Efficacy and Safety of Nipocalimab vs Efgartigimod in a Randomized, Open-Label, Phase 3b, Interventional Trial Including Within Class Switching from Efgartigimod to Nipocalimab (EPIC): Study Design

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EPIC
A Myasthenia Gravis study

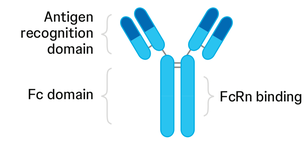
Key Takeaways

- **The EPIC trial addresses whether nipocalimab provides superior efficacy to efgartigimod in the latter part of efgartigimod cycles that cover most dosing patterns utilized in clinical practice**
- **This study is the first randomized trial comparing advanced treatments for patients with gMG and is designed to provide critical insights to inform clinical decisions when initiating or switching in the FcRn-targeting class**

Background

- Generalized myasthenia gravis (gMG) is a chronic, immunoglobulin G (IgG) autoantibody-mediated autoimmune neuromuscular disease associated with unpredictable, fluctuating muscle weakness[1,2]
- In the context of gMG, the neonatal fragment crystallizable receptor (FcRn) maintains high levels of pathogenic IgG and extends the half-life of IgG; therefore, FcRn inhibition constitutes a targeted approach for treatment of gMG[3–5]
- Nipocalimab and efgartigimod are FDA-approved FcRn-targeting treatments for gMG with differing molecular structures, binding affinities, and dosing (**Table 1**)[5–8]
- Currently, there are no trials directly comparing efficacy of nipocalimab vs efgartigimod and no data to inform switch strategies from efgartigimod to nipocalimab

Table 1. ***Nipocalimab and efgartigimod overview***



	Nipocalimab	Efgartigimod
Antibody	Fully human, aglycosylated, effectorless IgG1 mAb[6,7]	Human IgG1 Fc fragment[8]
Indications	Treatment of gMG in adult and pediatric patients 12 years of age and older who are anti-AChR or anti-MuSK antibody positive[7]	Treatment of gMG in adult patients who are anti-AChR antibody positive[8]
FcRn binding affinity[a]	Circulation (pH 7.4–7.6): 44 pM[6] Endosome (pH 6.0): 29 pM[6]	Circulation (pH 7.4–7.6): 320,000 pM[5] Endosome (pH 6.0): 14,200 pM[5]
Dosing	30 mg/kg IV initial dose followed by 15 mg/kg every 2 weeks thereafter[7]	10 mg/kg IV or 1000 mg SC once weekly for 4 weeks in each cycle; timing of subsequent treatment cycles is variable based on clinical evaluation and a minimum of 50 days[8] from the start of the previous cycle[8,9]

[a]*Endogenous IgG FcRn binding affinity is 370,000 pM.*[10] [b]*Safety of initiating subsequent cycles sooner than 50 days from the start of the previous treatment cycle has not been established.*[8] ***AChR****=acetylcholine receptor,* ***Fc****=fragment crystallizable,* ***FcRn****=neonatal Fc receptor,* ***gMG****=generalized myasthenia gravis,* ***IgG****=immunoglobulin G,* ***IV****=intravenous,* ***mAb****=monoclonal antibody,* ***MuSK****=muscle-specific tyrosine kinase,* ***SC****=subcutaneous.*

Objective

EPIC aims to evaluate the efficacy of nipocalimab vs efgartigimod in participants initiating FcRn treatment for gMG and to evaluate efficacy and safety of nipocalimab in participants switching from efgartigimod to nipocalimab

Study Rationale

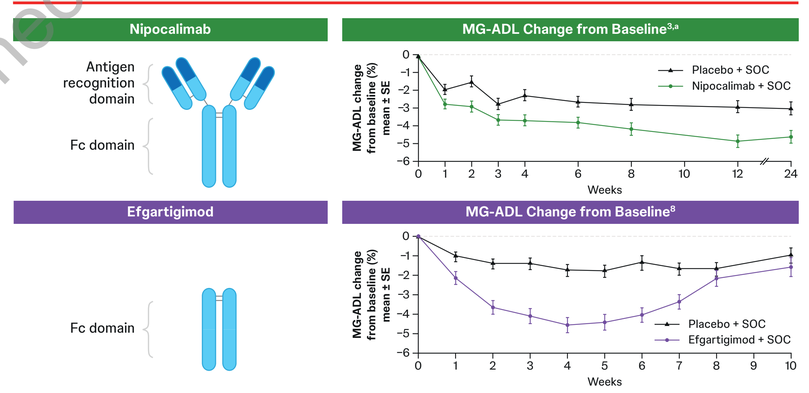
Efficacy of Nipocalimab vs Efgartigimod

- Differences in the molecular properties and dosing regimens between nipocalimab and efgartigimod may contribute in part to different profiles of IgG reduction and Myasthenia Gravis Activities of Daily Living (MG-ADL) score improvement reported in pivotal trials (**Figure 1**)[3,4,8]
  - Over the double-blind period of their pivotal trials, nipocalimab peak median IgG change from baseline (CFB) reduction occurred at 2 weeks (–74.6%) and this reduction remained sustained over the 24-week period (–68.8% at Week 24);[3] efgartigimod peak mean IgG CFB reduction occurred at 4 weeks (–61.3%) with a subsequent decline from peak and levels returning to baseline by Week 12[4]
  - However, variations in pivotal trial designs, timing, and patient populations limit the ability to make indirect efficacy comparisons using pivotal trial data, underscoring the need for a head-to-head clinical trial
- Nipocalimab is dosed consistently every 2 weeks while efgartigimod is dosed as cycles of 4 weekly infusions separated by variable intervals of time based on clinical evaluation of symptoms with a minimum safety period of 50 days from the start of the previous cycle[7,8]
- The majority of patients (~63%) on efgartigimod in the US have been re-dosed between Week 8 and Week 12 in clinical practice[11]
- Therefore, EPIC aims to compare efficacy outcomes 1) between Weeks 8 and 12 in the latter part of efgartigimod cycles that cover most dosing patterns utilized in clinical practice; 2) end of treatment (EoT)/end of cycle (EoC) based on clinical symptoms between Weeks 4 and 12, as in practice efgartigimod EoC could occur at any time after treatment with 4 weekly doses; and 3) at Week 8, when all participants have received the same number of drug administrations per unit time (i.e., 4 infusions in 8 weeks)

Switch from Efgartigimod to Nipocalimab

- For patients who want to stop efgartigimod treatment for any reason, current options include switching to an alternative treatment in the FcRn-class
- Currently, there is no data to inform on the efficacy and safety profile of nipocalimab in patients switching from efgartigimod
- In the treatment switch phase of EPIC (Arm 3), the timing of the switch between efgartigimod and nipocalimab aimed to balance 1) minimizing overlapping treatment effects between the two treatments, 2) minimizing the magnitude and duration of MG symptom return after an efgartigimod cycle, and 3) utilizing approved dosing for both treatments
- This switch strategy and alternative switch strategies were informed by modeling[12]

Figure 1. ***Nipocalimab and efgartigimod MG-ADL score profiles reported in pivotal trials***



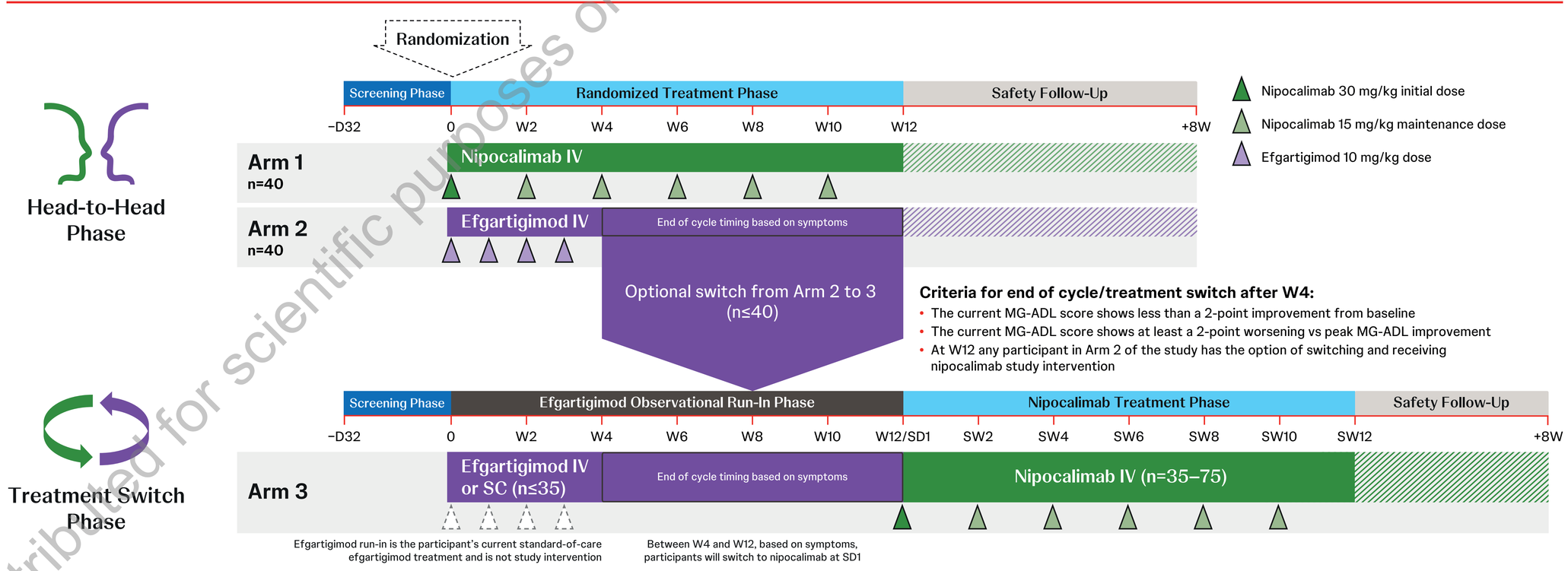
[a]*Adapted with permission from Antozzi et al. (2025, Lancet Neurol).*[3] © Elsevier Ltd.
Fc*=fragment crystallizable,* ***MG-ADL****=Myasthenia Gravis Activities of Daily Living,* ***SE****=standard error,* ***SOC****=standard of care.*

Methods

EPIC (NCT07217587) is a phase 3b, multicenter, randomized, open-label, active-controlled interventional study with parallel-group design including treatment switching in adult participants with gMG

- Participants must be adults with a diagnosis of gMG, MG-ADL score of ≥5 with <50% of symptoms coming from ocular MG-ADL subscores, and be positive for acetylcholine receptor (AChR) antibodies at screening (**Figure 2**)
  - Restriction to adults and AChR seropositive is to ensure participants are indicated for either treatment and to closely match the population eligible for either treatment during its pivotal trial
- The study consists of a screening phase of up to 32 days, a 12-week randomized open-label head-to-head phase (Arms 1 and 2) or an up to 12-week run-in phase and a 12-week open-label treatment switch phase (Arm 3), and an 8-week safety follow-up phase (**Figure 3**)
- FcRn-naïve participants (n=80) will be randomized 1:1 to receive nipocalimab (30 mg/kg initial dose followed by 15 mg/kg maintenance doses) every 2 weeks for 12 weeks (Arm 1) or efgartigimod every week (10 mg/kg) for 4 weeks (Arm 2)
- Participants in Arm 2 and additional participants with ≥1 on-label efgartigimod cycle (minimum n=35) can enroll in the treatment switch phase of the study to be followed on nipocalimab for 12 weeks (Arm 3)

Figure 3. ***EPIC study design***



D*=day,* ***IV****=intravenous,* ***MG-ADL****=Myasthenia Gravis Activities of Daily Living,* ***SC****=subcutaneous,* ***SD****=switch day,* ***SW****=switch week,* ***W****=week.*

Figure 2. ***Key inclusion and exclusion criteria***

Inclusion Criteria

All arms
- ≥18 years of age and <75 years of age
- Meets clinical criteria for gMG as defined by the MGFA Clinical Classification Class II a/b, III a/b, or IV a/b at screening
- AChR antibody positive
- MG-ADL score ≥5 with ≥50% as non-ocular

Arms 1 and 2 only
- Has suboptimal response to current stable therapy[a] for gMG according to the investigator
- Total IgG at screening ≥6 g/L

Arm 3 only
- Treatment with efgartigimod IV or SC for ≥1 cycle, and the final cycle is consistent with local label
- Participant and HCP agree it is appropriate for the participant to switch to nipocalimab

Exclusion Criteria

All arms
- Has received rituximab within 24 weeks prior to baseline
- Has received plasmapheresis, immunoadsorption therapy, or IVIg within 4 weeks prior to baseline

Arms 1 and 2 only
- Has received treatment for MG with an FcRn-targeting therapy
- Is currently taking IgG monoclonal antibody therapeutics, or Fc-conjugated therapeutic agents, including factor or enzyme replacement

Arm 3 only
- Is currently taking IgG monoclonal antibody therapeutics, or Fc-conjugated therapeutic agents, including factor or enzyme replacement, with the exception of efgartigimod

[a]*Stable therapy is defined as: 1) if taking an AChE inhibitor, receiving a stable dose and regimen for at least 2 weeks prior to baseline; 2) if taking a glucocorticosteroid, receiving a stable dose and regimen for at least 3 weeks prior to baseline; or 3) if currently receiving immunosuppressants, receiving the given immunosuppressant for ≥24 weeks and on a stable dose for ≥12 weeks prior to baseline. Allowed concomitant immunosuppressants are azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide.* ***AChE****=acetylcholinesterase,* ***AChR****=acetylcholine receptor,* ***Fc****=fragment crystallizable,* ***FcRn****=neonatal Fc receptor,* ***gMG****=generalized MG,* ***HCP****=healthcare provider,* ***IgG****=immunoglobulin G,* ***IV****=intravenous,* ***IVIg****=intravenous immunoglobulin,* ***MG****=myasthenia gravis,* ***MG-ADL****=Myasthenia Gravis Activities of Daily Living,* ***MGFA****=MG Foundation of America,* ***SC****=subcutaneous.*

Table 2. ***Primary and key secondary endpoints***

Study Phase		Description
	Primary Efficacy Endpoint	
	IgG[a]: CFB, W8–W12	Averaged mean percent CFB in total IgG over W8 to W12 between Arms 1 and 2
	Key Secondary Efficacy Endpoints	**Description**
	MG-ADL score[a]: CFB, W8–W12, EoT/EoC, and W8	Averaged mean CFB in MG-ADL total score over W8 to W12 between Arms 1 and 2 Mean CFB in MG-ADL total score between Arm 1 at EoT and Arm 2 at EoC based on clinical evaluation[b] Mean CFB in MG-ADL total score at W8 between Arms 1 and 2
	QMG score[a]: CFB, W8–W12, EoT/EoC, and W8	Averaged mean CFB in QMG total score over W8 to W12 between Arms 1 and 2 Mean CFB in QMG total score between Arm 1 at EoT and Arm 2 at EoC based on clinical evaluation[b] Mean CFB in QMG total score at W8 between Arms 1 and 2
	IgG[a]: CFB, EoT/EoC and W8	Mean percent CFB in total IgG between Arm 1 at EoT and Arm 2 at EoC based on clinical evaluation[b] Mean percent CFB in total IgG at Week 8 between Arms 1 and 2
	IgG: Change from SD1–SW12/EoT	Mean percent change in total IgG from pre-nipocalimab exposure (SD1) to end of nipocalimab study treatment (SW12/EoT) in Arm 3
	MG-ADL: Change from SD1–SW12/EoT	Mean change in MG-ADL total score from pre-nipocalimab exposure (SD1) to end of nipocalimab study treatment (SW12/EoT) in Arm 3
	Key Safety Endpoints	**Description**
	Incidence of AEs, SAEs, AESIs (infection, VTE, and hypoalbuminemia ≥Grade 3)	Percentage of participants with ≥1 AE occurrence, and descriptive analyses based on abnormal laboratory tests, vital signs and physical exam

[a]*Type I error rate controlled at the 2-sided 0.05 significance level using fixed sequence gatekeeper approach and Hochberg step-up procedure.* [b]*EoC based on clinical evaluation is defined as the timepoint after the fourth dose of efgartigimod when, based on MG-ADL score clinical criteria, the treatment decision would be made to start a second cycle of efgartigimod, an MG rescue medication, or Week 12/EoT, whichever occurs first.* ***AE****=adverse event,* ***AESI****=AE of special interest,* ***CFB****=change from baseline,* ***EoC****=end of cycle,* ***EoT****=end of treatment,* ***IgG****=immunoglobulin G,* ***MG****=myasthenia gravis,* ***MG-ADL****=Myasthenia Gravis Activities of Daily Living,* ***QMG****=quantitative myasthenia gravis,* ***SAE****=serious AE,* ***SD1****=switch day 1,* ***SW12****=switch week 12,* ***VTE****=venous thromboembolism,* ***W****=week.*

Statistical Analyses

Sample Size

- The sample size of 40 participants for each Arms 1 and 2 (1:1 randomization) is required to provide at least 90% power to detect a standardized effect size of 0.65 in the key secondary MG-ADL endpoint, and >95% power to detect a standardized effect size of 1.0 for the primary IgG endpoint
- For the treatment switch phase (Arm 3), assuming the expected mean change from time of switch in MG-ADL is 1.75 units with a significance level of 0.05, a sample size of 35 achieves approximately 84% power

Analysis Sets

- All efficacy and safety analyses will be based on the Full Analysis Sets (FAS)
  - FAS for Arms 1 and 2: All randomized participants who received at least 1 dose (partial or complete) of any study intervention
  - FAS for Arm 3: All participants who received at least 1 dose (partial or complete) of nipocalimab on or after Switch Day 1

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