Long-Term Safety and Efficacy of Nipocalimab in Generalized Myasthenia Gravis: Vivacity-MG3 Open-Label Extension Phase Results

Carlo Antozzi[1*], Tuan Vu[2], Sindhu Ramchandren[3], Richard J. Nowak[4], Constantine Farmakidis[5], Vera Bril[6], Jan De Bleecker[7], Huan Yang[8], Eduard Minks[9], Jin-Sung Park[10], Mariusz Grudniak[11], Marek Smilowski[12], Teresa Sevilla[13], Sarah Hoffmann[14], Kumaraswamy Sivakumar[15], Eriene Youssef[3], Panna Sanga[3], Keith Karcher[3], Yaowei Zhu[3], John Sheehan[3], Hong Sun[3¥]

[1]Neurology IV - Neuroimmunology and Neuromuscular Diseases Unit, Fondazione I.R.C.C.S. Istituto; Neurologico Carlo Besta, Milan, Italy; [2]Neurology, University of South Florida, Tampa, FL, USA; [3]Neuroscience, Johnson & Johnson, Titusville, NJ, USA; [4]Department of Neurology, Yale University School of Medicine, New Haven, CT, USA; [5]Neurology, University of Kansas Medical Center, Kansas City, KS, USA; [6]Neurology, University of Toronto, University Health Network, Toronto, Canada; [7]Neurology, Ghent University Hospital, Ghent, Belgium; [8]Neurology, Xiangya Hospital, Central South University, Changsha, China; [9]First Department of Neurology, Faculty of Medicine, Masaryk University and St. Anne's Hospital, Brno, Czech Republic; [10]Department of Neurology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, South Korea; [11]Neurology, Centrum Medyczne Neuro-Protect Ul, Warszawa, Poland; [12]Neurology, Silesian Neurology Medical Center, Katowice, Poland; [13]Neurology, Hospital Universitari i Politècnic and IIS La Fe/University of Valencia, Valencia, Spain; [14]Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [15]The Neuromuscular Research Center and Neuromuscular Clinic of Arizona, Phoenix, AZ, USA

*Presenting author
¥Affiliation at time of study

Introduction

- Nipocalimab is a fully human, aglycosylated investigational monoclonal antibody, designed to bind with high affinity and specificity to block neonatal fragment crystallizable receptor (FcRn); this decreases circulating immunoglobulin G (IgG) without causing broad immunosuppression[1-3]
- During the phase 3 Vivacity-MG3 placebo-controlled double-blind period, consistently-dosed nipocalimab + standard-of-care (SOC) resulted in rapid and substantial lowering of circulating IgG, including myasthenia gravis (MG) pathogenic antibodies, sustained over 6 months[4]
- IgG reduction was associated with rapid and sustained disease control over 6 months in a broad population of antibody-positive patients with generalized MG[4]
  - Least square (LS) mean change from baseline (CFB) (standard error [SE]) in Myasthenia Gravis-Activities of Daily Living (MG-ADL) score from baseline to weeks 22 to 24=−4.70 (0.329) for nipocalimab + SOC vs −3.25 (0.335) for placebo + SOC (difference −1.45 [95% CI −2.3 to −0.52]; p=0.0024)[4]

Objectives

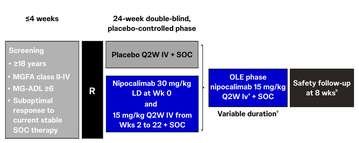
- To evaluate the long-term safety and efficacy of nipocalimab in patients with generalized MG enrolled in the open-label extension (OLE) study of Vivacity-MG3

Methods

- Vivacity-MG3 (NCT04951622) is a multicenter, randomized, double-blind, placebo-controlled study with an ongoing OLE phase, designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of nipocalimab in adults with generalized MG[4,a]
- Participants who completed the double-blind phase were eligible for OLE
- Results from the primary efficacy population (seropositive: anti-acetylcholine receptor [AChR]+, anti-muscle-specific kinase antibody [MuSK]+ and/or anti-low density lipoprotein receptor-related protein 4 [LRP4]+) participants are presented
- Participants could receive concomitant, stable SOC treatment during the trial[b]

[a]Randomization was stratified by autoantibody status (anti-AChR+ and/or anti-MuSK+, anti-AChR negative, and anti-MuSK negative), Day 1 MG-ADL total score (≤9 >9), and region (East Asia, US, rest of world); [b]SOC includes acetylcholinesterase inhibitor, glucocorticosteroid, and/or immunosuppressant.

Figure 1. Study Design[4]



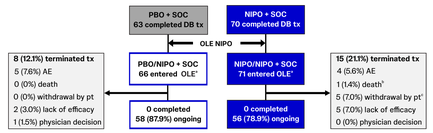
[c]Due to the COVID-19 pandemic, some participants from the Phase 2 study were unable to enter the Phase 2 OLE study. These participants could directly enter the Phase 3 OLE and their data will be disclosed later; [d]Participants who withdraw or discontinue after receiving any amount of study intervention are required to complete a safety follow-up visit 8 wks after their last dose; [e]In the EU, the OLE phase will be up to 240 wks.
COVID-19, coronavirus disease 2019; EU, European Union; IV, intravenous; LD, loading dose; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; OLE, open-label extension; Q2W, every 2 weeks; R, randomized 1:1; SOC, standard-of-care; wk(s), week(s).

Results

OLE Phase Patient Disposition

- Open-label phase is ongoing
- ~83% of participants entering the open-label phase are still receiving treatment at data cut-off

Figure 2. Disposition (Seropositive Population)



*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. Four patients discontinued the double-blind phase prior to Week 24, but entered the open-label phase: 3 PBO/NIPO and 1 NIPO/NIPO; †Cardiac failure (unrelated to treatment) occurred 2 days after the last dose of study treatment on study day 422; ‡Reasons for withdrawal: lack of improvement; participant was unsatisfied; travel to site was too tiring after surgery; personal reasons; and participant concern about poor vascular access
AE, adverse event; DB, double-blind; NIPO, nipocalimab; OLE, open-label extension; PBO, placebo; pt, participant; SOC, standard of care; tx, treatment.

Baseline Demographics and Characteristics

- DB baseline characteristics of participants entering the OLE are similar to the overall DB population

TABLE 1: Baseline Demographics and Characteristics (Seropositive Population)

Sample	Double-blind		Open-label	
	PBO + SOC	NIPO + SOC	PBO/ NIPO + SOC	NIPO/ NIPO + SOC
Analysis Set: Seropositive efficacy (DB and OLE)[a]	76	77	66	71
Age mean (range), years	52.3 (20, 81)	52.5 (20, 81)	51.6 (20, 81)	51.1 (20, 81)
Female, n (%)	42 (55.3%)	50 (64.9%)	38 (57.6%)	46 (64.8%)
Race, n (%)				
American Indian or Alaska native	0	1 (1.3%)	0	1 (1.4%)
Asian	25 (32.9%)	24 (31.2%)	21 (31.8%)	22 (31.0%)
Black/African American	1 (1.3%)	1 (1.3%)	1 (1.5%)	1 (1.4%)
White	47 (61.8%)	49 (63.6%)	41 (62.1%)	45 (63.4%)
Not reported	3 (3.9%)	2 (2.6%)	3 (4.5%)	2 (2.8%)
BMI, mean (SD), kg/m^2	28.5 (5.78)	27.6 (5.39)	28.6 (5.99)	27.5 (5.30)
Baseline MG-ADL total score, mean (SD)	9.0 (1.97)	9.4 (2.73)	9.0 (1.98)	9.3 (2.75)
Baseline QMG total score, mean (SD)	15.7 (4.92)	15.1 (4.78)[b]	15.6 (4.90)	15.2 (4.85)[c]
Anti-AChR+/ Anti-MuSK+/ Anti-LRP4+, n	71/4/1	63/12/2	61/4/1	59/10/2

[a]All randomized seropositive participants who received ≥1 dose of study intervention in the DB phase or all seropositive participants who received ≥1 dose of nipocalimab in the OL phase; [b]n=73; [c]n=67 AChR+, acetylcholine receptor antibody-positive; BMI, body mass index; DB, double-blind; gMG, generalized myasthenia gravis; LRP4+, low density lipoprotein receptor-related protein 4-positive; MG-ADL, Myasthenia Gravis-Activities of Daily Living; MuSK+, muscle-specific kinase antibody-positive; NIPO, nipocalimab; OLE, open-label extension; PBO, placebo; QMG, Quantitative Myasthenia Gravis; SD, standard deviation; SOC, standard-of-care.

Nipocalimab Exposure

- 137 antibody-positive participants were treated with nipocalimab during OLE phase
- Treatment at data cut-off, represents ~87-90 patient-years after completion of DB phase
- Among participants in OLE phase, follow-up duration was over 62 weeks

TABLE 2: Nipocalimab Exposure (Seropositive Population)

	Double-blind		Open-label	
	PBO + SOC	NIPO + SOC	PBO/ NIPO + SOC	NIPO/ NIPO + SOC
Analysis set: Seropositive efficacy (DB and OLE)	76	77	66	71
Treatment duration, median (range), weeks[a]	22.1 (0, 23)	22.1 (2, 23)	69.1 (8, 128)	62.1 (8, 128)
Number of administrations received, median (range)	12.0 (1, 12)	12.0 (2, 12)	35.0 (5, 57)	31.0 (5, 65)
Total treatment, participant-years, sum	29.2	30.4	86.8	90.3
Duration of follow-up, median (range), weeks[b]	24.0 (0, 31)	24.0 (10, 25)	69.7 (10, 128)	62.1 (16, 128)

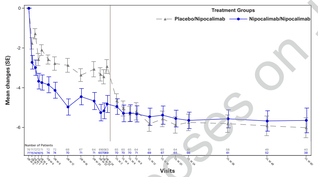
[a]Total duration of treatment=(date of last dose of study intervention minus date of first dose of study intervention) + 1; [b]Total duration of follow-up=(date of last contact minus date of first dose of study intervention) + 1.
DB, double-blind; NIPO, nipocalimab; OLE, open-label extension; PBO, placebo; SOC, standard-of-care.

Mean Change in MG-ADL and QMG Score

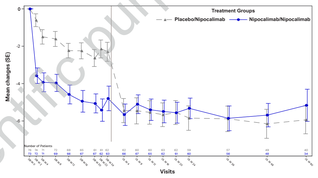
- At OLE Week 60, MG-ADL mean (SE) change from double-blind baseline: −6.01 (0.503) in PBO/NIPO + SOC and −5.64 (0.621) in NIPO/NIPO + SOC[a]
- At OLE Week 60, QMG mean (SE) change from double-blind baseline: −5.94 (0.749) in PBO/NIPO + SOC and −5.16 (0.860) in NIPO/NIPO + SOC[b]

FIGURE 3: CFB of MG-ADL and QMG Over Time (Seropositive Population)

(A) MG-ADL Total Score: Mean Changes from DB Baseline



(B) QMG Total Score: Mean Changes from DB Baseline



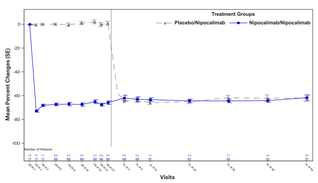
Note: P-value for comparison of MG-ADL and QMG total score change from baseline significantly different from zero using a one-sample t-test; [a]P<0.001, [b]P<0.001.
CFB, change from baseline; DB, double-blind; MG-ADL, Myasthenia Gravis-Activities of Daily Living; NIPO, nipocalimab; PBO, placebo; OL(E), open-label extension; QMG, Quantitative Myasthenia Gravis; SE, standard error; SOC, standard-of-care; W, week.

Total IgG Reduction

- At OLE Week 60, mean (SE) % CFB of IgG levels were −61.56 (2.297) in NIPO/NIPO + SOC and −61.96 (2.686) in PBO/NIPO + SOC groups

FIGURE 4: PD Biomarker: Total IgG Reduction from Baseline (Seropositive Population)

Mean Percent Changes from Baseline in IgG



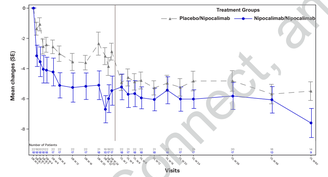
CFB, change from baseline; DB, double-blind; IgG, Immunoglobulin G; PD, pharmacodynamic; OL(E), open-label extension; SE, standard error; SOC, standard-of-care; W, week.

MG-ADL and QMG in Participants who Decreased/Discontinued Steroids

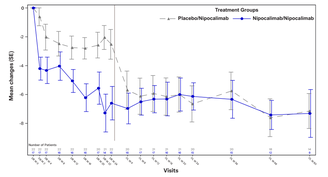
- 45% (40/89) of participants receiving steroids at open-label baseline were able to decrease or discontinue steroids at data cutoff[a]
  - Among these patients the mean dose of prednisone (mg eq per day) decreased from 23 to 10[b]
- Efficacy was maintained in participants who decreased/discontinued steroids

FIGURE 5: MG-ADL and QMG in Participants who Decreased/Discontinued Steroids (Seropositive Population)

(A) MG-ADL Total Score: Mean Changes from DB Baseline



(B) QMG Total Score: Mean Changes from DB Baseline



[a]Tapering one of the subject's concomitant MG medications Q4W was allowed in OLE phase if disease was stable in past 4 weeks based on MG-ADL scores and on investigator's discretion.
[b]Steroid dose equivalents were calculated as described[5,6].
CFB, change from baseline; DB, double-blind, MG-ADL, Myasthenia Gravis-Activities of Daily Living; OL, open-label extension; SE, standard error; QMG, Quantitative Myasthenia Gravis; Q4W, every 4 weeks; W, week.

Safety

- There were no unexpected adverse events during the OLE
- Adverse event rates including MACE were generally similar in the DB PBO and OLE All NIPO groups (Table 3)

TABLE 3: Safety and Tolerability (Seropositive Population)

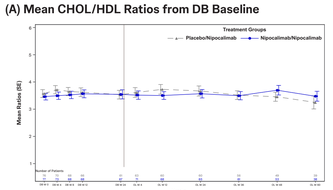
	DB PBO			DB NIPO			OLE All NIPO		
Analysis Set: Seropositive	76			77			137		
Average follow-up duration, wks	22.92			23.13			68.96		
P-Y[a]	33.4			34.1			181.1		
	Events/ P-Y[a]	Events, n	Pts, n[b]	Events/ P-Y[a]	Events, n	Pts, n[b]	Events/ P-Y[a]	Events, n	Pts, n[b]
All AE	6.98	233	62	8.41	287	64	5.10	924	124
Serious AE	0.57	19	11	0.35	12	5	0.28	51	31
Fatal AE	0.06	2[c]	2[c]	0.03	1[c]	1[c]	0.02	3[c,d]	3[c,d]
Tx discontinuation due to AE[e]	0.18	6	6	0.18	6	4	0.06	11	11
Infection and infestations	1.32	44	31	1.70	58	33	1.20	217	93
Infusion-related reaction	0	0	0	0.03	1	1	0.01	2	2
Adjudicated MACE, fatal	0.06	2	2	0	0	0	0.01	2	2
Adjudicated MACE, not fatal	0.03	1	1	0	0	0	0.04	7	1

[a]Participant-years of observation (P-Y) is calculated as the total duration of follow-up in days/365.25; [b]Participants with ≥1 AE are shown; [c]Investigator assessed death(s) as unrelated to treatment; [d]Investigator assessed 1 death as related to treatment (hemophagocytic lymphohistiocytosis); [e]Permanent discontinuation of treatment. Treatment discontinuation for an AE with onset in DB (or OLE) occurred in DB (or OLE)
AE, adverse event; DB, double-blind; MACE, major adverse cardiovascular event; NIPO, nipocalimab; n, number; OLE, open-label extension; PBO, placebo; Pt, participant; P-Y, participant-year; TEAE, treatment-emergent adverse events; Tx, treatment; wks, weeks.

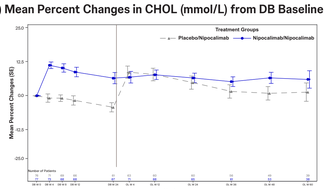
- From BL to DB Week 24, CHOL/HDL ratios (mean CFB) were stable in both the PBO/NIPO and NIPO/NIPO groups (−0.1 and 0, respectively)
- This ratio (mean CFB) remained stable at OLE Week 60 (−0.2 and +0.2, respectively)
  - Ratios remained stable because similar percent increases in both HDL and LDL were observed with nipocalimab

FIGURE 6: Lipids Over Time (Seropositive Population)

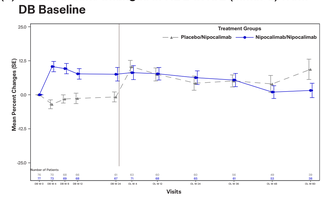
(A) Mean CHOL/HDL Ratios from DB Baseline



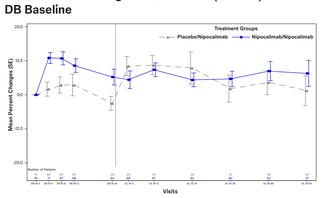
(B) Mean Percent Changes in CHOL (mmol/L) from DB Baseline



(C) Mean Percent Changes in HDL CHOL (mmol/L) from DB Baseline



(D) Mean Percent Changes in LDL CHOL (mmol/L) from DB Baseline



BL, baseline; CFB, change from baseline; CHOL, cholesterol; DB, double-blind; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIPO, nipocalimab; OL(E), open-label extension; PBO, placebo; SE, standard error.

Key Takeaway

Nipocalimab demonstrated sustained, clinically meaningful disease control over 84 weeks in a broad population of autoantibody-positive gMG patients, while maintaining an acceptable safety profile

Conclusions

- Nipocalimab treatment resulted in sustained, clinically meaningful disease control over 84 weeks across the double-blind and open-label phases in a broad population of autoantibody-positive adults with gMG
- 45% of patients receiving corticosteroids for gMG steroids at baseline decreased/discontinued corticosteroids; the nipocalimab efficacy benefit was preserved in these patients
- There are no new safety concerns despite continuous IgG lowering and event rates were comparable in the double-blind placebo and open-label extension phases

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Autoantibody: gMG