Predicting Total Immunoglobulin G Change From Baseline When Switching From Efgartigimod to Nipocalimab

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Background

- Myasthenia gravis (MG) is a chronic autoimmune disorder with elevated levels of autoimmune antibodies, impaired neuromuscular junction transmission, characterized by muscle weakness and fatigability of ocular, skeletal and bulbar muscles.[1]
- Neonatal fragment crystallizable (Fc) receptor (FcRn) interacts with the Fc portion of immunoglobulin G (IgG) and extends the IgG half-life by preventing its lysosomal degradation.[2] Neonatal FcRn is a promising target for treatment of autoimmune diseases such as generalized myasthenia gravis (gMG).
- Current treatment options for autoimmune diseases like gMG include FcRn blockers such as nipocalimab and efgartigimod which increase IgG clearance and reduce circulating IgG, including pathogenic IgG antibodies.[3]

Objective

We simulated total serum IgG reductions when switching from efgartigimod to nipocalimab to inform the upcoming EPIC clinical trial (NCT05327114) and switch strategies in clinical practice.

Methods

- Available population pharmacokinetic (PK)/pharmacodynamic (PD) models for both efgartigimod and nipocalimab were combined. IgG turnover was described as a combination of intrinsic catabolic rate k_{deg} and FcRn-mediated recycling rate k_{rec}. FcRn-mediated recycling is inhibited by the FcRn inhibitor through a drug-specific function.

$$\frac{dIgG}{dt} = k_{syn} - (k_{deg} - k_{rec} * Inhib) * IgG$$

- **Nipocalimab drug effect:** Nipocalimab inhibits IgG recycling dependent on the fraction of free FcRn receptor (*$FcRn_{free}$*) relative to its baseline value *(FcRn0)*.

$$Inhib = \frac{FcRn_{free}}{FcRn0}$$

- **Efgartigimod model:** Efgartigimod inhibits IgG recycling based on a sigmoidal model determined by a maximum x-fold increase (EMax) and efgartigimod serum concentration relative to the concentration of 50% effect size (EC_{50}).

$$Inhib = 1 - \frac{Conc}{EC_{50}+Conc}$$

Dosing:

- Nipocalimab and efgartigimod dosing were simulated according to the approved US label regimen: 30 mg/kg LD followed by continuous 15 mg/kg Q2W for nipocalimab, and repeating cycles of 4 doses of 10 mg/kg QW followed by 4 weeks off period for efgartigimod dosing.

Conc=concentration, **EC_{50}**=half-maximal effective concentration, **FcRn**=neonatal fragment crystallizable receptor, **IgG**=immunoglobulin G, **Inhib**=inhibition, **k_{deg}**=degradation rate constant, **k_{rec}**=recyling rate constant, **k_{syn}**=production rate constant.

Key Takeaways

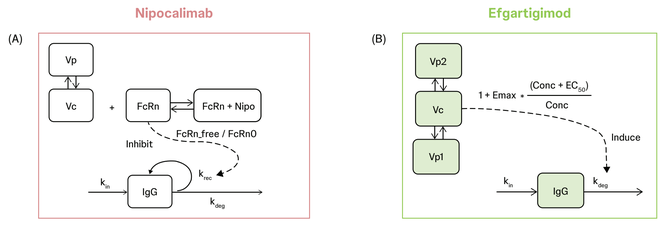
- **A combined population PK/PD model predicts there are multiple switch strategies from efgartigimod to nipocalimab that can achieve IgG reductions consistent with the nipocalimab's target IgG reduction profile, while avoiding IgG oversuppression:**
  - **Switching to nipocalimab 30 mg/kg LD + 15 mg/kg Q2W maintenance ≥8 weeks after the initiation of an efgartigimod cycle.**
  - **Switching to nipocalimab 15 mg/kg Q2W maintenance dose (without LD) 4 weeks after the initiation of an efgartigimod cycle.**
- **In the absence of robust clinical trial switch data, these models may inform switch strategies in clinical practice, and they were utilized to design the switch portion of the EPIC clinical trial.**

Results

Individual treatments

- Nipocalimab PK and receptor occupancy was described using an open two-compartment distribution model, with parallel linear (CL) and target-mediated clearance. An indirect-response model was used to describe the time course of total serum IgG concentrations, with IgG loss composed of natural catabolism k_{deg} and an FcRn-mediated endosomal recycling rate k_{rec}. K_{rec} was inhibited depending on the fraction of free FcRn receptor $FcRn_{free}$ relative to its baseline value FcRn0.
- Efgartigimod PK was described using an open three-compartment distribution model with linear clearance. Similar to nipocalimab model, an indirect-response model was used to describe the time course of total serum IgG concentrations, with efgartigimod inducing IgG loss through a sigmoidal Emax model.

FIGURE 1: Individual treatments of (A) Nipocalimab and (B) Efgartigimod



Conc=concentration, **EC_{50}**=half-maximal effective concentration, **FcRn**=neonatal fragment crystallizable receptor, **IgG**=immunoglobulin G, **k_{deg}**=degradation rate constant, **k_{in}**=production rate constant, **k_{rec}**=recyling rate constant, **Nipo**=nipocalimab, **Vc**=central volume of distribution, **Vp**=peripheral volume of distribution.

Comparison of systemic IgG parameters with both treatments

- Systemic IgG parameters were equivalent for both nipocalimab and efgartigimod (**Table 1**).

TABLE 1: Systemic parameters comparison for nipocalimab and efgartigimod

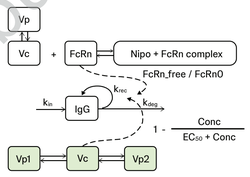
Systemic parameters	Nipocalimab popPKPD model[4]	Efgartigimod popPKPD model[5]
Baseline IgG µmol/L	59.8	51.63
Baseline IgG µg/L	8970	7744
Maximal % IgG	-84.3	-82.8
Time (d) until 80% of maximal reduction	6.3	5.7
k_{deg} IgG degradation rate at full FcRn inhibition (1/day)	0.252	0.279
k_{rec} IgG recycling rate (1/day)	0.213	0.231
k_{out} IgG degradation rate with uninhibited FcRn (1/day)	0.0394	0.0475
Synthesis rate at baseline (µmol/L/day)	2.36	2.45

FcRn=neonatal fragment crystallizable receptor, **IgG**=immunoglobulin G, **k_{deg}**=degradation rate constant, **k_{out}**=loss, **k_{rec}**=recyling rate constant, **popPKPD**=population pharmacokinetic pharmacodynamic.

Combined model

- The PK models for nipocalimab and efgartigimod were simulated in parallel, assuming no interaction on PK. The efgartigimod IgG model was adapted from an induction of IgG loss to an inhibition of IgG recycling. This allowed the IgG models for both compounds to merge into one. As nipocalimab has between 450- and 5500-fold higher FcRn binding affinity compared to efgartigimod, the impact of any remnant efgartigimod at the time of nipocalimab dosing was considered negligible.

FIGURE 2: Combined model

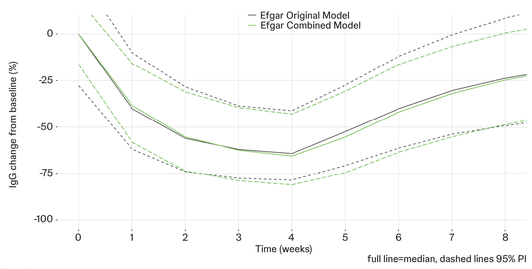


Conc=concentration, **EC_{50}**=half-maximal effective concentration, **FcRn**=neonatal fragment crystallizable receptor, **IgG**=immunoglobulin G, **k_{in}**=production rate constant, **k_{deg}**=degradation rate constant, **k_{rec}**=recyling rate constant, **Nipo**=nipocalimab, **Vc**=central volume of distribution, **Vp**=peripheral volume of distribution.

Comparison of efgartigimod with original and combined models

- Results of IgG change from baseline with efgartigimod monotherapy matched when using original efgartigimod model and combined model using nipocalimab-estimated IgG systemic parameters (**Figure 3**).

FIGURE 3: Overlay of efgartigimod alone using the combined and the original model



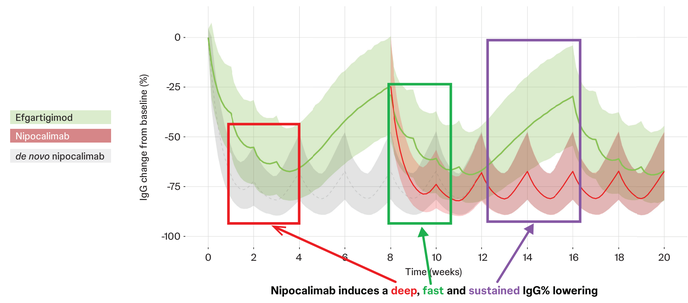
full line=median, dashed lines 95% PI

Efgar=efgartigimod, **IgG**=immunoglobulin G, **PI**=prediction interval.

Simulate base case: switch at W8, with 30 mg/kg LD

- Efgartigimod cycles (4W on/4W off), 10 mg/kg once weekly (QW) followed by nipocalimab 30 mg/kg LD + 15 mg/kg Q2W was compared with *de novo* nipocalimab steady state 30 mg/kg LD + 15 mg/kg Q2W and with efgartigimod (4W on/4W off) (**Figure 4**).
- The *de novo* initiation of nipocalimab IV 30 mg/kg LD + 15 mg/kg Q2W resulted in a rapid initial IgG reduction of 72% at W2 and subsequently alternated between 81% (odd weeks) and 67% (prior to next dose).
- Efgartigimod cycles (4W on/4W off) yielded IgG reductions of 65% at W4 and 24% at W8.
- Switching to nipocalimab after 8W efgartigimod therapy resulted in robust (>70%) IgG reduction within 1W of the switch and a 74% reduction at W2, indicating no significant additional reduction in IgG compared to *de novo* initiation.

FIGURE 4: Comparison of switch at Week 8 between nipocalimab and efgartigimod

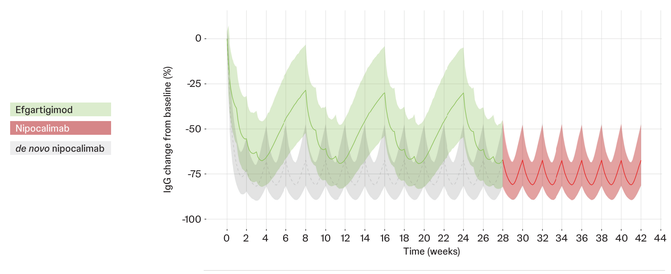


IgG=immunoglobulin G.

Early switch: switch at W4, without LD

- Efgartigimod 4x10 mg/kg QW followed by nipocalimab 15 mg/kg Q2W was compared with *de novo* nipocalimab steady state 30 mg/kg LD + 15 mg/kg Q2W and with efgartigimod (4W on/4W off) (**Figure 5**).
- Switching from efgartigimod to nipocalimab IV 15 mg/kg Q2W resulted in a profile that was identical to nipocalimab steady-state.
- Based on the semi-mechanistic model, no relevant interactions between nipocalimab and residual efgartigimod concentrations are expected.
- The model predicts that IgG is not reduced below the levels of nipocalimab steady-state.

FIGURE 5: Switch to nipocalimab four weeks after start of last efgartigimod cycle by dose

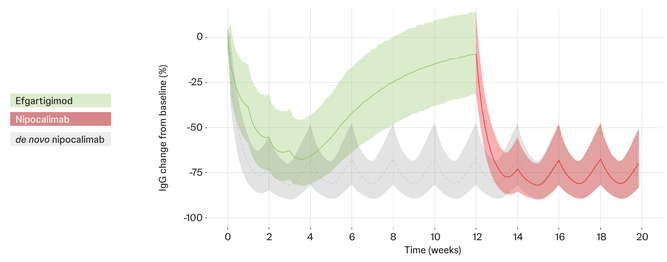


Patients can switch to nipocalimab at Week 5 after efgartigimod initiation, ensuring sustained IgG reductions during the transition. **IgG**=immunoglobulin G.

Simulate more delay: switch at W12, including LD

- Efgartigimod cycles (4W on/4W off), 10 mg/kg QW was followed by 4 weeks of no treatment, then initiation of nipocalimab 30 mg/kg LD followed with 15 mg/kg Q2W began. This was compared with *de novo* nipocalimab steady state 30 mg/kg LD + 15 mg/kg Q2W (**Figure 6**).
- If switching to nipocalimab is delayed, such as at W12, when IgG levels return to baseline following the start of an efgartigimod cycle, the IgG profile post-switching matched that predicted after *de novo* initiation. A robust IgG reduction (71%) occurred within 1 week after the switch.

FIGURE 6: Switch to nipocalimab 12 weeks after start of efgartigimod



IgG=immunoglobulin G.

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