

Immunogenicity Assessment With Nipocalimab Treatment in Patients With Generalized Myasthenia Gravis

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Introduction

- Generalized myasthenia gravis (gMG), a rare chronic condition, is characterized by pathogenic immunoglobulin G (IgG) autoantibody-mediated impairment of neurotransmission leading to fatigable muscle weakness^{1,2}
- 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^{3,4}
- 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 in patients with gMG who are seropositive (acetylcholine receptor [AChR]+, muscle-specific receptor tyrosine kinase [MuSK]+, or low-density lipoprotein receptor-related protein 4 [LRP4]+)⁵
- The immunogenicity of nipocalimab was evaluated in Vivacity-MG3 study as a secondary objective

Objective

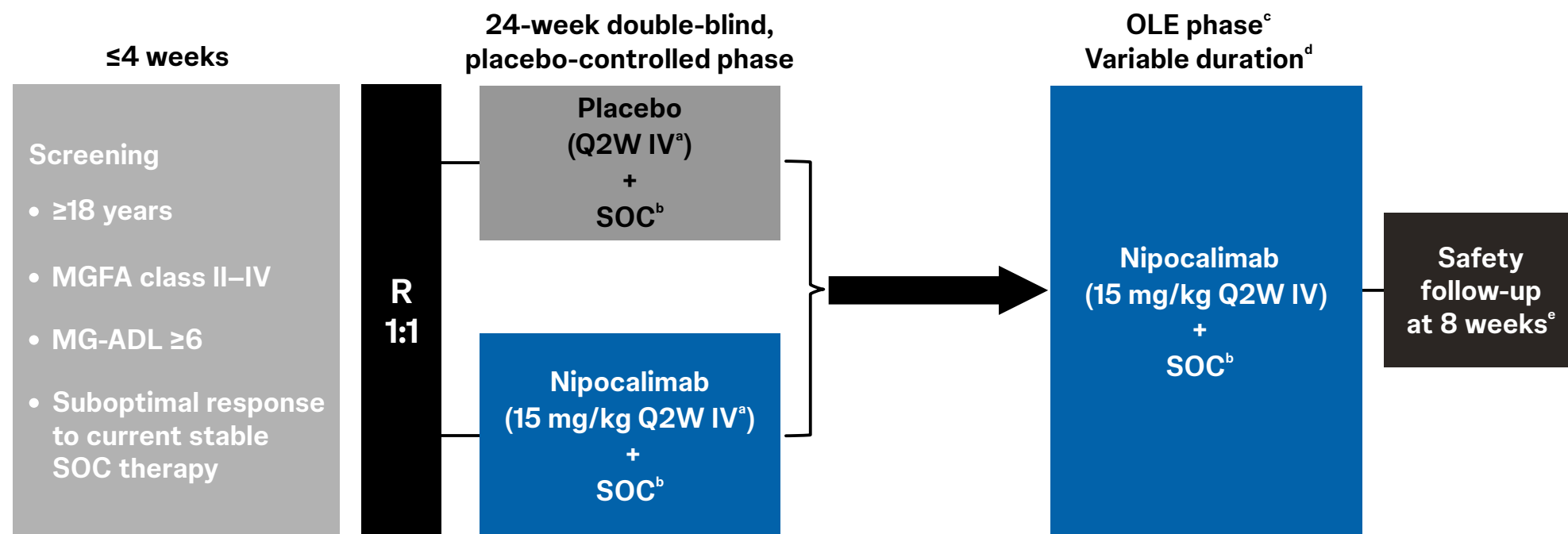
To evaluate the occurrence of anti-drug antibodies (ADA) and neutralizing-antibodies (NAb) to nipocalimab, and impact on pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety in patients with gMG in Vivacity-MG3

Methods

Study design

- Vivacity-MG3 (NCT04951622) is a double-blind, randomized, placebo-controlled, multicenter, phase 3 study evaluating efficacy and safety of nipocalimab in adults with gMG (**Figure 1**)⁵
 - Patients were randomized to intravenous nipocalimab + SOC or placebo + SOC for 24 weeks in the double-blind phase, followed by an option to enter the open-label extension (OLE) phase

Figure 1. Study Design



*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. †Due to the COVID-19 pandemic, some participants from the phase 2 study (NCT03772587) were unable to enter the phase 2 OLE study (NCT03896295). These participants could directly enter the Phase 3 OLE. ‡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. EU=European Union, IV=intravenous, MG-ADL=Myasthenia Gravis Activities of Daily Living, MGFA=Myasthenia Gravis Foundation of America, OLE=open-label extension, Q2W=every 2 weeks, R=randomized, SOC=standard of care.

Immunogenicity analyses

- Serum samples were collected at selected time points up to Week 96 after nipocalimab initiation
- Incidence of antibodies to nipocalimab and peak titers of ADAs were evaluated in all patients who received at least 1 dose (partial or complete) of nipocalimab in either the double-blind or OLE phase and have at least 1 post-dose serum sample evaluable for antibodies to nipocalimab (immunogenicity analysis set)
- ADAs were detected using a specific, highly sensitive and drug tolerant electrochemiluminescence immunoassay (ECLIA) method
- ADA positive samples in ADA positive patients were further analyzed for NAb using a non-cell based competitive ligand binding ECLIA assay
- The impacts of treatment-emergent (TE) ADA were assessed on the following endpoints: PK (serum nipocalimab concentrations), PD (changes from baseline in total IgG/anti-AChR binding autoantibody levels), efficacy (Myasthenia Gravis Activities of Daily Living [MG-ADL] total scores), and safety (infusion-related reactions [IRRs])
 - Of note, the TE-ADA includes patients who had treatment-boosted or treatment-induced ADA at any time after their first nipocalimab administration through the end of study visit

Results

Incidences of ADA and NAb to nipocalimab

- A total of 194 patients treated with nipocalimab had post-treatment serum samples evaluated for ADA
- The overall incidence of treatment-emergent ADA up to Week 96 was 42.8% (83/194), with generally low titers (**Table 1**)
 - The majority (92.8% [77/83]) of ADA positive patients had peak titer levels ≤1:80; 75.9% (63/83) had peak titer levels ≤1:20
- All 83 patients who were ADA positive had post-treatment serum samples available for NAb assessment
- The overall incidence of NAb to nipocalimab was 22.7% (44/194)

Table 1. Incidences of ADA and NAb to nipocalimab

	Nipocalimab/ Nipocalimab	Placebo/ Nipocalimab	Nipocalimab (OL)*	All Nipocalimab
Immunogenicity analysis set	97	78	19	194
Positive for ADA	48 (49.5%)	24 (30.8%)	11 (57.9%)	83 (42.8%)
Peak titers				
1:10	25	9	6	40
1:20	14	6	3	23
1:40	3	1	1	5
1:80	4	5	0	9
1:160	1	1	0	2
1:320	1	1	0	2
1:640	0	1	0	1
1:1280	0	0	0	0
1:2560	0	0	0	0
1:5120	0	0	0	0
1:10240	0	0	1	1
Positive for NAb	19 (19.6%)	17 (21.8%)	8 (42.1%)	44 (22.7%)

*Participants from phase 2 studies (NCT03772587, NCT03896295) who entered the Vivacity-MG3 OLE phase directly. ADA=anti-drug antibody, NAb=neutralizing antibody, OL=open-label.

ADA and study discontinuation

- Development of ADA was not associated with study discontinuation
- Among 36 patients who discontinued the study, 13 (36.1%) were ADA positive and 23 (63.9%) were ADA negative (**Table 2**)

Table 2. Incidence of ADA in patients who discontinued the study

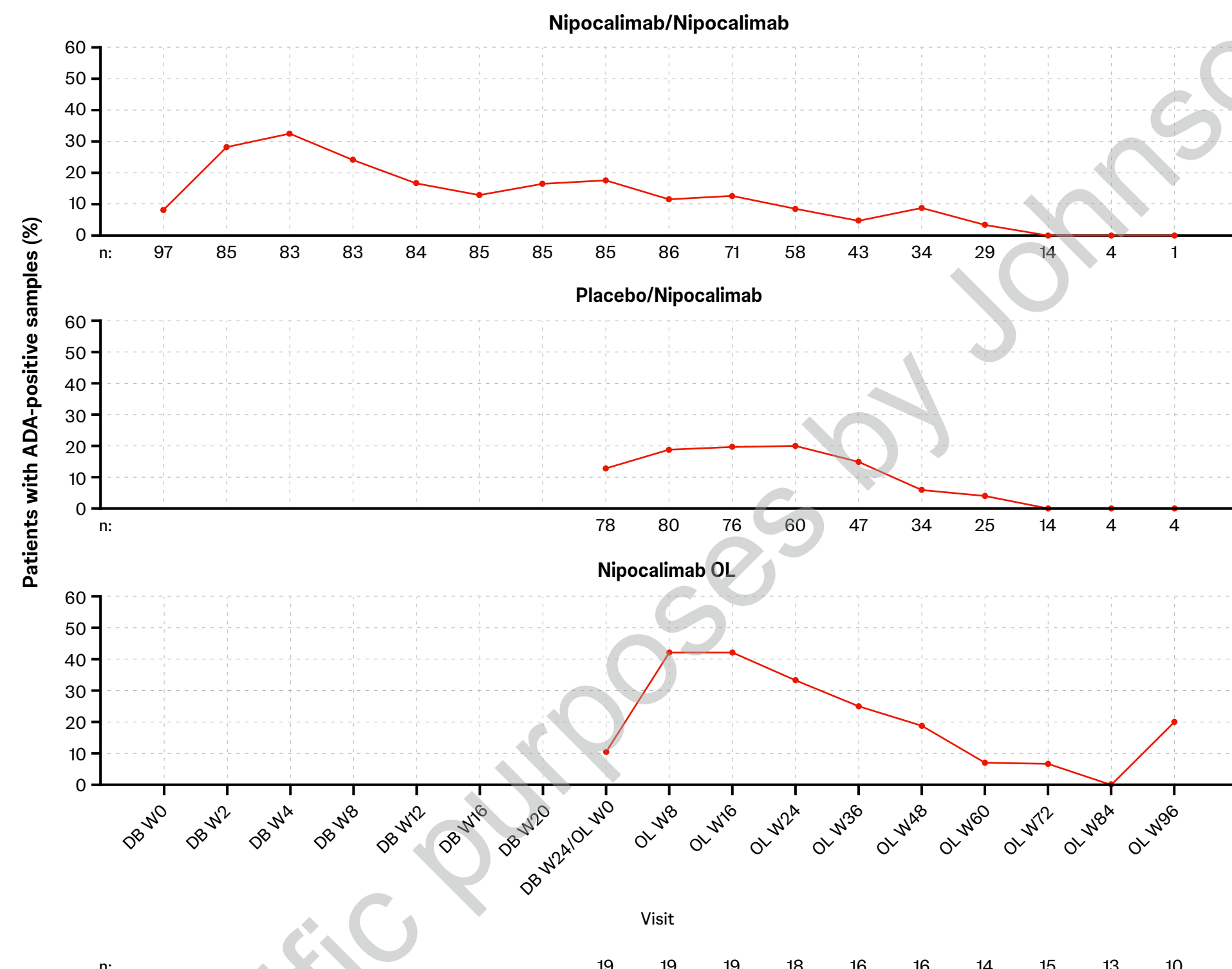
	Nipocalimab/ Nipocalimab	Placebo/ Nipocalimab	Nipocalimab (OL)	All Nipocalimab
Immunogenicity analysis set	97	78	19	194
Terminated study participation prematurely	22	10	4	36
ADA positive*	10 (45.5%)	1 (10.0%)	2 (50.0%)	13 (36.1%)
ADA negative*	12 (54.5%)	9 (90.0%)	2 (50.0%)	23 (63.9%)

*Patients positive for treatment-emergent antibodies to nipocalimab includes all patients who were positive (treatment-boosted or treatment-induced) at any time after their first nipocalimab administration through OL phase. Patients with baseline positive samples and without at least 4-fold increased titer after treatment are not considered treatment-boosted or treatment-emergent. *Excludes patients who were treatment-emergent positive at any time through OLE phase. ADA=anti-drug antibody, NAb=neutralizing antibody, OL=open-label.

Frequency of ADA-positive samples by visit through open-label phase

- Antibodies to nipocalimab were transiently developed
- Most of the ADA positive patients developed ADA earlier (as early as Week 2) but became ADA negative at later time points (**Figure 2**)
- Therefore, the incidence of sample-level ADA was diminished over time
 - The diminishing of ADA over time is not unexpected. As a monoclonal antibody against FcRn, nipocalimab is expected to reduce IgG levels, including ADA to nipocalimab (generally IgG-based)

Figure 2. ADA status per visit

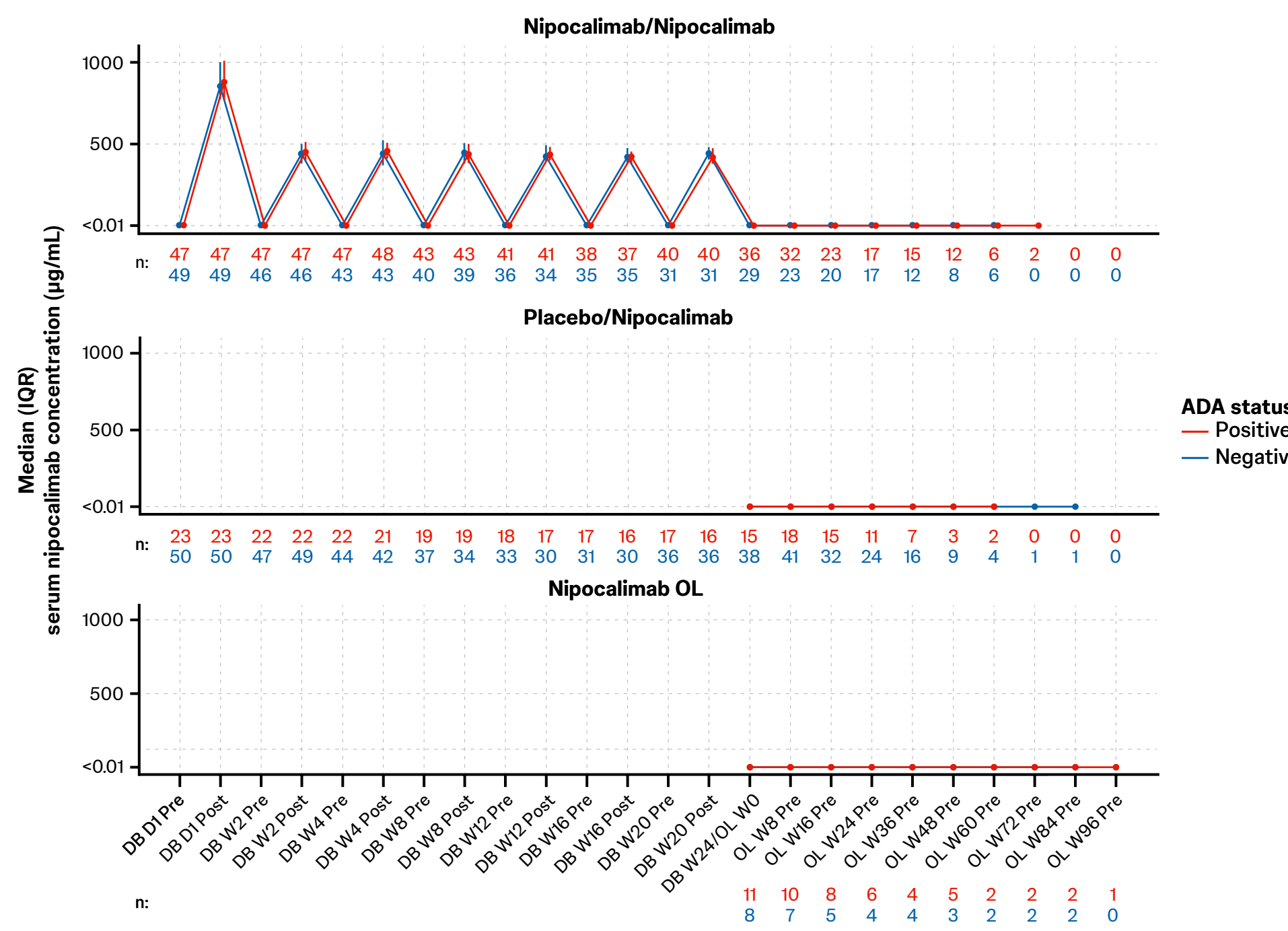


n numbers indicate number of patients with appropriate samples at the visit. X axis represents visit, and is not scaled linearly with duration between visits. DB=double-blind, OL=open-label, W=week.

Impact of ADA on serum nipocalimab concentration

- The presence of ADA to nipocalimab did not alter the PK of nipocalimab (**Figure 3**)
 - Median and mean serum nipocalimab concentrations in ADA positive patients were comparable to those in ADA negative patients at respective sampling time points
 - No trend in decreasing serum nipocalimab concentrations were observed in ADA positive patients when compared with ADA negative patients
- Similar findings were observed between NAb positive and NAb negative patients

Figure 3. Serum nipocalimab concentration by ADA status

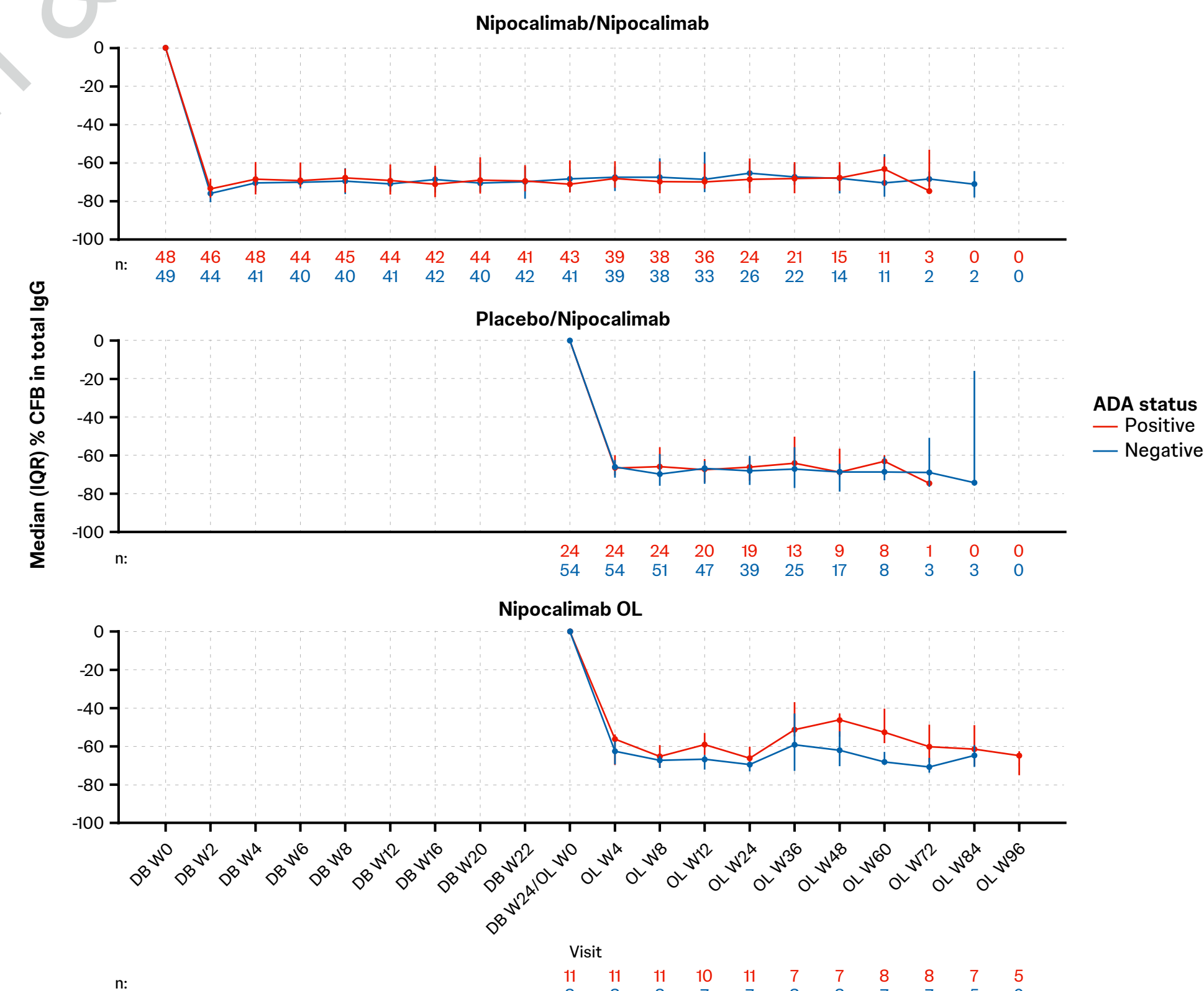


X axis represents visit, and is not scaled linearly with duration between visits. Of note, only trough (pre-dose) serum samples were taken during the OL period and all median trough (pre-dose) serum nipocalimab concentrations were below the limit of quantification. ADA=anti-drug antibody, DB=double-blind, OL=open-label, IQR=interquartile range, W=week.

Impact of ADA on IgG reduction

- The presence of ADA to nipocalimab did not reduce the % change in total IgG levels from baseline (**Figure 4**)
 - Median % changes in total IgG from baseline in ADA positive patients were comparable to those in ADA negative patients at respective sampling time points
- Similar findings were observed between NAb positive and NAb negative patients

Figure 4. Change from baseline in total IgG by ADA status

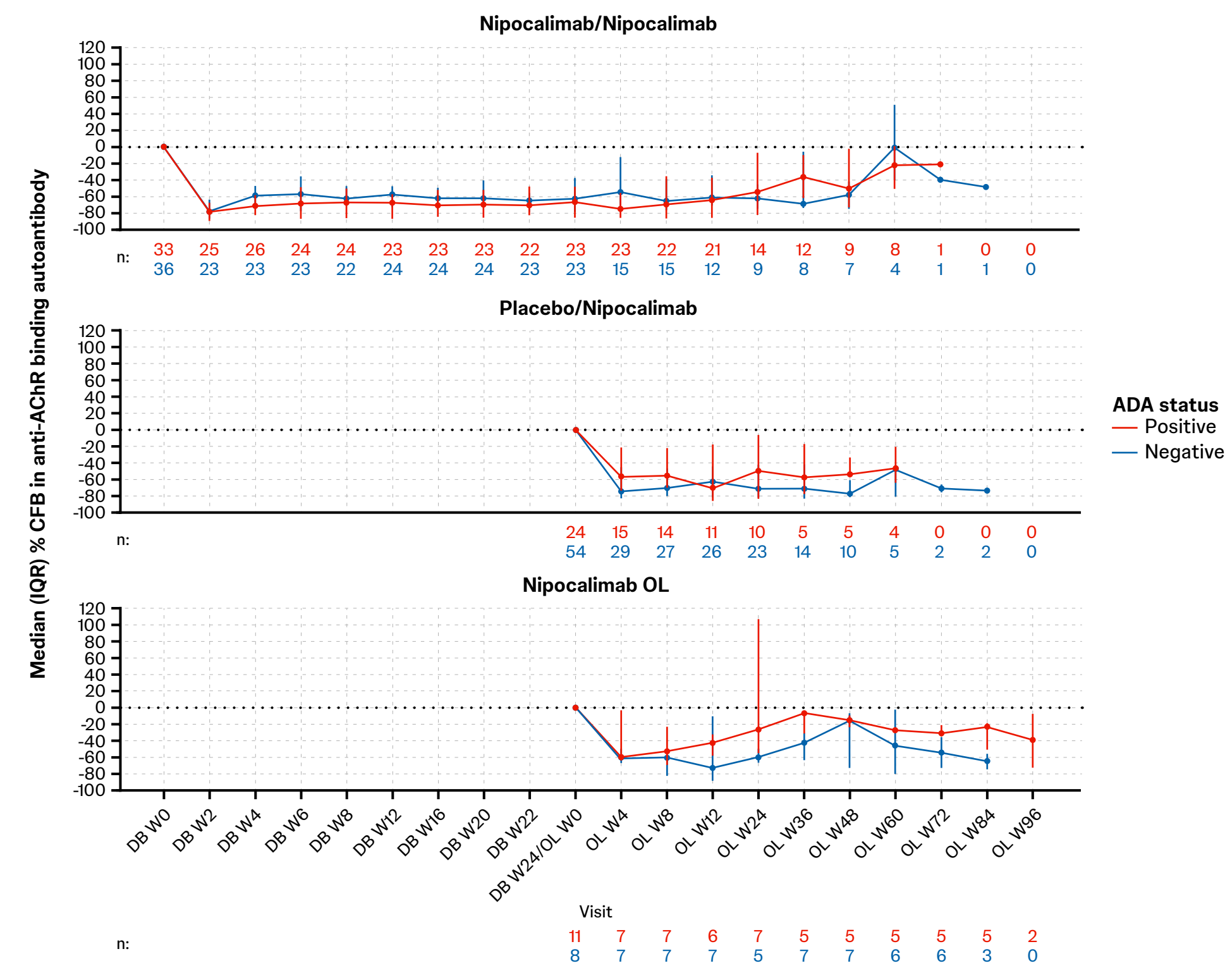


X axis represents visit, and is not scaled linearly with duration between visits. ADA=anti-drug antibody, CFB=change from baseline, DB=double-blind, OL=open-label, IgG=immunoglobulin G, IQR=interquartile range, W=week.

Impact of ADA on pathogenic autoantibody reduction

- The presence of ADA to nipocalimab did not reduce the % change in anti-AChR binding autoantibody levels from baseline (**Figure 5**)
 - Median % changes in anti-AChR binding autoantibody level from baseline in ADA positive patients were comparable to those in ADA negative patients at respective sampling time points
- Similar findings were observed between NAb positive and NAb negative patients

Figure 5. Change from baseline in anti-AChR binding autoantibody levels by ADA status



X axis represents visit, and is not scaled linearly with duration between visits. AChR=acetylcholine receptor, ADA=anti-drug antibody, CFB=change from baseline, DB=double-blind, OL=open-label, IQR=interquartile range, W=week.

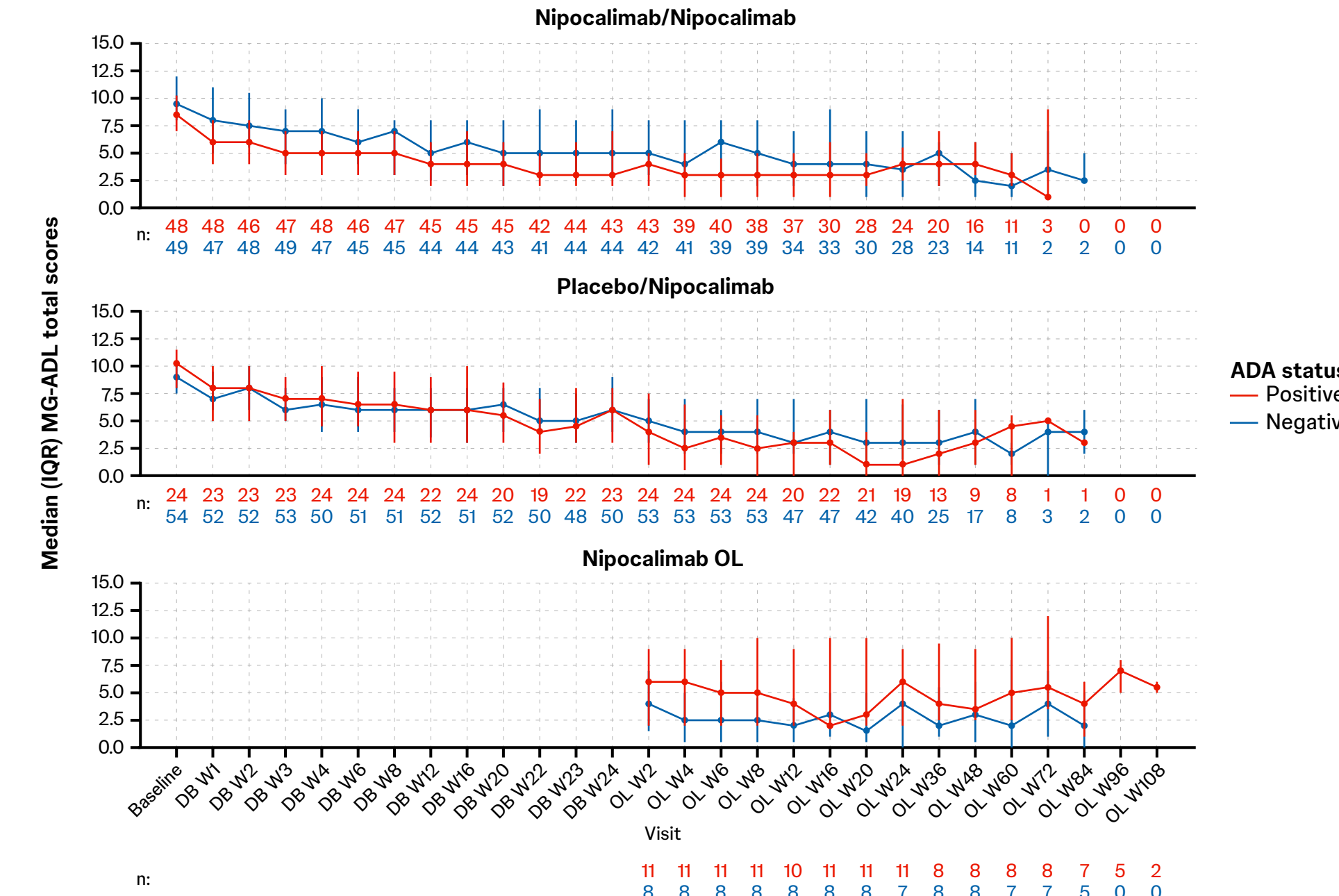
Key Takeaways

- Development of ADA was transient in nipocalimab-treated patients, and the incidence of ADA positive samples appeared to be diminished over time
- The presence of ADA and NAb to nipocalimab did not alter the PK, PD, efficacy, or safety profiles of nipocalimab
- Development of ADA was not associated with discontinuation from study participation
- The immunogenicity of nipocalimab is not clinically relevant in patients with gMG

Impact of ADA on nipocalimab efficacy

- The presence of ADA to nipocalimab was not associated with reduced efficacy (**Figure 6**)
 - Median changes in MG-ADL total score from baseline over time in ADA positive patients appeared to be generally comparable to those in ADA negative patients at respective sampling time points
 - No trend in decreasing efficacy was observed in ADA positive vs ADA negative patients
- Similarly, no impact of NAb on nipocalimab efficacy was observed
- MG-ADL non-responders did not show higher incidence of ADA compared with MG-ADL responders
 - In the nipocalimab/nipocalimab group, incidence of ADA was 55.4% (36/65) among MG-ADL responders and 37.5% (12/32) among MG-ADL non-responders at double-blind Week 24
- Among AChR+ and MuSK+ patients in the nipocalimab/nipocalimab group, 75.0% (30/40) of ADA positive vs 62.2% (23/37) of ADA negative patients achieved at least 2 points MG-ADL improvement at double-blind Week 24

Figure 6. MG-ADL total score by ADA status

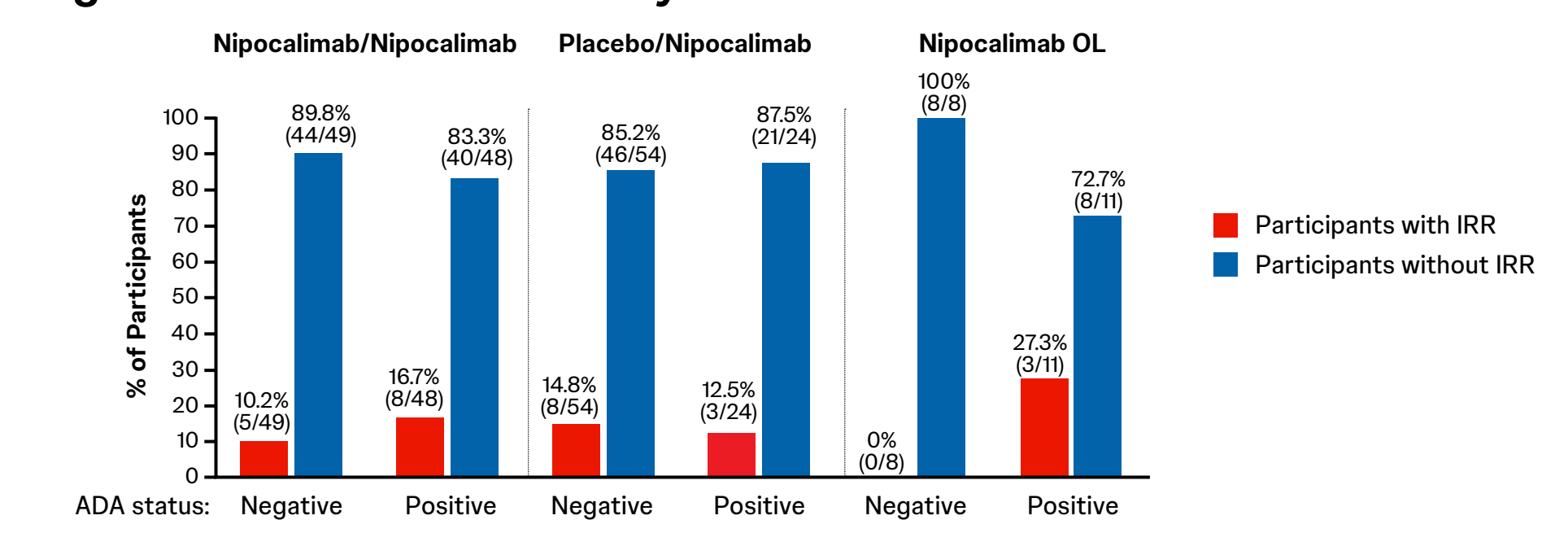


X axis represents visit, and is not scaled linearly with duration between visits. ADA=anti-drug antibody, DB=double-blind, MG-ADL=Myasthenia Gravis Activities of Daily Living, OL=open-label, IQR=interquartile range, W=week.

Impact of ADA on infusion-related reactions

- The development of ADA to nipocalimab did not appear to be associated with the occurrence of infusion-related reactions (IRRs) (**Figure 7**)
 - Through the OLE phase, 14 (16.9%) of the 83 ADA positive patients had an IRR, while 13 (11.7%) of the 111 ADA negative patients had IRRs
 - 23 (1.0%) of the 2,248 nipocalimab infusions in ADA positive patients were associated with an IRR, while 10 (0.4%) of the 2,716 nipocalimab infusions in ADA negative patients were associated with IRRs
- All IRRs were mild (infusion-site pain, erythema, bruising, hematoma, or extravasation) without any severe or serious IRRs, or IRRs leading to discontinuation
- Similar findings were observed between NAb positive and NAb negative patients

Figure 7. Incidence of IRRs by ADA status



ADA=anti-drug antibody, OL=open-label, IRR=infusion-related reaction.