

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

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Introduction

- Myasthenia gravis (MG) is characterized by pathogenic immunoglobulin G (IgG) autoantibody-mediated impairment of neurotransmission leading to fatigable muscle weakness¹
- Acetylcholine receptor (AChR) antibodies are detected in up to 85% of patients with MG¹
 - 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 membrane¹
- Nipocalimab is a fully human monoclonal antibody that binds to the neonatal Fc receptor 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

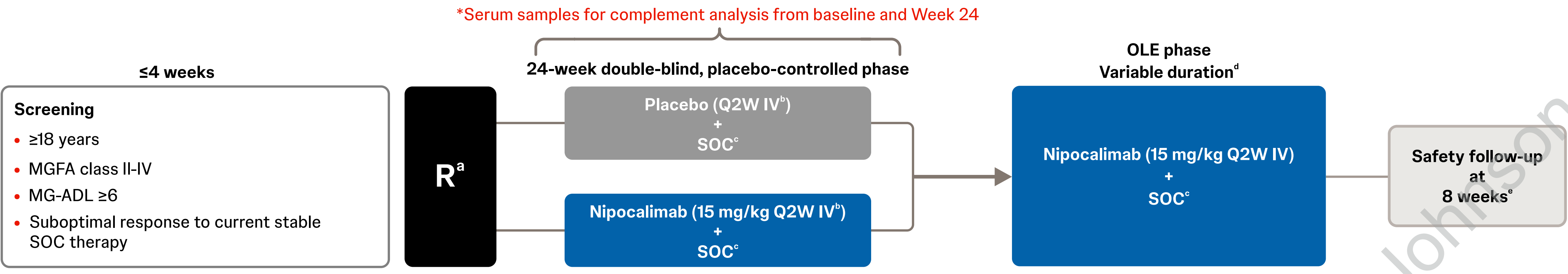
Objective

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 gMG²

Figure 3. Study Design



*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. *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. *SOC includes acetylcholinesterase inhibitor, glucocorticosteroid, and/or immunosuppressant. *In the EU, the OLE phase will be up to 240 weeks. *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. *AChR+=anti-acetylcholine receptor antibody-positive, EU=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.

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

	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)

AChR=anti-acetylcholine receptor, LRP4=low-density lipoprotein receptor-related protein 4, MuSK+=anti-muscle-specific tyrosine kinase antibody-positive.

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

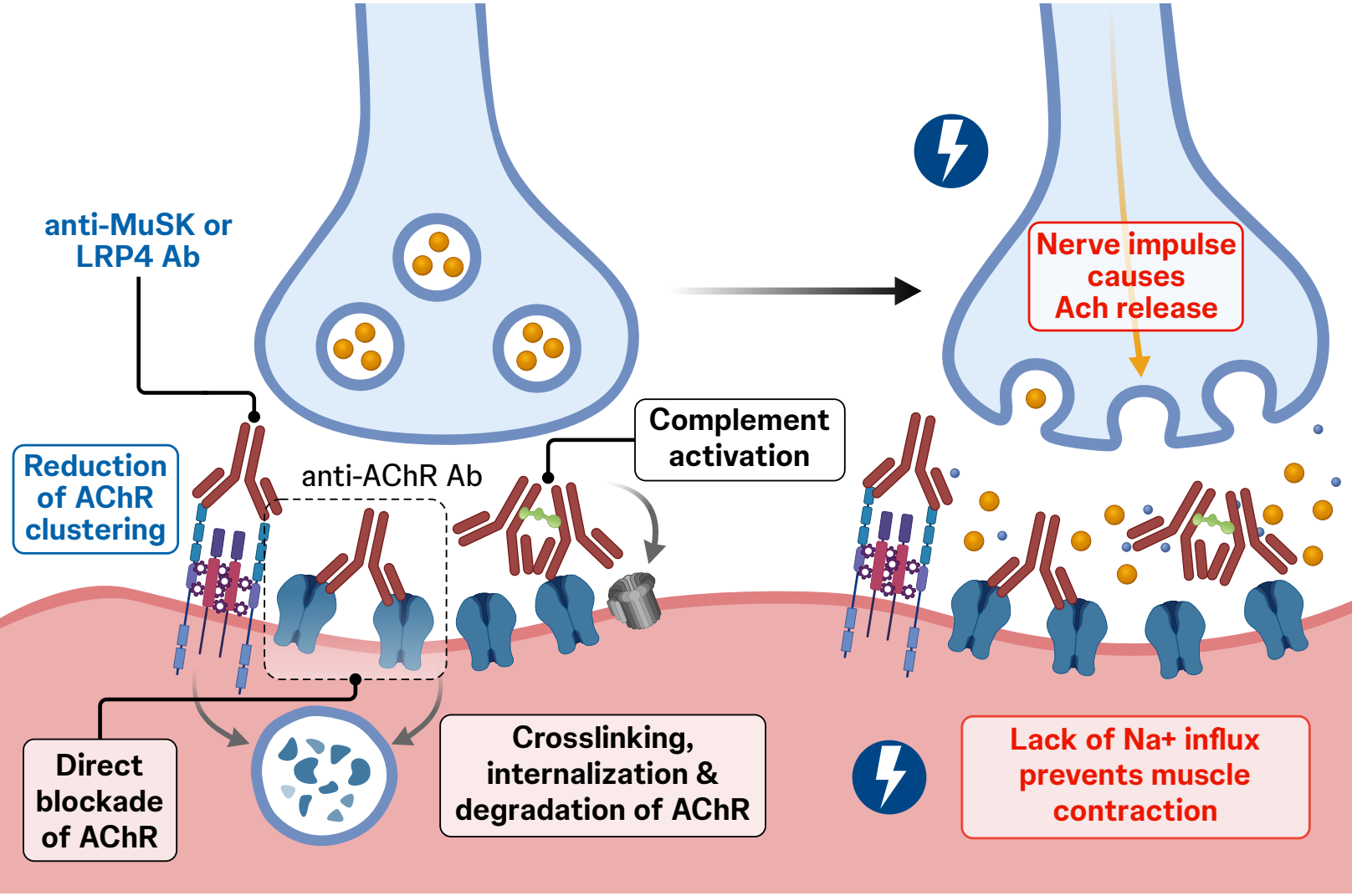
- At Week 24, nipocalimab was associated with substantial and sustained reductions in IgG1/2/3/4, and anti-AChR titers (Table 2; Figure 4)

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]

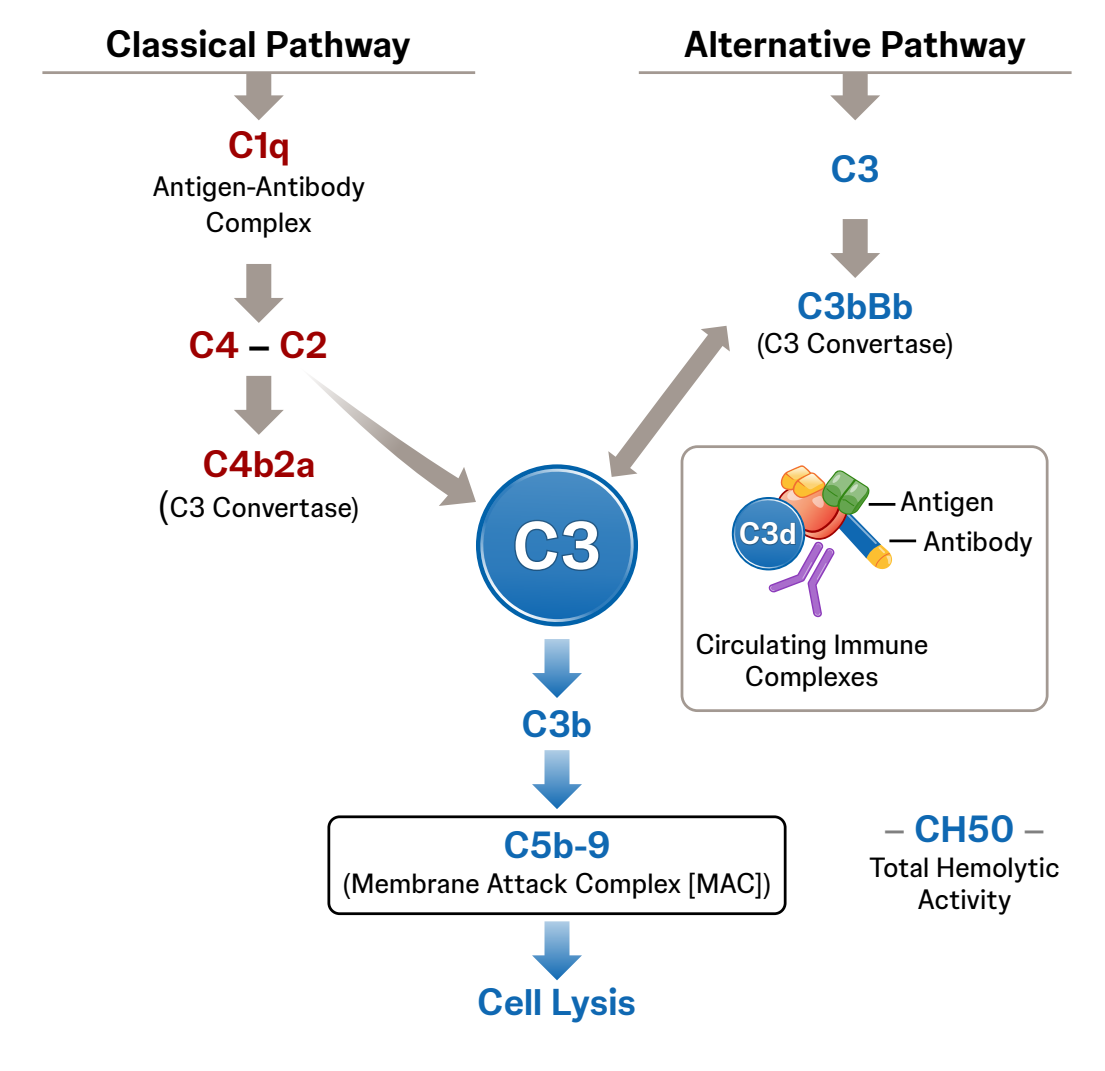
N indicates number of seropositive patients with samples available for modelling of antibody titers. AChR=anti-acetylcholine receptor, IgG=immunoglobulin G, vpcPI=visual predictive check prediction interval—a measure of model certainty in nonlinear mixed models.

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 box □). MuSK and LRP4 antibodies may reduce AChR clustering (blue box □). These result in impaired neural transmission at the neuromuscular junction (red box □).

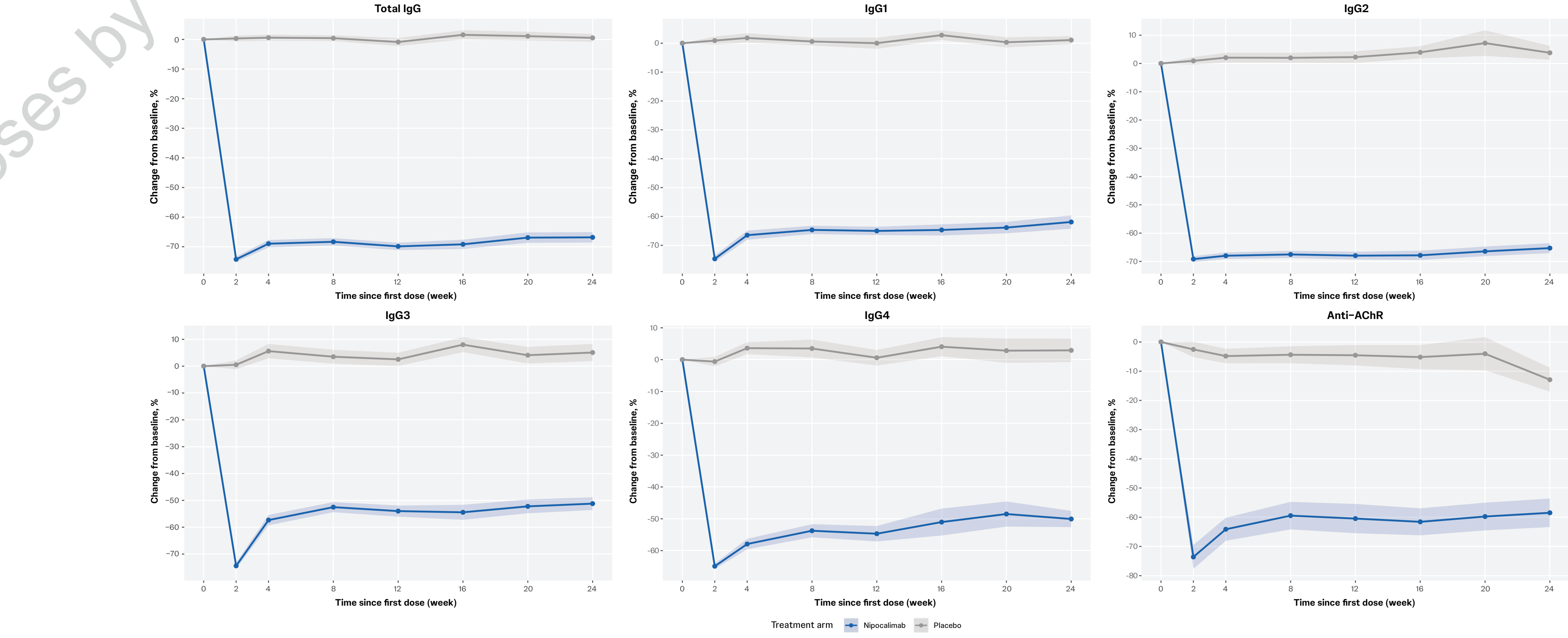
Figure 2. Complement pathway overview



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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 means; shaded areas depict standard error. AChR=anti-acetylcholine receptor, IgG=immunoglobulin G.

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				p-value	FDR**
		N	LS means*±SD	N	LS means*±SD		
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.