distinct muscle function groups.**

Methods

VIVACITY MG3 (NCT04951622) - Study design and treatment

- The VIVACITY-MG3 study enrolled adult participants with gMG who had an insufficient clinical response (MG-ADL score of ≥6 at baseline, and a Myasthenia Gravis Foundation of America [MGFA] Clinical Classification Class II a/b, III a/b, or IV a/b at screening) to ongoing, stable SOC.
- The study consisted of a screening period of up to 4 weeks, a 24-week double-blind PBO-controlled phase and an open-label extension phase of variable duration.
  - Participants on stable SOC treatment were randomized (1:1) to either PBO or nipocalimab 30 mg/kg loading dose, followed by 15 mg/kg administered intravenously every 2 weeks.
- Randomization was stratified by antibody status, Day 1 MG-ADL total score (≥6 to ≤9, >9), region (East Asia, United States [US], Rest of World [ROW]).

Assessments

- QMG is a 13-item, objective, physician-assessed measure of muscle strength across 4 domains scored from 0 (not affected) to 3 (severely affected) with total score range 0–39 (**Figure 1**).
  - A 1- to 2-point change on the QMG for a participant may be the difference between normal swallowing and severe choking on food.
- Thus, a meaningful within-person improvement threshold (MWPI) for an individual participant was defined for:
  - Items: Individual participant achieving ≥1-point improvement from baseline.
  - Domains: Individual participant achieving ≥2-points improvement from baseline, except for 1-item respiratory domain which was ≥1-point from baseline.

Figure 1: QMG score interpretation[a]

Domain function	Test Item	None	Mild	Moderate	Severe
Bulbar	Grade	0	1	2	3
	Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat cleaning	Severe coughing/ choking or nasal regurgitation	Cannot swallow/ test not attempted
	Speech counting from 1–50	None at 50	Dysarthria at 30–49	Dysarthria at 10–29	Dysarthria at 1–9
Respiratory	FVC, %	≥80	65–79	50–64	<50
Limb	Right arm at 90°, sec	240	90–239	10–89	0–9
	Left arm at 90°, sec	240	90–239	10–89	0–9
	Right hand grip, kg – Men	≥45	15–44	5–14	0–4
	– Women	≥30	10–29	5–9	0–4
	Left hand grip, kg – Men	≥35	15–34	5–14	0–4
	– Women	≥25	10–24	5–9	0–4
	Head lift 45°, sec	120	30–119	1–29	0
	Right leg outstretched (45°), sec	100	31–99	1–30	0
	Left leg outstretched (45°), sec	100	31–99	1–30	0
Ocular	Double vision on lateral gaze (R or L), sec	61	11–60	1–10	Spontaneous
	Ptosis	61	11–60	1–10	Spontaneous

[a]Adapted from https://studylib.net/doc/18260173/the-qmg---myasthenia-gravis-foundation-of-america.
FVC=forced vital capacity, **L**=left, **QMG**=Quantitative Myasthenia Gravis, **R**=right.

Analyses

- Primary efficacy analysis set which included all randomized anti-acetylcholine receptor (AChR)+, anti-muscle-specific kinase (MuSK)+, and anti-low-density lipoprotein receptor-related protein 4 (LRP4)+ participants who received ≥1 dose of any study intervention was used for this post-hoc analyses.
- Baseline demographics and disease characteristics were summarized.
- Baseline floor effects (score=0) for QMG items/domains were evaluated using item-level frequency distributions and mean domain scores.
- Analysis of covariance models, along with fixed effects for treatment group, autoantibody status, region, and baseline value as covariates compared mean change from baseline (CFB) in four domains at 24 weeks between nipocalimab + SOC and PBO + SOC.
- Odds of achieving 1-point improvement in QMG items and 2-point improvement in QMG domains over 24 weeks were analyzed using Generalized Estimating Equations (GEE) with repeated measures with treatment and visit as fixed-effect factors and interaction.
- Statistical analyses were conducted using SAS (Cary, NC, USA), version 9.04, and R, version 4.2.1.

Results

Baseline demographics

- Of 153 antibody-positive participants, 77 and 76 received nipocalimab and PBO, respectively (**Table 1**).
- Mean age was 52.4 years (range 20–81) and 60.1% of participants were female.

Table 1: Baseline demographics and disease characteristics

	Nipocalimab + SOC N=77	Placebo + SOC N=76	Total N=153
Age, years			
Mean (SD)	52.5 (15.66)	52.3 (16.37)	52.4 (15.97)
Range	20–81	20–81	20–81
Sex, n (%)			
Female	50 (64.9)	42 (55.3)	92 (60.1)
QMG total score			
Mean (SD)	15.1 (4.78)	15.7 (4.92)	15.4 (4.85)
QMG domains			
N	76	73	149
Bulbar, mean (SD)	1.5 (1.36)	1.2 (1.36)	-
Median (range)	1 (0–5)	1 (0–6)	-
Ocular, mean (SD)	4.3 (2)	4 (1.9)	-
Median (range)	4.5 (0-8)	4.3 (0–8)	-
Limb/gross motor domain, mean (SD)	8.8 (3.36)	9.8 (3.45)	-
Median (range)	9 (2–16)	10 (1–20)	-
Respiratory, mean (SD)	0.6 (0.82)	0.7 (0.92)	-
Median (range)	0 (0–3)	0 (0–3)	-

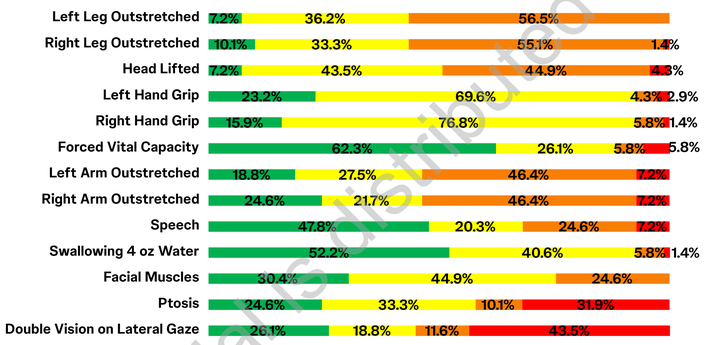
PBO=placebo, **QMG**=Quantitative Myasthenia Gravis, **SD**=standard deviation, **SOC**=standard-of-care.

Baseline QMG items

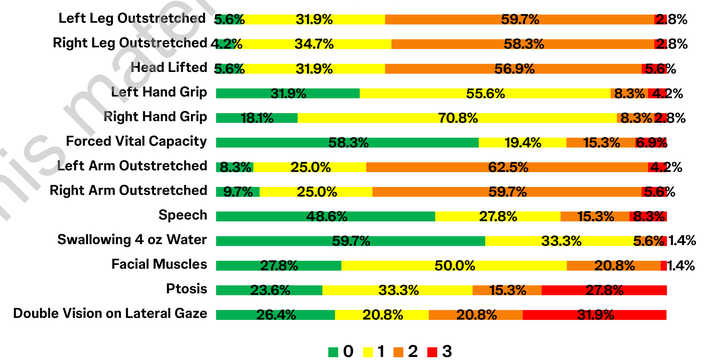
- Median baseline QMG item scores were 1.0–2.0; proportion with item-level floor effects (score=0) at baseline ranged from 7.2% (left leg outstretch/head lifted) to 62.3% (forced expiratory volume) (**Figure 2**)

Figure 2: Baseline QMG item score distribution

A. QMG Item Distribution at baseline: Nipocalimab + SOC (n=77)



B. QMG Item Distribution at baseline: PBO + SOC (n=76)

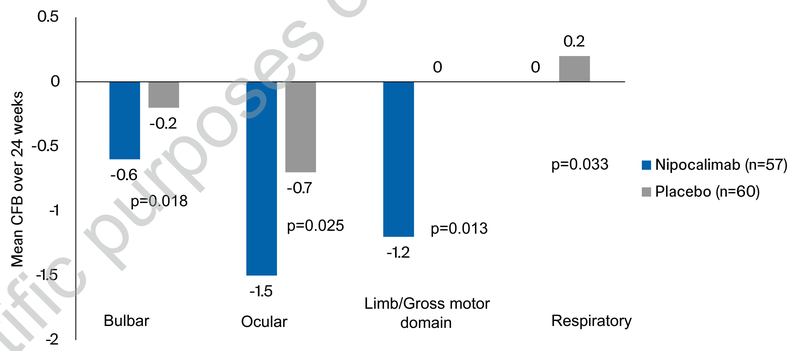


PBO=placebo, **QMG**=Quantitative Myasthenia Gravis, **SOC**=standard-of-care.

Mean change from baseline for domains

- Nipocalimab + SOC demonstrated significant improvements in mean CFB for bulbar, ocular and limb/gross motor domains versus PBO + SOC (p<0.05) over 24 weeks; nipocalimab + SOC showed stabilization of respiratory domain but got worse with PBO + SOC (**Figure 3**).

Figure 3: Improvement in LS-mean CFB over 24 weeks for QMG domains



Baseline mean (range) domain scores in nipocalimab + SOC and PBO + SOC were: bulbar (0.8 [0–5]; 1.2 [0-6]), limb (8.8 [2–16]; 9.8 [1–20]), ocular (4.3 [0–8]; 4.0 [0–8]), respiratory (0.6 [0–3]; 0.7 [0–3]), respectively. **CFB**=change from baseline, **LS-Mean**=least squares mean, **QMG**=Quantitative Myasthenia Gravis..

Mean changes from baseline in QMG items

- Statistically significant improvement was reported in CFB in QMG total score in nipocalimab + SOC versus PBO + SOC over W22 and W24 (p <0.001).
- At W22, CFB of QMG item scores was numerically greater with nipocalimab versus PBO for all items (**Figure 4A**); similar observations were made for W24, except right hand grip (**Figure 4B**).

Figure 4A: Mean CFB in QMG items at 22 weeks

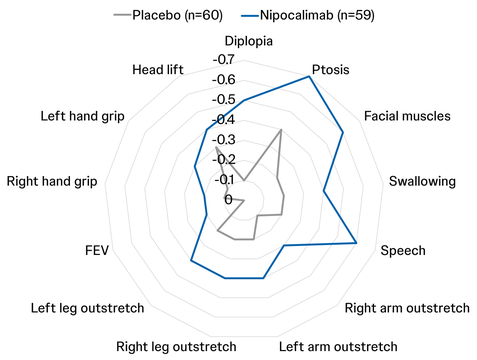
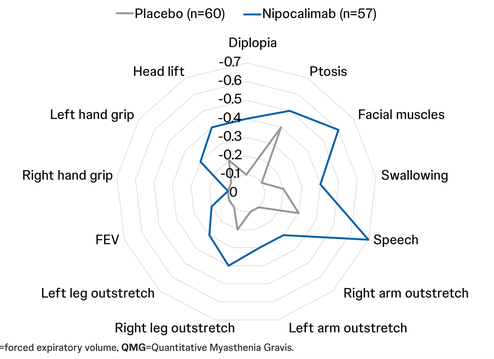


Figure 4B: Mean CFB in QMG items at 24 weeks

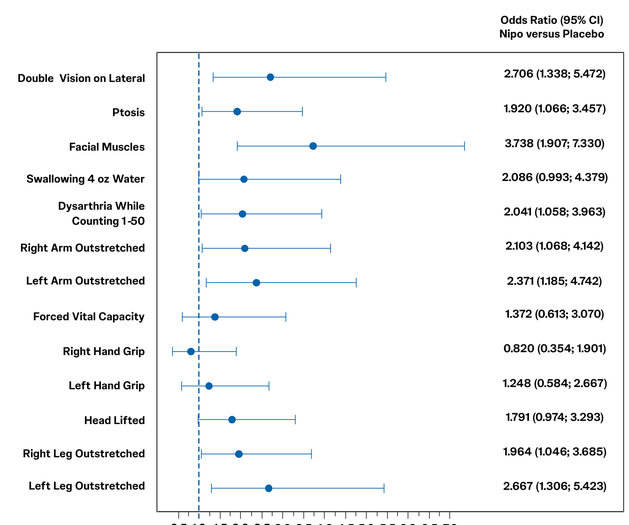


CFB=change from baseline, **FEV**=forced expiratory volume, **QMG**=Quantitative Myasthenia Gravis.

QMG item response

- Likelihood of achieving item response (≥1-point improvement) was greater with nipocalimab + SOC versus PBO + SOC over 24 weeks (odds ratio [OR]: 1.3 [left-hand grip] to 3.7 [facial muscles]), except right hand grip (OR=0.8) (**Figure 5**).

Figure 5: Achieving QMG item response

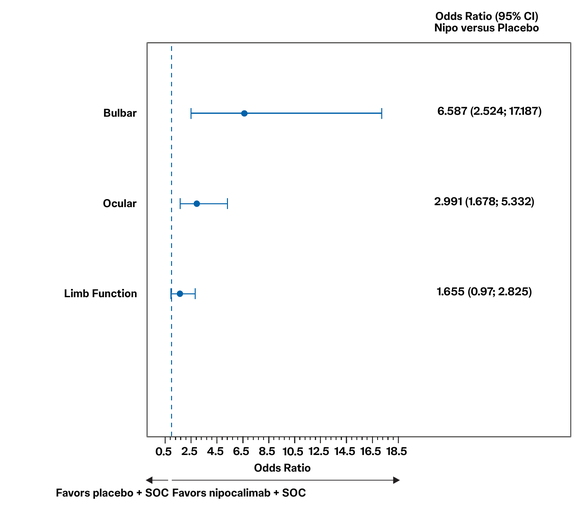


CI=confidence interval, **QMG**=Quantitative Myasthenia Gravis.

QMG domain response

- Likelihood of achieving domain response (≥2-point improvement) was greater with nipocalimab + SOC versus PBO + SOC over 24 weeks (OR: bulbar 6.6 [2.5–17.2]; limb 1.7 [1.0–2.8]; ocular 3.0 [1.7–5.3]; respiratory 1.4 [0.6–3.1]) generally favoring nipocalimab (**Figure 6**).

Figure 6: Achieving QMG domain response



Respiratory domain has a single item responder, i.e., forced vital capacity. This is included in the QMG items figure as the meaning within person improvement (MWPI) is ≥1-point. **CI**=confidence interval, **QMG**=Quantitative Myasthenia Gravis.

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