Nipocalimab Effects on Immunoglobulin G Subclasses in Patients with Generalized Myasthenia Gravis

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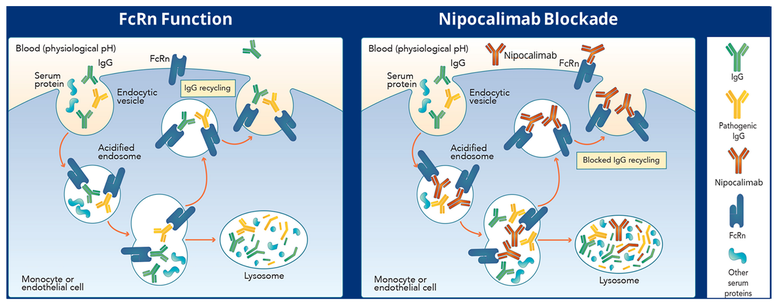
Key Takeaways

- **Nipocalimab significantly inhibits FcRn-mediated IgG recycling, leading to rapid, greater, and sustained reductions in all IgG subclasses and pathogenic anti-AChR autoantibodies in gMG compared with efgartigimod and rozanolixizumab, highlighting the therapeutic potential of nipocalimab.**
- **These findings enhance our understanding of effects of nipocalimab on the pathogenic autoantibodies involved in gMG and support further exploration of therapeutic potential of nipocalimab for IgG-driven, autoantibody- and alloantibody-mediated diseases.**

Background

- Nipocalimab is a fully human immunoglobulin G (IgG)1 monoclonal antibody that selectively binds to human neonatal fragment crystallizable receptor (FcRn), and inhibits the recycling of IgG and reduces half-life and levels of circulating IgG, including IgG-based pathogenic autoantibodies in generalized myasthenia gravis (gMG) **(Figure 1)**.[1-4]
- Phase 2 and Phase 3 studies have shown that nipocalimab effectively decreases total IgG in a dose-dependent manner, improves clinical outcomes, and has a favorable safety profile.[1,2]
- Challenges exist in understanding the extent of nipocalimab effects on specific autoantibodies due to low antibody levels.

Figure 1: Nipocalimab's Mechanism of Action in FcRn-Mediated IgG Recycling



Vu T, et al. Presented at American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting; Savannah GA, USA; October 15–October 18; 2024. **FcRn**=neonatal fragment crystallizable receptor, **IgG**=immunoglobulin G.

Objective

- **To characterize the effects of nipocalimab on IgG subclasses (IgG1, IgG2, IgG3, and IgG4) and anti-acetylcholine receptor (AChR) autoantibodies to gain indirect insights on the impact of nipocalimab on pathogenic autoantibodies in patients with gMG, and to compare the results from nipocalimab with those observed in efgartigimod and rozanolixizumab studies.**

Methods

Nipocalimab Clinical Studies Included in Population Pharmacokinetic (PPK) Analyses

- Data from nipocalimab Phase 2 and Phase 3 studies in patients with gMG were pooled to develop a longitudinal pharmacokinetic (PK)-pharmacodynamic (PD) model. Key study design elements and pharmacokinetic sampling are provided in **Table 1**.

Table 1: Overview of Nipocalimab Studies Included in the PPK Analysis.

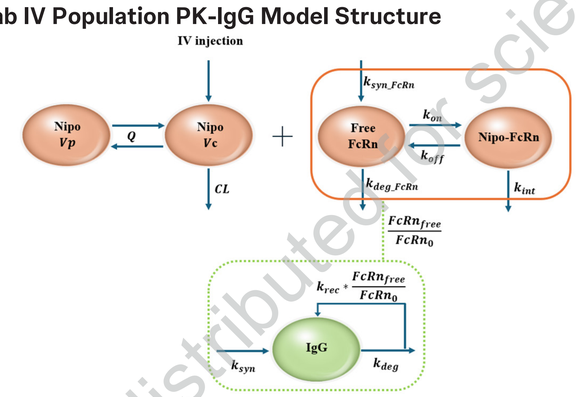
Phase, Study Name	Dose, Regimen, Route of Administration, Number of Participants	Sampling Timepoints
Phase 3 Vivacity-MG3[2] NCT04951622	N=196; Nipocalimab IV 30 mg/kg loading dose, 15 mg/kg Q2W for 24 weeks: N=98, Placebo: N=98	• PK: Pre-dose and post-dose (45 minutes after infusion) on Day 1 and Weeks 2, 4, 8, 12, 16, 20, and 24. • Total serum IgG, IgG subclasses, and anti-AChR: screening, baseline (Day 1), and pre-dose on Weeks 2, 4, 6, 8, 12, 16, 20, 22, and 24.
Phase 2 Vivacity-MG[1] NCT03772587	N=68 (nipocalimab 54; placebo 14); Single IV dose: 60 mg/kg, N=13 Multiple IV doses: 5 mg/kg Q4W (x3), N=14 30 mg/kg Q4W (x3), N=13, 60 mg/kg Q2W (x5), N=14, Placebo Q2W: N=14	• PK: Pre-dose and post-dose on Day 1, pre-dose on Day 15, 29, 43, 57, post-dose on Day 57, and Day 85. • Total serum IgG, IgG subclasses, and anti-AChR: screening, baseline (Day 1), Day 15, 29, 43, 57, 85, and 113. • Serum IgG subclasses and anti-AChR also sampled on Day 8.

Anti-AChR=anti-acetylcholine receptor, **IgG**=immunoglobulin G, **IV**=intravenous, **PPK**=population pharmacokinetics, **Q2W**=every two weeks, **Q4W**=every four weeks.

Population Pharmacokinetic (PPK) Modeling

- The PPK analysis was performed using nonlinear mixed-effects modeling approach (NONMEM 7.4.3).
- The PPK of nipocalimab and FcRn receptor occupancy (RO) parameters were fixed based on the previously established model[5] shown in **Figure 2**. The available PK-RO data allow for the estimation of individual empirical Bayes estimates, which were then used as inputs to develop the PK-PD models for the IgG subclassess. The population model parameters for IgG/anti-AChR were estimated from the developed model.

Figure 2. Nipocalimab IV Population PK-IgG Model Structure



The figure was adapted from Valenzuela B, Neyens M, Zhu Y, et al. Nipocalimab Dose Selection in Generalized Myasthenia Gravis. CPT Pharmacometrics Syst Pharmacol. 2025 Sep 17. doi: 10.1002/psp4.70109. Online ahead of print

CL=linear clearance, **FcRn**=neonatal Fc receptors, **IgG**=immunoglobulin G, **IV**=intravenous, k_{deg}=degradation rate constant of IgG, k_{deg_FcRn}=degradation rate constant of **FcRn**, k_{int}=internalization rate constant, k_{off}=off-rate of ligand from receptor, k_{on}=on-rate of receptor-ligand complex formation binding, k_{rec}=FcRn-medicated recycling rate, $FcRn_{free}$=free FcRn receptor available, $FcRn_0$=baseline FcRn receptor available, k_{syn}=synthesis rate of IgG, k_{syn_FcRn}=synthesis rate of FcRn, **Nipo**=nipocalimab, **PK**=pharmacokinetic(s), **Q**=intercompartmental clearance, **Vc** =central compartment, **Vp** = peripheral compartment.

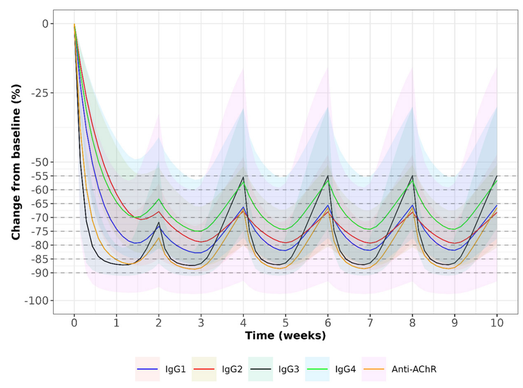
Model-based Simulations

- Model-based simulations of 1000 virtual patients with gMG were conducted for total IgG, IgG subclasses and anti-AChR over 14 weeks, following the United States Food and Drug Administration (FDA) approved nipocalimab intravenous (IV) dose regimen (loading dose of 30 mg/kg, followed by 15 mg/kg every two weeks [Q2W] thereafter).[5] The predicted reductions in total IgG, IgG subclassess and anti-AChR concentrations over time were graphically depicted to illustrate the impact of nipocalimab.
- Simulated and observed profiles of total IgG, IgG subclassess, and anti-AChR antibody for nipocalimab were also compared with observed data from efgartigimod and rozanolixizumab studies. For nipocalimab, the observed data from Vivacity-MG3[2] with the FDA-approved nipocalimab IV dose regimen were used, and supplemented with rich model-predicted profiles. For efgartigimod, the observed data from a Phase 2 study with the recommended efgartigimod IV dose of 10 mg/kg every week (QW) for 4 weeks were used.[6] For rozanolixizumab, the observed data from a Phase 3 study with doses of 7 mg/kg and 10 mg/kg subcutaneous (SC) QW for 6 weeks were used.[7]

Results

- **Model-based typical value simulations** showed that IgG3 dropped most rapidly with a degradation rate of 0.847 d^{-1}, reached the deepest nadir of 87.3% reduction from baseline and the level recovered to 54.9% reduction from baseline prior to the next dose at steady state.
- In contrast, IgG4 exhibited shallowest decrease with a degradation rate of 0.257 d^{-1} with the slowest recovery, reaching a nadir of 74.8% reduction from baseline and recovering to 56.6% reduction from baseline at steady-sate pre-dose, which was generally comparable to IgG3.
- Overall, IgG1 and IgG2 exhibited similar profiles over time with nadirs of 82.2% and 79.6% reductions, respectively, and steady-state pre-dose levels of 65.6% and 68.1% reductions, respectively (**Figure 3**).

Figure 3: Comparison of the Simulated IgG Subclasses, Total IgG, and Anti-AChR Autoantibody Serum Concentration Changes from Baseline Over Time After Nipocalimab IV 30 mg/kg Loading Dose Followed by 15 mg/kg Q2W in Participants With gMG

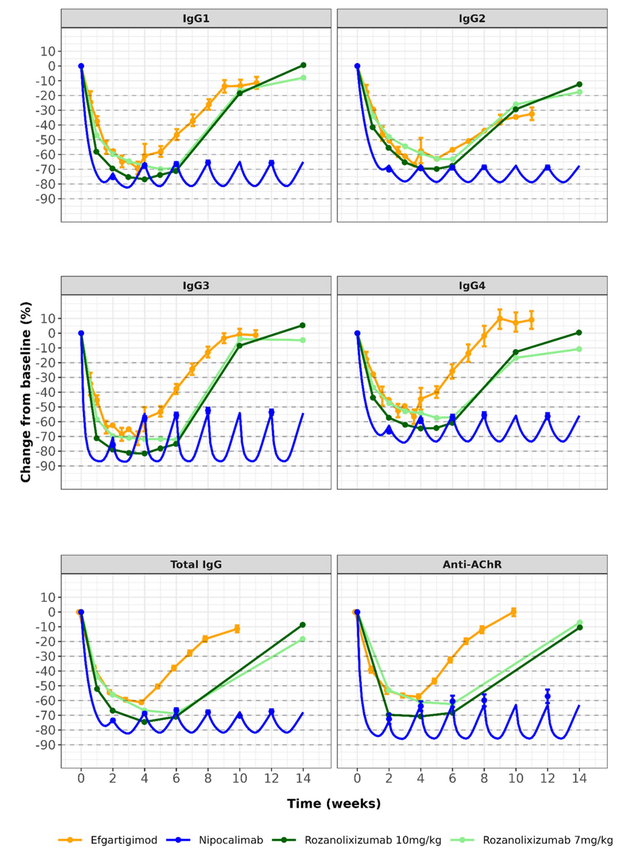


Colored solid lines and shaded areas represent medians and 90% prediction intervals of each IgG subclass or pathogenic anti-AChR autoantibody change from baseline, respectively.

Anti-AChR=anti-acetylcholine receptor, **gMG**=generalized myasthenia gravis **IgG**=immunoglobulin G, **IV**=intravenous, **QW**=every week.

- Total IgG experienced a nadir of 82.6% reduction from baseline and recovered to a pre-dose level of 68.6% reductions from baseline at steady state.
- The degradation rate of anti-AChR was 0.584 d^{-1}, similar to the median degradation rate of IgG1 and IgG3.
- Anti-AChR reached a nadir of 88.8% reduction from baseline, closely matched the nadir of IgG3, and subsequently recovered to a pre-dose level of 66.5% reduction from baseline at steady state (**Figure 3**).

Figure 4. Percent Changes from Baseline in Serum Concentrations of IgG Subclasses, Total IgG, and Anti-AChR Autoantibody Over Time Following Nipocalimab, Efgartigimod, and Rozanolixizumab Dosing Regimens in Patients with gMG



The blue, orange, and green points and error bars represent the mean (±SE) of observed IgG subclasses, total IgG, and anti-AChR autoantibody serum concentration change from baseline after administration of nipocalimab, efgartigimod, and rozanolixzumab, respectively.

Nipocalimab 30 mg/kg loading dose followed by 15 mg/kg IV Q2W (blue): The blue line represents the model-simulated mean values.

Efgartigimod 10 mg/kg IV QW for 4 weeks followed by 7 weeks of observation (orange): The orange line connects the observed mean values.

Rozanolixizumab 7 mg/kg (light green) and 10 mg/kg (dark green) SC QW for 6 weeks followed by 8 weeks of observation. The green line connects the observed mean values.

Anti-AChR=anti-acetylcholine receptor, **IgG**=immunoglobulin G, **IV**=intravenous, **SC**=subcutaneous, **QW**=every week, **Q2W**=every two weeks.

- With the recommended dose regimens, nipocalimab demonstrated faster, stronger, and more sustained reductions in total IgG, IgG subclasses, and anti-AChR autoantibody levels when compared with efgartigimod and rozanolixizumab (**Figure 4**).
- Following nipocalimab treatment, IgG subclasses and anti-AChR autoantibody were predicted to reach their lowest levels before Week 3, one week earlier than those observed with efgartigimod treatment.
- In addition, nipocalimab was expected to achieve a median reduction of 82.6% in total IgG, 74.8%–87.3% in IgG subclasses, and 88.6% in anti-AChR at nadir, while efgartigimod resulted in shallower reductions, i.e., 61% in total IgG, 57%–71% in IgG subclasses, and 57% in anti-AChR.
- Rozanolixizumab also resulted in shallower reductions, i.e., 69% in total IgG, 57%–72% in IgG subclasses, and 62% in anti-AChR with 7 mg/kg SC QW; and 75% in total IgG, 65%–82% in IgG subclasses, and 71% in anti-AChR with 10 mg/kg SC QW for 6 weeks.[7,8]

PRESENTED AT: 2025 Myasthenia Gravis Foundation of America (MGFA) Scientific Session at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting; San Francisco, CA, USA; October 29, 2025. **REFERENCES: 1.** Antozzi C, et al. *Neurology.* 2024;102(2):e207937. **2.** Antozzi C, et al. *Lancet Neurol.* 2025;24(2):105–116. **3.** Ling LE, et al. *Clin Pharmacol Ther.* 2019;105(4):1031-1039. **4.** Seth NP, et al. *MAbs.* 2025;17(1):2461191. **5.** IMAAVY™ (nipocalimab-aahu) injection, for intravenous use. Full Prescribing Information. Johnson & Johnson. 2025. **6.** https://static.seekingalpha.com/uploads/sa_presentations/586/25586/original.pdf. Accessed June 18, 2025, et al. *American Academy of Neurology.* Los Angelis, CA, 2018. **7.** Bril V, et al. *Lancet Neurol.* 2023;22(5):383–394. **8.** Habib A, et al. *Ther Adv Neurol disord.* 2024;17:17562864241273036. **ACKNOWLEDGMENTS:** The authors thank the participants and investigators for their participation in the study. Priyanka Grandhi and Doyel Mitra, PhD (Johnson & Johnson) provided editorial assistance. Layout design for this presentation was provided by Samita Warang (SIRO Medical Writing Pvt. Ltd., India), with funding from Johnson & Johnson. This study was sponsored by Johnson & Johnson. **DISCLOSURES: Xia Li, Juan-José Pérez-Ruixo, Yaowei Zhu, Jocelyn H. Leu, John J. Sheehan, Ruben Faelens:** Employees of Johnson & Johnson and may own stock or stock options in Johnson & Johnson.