

Effect of Nipocalimab on Pathogenic IgG and Circulating Immune Complex Levels: A Role in Myasthenia Gravis-Activities of Daily Living Score Improvement in Patients With Generalized Myasthenia Gravis

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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 (**Figure 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^{2,3}
- Nipocalimab is approved for the treatment of generalized MG (gMG) in adult and adolescent (≥12 years of age) patients who are AChR positive or anti-muscle-specific tyrosine kinase (MuSK) antibody positive^{4,5}
- In the phase 3 Vivacity-MG3 study, nipocalimab added to standard-of-care (SOC) substantially reduced circulating IgG, including pathogenic autoantibodies, and demonstrated rapid and sustained disease control over 24 weeks in seropositive patients with gMG⁶
 - Reductions in complement components, including C3d circulating immune complex (CIC), were also observed with nipocalimab⁷

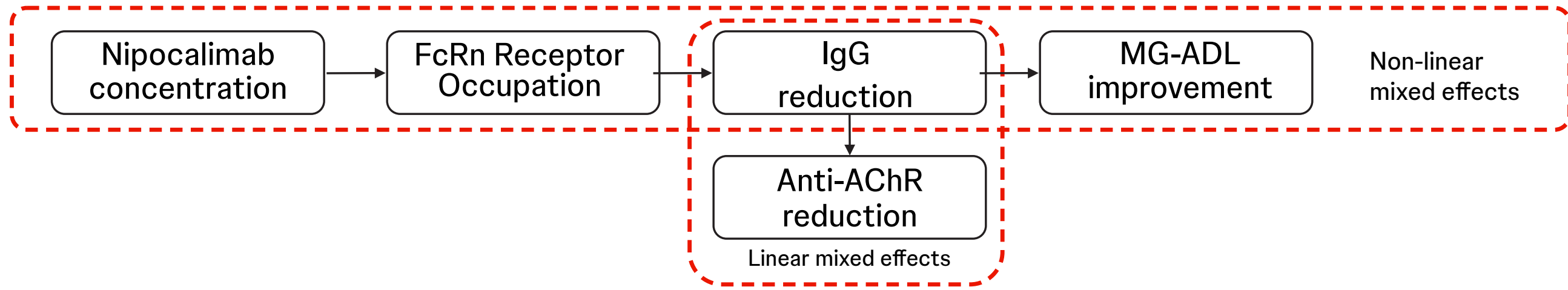
Objective

To quantify the effect of nipocalimab-induced total and pathogenic anti-AChR IgG reduction on complement C3d immune complex levels and their associative roles in Myasthenia Gravis-Activities of Daily Living (MG-ADL) improvement in patients with gMG

Methods

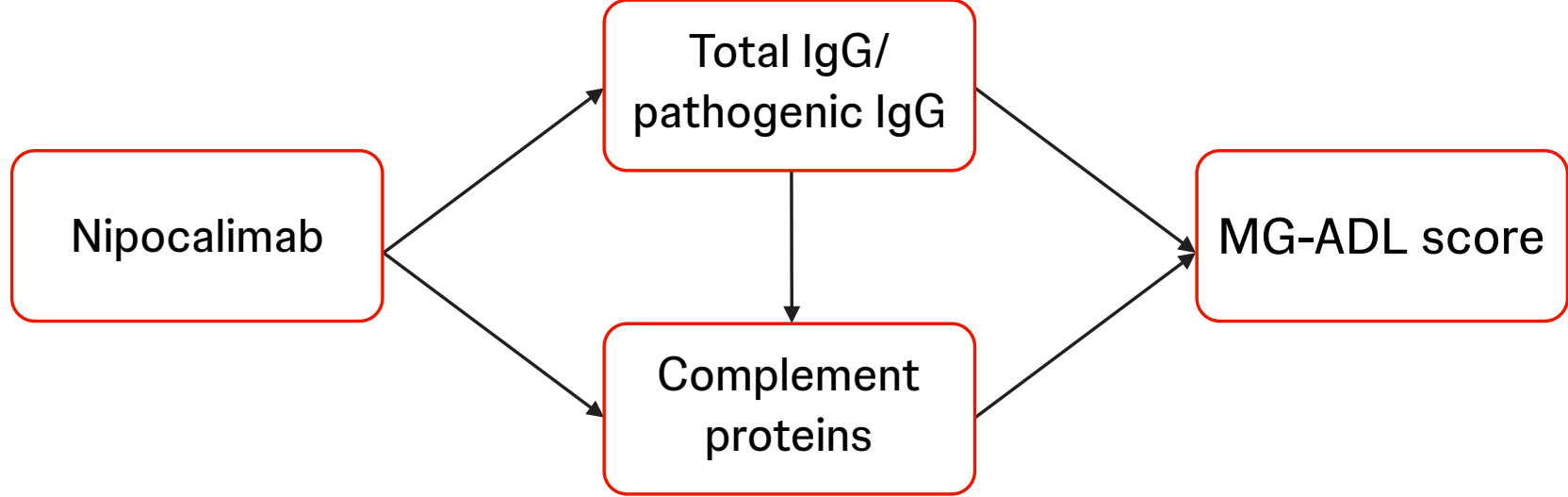
- A previously published non-linear mixed effects model^{8,9} describing nipocalimab serum concentrations, FcRn receptor occupancy, total IgG reductions and MG-ADL score improvements was fitted to all available data (**Table 1**). A linear relationship between total IgG reduction and anti-AChR concentration was further identified in Vivacity-MG3 data through linear mixed effects modeling (**Figure 2**)
- Linear models were fitted through causal mediation and used to describe the sequential reduction of total IgG, anti-AChR, and C3d levels, and explore association with MG-ADL improvement at Week 24 of Vivacity-MG3 (**Figure 3**)

Figure 2. High-level longitudinal model structure showing non-linear mixed effects relationships between nipocalimab serum concentration, FcRn receptor binding, IgG reduction through blocking FcRn-mediated recycling, and subsequent MG-ADL improvement. IgG reduction was also linearly linked to anti-AChR reduction



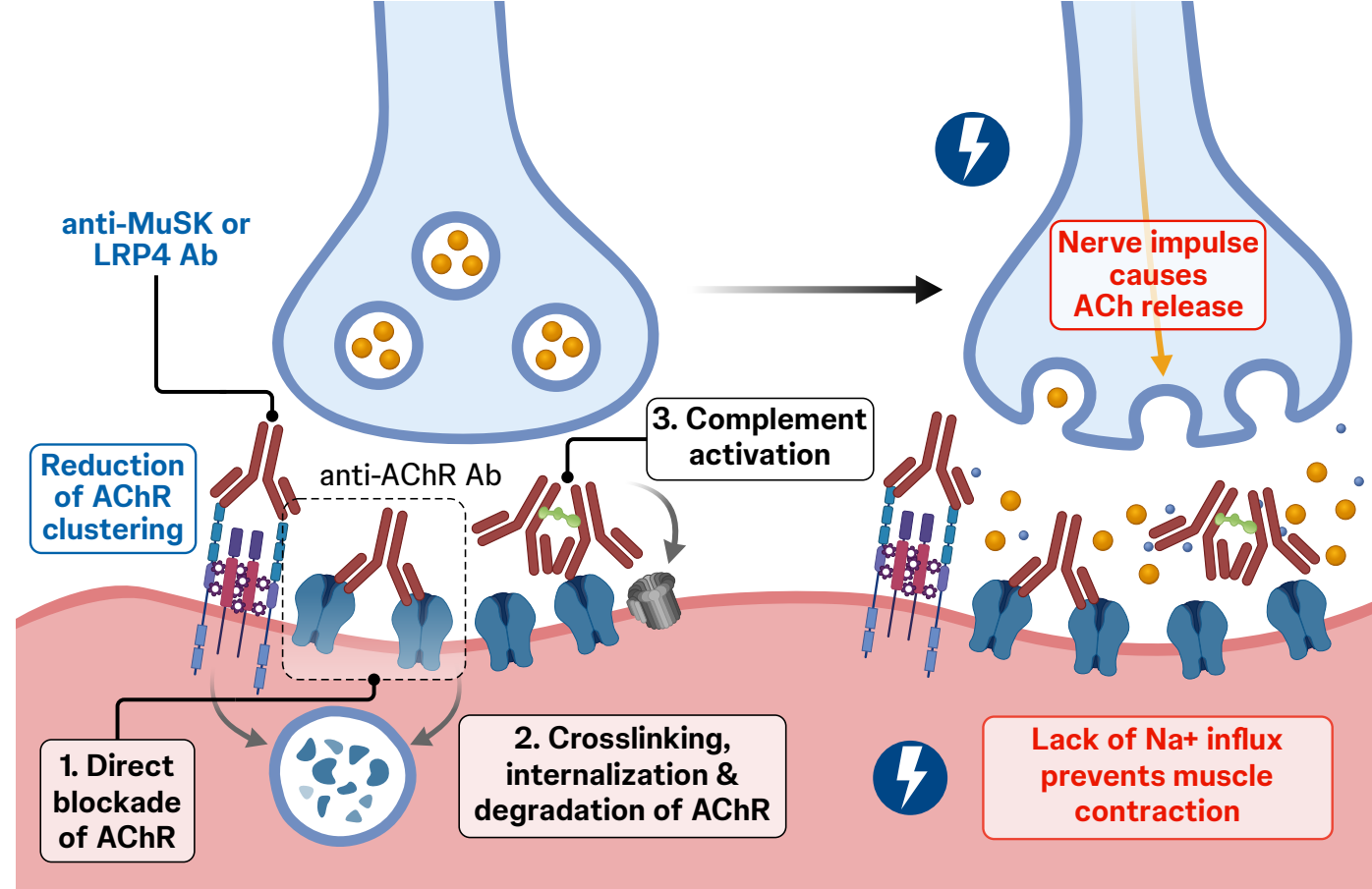
Anti-AChR=anti-acetylcholine receptor; FcRn=neonatal Fc receptor; IgG=immunoglobulin G.

Figure 3. Potential relationships between IgG reduction, complement reduction, and MG-ADL improvement by nipocalimab



IgG=immunoglobulin G, MG-ADL=Myasthenia Gravis-Activities of Daily Living.

Figure 1. Mechanisms of MG pathogenesis



MG has several mechanisms of pathogenicity. AChR-related effector mechanisms include 1) direct blockade of AChR; 2) crosslinking, internalization, and degradation of AChR; and 3) 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**). Ab=antibody; ACh=acetylcholine; AChR=acetylcholine receptor; Anti-AChR=anti-acetylcholine receptor; Anti-MuSK=anti-muscle-specific tyrosine kinase; LRP4=low-density lipoprotein receptor-related protein 4; MG=myasthenia gravis; Na⁺=sodium ions.

Table 1. Data sources for non-linear mixed effects model, linear mixed effects model and causal mediation analysis

Studies	Dosing	Participants	Samples	Used in
Phase 1 studies (N=5)	Single IV doses from 0.3 to 60 mg/kg, flat doses of 300 and 1200 mg. Multiple IV doses: 15 mg/kg QW (x4) 30 mg/kg QW (x4)	N=160 (126 treated, 34 placebo)	PK: Rich PK profiles. RO: Sampled in M281-001, ED1H001, and ED1H002. Total serum IgG: Rich sampling.	PK-RO-IgG model
Vivacity-MG Phase 2	Placebo, 5mg/kg Q4W, 30mg/kg Q4W and 60mg/kg Q2W	N=68 (54 treated, 14 placebo)	PK: Day 1 predose and postdose, Day 15 predose, Day 29 predose, Day 43 predose, Day 57 predose and postdose, Day 85. RO: Not sampled. Total serum IgG: Screening, baseline (Day 1), Day 15, 29, 43, 57, 85, and 113. MG-ADL: Screening, baseline (Day 1), Day 15, 29, 43, 57, 85, and 113.	PK-RO-IgG-MGADL model
Vivacity-MG3 Phase 3	Placebo, 15 mg/kg Q2W	N=196 (98 treated, 98 placebo)	PK: Predose and postdose (45 minutes after the end of infusion) on Day 1 and Weeks 2, 4, 8, 12, 16, 20, and 24. RO: Not sampled. Total serum IgG: Screening, baseline (Day 1) and predose on Weeks 2, 4, 6, 8, 12, 16, 20, 22, and 24. Anti-AChR autoantibodies: Screening, baseline (Day 1) and predose on Weeks 2, 4, 6, 8, 12, 16, 20, 22, and 24. MG-ADL: Screening, baseline (Day 1), Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 22, 23, and 24.	PK-RO-IgG-MGADL model, IgG-Anti-AChR model Causal mediation analysis (Week 24 data only)

AChR=acetylcholine receptor; IgG=immunoglobulin G, IV=intravenous, MG-ADL=Myasthenia Gravis Activities of Daily Living, PK=pharmacokinetics, Q2W=every 2 weeks, Q4W=every 4 weeks, QW=once weekly, RO=receptor occupancy.

Results

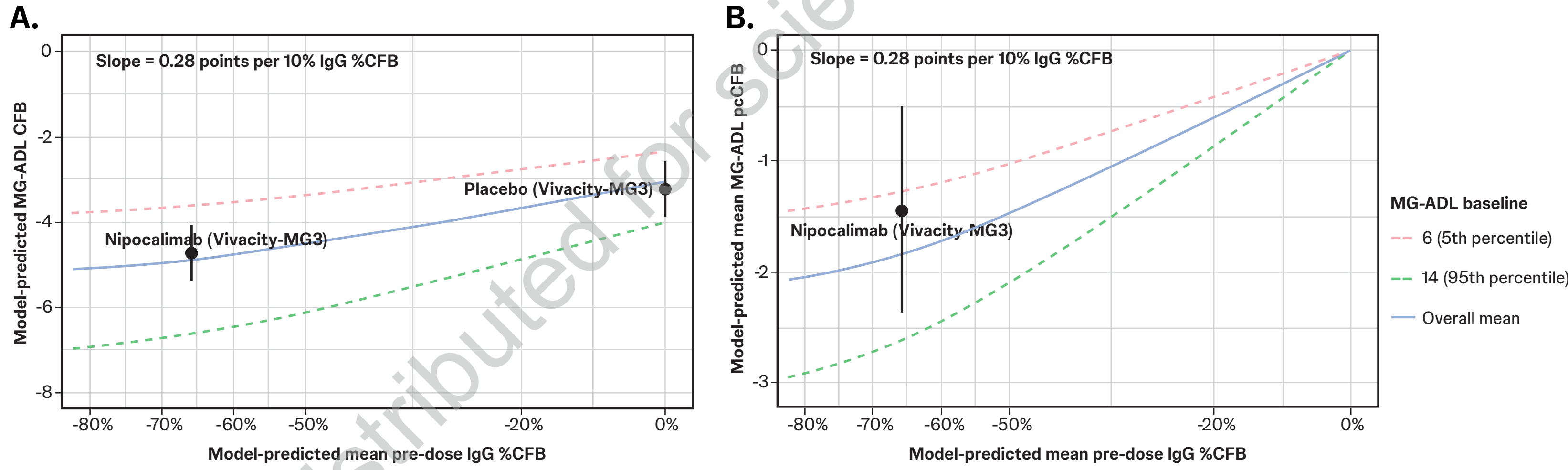
Simulated change in IgG and anti-AChR antibodies, and MG-ADL scores

- NLME simulations predicted nipocalimab 15mg/kg Q2W (approved maintenance dose⁴) results in mean % change from baseline (CFB) -65.9% pre-dose IgG, mean %CFB -64.8% anti-AChR, and mean %CFB -1.84 points MG-ADL (placebo-corrected) at steady-state

Relationship between total serum IgG and MG-ADL

- In the NLME model, %CFB total IgG predicted the overall average effect on MG-ADL CFB (105%; **Figure 4**)
 - The predicted Vivacity-MG3 averaged mean pcCFB was -1.84 points
 - Proportion of treatment effect (PTE) explained by the mediator >100% due to sampling variability; the true PTE is likely close to 100%
- Between-patient variability was high, with standard deviations of ±1.87 points on initial placebo effect, ± 0.31 points per 10% IgG %CFB on the drug effect slope, and a further additive residual error of ±1.43 SD

Figure 4. Model-predicted relationship between mean %CFB in total serum IgG and (A) MG-ADL CFB and (B) MG-ADL placebo-corrected CFB at Week 24

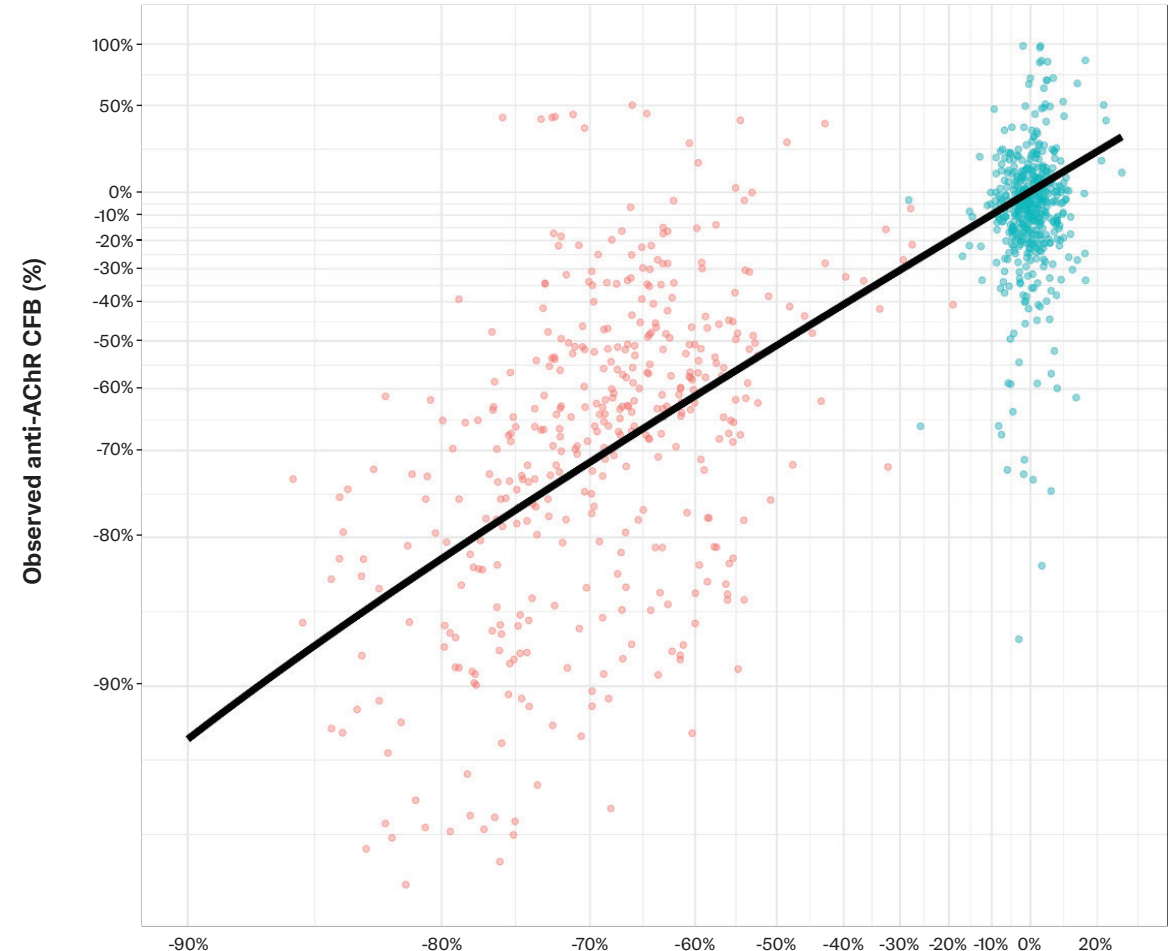


CFB=change from baseline, IgG=immunoglobulin G, MG-ADL=Myasthenia Gravis-Activities of Daily Living.

Relationship between total serum IgG and anti-AChR

- Total IgG %CFB was linearly correlated with anti-AChR %CFB, with a slope of 1.03 (**Figure 5**) and intercept of -0.0250. Inter-individual variability on the slope was 39.5%, and residual error was 21.5% (proportional) and 4.95 nmol/L (additive)

Figure 5. Relationship between total serum IgG and anti-AChR %CFB

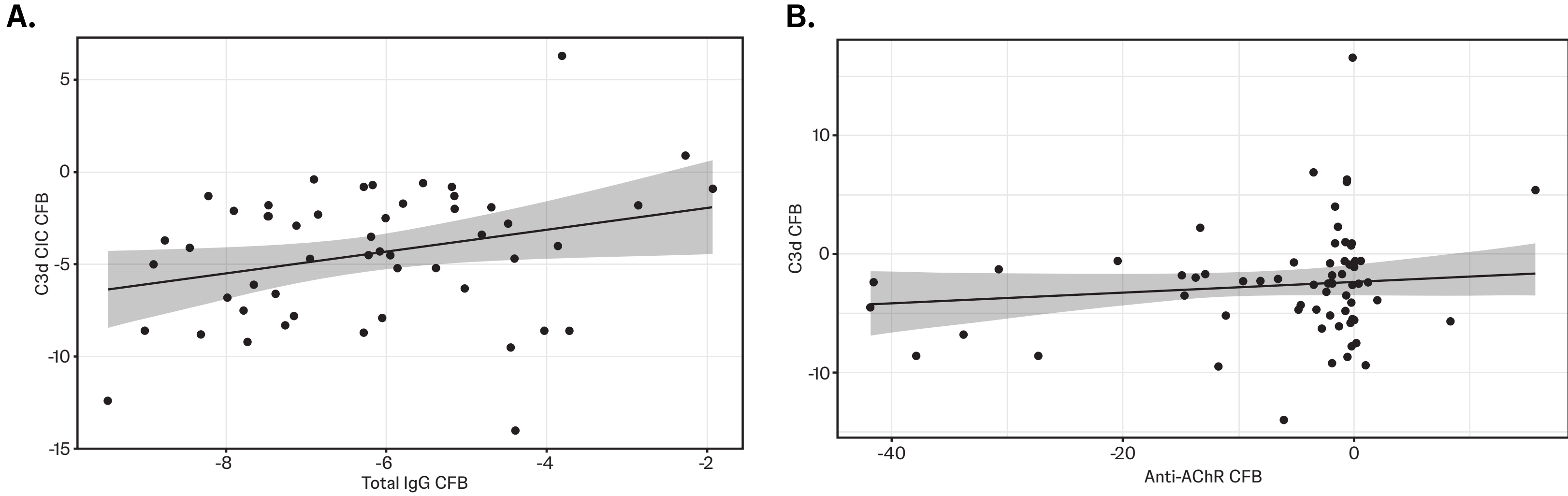


Dots are observed IgG and anti-AChR CFB (%) in Vivacity-MG3. Black line shows typical model prediction at %anti-AChR=1.03*%IgG-0.025. Anti-AChR=anti-acetylcholine receptor, CFB=change from baseline, IgG=immunoglobulin G.

Relationship between CFB of total IgG, anti-AChR and C3d

- At Week 24, CFB of total IgG was associated with C3d CIC reduction (p=0.042, 108%; **Figure 6A**)
- There was a trend for an association between anti-AChR reduction and C3d CIC reduction (p=0.2, 10%; **Figure 6B**)

Figure 6. Relationship between (A) IgG CFB and (B) anti-AChR CFB to C3d CIC CFB

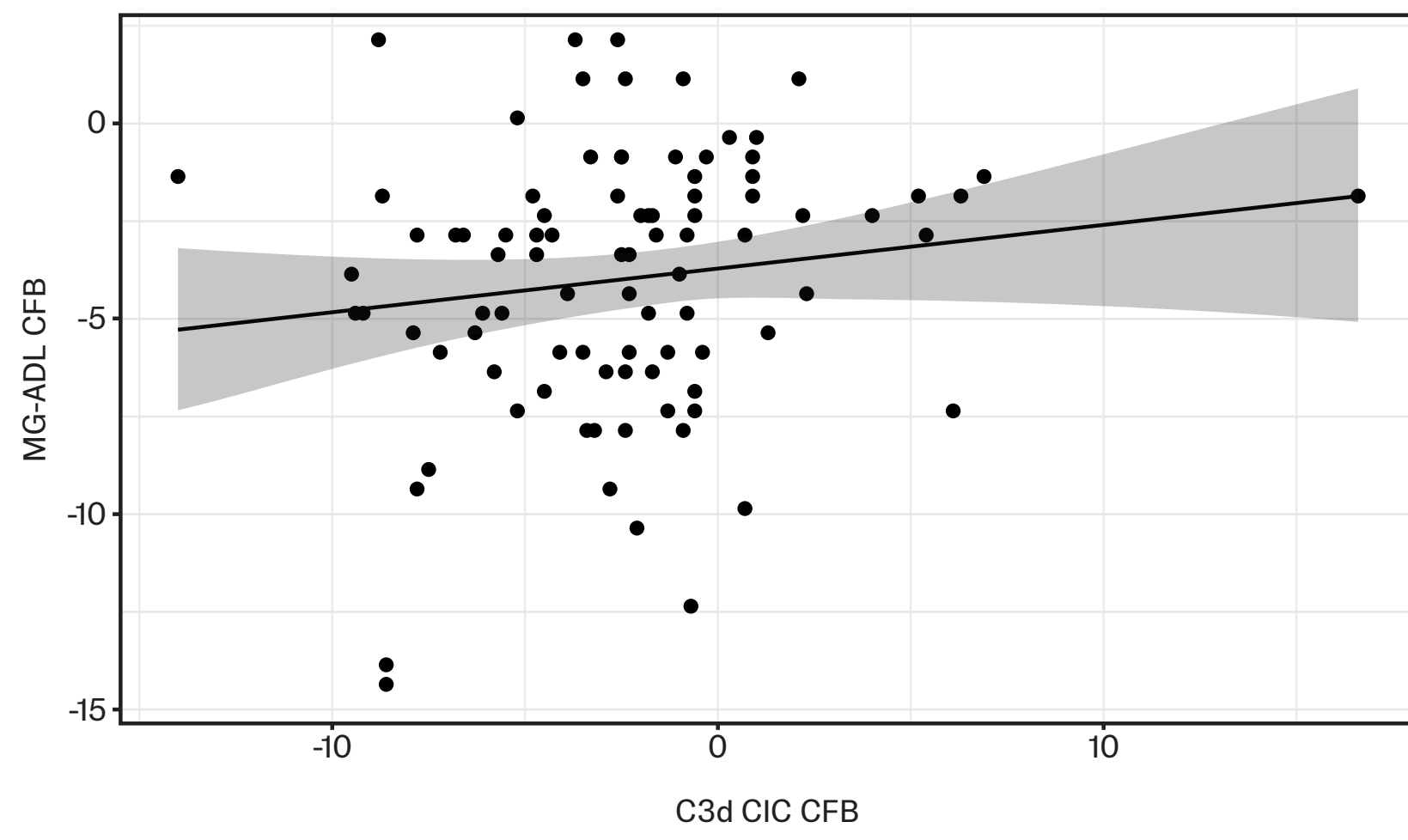


Mean C3d %CFB versus mean anti-AChR %CFB with pointwise bootstrap 95% confidence intervals. Adjustment for baseline confounders using parametric g-estimation. Anti-AChR=anti-acetylcholine receptor, C3d=complement component 3d, CIC=circulating immune complexes, CFB=change from baseline, IgG=immunoglobulin G.

Relationship between C3d and MG-ADL

- C3d CIC reduction at Week 24 did not significantly explain MG-ADL reduction (p=0.232, 28.6%); analysis of more timepoints is needed to fully explore this relationship (**Figure 7**)

Figure 7. Relationship between C3d CIC CFB and MG-ADL CFB



Mean MG-ADL CFB versus mean C3d CIC CFB with pointwise bootstrap 95% confidence intervals. Adjustment for baseline confounders using parametric g-estimation. C3d=complement component 3d, CIC=circulating immune complexes, CFB=change from baseline, MG-ADL=Myasthenia Gravis-Activities of Daily Living.