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Assessing Relationship Between IgG-Levels and Infection Rate in Nipocalimab-Treated Patients With Generalized Myasthenia Gravis (Vivacity-MG3)

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Key Takeaways

- **Nipocalimab reduced levels of IgG in the Vivacity-MG3 study, incidence of infection was comparable with placebo**
- **ROC and threshold analyses consistently showed no predictive association between IgG levels and infection risk**
- **In patients with lower levels of IgG during the Vivacity-MG3 study, there was no increased risk of occurrence of infections**

Introduction

- Nipocalimab, is the first approved FcRn blocker for the treatment of gMG in adult and adolescent (≥12 years of age) patients who are anti-AChR or anti-MuSK antibody positive[1,2]
- Nipocalimab is a fully human monoclonal antibody that binds the neonatal Fc receptor (FcRn) with high affinity and specificity. This FcRn blockade reduces IgG recycling and circulating IgG levels without affecting other immunoglobulin classes or cellular immune function[3]
- Nipocalimab + standard-of-care (SOC) vs placebo+SOC has demonstrated sustained disease control in the 24-week phase 3, double-blind (DB) Vivacity-MG3 study in seropositive patients with gMG[4,5]
  - Nipocalimab also demonstrated rapid and substantial IgG reduction while overall incidence of infection was similar between nipocalimab+SOC and placebo+SOC treatment groups

Objectives

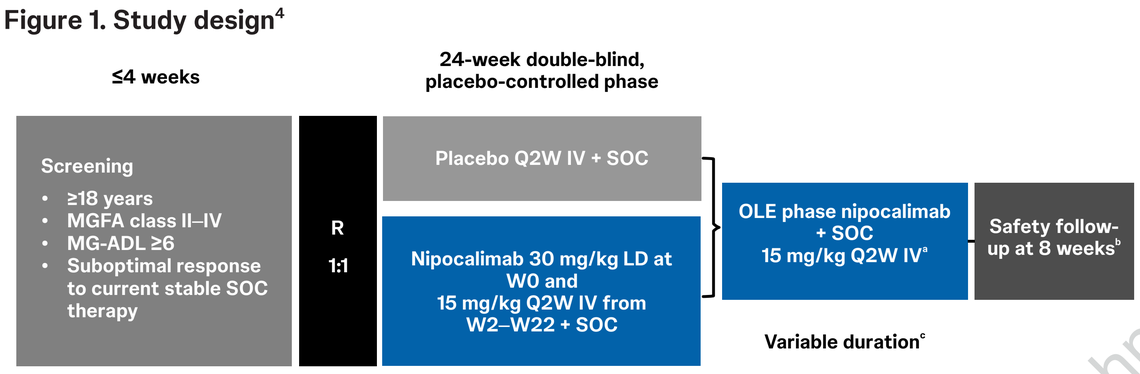
To evaluate the relationship between reduced IgG levels and infection rates in patients with gMG and treated with nipocalimab+SOC across the DB phase of Vivacity-MG3

Methods

Analysis population

- Patients with gMG from efficacy analysis set of Vivacity-MG3 study (**Figure 1**)
  - All patients who received ≥1 dose of nipocalimab+SOC or placebo+SOC in the DB phase and were antibody positive for a gMG-related pathogenic antibody (anti-AChR, anti-MuSK, or anti-LRP4)

Figure 1. Study design[4]



[a]Due to the COVID-19 pandemic, some participants from the Phase 2 study (NCT03772587) were unable to enter the Phase 2 OLE study (NCT03896295). These participants could directly enter the Phase 3 OLE and their data will be disclosed later. [b]Participants who withdraw or discontinue after receiving any amount of study intervention are required to complete a safety follow-up visit 8 weeks after their last dose. [c]In the EU, the OLE phase will be up to 240 weeks.
***COVID-19**=coronavirus disease 2019, **EU**=European Union, **IV**=intravenous, **LD**=loading dose, **MG-ADL**=Myasthenia Gravis-Activities of Daily Living, **MGFA**=Myasthenia Gravis Foundation of America, **OLE**=open-label extension, **Q2W**=every 2 weeks, **R**=randomized, **SOC**=standard-of-care, **W**=week.*

Assessments

ROC analysis

- Receiver Operating Characteristic (ROC) analysis assessed the relationship between IgG levels (evaluated as a continuous variable) and infection rates
- Area under the curve (AUC) values were calculated using logistic regression ROC analysis with treatment group, maximum change from baseline in IgG, and baseline IgG as covariates
- AUC values range from 0–1, with 0.5–≤0.7 indicating no/poor discrimination[6] (**Table 1**)

Table 1. Interpretation of AUC values

wAUC value (g/L)	Interpretation
0.5	No discrimination (equivalent to chance) – IgG levels do not predict infection
>0.5 to ≤0.7	Poor discrimination – weak predictive association
>0.7 to <0.8	Acceptable discrimination – moderate predictive association
≥0.8 to ≤0.9	Excellent discrimination – strong predictive association
>0.9 to 1.0	Outstanding discrimination – very strong predictive association

***AUC**=area under the curve, **IgG**=immunoglobulin G.*

Threshold-based analysis

- Incidence of infection was ascertained across treatment groups by IgG threshold levels
- Proportion of patients with infection treatment-emergent adverse events (TEAEs) was evaluated at lowest IgG thresholds (≤5, ≤4, ≤3, and ≤2 g/L)
- Patients were stratified as with low IgG (lowest IgG threshold) vs. without low IgG (lowest IgG threshold), and incidence of infection was compared between nipocalimab and placebo groups

Results

AUC analysis

- AUC values for IgG thresholds ≤5 g/L to ≤2 g/L are ~0.51–0.69, which fall within the no/poor discrimination range. (**Table 1**). Thus, ROC analysis indicated no real predictive association between reduced IgG levels (as low as ≤2 g/L) with nipocalimab treatment and infection rates (**Table 2**)
- Patient numbers at the ≤1 g/L threshold were too low (N=8) to draw any meaningful conclusions regarding the association between IgG reduction and infection rates at this level

Table 2. Summary of AUC analysis comparing all infections and maximum change from baseline in IgG (g/L) in nipocalimab treated patients

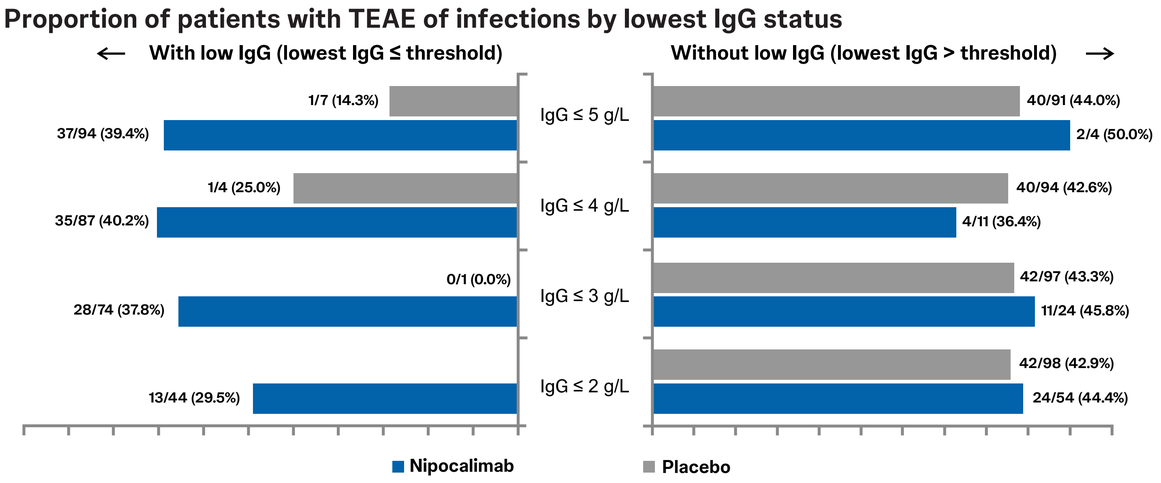
Post-baseline level of IgG (g/L)	N	P-Y exposure	AUC[a] (SE) for Maximum Change from Baseline in IgG and Infection[b]	95% CI
≤5 g/L	94	105.51	0.510 (0.062)	(0.389, 0.631)
≤4 g/L	87	97.92	0.523 (0.064)	(0.397, 0.649)
≤3 g/L	74	72.40	0.533 (0.070)	(0.395, 0.670)
≤2 g/L	44	30.00	0.686 (0.082)	(0.525, 0.848)

[a]AUC scores range from 0-1, where a score of 0.5 would indicate no discrimination and that the association is equivalent to chance while a score of 1 indicates a perfect predictive value.
Generally, scores above 0.8 indicate excellent predictive value and above 0.9 indicate outstanding predictive value.
[b]Infection occurred after the timepoint when maximum change from baseline in IgG occurred.
Note: Area under the curve was calculated using a logistic regression receiver operator curve analysis with maximum change from baseline in IgG, treatment group and baseline IgG as covariates.
Note: Duration of exposure includes follow-up period.
***AUC**=area under the curve, **CI**=confidence interval, **IgG**=immunoglobulin G, **P-Y**=patient-year, **SE**=standard error.*

Proportion of patients with infections

- Despite rapid and substantial IgG lowering with nipocalimab, lower IgG levels were not associated with higher infection risk in Vivacity-MG3
- The threshold-based infection results among nipocalimab-treated patients shows that the proportion with infection TEAEs was 39.4% at ≤5 g/L, 40.2% at ≤4 g/L, 37.8% at ≤3 g/L, and 29.5% at ≤2 g/L, which does not show a pattern of increasing infection frequency with lower IgG levels (**Figure 2**)
- Overall infection incidence was similar between nipocalimab and placebo groups (43% each), and ROC/AUC analyses showed no meaningful predictive relationship between post-baseline IgG level and infection occurrence

Figure 2. Proportion of patients with TEAE of infections by lowest IgG status



Note: Infections and infestations occurred after the timepoint when lowest IgG level occurred. Bar labels show n/N (%) of patients with TEAE Infections/Infestations. Axes mirrored 0–55%.
***IgG**=immunoglobulin G, **TEAE**= treatment-emergent adverse event.*

Summary of infections in patients with ≤1 g/L of IgG level

- In nipocalimab+SOC-treated patients with lowest IgG ≤1 g/L, 8 events of TEAEs of infection/infestation were reported in 5 patients
- All events were mild-to-moderate in severity except 1 serious event (pneumonia) which was resolved
- All events were assessed by investigators as not related to nipocalimab treatment
- No treatment modification was required for most events; temporary treatment interruption occurred for 2 events (COVID-19 and pneumonia)
- All reported events recovered/resolved

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