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Effect of Nipocalimab on Pathogenic IgG and Complement Markers in Patients with Seropositive gMG: Exploratory Analysis in Vivacity-MG3 study

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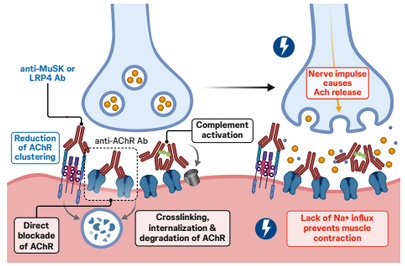
Key Takeaways

- **Nipocalimab led to sustained reductions in IgG subclasses and anti-AChR titers, accompanied by rapid and significant decreases in the levels of selected immune complex–associated complement markers (C3d-CIC and C1q-ICB)**
- **These data indicate changes in selected circulating complement-related markers following nipocalimab treatment; further exploration is needed to better understand the clinical relevance**

Introduction

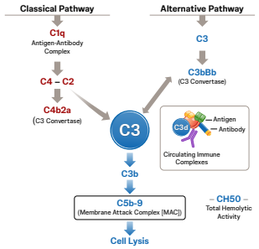
- Myasthenia gravis (MG) is characterized by pathogenic immunoglobulin G (IgG) autoantibody-mediated impairment of neurotransmission leading to fatigable muscle weakness[1]
- Acetylcholine receptor (AChR) antibodies are detected in up to 85% of patients with MG[1]
  - These antibodies bind to AChR and can directly block the action of ACh, or cross-link the receptors, leading to their endocytosis and degradation (**Figure 1**)
  - AChR antibodies belong to the IgG1 and IgG3 subclasses, and can also activate complement at the neuromuscular junction, leading to destruction of the muscle end plate (**Figure 2**)
- In some cases of MG, antibodies against muscle-specific receptor tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4) can reduce AChR clustering, resulting in damage to the post-synaptic membrane[1]
- Nipocalimab is a fully human monoclonal antibody that binds to the neonatal Fc receptor (FcRn) with high affinity and specificity, reducing circulating levels of IgG, including pathogenic IgG-based autoantibodies
- In the phase 3 Vivacity-MG3 study, nipocalimab added to standard-of-care (SOC) demonstrated substantial reduction in circulating IgG, with rapid and sustained disease control over 24-weeks in seropositive patients with generalized MG (gMG)[2]

Figure 1. Mechanisms of MG pathogenesis



*MG has several mechanisms of pathogenicity. AChR-related effector mechanisms include direct blockade of AChR; crosslinking, internalization, and degradation of AChR; and complement activation (**black boxes**). MuSK and LRP4 antibodies may reduce AChR clustering (**blue box**). These result in impaired neural transmission at the neuromuscular junction (**red box**).*

Figure 2. Complement pathway overview



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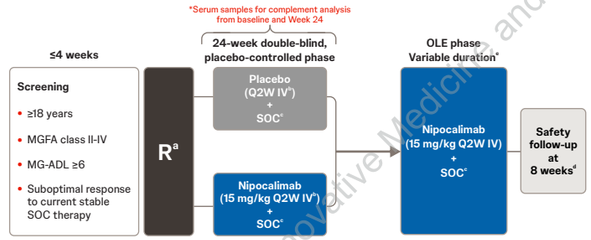
Objective

- **The purpose of this post-hoc analysis of Vivacity-MG3 was to evaluate whether nipocalimab reduces circulating complement components and activity indicative of complement activation.**

Methods

- Vivacity-MG3 (NCT04951622) is a double-blind, randomized, placebo-controlled, multicenter, phase 3 study evaluating efficacy and safety of nipocalimab in adults with gMG[2]

Figure 3. Study Design



[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). The analysis plan, however, grouped all seropositives together (AChR+, MuSK+, or LRP4+) vs triple seronegatives. [b]All patients received the loading dose of placebo or nipocalimab 30 mg/kg at Week 0 and then started placebo or nipocalimab 15 mg/kg Q2W IV from Week 2 to Week 24. [c]SOC includes acetylcholinesterase inhibitor, glucocorticosteroid, and/or immunosuppressant. [d]Participants who withdraw or discontinue after receiving any amount of study intervention are required to complete a safety follow-up visit 8 weeks after their last dose. *In the ELI, the OLE phase will be up to 240 weeks. ***AChR***=anti-acetylcholine receptor antibody-positive, ***ELI***=European Union, ***gMG***=generalized myasthenia gravis, ***IV***=intravenous, ***MG-ADL***=Myasthenia Gravis Activities of Daily Living, ***MGFA***=Myasthenia Gravis Foundation of America, ***MuSK***=anti-muscle-specific tyrosine kinase antibody-positive, ***OLE***=open-label extension, ***Q2W***=every 2 weeks, ***R***=randomized, ***SOC***=standard-of-care.

- In this exploratory analysis, available serum samples from seropositive participants were analysed at baseline and Week 24
  - Seropositive: positive for AChR/MuSK/LRP4
  - Least square means were compared between placebo and nipocalimab using linear mixed model
- Complement markers measured were: C3d circulating immune complexes (C3d-CIC), C1q immune complex binding (C1q-ICB), C3, C4, C5a, and total complement activity (CH50)
- Parallel assays quantified total IgG, IgG1/2/3/4, and anti-AChR titers, which informed a nonlinear mixed-model previously presented[3]

Results

Distribution of seropositive status

- Among 153 randomized and treated patients in VIVACITY-MG3 who were antibody-positive, 134 (88%) were antibody-positive for AChR, 16 (10%) for MuSK, and 3 (2%) for LRP4 (**Table 1**)[2]

Table 1. Distribution of anti-AChR, anti-MuSK, and anti-LRP4 status among patients who were antibody-positive at screening

	Placebo	Nipocalimab
Antibody-positive at screening (n)	76	77
Anti-AChR+, n (%)	71 (93)	63 (82)
Anti-MuSK+, n (%)	4 (5)	12 (16)
Anti-LRP4+, n (%)	1 (1)	2 (3)

Change from baseline in IgG and anti-AChR antibodies in seropositive patients

- At Week 24, nipocalimab was associated with substantial and sustained reductions in IgG1/2/3/4, and anti-AChR titers (**Table 2; Figure 4**).

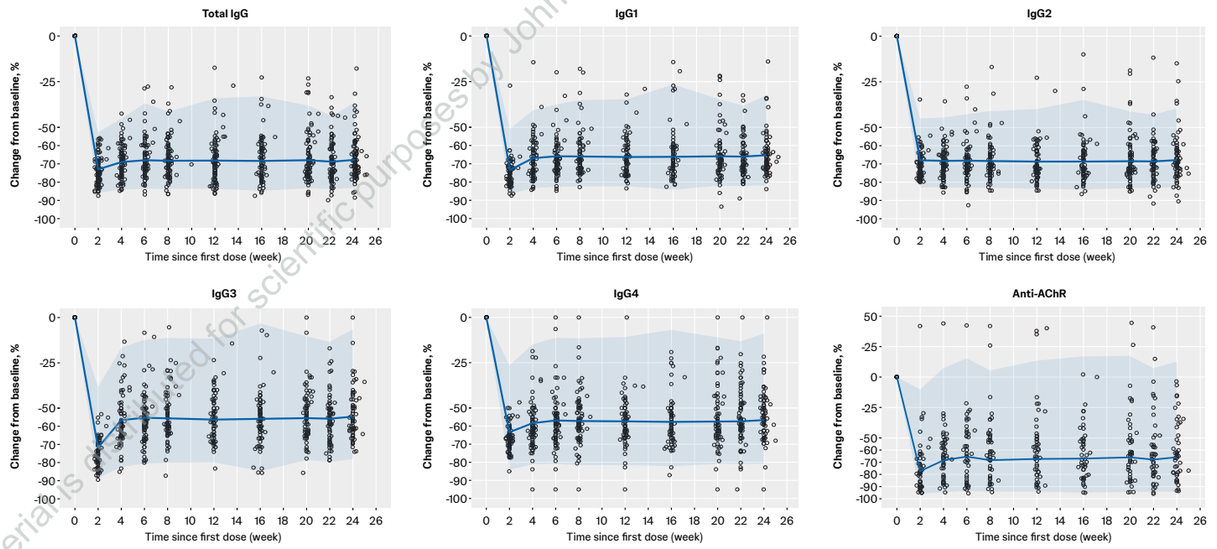
Table 2. Relative change from baseline of IgG and anti-AChR antibodies in seropositive patients with gMG at Week 24

Titer	Placebo		Nipocalimab	
	N	Observed mean % reduction [95% vpcPI]	N	Observed mean % reduction [95% vpcPI]
Total IgG	63	1.3 [−3.2; 3.3]	69	−67.9 [−69.9; −64.8]
IgG1	55	−2.0 [−4.0; 4.4]	54	−64.8 [−68.3; −62.4]
IgG2	55	1.8 [−4.7; 4.9]	54	−67.0 [−70.4; −65.1]
IgG3	55	3.1 [−5.4; 5.6]	54	−55.2 [−58.7; −49.9]
IgG4	55	−2.0 [−6.1; 6.5]	54	−54.0 [−62.0; −51.5]
Anti-AChR	46	−12.2 [−8.7; 9.6]	46	−65.1 [−72.9; −58.6]

N indicates number of seropositive patients with samples available for modelling of antibody titers.
***vpcPI**=visual predictive check prediction interval—a measure of model certainty in nonlinear mixed models.*

Simulated change in IgG and anti-AChR antibodies

Figure 4. Simulated change in total IgG, anti-AChR, and IgG1/2/3/4 with nipocalimab



Lines depict medians; areas depict 5th to 95th population quantiles; points depict observations.

Complement marker analysis in seropositive patients

- Baseline levels of complement markers were comparable across nipocalimab and placebo groups (**Table 3**)
- Concomitant decreases were observed in selected immune complex–associated complement markers (C3d-CIC and C1q-ICB, $p<0.05$; **Table 3**)
- A trend towards reductions in CH50 and C5a were detected with nipocalimab, which did not reach statistical significance (**Table 3**)

Table 3. Characteristics of complement protein measurements among seropositive patients

Complement proteins	Treatment	Time points: Baseline N	Baseline LS means*±SD	Week 24 N	Week 24 LS means*±SD	*p*-value	FDR**
CH50, activity units	Placebo	50	100.21 ± 5.65	49	101.22 ± 5.71	0.08	0.24
	Nipocalimab	52	103.48 ± 5.92	52	95.34 ± 6.00		
C1q ICB, µg Eq/mL	Placebo	14	6.15 ± 1.69	13	6.87 ± 1.71	0.01	0.04
	Nipocalimab	24	7.40 ± 1.78	13	5.50 ± 1.79		
C3d CIC, µg Eq/mL	Placebo	47	7.58± 0.90	47	7.25 ± 0.92	<0.001	<0.001
	Nipocalimab	51	7.60 ± 0.94	48	2.64 ± 0.96		
C3, g/L	Placebo	51	1.21 ± 0.04	50	1.21 ± 0.04	0.79	0.80
	Nipocalimab	54	1.22 ± 0.05	54	1.23 ± 0.05		
C4, g/L	Placebo	35	0.30 ± 0.02	35	0.29 ± 0.02	0.80	0.80
	Nipocalimab	33	0.28 ± 0.02	32	0.27 ± 0.02		
C5a, ng/mL	Placebo	50	9.46 ± 1.56	49	9.57 ± 1.60	0.12	0.18
	Nipocalimab	51	10.75 ± 1.64	49	7.98 ± 1.67		

*Note: N indicates number of seropositive patients with non-missing data for complement proteins.*LS means: adjusted values after accounting for confounding factors including age, sex, BMI, immunosuppressant, race, treatment arm, time point and treatment arm*time point. **FDR: multiple testing adjustment across the six complement proteins.*
***BMI**=body mass index, **CIC**=circulating immune complex, **FDR**=false discovery rate, **ICB**=immune complex binding, **LS**=least square, **SD**=standard deviation.*

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