

# Assessing the Relationship Between Immunoglobulin G Level and Efficacy of Nipocalimab Measured Using the Myasthenia Gravis Activities of Daily Living Scale

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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<sup>1,2</sup>
- Nipocalimab, a fully human monoclonal antibody, binds the neonatal Fc receptor (FcRn) with high affinity, inhibiting IgG recycling and thereby reducing circulating total IgG, including pathogenic IgG autoantibodies<sup>3,4</sup>
- Nipocalimab is approved for the treatment of gMG in anti-acetylcholine receptor (AChR) and anti-muscle-specific tyrosine kinase-(MuSK)-antibody-positive adult and adolescent patients in the United States and the EU<sup>5,6</sup>
  - In the phase 3 Vivacity-MG3 study (NCT04951622), nipocalimab added to standard-of-care (SOC) demonstrated substantial reduction in circulating IgG with rapid and sustained disease control over 24-weeks in a population of seropositive patients with gMG<sup>7</sup>
- Total serum IgG serves as a direct pharmacodynamic marker and an indirect marker of clinical improvement for anti-FcRn treatments in gMG and development of pharmacometrics model quantifying this relationship could help assess between-patient variability and evaluate whether dose adjustments are needed in specific patient subgroups<sup>8</sup>

## Objective

To characterize the longitudinal relationship between reduction in total serum IgG level and clinical efficacy, measured by change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score, using semi-mechanistic pharmacometrics modeling

## Methods

### Data

- Data were pooled from 7 clinical studies of nipocalimab
  - 5 phase 1 studies in healthy volunteers
  - 1 phase 2 study (Vivacity-MG) in patients with gMG<sup>9</sup>
  - 1 phase 3 study (Vivacity-MG3)<sup>7</sup> in patients with gMG: total of 196 patients, of which 153 were seropositive (anti-AChR+, anti-MuSK+, and/or anti-LRP4+)

| Dataset                          | Sample size                |
|----------------------------------|----------------------------|
| Serum nipocalimab concentrations | 3,429 samples (n=277)      |
| FcRn receptor occupancy          | 1,247 samples (n=78)       |
| Total serum IgG concentrations   | 4,441 samples (n=421)      |
| MG-ADL change from baseline      | 2,317 observations (n=220) |

### Pharmacokinetic/Pharmacodynamic Modeling

- A previously developed nonlinear mixed-effects model was used (NONMEM v7.4.3)<sup>10</sup>
- Investigated nipocalimab intravenous (IV) dose regimens:
  - 0.3, 3, 10, 15, 30, 45, 60 mg/kg, 300 mg, and 1200 mg single dose; 15 mg/kg once weekly (QW) and 30 mg/kg QW in healthy volunteers; 5 mg/kg every 4 weeks (Q4W), 30 mg/kg Q4W, 60 mg/kg single dose, and 60 mg/kg every 2 weeks (Q2W) in the phase 2 study
  - 30 mg/kg loading dose followed by 15 mg/kg Q2W in the phase 3 study

Figure 1. Schematic of the nipocalimab PK/RO/IgG/MG-ADL model<sup>10</sup>

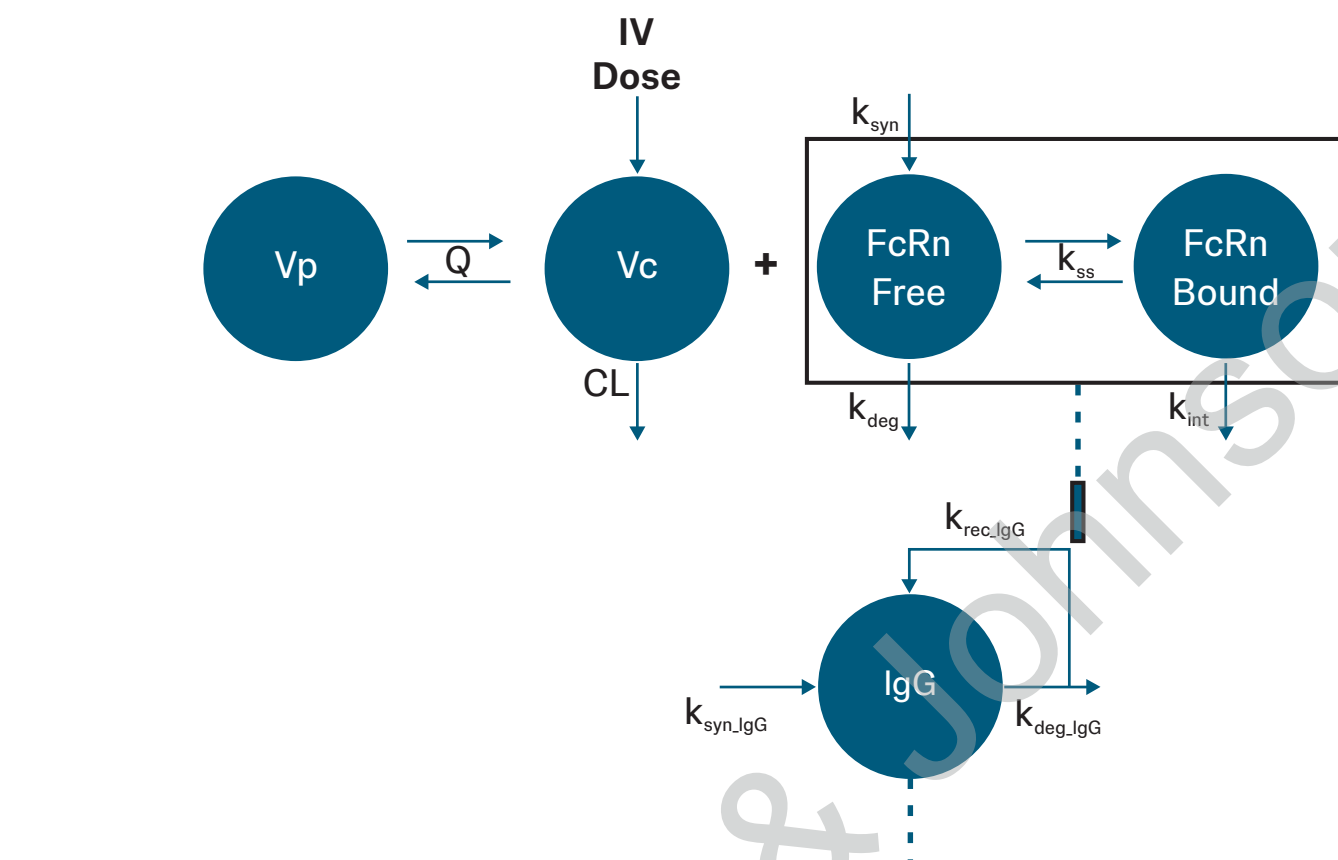


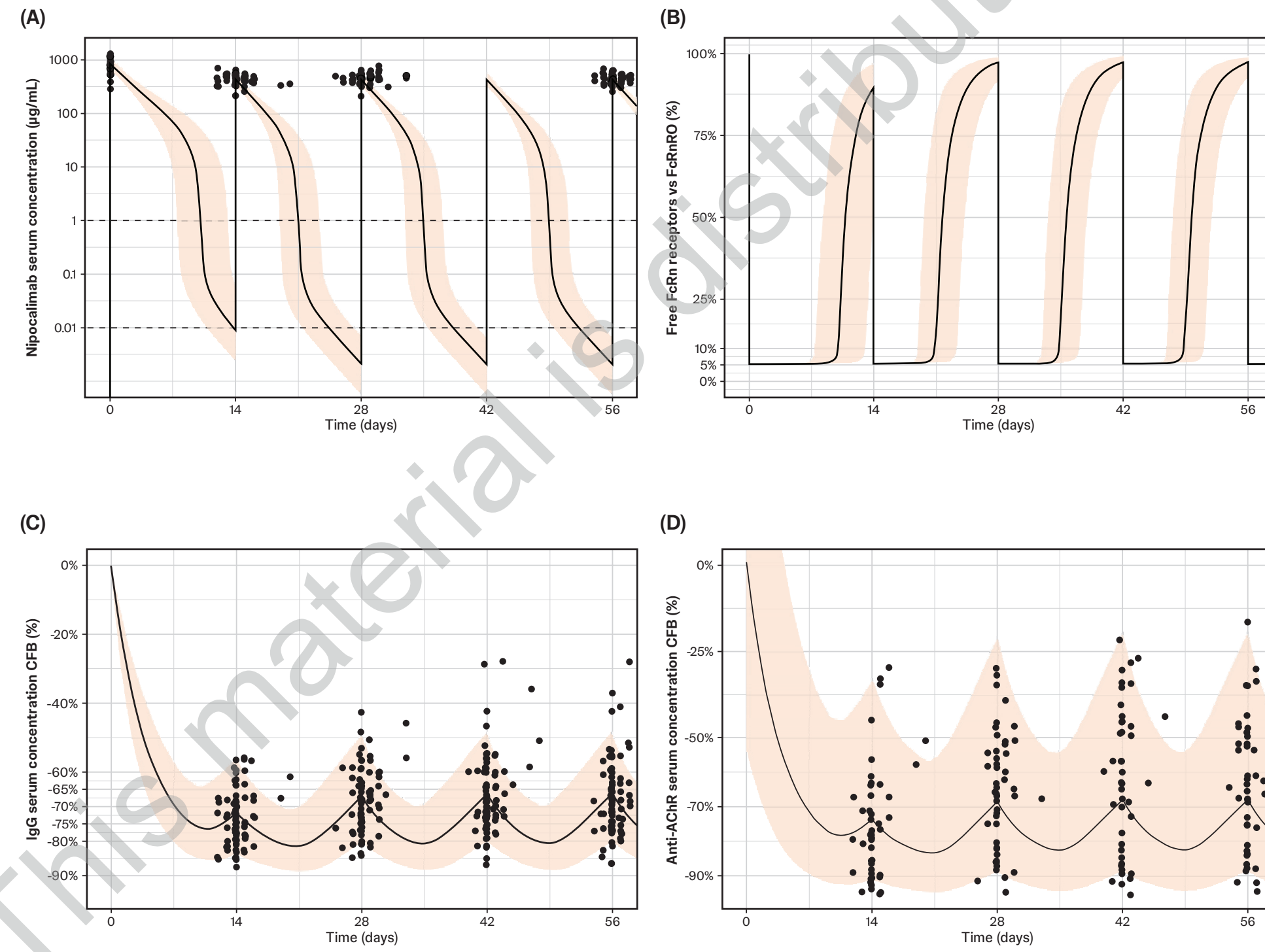
Figure reproduced with permission from Valenzuela B, et al. CPT Pharmacometrics Syst Pharmacol. 2025;14(12):2074–2085. CL=linear clearance, FcRn bound=FcRn receptor bound to nipocalimab, FcRn free=FcRn receptor available for nipocalimab binding, IgG=total serum immunoglobulin G, IV=intravenous, kdeg=first-order degradation rate constant of the free FcRn, kdeg\_ig=first-order IgG degradation rate constant for FcRn-nipocalimab complex, krec=internalization rate constant for FcRn-nipocalimab complex, krec\_ig=first-order IgG recycling rate constant, kss=quasi-steady-state FcRn-nipocalimab dissociation equilibrium constant, Ksyn=zero-order FcRn free production rate, Ksyn\_ig=zero-order IgG production rate, MG-ADL=Myasthenia Gravis Activities of Daily Living, MG-ADL\_0=MG-ADL at baseline, Q=intercompartmental clearance, RO=FcRn receptor occupancy, Vc=central volume of distribution, Vp=peripheral volume of distribution, ΔMG-ADL\_0=MG-ADL change from baseline in absence of nipocalimab, ΔΔMG-ADL\_drug=placebo-corrected MG-ADL change from baseline in presence of nipocalimab.

## Results

### Pharmacokinetics

- Pharmacokinetics (PK) of nipocalimab were well described using a two-compartment target-mediated drug disposition model (Figure 2A)
- Elimination occurred through both: linear catabolic clearance and nonlinear FcRn-mediated clearance
- Estimated central volume of distribution was 2.41 L and total volume of distribution 3.17 L in patients with gMG from Vivacity-MG3
- No systemic accumulation of nipocalimab was observed with repeated Q2W IV dosing of nipocalimab
- Inter-individual variability in model-predicted PK parameters was low to moderate (<20%)

Figure 2. Time profiles for (A) nipocalimab serum concentration (B) FcRn RO (C) total serum IgG reduction from baseline (D) anti-AChR autoantibody reduction from baseline in patients with gMG from the Vivacity-MG3 study<sup>7</sup>

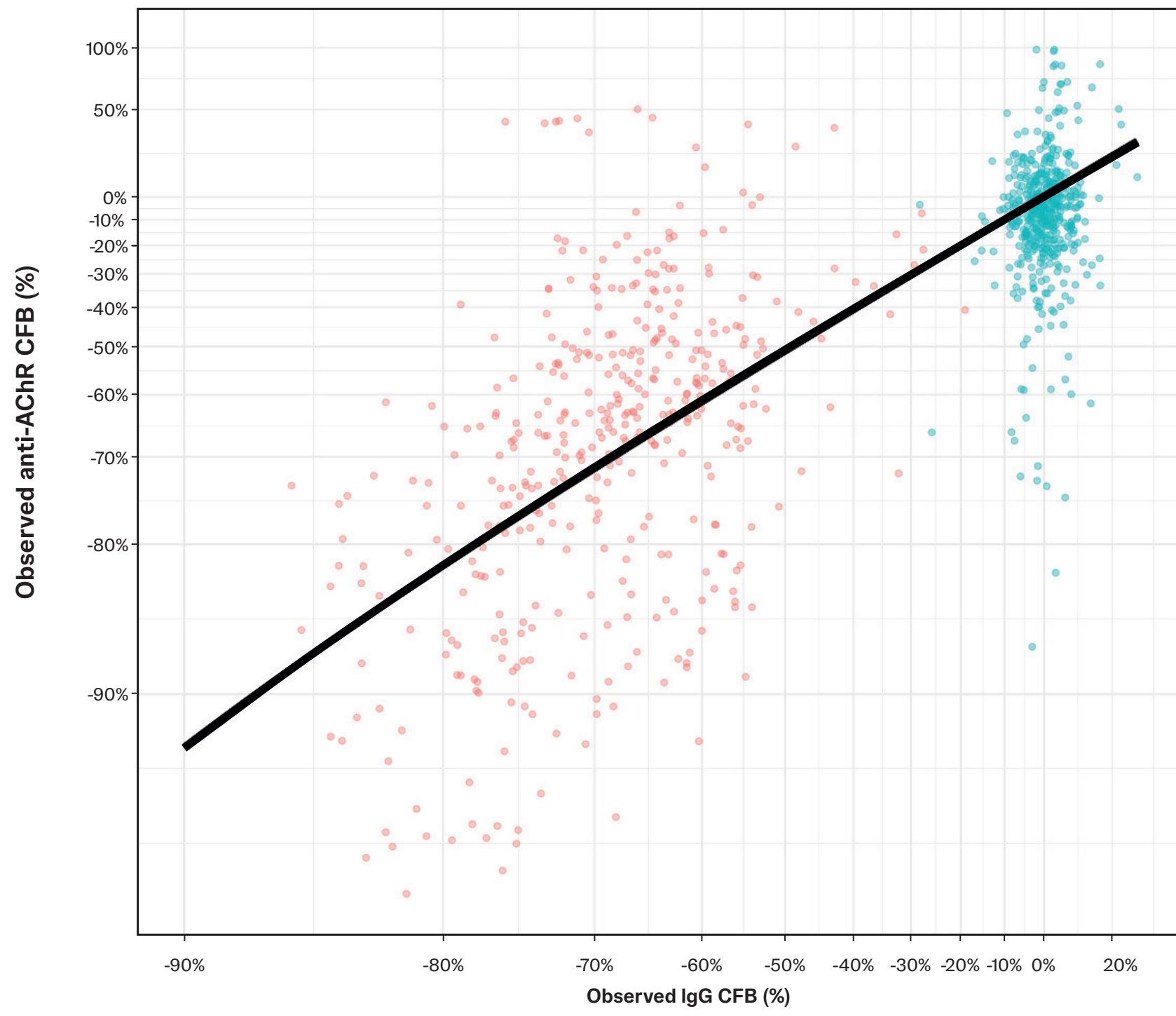


Black line represents model-predicted median and shaded areas represent 95% prediction intervals. Dots represent observed post-dose PK, pre-dose IgG %CB and pre-dose anti-AChR %CB data. Pre-dose PK not shown because of high fraction below limit of quantification (BLOQ) data. Anti-AChR=anti-acetylcholine receptor, CFB=change from baseline, FcRn RO=FcRn receptor occupancy, gMG=generalized myasthenia gravis, IgG=immunoglobulin G, PK=pharmacokinetics.

### Pharmacokinetics of nipocalimab and relationship with total serum IgG reduction

- Nipocalimab Q2W dosing demonstrated rapid, substantial and sustained reductions in total serum IgG, well described by the model (Figure 2C)
- Model-predicted mean (SD) reductions in total serum IgG:
  - Week 2 reduction after loading dose: -71.2% (7.08)
  - Pre-dose steady-state: -65.9% (8.22)
  - Average steady-state: -74.7% (6.21)
  - Maximum predicted IgG reduction, steady state: -80.4% (4.95)
- FcRn blockade with nipocalimab reduced IgG half-life from 17.6 days to 2.75 days
- Total serum IgG concentrations were predicted to return to >90% of baseline approximately 9 weeks after the last dose following treatment discontinuation
- Percent change from baseline (CFB) in anti-AChR linearly correlated with %CFB in total serum IgG, with a slope not significantly different from 1 (Figure 3)

Figure 3. Relationship between total serum IgG and anti-AChR %CFB in adult patients with gMG<sup>7</sup>



Dots are observed IgG and anti-AChR CFB (%). Black line shows typical model prediction at %anti-AChR=1.03\*\*IgG-0.0250. anti-AChR=anti-acetylcholine receptor, CFB=change from baseline, gMG=generalized myasthenia gravis, IgG=immunoglobulin G, IV=intravenous, LD=loading dose, Q2W=every 2 weeks.

## Key Takeaways

- The model predicted rapid, deep, and sustained reduction in total serum IgG with nipocalimab and this was confirmed in seropositive patients with gMG
- The model confirmed that total serum IgG (percent change from baseline) drives the clinical effect of nipocalimab (changes from baseline in MG-ADL) in seropositive patients with gMG

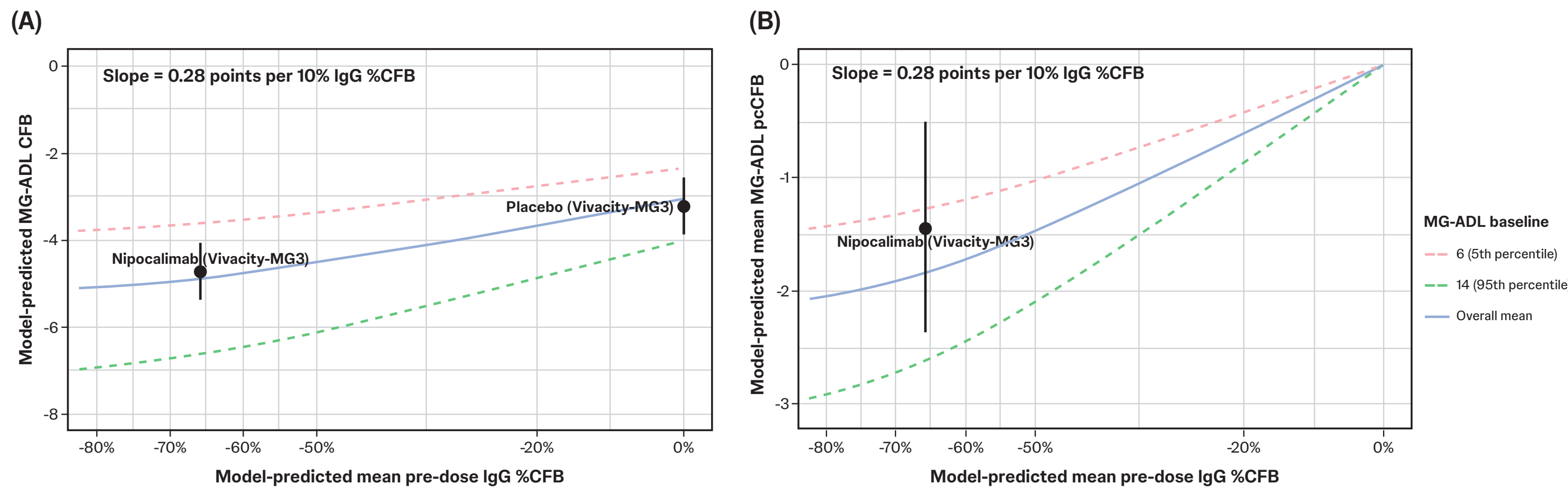
## Conclusions

- The PK of nipocalimab was well described by a two-compartment non-linear target-mediated drug disposition model
- Treatment with nipocalimab (30 mg/kg loading, then 15 mg/kg Q2W) demonstrated rapid, substantial, and sustained reductions in total serum IgG and pathogenic AChR-IgG autoantibodies when dosing was maintained at 15 mg/kg Q2W
- A linear relationship between total serum IgG reduction and MG-ADL improvement was identified whereby a 70% reduction in total serum IgG resulted in ~2-point improvements in MG-ADL when adjusted for placebo effect
- Collectively, the model predicted that nipocalimab produces a substantial reduction in total serum IgG, correlating with a clinical improvement representing the minimal clinically important difference in MG-ADL, which was confirmed in the phase 3 Vivacity-MG3 study in seropositive patients with gMG

### IgG–MG-ADL relationship

- Placebo-corrected CFB in MG-ADL linearly correlated with an IgG-reduction effect compartment (T<sub>1/2</sub>=5.87 days)
- The estimated slope was 0.28 points MG-ADL improvement per 10% reduction in total serum IgG (Figure 4)
- When adjusted for placebo effect, model simulations predicted that a 70% reduction in total serum IgG would result in an additive ~2-point MG-ADL reduction in patients with gMG
- The magnitude of predicted clinical improvement was dependent on the baseline MG-ADL score
- Differences in predicted MG-ADL improvement across tertiles of the nipocalimab-induced reduction in total serum IgG in the phase 3 study were minimal

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



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

- The longitudinal MG-ADL model adequately reproduced placebo-corrected outcomes (i.e., between-group differences vs placebo) for multiple clinical endpoints in the gMG population from the Vivacity-MG3 study<sup>7</sup> (Table 1)
- Predicted improvement was observed when adjusted for age, body weight, sex, race/ethnicity, renal and hepatic impairments, autoantibody status and concomitant gMG therapy

Table 1. Numerical predictive check of clinical endpoints<sup>7</sup>

| Clinical endpoint                     | Nipocalimab |                           | Placebo  |                           | Between-group difference |                           |
|---------------------------------------|-------------|---------------------------|----------|---------------------------|--------------------------|---------------------------|
|                                       | Observed    | Model prediction (95% CI) | Observed | Model prediction (95% CI) | Observed                 | Model prediction (95% CI) |
| MG-ADL CFB (Weeks 22 to 24)           | -4.98       | -4.77 (-3.81; -5.67)      | -3.22    | -2.84 (-2.08; -3.56)      | -1.75                    | -1.93 (-3.07; -0.67)      |
| Responders (Weeks 22 to 24), %        | 82.6        | 75.4 (63.8; 85.5)         | 66.1     | 59.7 (48.4; 72.6)         | 16.5                     | 15.3 (-1.8; 31.2)         |
| Early responders (≤2 weeks), %        | 62.3        | 72.7 (63.6; 81.8)         | 56.2     | 60.3 (47.9; 71.2)         | 6.2                      | 12.7 (-1.2; 28.4)         |
| Sustained response (Weeks 4 to 24), % | 60.5        | 52.6 (42.1; 63.2)         | 34.2     | 30.1 (20.5; 39.7)         | 26.3                     | 22.6 (9.0; 37.1)          |
| ≥50% improvement in MG-ADL, %         | 56.5        | 50.7 (39.1; 62.3)         | 32.3     | 29.0 (19.3; 41.9)         | 24.3                     | 21.7 (4.6; 38.1)          |

Observed data were derived through t-test (for continuous endpoints) and chi-squared test (for dichotomous endpoints) based on the Vivacity-MG3 PK/PD analysis dataset. Simulations were performed for 2,000 study replicates of same sample size as the phase 3 Vivacity-MG3 study. Responders were patients with ≥2-point improvement (vs baseline) in average improvement in MG-ADL total score over Weeks 22, 23, and 24 of the double-blind placebo-controlled phase. CFB=change from baseline, CI=confidence interval, MG-ADL=Myasthenia Gravis Activities of Daily Living, PK=pharmacokinetics, PD=pharmacodynamics.