Nipocalimab Effect on IgG Subclasses in Patients with Generalized Myasthenia Gravis

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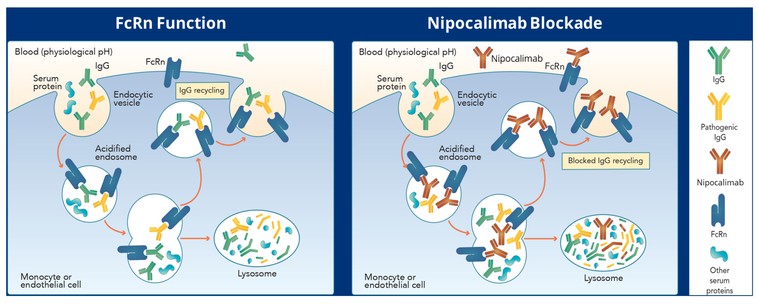
BACKGROUND AND OBJECTIVES

Nipocalimab is a fully human IgG1 monoclonal antibody that selectively binds to human FcRn, inhibiting the recycling of IgG and reducing half-life and levels of circulating IgG subclasses, including pathogenic autoantibodies in generalized myasthenia gravis (gMG), (**Figure 1**). Phase 2 and Phase 3 studies have shown nipocalimab effectively decreases total IgG in a dose-dependent manner, improves clinical outcomes, and has a favorable safety profile [1,2].

Although challenges in understanding nipocalimab effects on specific autoantibodies remain due to low antibody levels and limited samples, particularly concerning anti-MuSK (IgG4) and anti-LRP4 (IgG1 and IgG2), we investigated the effects of nipocalimab on IgG subclasses and anti-AChR antibodies (IgG1 and IgG3), using a mechanistic PKPD model, to gain indirect insights into nipocalimab's impact on pathogenic autoantibodies within the gMG.

Figure 1 Nipocalimab's mechanism of action in FcRn-mediated IgG recycling



METHODS

Clinical studies. Data from the Phase 2 and pivotal Phase 3 studies in gMG patients were pooled. Key study design elements and PK sampling are provided in **Table 1**.

Table 1. Overview of Studies Included inthe PPK Analysis.

Phase, Study Number	Dose, Regimen, Route of Administration, Number of Participants	Sampling
Phase 3 Vivacity-MG3	N=196 Nipocalimab IV 30 mg/kg at first infusion, 15 mg/kg Q2W for 24 weeks: N=98 Placebo: N=98	PK Predose and postdose (45 minutes after infusion) on Day 1 and Weeks 2, 4, 8, 12, 16, 20, and 24. ADA and Nab were also assessed. PK and ADA/Nab ECLIA bioanalytical assay. Total serum IgG and IgG subclasses Screening, baseline and predose on Weeks 2, 4, 6, 8, 12, 16, 20, 22, and 24. Anti-AChR, Anti-MuSK, Anti-LRP4 autoantibodies Screening, baseline and predose on Weeks 2, 4, 6, 8, 12, 16, 20, 22, and 24.
Phase 2 Vivacity-MG	N=68 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 Day 1 predose and postdose, Day 15 predose, Day 29 predose, Day 43 predose, Day 57 predose and postdose, Day 85. ADA/Nab were also assessed. PK and ADA ELISA bioanalytical assay. Total serum IgG and IgG subclasses 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.

Population Pharmacokinetic Modeling

The PPK analysis was performed using nonlinear mixed-effects modeling (NONMEM 7.4.3). The population PK of nipocalimab and FcRn RO parameters were fixed based on the previously established model [3] in **Figure 2**, allowing for the estimation of individual empirical Bayes estimates, which were then used as an input to develop the IgG subclass model. The indirect response model was utilized to characterize the serum IgG subclass concentration time course**.** Exploratory analysis, diagnostic graphics [**Figure 3**], and post-processing of analysis results were carried out using R.

PK/PD Simulations

Model-based simulations of 1000 virtual patients with gMG were conducted for IgG subclasses and anti-AChR over 14 weeks, following the IV loading dose regimen of 30 mg/kg and 15 mg/kg Q2W thereafter.

The predicted reductions in IgG subclass concentrations over time were graphically depicted to illustrate the impact of nipocalimab, compared to IgG subclass profiles observed in phase 2 study with the recommended efgartigimod dose of 10 mg/kg as well as total IgG and anti-AChR autoantibody observed in phase 3 study with the rozanolixizumab at doses of 7 and 10 mg/kg [4,5].

RESULTS & DISCUSSION

Figure 2. Nipocalimab IV Population PK-IgG Model Structure

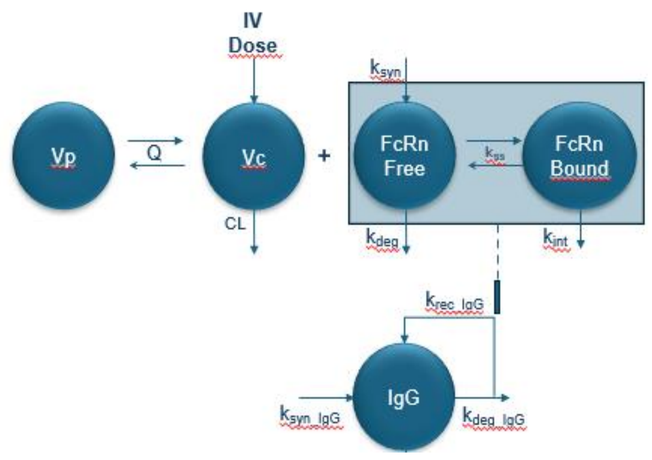


Figure 3. Goodness-of-fit Plots for the Final PK-IgG Model

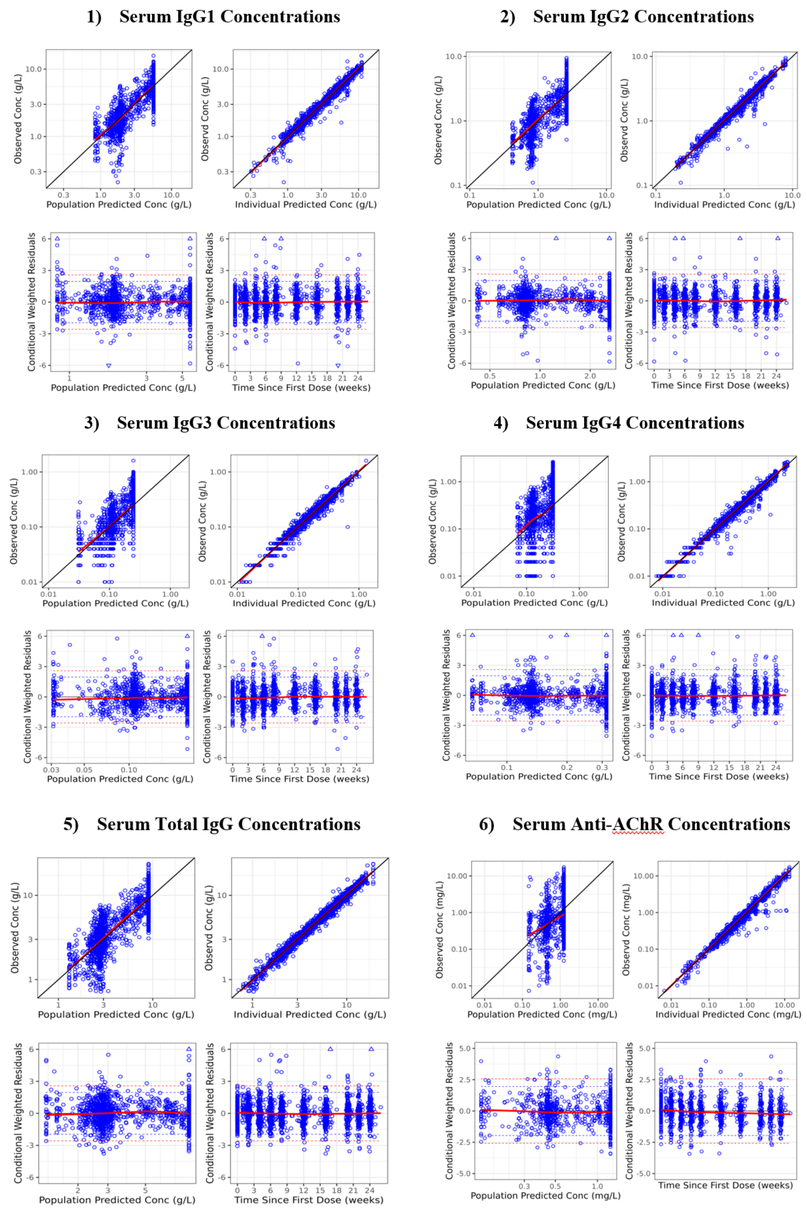
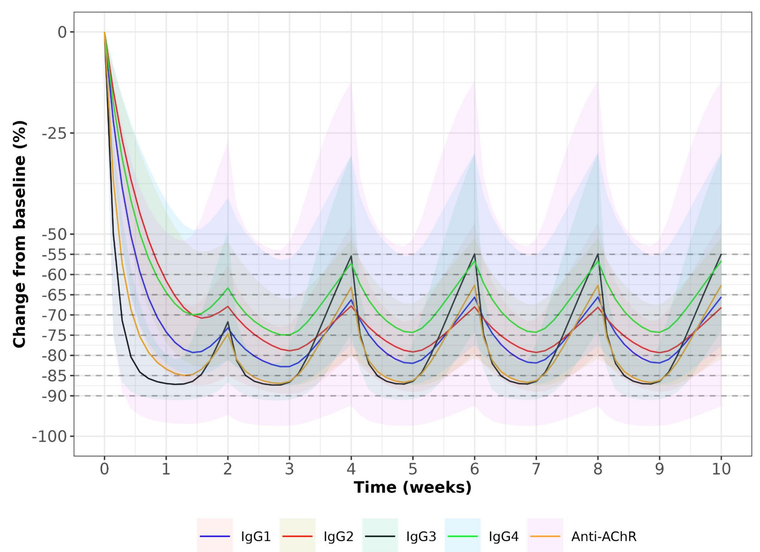
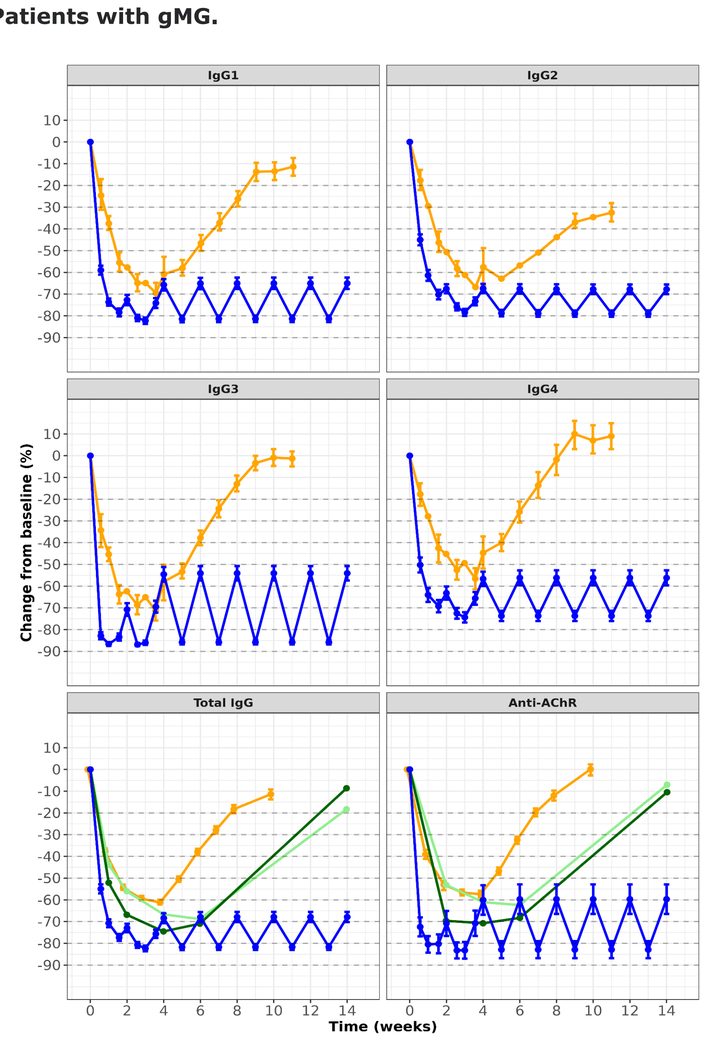


Figure 4. Comparison of the Simulated IgG Subclasses, Total IgG, and Anti-AChR Autoantibody Serum Concentration Changes from Baseline



Model-based simulations showed that IgG3 dropped the most rapidly, reached the deepest nadir and recovered to the highest predose level prior to the next dose, indicating IgG3 had the shortest half-life. In contrast, IgG4 exhibited a less pronounced decrease, reaching a nadir of 73.9% and recovering to pre-dose levels comparable to IgG3. Overall, IgG1 and IgG2 exhibited similar profile over time, maintaining comparable pre-dose and nadir levels at steady state (**Figure 4**).

Figure 5. Time Course of IgG Subclasses, Total IgG, and Anti-AChR Autoantibody Serum Concentration Changes from Baseline over Time Following Nipocalimab, Efgartigimod, and Rozanolixizumab Dosing Regimens Supporting Approval in Patients with gMG.



Efgartigimod (10 mg/kg QW IV [orange]): mean (±SD) of observed IgG subclasses, total IgG, and anti-AChR autoantibody CFB after 4 weeks of treatment followed by 7 weeks of observation.

Rozanolixizumab (7 mg/kg [light green] and 10 mg/kg [dark green] QW SC): mean of observed total IgG and anti-AChR autoantibody CFB after 6 weeks of dosing followed by 8 weeks of observation.

Nipocalimab (30 mg/kg loading dose followed by 15 mg/kg Q2W IV [blue]): the simulated mean (±SD) of observed IgG subclasses, total IgG, and anti-AChR autoantibody CFB after the treatment.

Nipocalimab demonstrated a faster, stronger and more sustained effect compared with efgartigimod and rozanolixizumab (**Figure 5**). Following nipocalimab treatment, IgG subclasses and anti-AChR autoantibody were predicted to reach their lowest levels before week 3, one week earlier than with efgartigimod treatment. Furthermore, nipocalimab achieved a reduction of 74-87% at nadir in IgG subclasses, 82% in total IgG and 83% in anti-AChR, while efgartigimod resulted in a smaller reduction, i.e. 57-71% in IgG subclasses, 61% in total IgG and 57% in anti-AChR. Rozanolixizumab also resulted in a smaller reduction of 69% in total IgG and 62% in anti-AChR with 7 mg/kg QW SC; and 75% and 71% with 10 mg/kg QW SC for 6 weeks.

CONCLUSION

Nipocalimab selectively binds to FcRn, effectively inhibiting FcRn-mediated IgG recycling. This results in rapid, deep and sustained reductions in IgG subclasses as well as pathogenic anti-AChR autoantibodies in patients with gMG. These findings enhance our understanding of nipocalimab's effects on the pathogenic autoantibodies involved in the gMG disease and support further exploration of nipocalimab's therapeutic potential for IgG-driven, autoantibody- and alloantibody-mediated diseases.

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