Safety Profile of Nipocalimab, a New Neonatal Fragment Crystallizable Receptor Blocker in the Phase 3 Vivacity Study

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Background

- Myasthenia gravis (MG) is a rare autoimmune disorder causing muscle weakness and reduced quality of life.
  - Limitations of current therapies highlight the need for safe, more effective treatment options for sustained disease control.[1,2]
- Nipocalimab, a neonatal fragment crystallizable receptor (FcRn) blocker has demonstrated reduction in levels of circulating immunoglobulin G (IgG) and anti-acetylcholine receptor (anti-AChR) antibodies while preserving immune function.[3]
- Nipocalimab, added to standard-of-care (SOC), signifi antly reduced IgG levels from baseline in a phase 1 study[3] and demonstrated meaningful clinical improvements with a tolerable safety profile n the phase 2 Vivacity-MG study[4] in patients with generalized MG.
- The safety profile f nipocalimab + SOC versus placebo + SOC was evaluated in the phase 3 Vivacity-MG3, a randomized, double-blind (DB), placebo-controlled study.[5]

Objective

- **To report a comprehensive safety profile of nipocalimab, a novel FcRn blocker, from the phase 3 Vivacity-MG3 study and open-label extension (OLE) phase in adult patients with generalized MG.**

Methods

Vivacity-MG3 study

- Vivacity-MG3 (NCT04951622) is a multicenter, randomized, DB, placebo-controlled phase 3 study with an ongoing OLE phase, designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of nipocalimab in adults with generalized MG.
- Patients who completed or terminated treatment in the DB phase were eligible to enter the ongoing OLE phase.

Safety assessments

- Treatment-emergent adverse events (TEAEs), TEAEs of interest, serious AEs (SAEs), and AEs leading to treatment discontinuation were summarized for DB phase and OLE phase.
- Additionally, changes and clinically meaningful changes in laboratory values, vital signs, and cardiovascular (CV) risk (Systematic Coronary Risk Evaluation 2 [SCORE2]) were reported.
- TEAEs were coded in accordance with MedDRA, Version 26.1.

Analysis

- Safety (DB) analysis set: participants who received at least 1 dose (partial or complete) of any study intervention in the DB phase.
- Safety (OLE) analysis set: participants who received at least 1 dose (partial or complete) of nipocalimab in the OLE phase.
- 10-year coronary risk was estimated using the SCORE2 algorithm from the European Society of Cardiology (key inputs were: systolic blood pressure, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]).
- As the duration of DB and OLE phases were different, exposure adjusted incidence rates of AEs are presented.

Key Takeaways

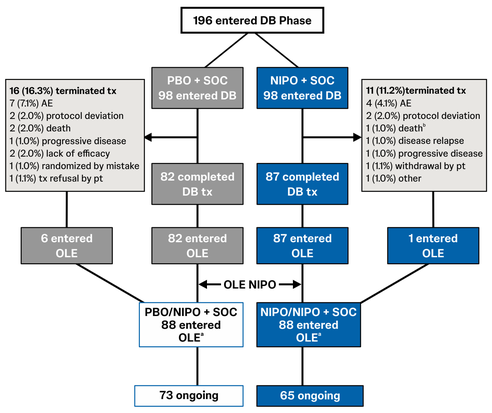
- **Nipocalimab + SOC was generally well-tolerated during the DB and OLE phases.**
  - **The proportion of patients with AEs, SAE, discontinuation due to AEs, and fatal AEs was similar in nipocalimab + SOC and placebo + SOC.**
  - **Muscle spasm and peripheral edema were more common in the nipocalimab + SOC group, and events were mild to moderate in severity.**
  - **During the long-term OLE phase, there were no evidence of new safety risk with nipocalimab + SOC treatment.**
  - **Exposure adjusted rates of AEs and SAEs were generally lower in the OLE phase compared with the DB phase.**
- **In the nipocalimab + SOC group, mild increases were observed for total cholesterol, HDL, and LDL which decreased and plateaued by Week 24 of the DB phase.**
  - **Most patients remained within the same LDL risk category as their initial category.**
  - **A few patients who initiated lipid-lowering agents demonstrated a rapid reduction of LDL to baseline levels or lower.**
  - **No difference in rate of MACE or CV risk was observed across patients receiving nipocalimab + SOC and placebo + SOC.**

Results

DB and OLE phase patient disposition

- Total of 196 (nipocalimab + SOC: 98; placebo + SOC: 98) entered the DB phase of which, 82 in placebo + SOC and 87 in nipocalimab + SOC group completed the DB phase (**Figure 1**).
- In OLE phase (**Figure 1**):
  - 88 patients from DB placebo + SOC group (82 completed + 6 from those who discontinued DB) entered OLE phase.
  - 88 patients from DB nipocalimab + SOC group (87 completed + 1 from those who discontinued DB) and entered OLE phase.

Figure 1: Patient disposition (DB and OLE safety analysis set)



[a]Per protocol, participants requiring rescue treatment during the DB phase completed the DB end-of-phase visit and were eligible to enter the OLE per investigator's discretion. Eight patients discontinued the double-blind phase prior to Week 24, but entered the open-label phase: 5 PBO/NIPO and 1 NIPO/NIPO; [b]Cardiac failure (unrelated to treatment) occurred 2 days after the last dose of study treatment on study day 422. **AE**=Adverse event, **DB**=Double-blind, **NIPO**=Nipocalimab, **OLE**=Open-label extension, **PBO**=Placebo, **pt**=Patient, **SOC**=Standard-of-care, **tx**=Treatment

- DB baseline characteristics of patients entering the OLE are similar to the overall DB population (**Table 1**).

Table 1: Double-blind baseline demographic and clinical characteristics

Characteristics	DB phase		OLE phase	
	PBO + SOC	NIPO + SOC	PBO/NIPO + SOC	NIPO/NIPO + SOC
Analysis set: Safety (DB and OLE)[a]	98	98	88	88
Age, mean (range), years	52.7 (20; 81)	52.9 (20; 81)	52.2 (20; 81)	52.1 (20; 81)
Female, n (%)	56 (57.1%)	66 (67.3%)	52 (59.1%)	59 (67.0%)
Race, n (%)				
American Indian or Alaska native	0	1 (1.0%)	0	1 (1.0%)
Asian	29 (29.6%)	28 (28.6%)	25 (28.4%)	25 (28.4%)
Black/African American	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
White	65 (66.3%)	66 (67.3%)	59 (67.0%)	59 (67.0%)
Not reported	3 (3.1%)	2 (2.0%)	3 (3.4%)	2 (2.3%)
BMI, mean (SD), kg/m^2	28.8 (6.7)	27.8 (5.9)	28.9 (6.9)	27.7 (5.9)
Baseline MG-ADL total score, mean (SD)	9.3 (2.0)	9.5 (2.7)	9.3 (2.0)	9.5 (2.7)
Baseline QMG total score, mean (SD)	15.6 (4.7)	15.0 (4.8)	15.5 (4.7)[b]	15.1 (5.0)
Autoantibody status at screening				
Seronegative, n (%)	22 (22.4%)	21 (21.4%)	22 (25.0%)	17 (19.3%)
Seropositive, n (%)	76 (77.6%)	77 (78.6%)	66 (75.0%)	71 (80.7%)
Anti-AChR[+]	71 (72.4%)	63 (64.3%)	61 (69.3%)	59 (67.0%)
Anti-MuSK[+]	4 (4.1%)	12 (12.2%)	4 (4.5%)	10 (11.4%)
Anti-LRP4[+]	1 (1.0%)	2 (2.0%)	1 (1.1%)	2 (2.3%)

[a]N's for each parameter refl ct non-missing values. **AChR**=Acetylcholine receptor antibody-positive, **BMI**=Body mass index, **DB**=Double-blind, **LRP4**=Low density lipoprotein receptor-related protein 4-positive, **MG-ADL**=Myasthenia Gravis-Activities of Daily Living, **MuSK**=Muscle-specific inase antibody-positive, **NIPO**=Nipocalimab, **OLE**=Open-label extension, **PBO**=Placebo, **QMG**=Quantitative Myasthenia Gravis, **SD**=Standard deviation, **SOC**=Standard-of-care

Overall safety profile

- For 196 patients in the DB phase (nipocalimab + SOC: 98; placebo + SOC: 98), median follow-up was 24 weeks.
- For 176 patients in the OLE phase (NIPO/NIPO + SOC: 88; PBO/NIPO + SOC: 88), median follow-up was 72 weeks.
- In the DB phase, the proportion of patients experiencing ≥1 AEs was similar between the nipocalimab + SOC (83.7%) and placebo + SOC (83.7 %) groups.
- In the OLE phase, the proportion of patients experiencing ≥1 AEs was similar between (NIPO/NIPO + SOC (89.8%) and PBO/NIPO + SOC (90.9%) groups, **Table 2**).
- 7 deaths (DB phase: n=3; OLE phase: n=4) were reported:
  - None of the deaths in DB phase were related to study treatment (nipocalimab + SOC: n=1; placebo + SOC: n=2).
  - Of the 4 deaths in the OLE phase:
    - 3 deaths were not considered treatment related and occurred in older patients who had CV comorbidities.
    - 1 death was considered treatment-related (Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in a patient receiving concomitant tacrolimus; death occurred on study day 224, and 18 days after the last dose of study treatment).

Table 2: Overall patient proportion summary of AEs (DB and OLE safety analysis set)

Safety analysis set	DB phase		OLE phase	
	PBO + SOC (n=98), n (%)	NIPO + SOC (n=98), n (%)	PBO/NIPO + SOC (n=88), n (%)	NIPO/NIPO + SOC (n=88), n (%)
AEs	82 (83.7)	82 (83.7)	80 (90.9)	79 (89.8)
Related AEs[a]	27 (27.6)	28 (28.6)	35 (39.8)	37 (42.0)
SAEs	14 (14.3)	9 (9.2)	21 (23.9)	25 (28.4)
Related SAEs	1 (1.0)	1 (1.0)	4 (4.5)	2 (2.3)
AEs leading to permanent discontinuation of study treatment[b]	7 (7.1)	5 (5.1)	8 (9.1)	5 (5.7)

[a]An AE is assessed by the investigator as related to study agent. [b]AEs leading to permanent discontinuation of study treatment is based on AE action taken of drug withdrawn. Treatment discontinuation for an AE with onset in DB occurred in DB. **AE**=Adverse event, **DB**=Double-blind, **MG**=Myasthenia Gravis, **OLE**=Open-label extension, **NIPO**=Nipocalimab, **PBO**=Placebo, **SAEs**=Serious adverse events, **SOC**=Standard-of-care

AEs in either arm in DB or OLE (events per-patient per-year)

- There were no unexpected AEs during the DB or OLE phase.
- Rates of AEs were generally similar in the DB PBO and OLE nipocalimab combined group.

Table 3: Safety and tolerability (exposure adjusted incidence rate)

Safety analysis set	DB phase						OLE phase		
	PBO + SOC (n=98)			NIPO + SOC (n=98)			NIPO combined (n=176)		
Average follow-up duration, wks	23			23			70.53		
P-Y[a]	43.3			43.2			237.9		
	Events/ P-Y[a]	Events, n	Pts, n[b]	Events/ P-Y[a]	Events, n	Pts, n[b]	Events/ P-Y[a]	Events, n	Pts, n[b]
All AEs	7.54	326	82	8.73	377	82	5.59	1331	159
Serious AEs	0.60	26	14	0.42	18	9	0.31	74	46
Fatal AEs	0.05	2	2	0.02	1	1	0.02	4	4
Tx discontinuation due to AE[c]	0.25	11	7	0.16	7	5	0.05	13	13
Infection and infestations	1.14	61	42	1.64	71	42	1.39	330	125
Infusion-related reactions[d]	0.62	27	11	0.37	16	10	0.07	17	10
Adjudicated MACE, fatal	0.05	2	2	0	0	0	0.01	3	3
Adjudicated MACE, not fatal	0.02	1	1	0	0	0	0.03	7	1

[a]Participant-years of observation (P-Y) is calculated as the total duration of follow-up in days/365.25. [b]Patients with ≥1 AE are shown. [c]Permanent discontinuation of treatment. Treatment discontinuation for an AE with onset in DB (or OLE) occurred in DB (or OLE). [d]Indicated as infusion reaction by investigator on eCRF and relationship to study intervention="Related". **AE**=Adverse event, **DB**=Double-blind, **eCRF**=Electronic case report form, **MACE**=Major adverse cardiovascular event, **NIPO**=Nipocalimab, **OLE**=Open-label extension, **PBO**=Placebo, **Pt**=Patient, **P-Y**=Participant-year, **SOC**=Standard-of-care, **Tx**=Treatment, **Wks**=Weeks

AEs with a rate of at least 1 patient in 10 per year (exposure adjusted incidence rate)

- Exposure adjusted incidence rates showed that the overall incidence of AE rates were generally lower in the OLE phase compared to the DB phase.

Table 4: AEs by preferred term in at least 0.1 events per P-Y of pts in either arm in DB or OLE (exposure adjusted incidence rate)

Safety analysis set	DB phase						OLE phase		
	PBO + SOC (n=98)			NIPO + SOC (n=98)			NIPO combined (n=176)		
P-Y[a]	43.3			43.2			237.9		
	Events/ P-Y	Events, n	Pts, n[a]	Events/ P-Y	Events, n	Pts, n[a]	Events/ P-Y	Events, n	Pts, n[a]
Upper respiratory tract infection	0.18	8	8	0.14	6	6	0.21	50	39
Nasopharyngitis	0.25	11	10	0.21	9	9	0.18	44	33
COVID-19	0.25	11	10	0.3	13	13	0.11	25	23
Urinary tract infection	0.05	2	2	0.12	5	5	0.12	28	19
Back pain	0.12	5	5	0.21	9	8	0.09	22	18
Muscle spasms	0.07	3	3	0.3	13	12	0.08	19	12
Pain in extremity	0.09	4	3	0.12	5	5	0.05	11	10
Arthralgia	0.16	7	5	0.05	2	2	0.08	18	13
Myasthenia gravis	0.37	16	12	0.35	15	12	0.20	48	31
Headache	0.74	32	17	0.51	22	14	0.21	50	29
Dizziness	0.02	1	1	0.14	6	5	0.02	5	4
Peripheral edema	0	0	0	0.3	13	11	0.04	10	9
Pyrexia	0.02	1	1	0.19	8	7	0.05	11	10
Diarrhea	0.07	3	3	0.16	7	7	0.08	20	20
Nausea	0.07	3	2	0.14	6	5	0.04	10	8
Cough	0.09	4	3	0.19	8	7	0.04	10	9
Rash	0.12	5	3	0.02	1	1	0.02	5	4
Anaemia	0.12	5	4	0.09	4	4	0.03	7	7
Insomnia	0.05	2	2	0.12	5	5	0.02	4	4

Note: NIPO combined group represent all the patient from PBO/NIPO + SOC (n=88) and NIPO/NIPO + SOC (n=88) who entered OLE phase.
Participant-Years of Observation (P-Y) is calculated as the total duration of follow-up in days/365.25.
[a]Patients with ≥1 AE are shown; Event Rate=Number of Events/PY. Adverse Events listed where system organ class event rate is ≥0.1 or preferred term event rate is ≥0 in either treatment group. **AE**=Adverse event, **DB**=Double-blind, **NIPO**=Nipocalimab, **OLE**=Open-label extension, **PBO**=Placebo, **Pt**=Participant, **P-Y**=Participant-year, **SOC**=Standard-of-care

Specific AEs: Muscle spasm and peripheral edema

- A total of 12 (12.2%) in the nipocalimab + SOC group in the DB phase and 12 (6.8%) in the nipocalimab combined group had mild to moderate muscle spasm; 11 (11.2%) in the nipocalimab + SOC group in the DB phase and 9 (5.1%) in the nipocalimab combined group had mild to moderate peripheral edema.
- There were no patients who experienced severe muscle spasm or peripheral edema during the DB or OLE phases.

Table 5: Number of patients with treatment-emergent muscle spasms or peripheral edema adverse events

Safety analysis set	DB phase		OLE phase
	PBO + SOC (n=98)	NIPO + SOC (n=98)	NIPO combined (n=176)
Preferred Term[a] Severity[b]			
Muscle Spasms, n (%)	3 (3.1)	12 (12.2)	12 (6.8)
Mild	2 (2.0)	9 (9.2)	11 (6.3)
Moderate	1 (1.0)	3 (3.1)	2 (1.1)
Peripheral edema, n (%)	0	11 (11.2)	9 (5.1)
Mild	0	9 (9.2)	8 (4.5)
Moderate	0	2 (2.0)	2 (1.1)

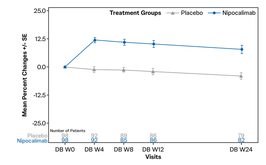
Note: NIPO combined group represent all the patient from PBO/NIPO + SOC (n=88) and NIPO/NIPO + SOC (n=88) who entered OLE phase.
[a]Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
[b]Patients may be counted more than once for any given event. **DB**=Double-blind, **NIPO**=Nipocalimab, **OLE**=Open-label extension, **PBO**=Placebo, **SOC**=Standard-of-care

Lipid levels (DB phase)

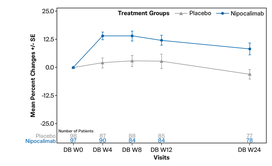
- Mild increases in total cholesterol, HDL, and LDL were observed in patients receiving nipocalimab, by DB Week 24, levels decreased and plateaued (**Figure 2A-2C**).
- The total Cholesterol/HDL ratio remained under 4 and was similar across treatment groups (**Figure 2D**).
- A total of 7 patients initiated lipid-lowering agents (usually statins) and a similar rapid reduction of LDL to baseline or lower levels was observed among these patients in both treatment arms (**Figure 2E**).
- Among placebo + SOC patients, those who had low LDL levels (<4.1 mmol/L) at baseline, 95% maintained low levels at Week 24. Similarly, among the nipocalimab + SOC patients with low LDL levels at baseline, 89% were able to sustain those levels at Week 24.
- Throughout the 24 week DB and OLE phases, there was no difference in rate of major adverse cardiovascular events (MACE) across participants receiving nipocalimab and placebo.

Figure 2: Lipids over time during the DB phase (safety analysis set)

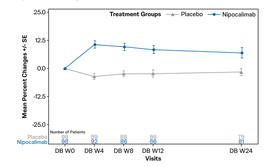
(A) Mean percent changes in CHOL (mmol/L) from DB baseline



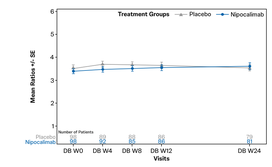
(B) Mean percent changes in LDL CHOL (mmol/L) from DB baseline



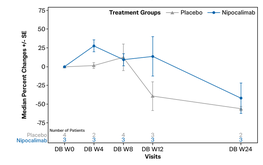
(C) Mean percent changes in HDL CHOL (mmol/L) from DB baseline



(D) Mean CHOL/HDL ratios from DB baseline



(E) Median percent changes in LDL CHOL (mmol/L) from DB baseline with lipid-lowering agents use started in DB phase



CHOL=Cholesterol, **DB**=Double-blind, **HDL**=High-density lipoprotein, **LDL**=Low-density lipoprotein, **SE**=Standard error, **W**=Week

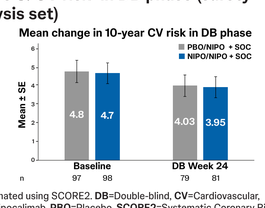
Mean change in systolic blood pressure

- At Week 24 of the DB phase, mean (SD) change from baseline (CFB) in systolic blood pressure was −4.1 (14.76) mmHg for the nipocalimab + SOC group and −2.2 (12.51) mmHg for the placebo + SOC group.
- At Week 24 of the OLE phase, the mean (SD) CFB in systolic blood pressure was: −3.6 (14.00) mmHg for NIPO/NIPO + SOC and −2.2 (12.86) mmHg for PBO/NIPO + SOC.
- At Week 48 of the OLE phase, the mean (SD) CFB in systolic blood pressure was: −3.5 (16.24) mmHg for NIPO/NIPO + SOC and −5.0 (12.64) mmHg for PBO/NIPO + SOC.

CV risk (SCORE2)

- During the DB phase, the 10-year cumulative CV risk estimate remained similar for nipocalimab + SOC group and for placebo + SOC group after 24 weeks of exposure (**Figure 3**).
- The trends observed on the calculated 10-year CV risk following 24 weeks of nipocalimab + SOC treatment during the DB phase were preserved for up to 72 weeks of follow-up through OLE phase.
  - mean (SE) 10-year CV risk change after 48 weeks of exposure (i.e., OLE Week 24): −0.21 (0.111).
  - mean (SE) 10-year CV risk change after 72 weeks of exposure (i.e., Week 48 of OLE): −0.28 (0.180).

Figure 3: CV risk[a] in DB phase (safety analysis set)



[a]As estimated using SCORE2. **DB**=Double-blind, **CV**=Cardiovascular, **NIPO**=Nipocalimab, **PBO**=Placebo, **SCORE2**=Systematic Coronary Risk Evaluation 2, **SOC**=Standard-of-care, **SE**=Standard error

PRESENTED AT: Myasthenia Gravis Foundation of America (MGFA) Scientific Session 2025; San Francisco, California, USA; October 29, 2025. **REFERENCES: 1.** Gilhus NE, et al. Myasthenia gravis. *Nat Rev Dis Primers.* 2019;5:30. **2.** Dresser L, et al. *J Clin Med.* 2021;10:2235. **3.** Ling LE, et al. *Clin Pharmacol Ther.* 2019;105(4):1031-1039. **4.** Antozzi, et al. *Neurology.* 2024;102(2):e207937. **5.** Antozzi C, et al. *Lancet Neurol.* 2025;24(2):105-116. **ACKNOWLEDGMENTS:** The authors thank the participants and investigators for their participation in the study. Kalpana Tilekar, PhD (SIRO Medical Writing Pvt. Ltd.) and Doyel Mitra, PhD (Johnson & Johnson) provided editorial assistance. Layout design and reformatting for this encore presentation were provided by Amit Kavle (SIRO Medical Writing Pvt. Ltd., India), with funding from Johnson & Johnson. This study was sponsored by Johnson & Johnson. **DISCLOSURES: Hans Katzberg:** Consultant to Octapharma, UCB, Alnylam, CSL Behring, Alexion, argenX, Dyne, Roche, Takaeda, Dianthus, Merz; he has been on the DSMB for Alexion, UCB, Abcuro, Octapharma, and argenX and has received clinical trial support from Takaeda, CSL Behring, Roche and, argenX. **Ibrahim Turkoz, Kavita Gandhi,** and **Sindhu Ramchandren:** are employees, contractors, or consultants for Johnson & Johnson and may hold stock or stock options in Johnson & Johnson. **Maria Ait-Tihyaty:** was an employee of Johnson & Johnson at the time of the study and may hold stock or stock options in Johnson & Johnson. Some of these results were previously presented at the American Academy of Neurology (AAN) Annual Meeting; San Diego, IL, USA; April 5–9, 2025.