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

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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.**

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, 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.[3,4]
- 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.[5,6]
  - 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.[7]
- 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.[8]

Objectives

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

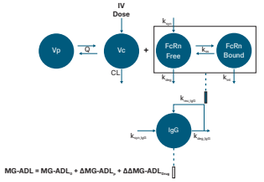
- Data were pooled from 7 clinical studies of nipocalimab.
  - 5 phase 1 studies in healthy volunteers
  - 1 phase 2 study (Vivacity-MG) in patients with gMG[9]
  - 1 phase 3 study (Vivacity-MG3)[7] in patients with gMG: total of 196 patients, of which 153 were seropositive (anti-AChR+, anti-MuSK+ and/or 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).[10]
- Investigated nipocalimab 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[10]



MG-ADL = $MG\text{-}ADL_0$ + $\Delta MG\text{-}ADL_s$ + $\Delta\Delta MG\text{-}ADL_{Drug}$

- After dosing, nipocalimab concentration was distributed into a central compartment (Vc) and peripheral compartment (Vp). It was subject to linear catabolism (CL), as well as binding to FcRn and subsequent internalization of the bound FcRn-nipocalimab complex.
- IgG dynamics were described by a turnover model with synthesis rate (K_{syn}) and a natural degradation composed of catabolism (K_{deg}) and an FcRn-mediated recycling rate (K_{rec}), which was dependent on the available free FcRn compared to baseline FcRn.
- MG-ADL was described by baseline ($MG\text{-}ADL_0$), a placebo signal ($MG\text{-}ADL_s$) and a drug effect ($MG\text{-}ADL_{Drug}$) that linearly scaled with IgG reduction from baseline.
- Impact of age, body weight, sex, race/ethnicity, renal and hepatic impairments, autoantibody status and concomitant gMG therapy on the model parameters was evaluated.

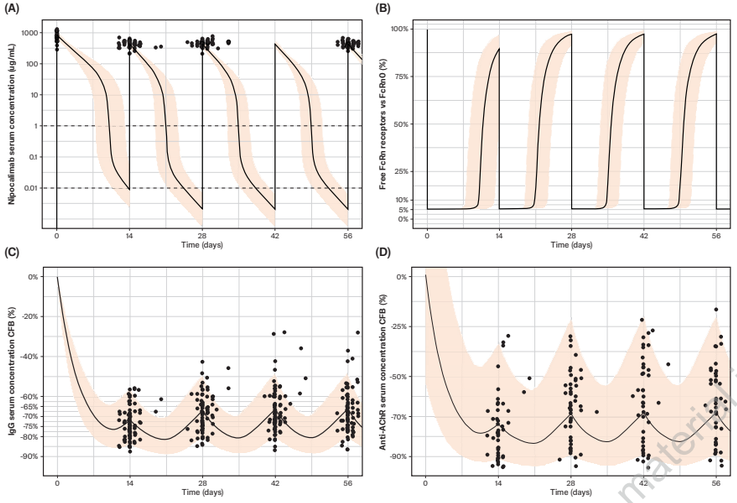
Figure reproduced with permission from Valenzuela B, et al. *CPT Pharmacometrics Syst Pharmacol.* 2025;14(12):2074-2085. CL, linear clearance; FcRn, neonatal fragment crystallizable receptor; FcRn bound, FcRn receptor bound to nipocalimab; FcRn free, FcRn receptor available for nipocalimab binding; IgG, total serum immunoglobulin G; IV, intravenous; MG-ADL, Myasthenia Gravis Activities of Daily Living MG-ADL; $MG\text{-}ADL_0$, MG-ADL at baseline; k_{deg}, first-order degradation rate constant of the free FcRn; $k_{deg,IgG}$, first-order IgG degradation rate constant; k_{in}, quasi-steady-state FcRn–nipocalimab dissociation equilibrium constant; k_{in}, zero-order FcRn free production rate; k_{int}, internalization rate constant for FcRn-nipocalimab complex; $k_{syn,IgG}$, zero-order IgG production rate; k_{rec}, first-order IgG recycling rate constant; Q, intercompartmental clearance; RO, FcRn receptor occupancy; Vc, central volume of distribution; Vp, peripheral volume of distribution; $\Delta MG\text{-}ADL_s$, MG-ADL change from baseline in absence of nipocalimab; $\Delta\Delta MG\text{-}ADL_{Drug}$, placebo-corrected MG-ADL change from baseline in presence of nipocalimab.

Results

Pharmacokinetics

- Nipocalimab PK 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[7]

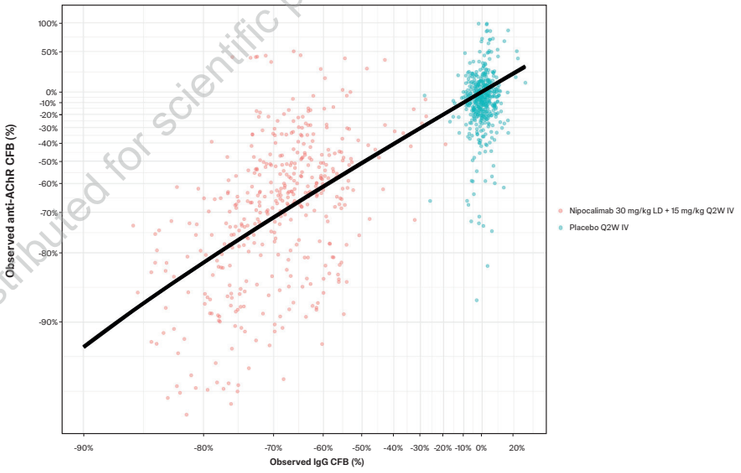


Black line represents model-predicted median and shaded areas represent 95% prediction intervals. Dots represent observed post-dose pharmacokinetics, pre-dose IgG %CFB and pre-dose anti-AChR %CFB data. Pre-dose pharmacokinetics not shown because of high fraction below limit of quantification (BLOQ) data.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

Pharmacokinetics of nipocalimab and relationship with total serum Immunoglobulin G 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[7]

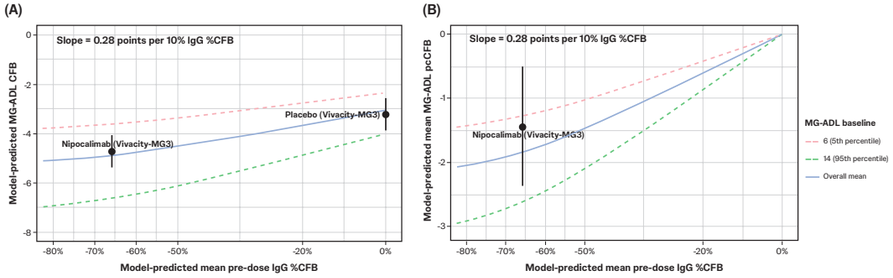


Dots are observed IgG and anti-AChR CFB (%). Black line shows typical model prediction at %anti-AChR=103*%IgG−0.0250. AChR, anti-acetylcholine receptor; CFB, change from baseline; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IV, intravenous; LD, loading dose; Q2W, every 2 weeks.

IgG–MG-ADL relationship

- Placebo-corrected CFB in MG-ADL linearly correlated with an IgG-reduction effect compartment ($T_{1/2}$ =5.87 days).
- The estimated slope was 0.28 points MG-ADL improvement per 10% reduction in total serum IgG.
- 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; pcCFB, 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.[7]

Table 1: Numerical predictive check of clinical endpoints[7]

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 (Week 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.

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