Relationship Between IgG Levels and Infection Rates in Nipocalimab Treated Participants With Systemic Lupus Erythematosus (SLE) in the Phase 2 JASMINE-SLE Study

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Key Takeaways

- **While nipocalimab reduced levels of IgG in the JASMINE-SLE study, the incidence of infection was comparable with placebo**
- **Neither ROC nor threshold analyses showed predictive associations between IgG levels and infection risk**
- **This exploratory analysis in the small sample of participants in the JASMINE-SLE study did not show an increased infection risk with low IgG levels; evaluation in a larger population will be necessary to confirm these findings**

Background

- Nipocalimab is a fully human immunoglobulin G (IgG)1 monoclonal antibody that selectively blocks the neonatal Fc receptor (FcRn),[1] thereby preventing IgG recycling and leading to a rapid and substantial reduction in all IgG subclasses, including pathogenic autoantibodies and circulating immune complexes[2,3]
- In the phase 2 JASMINE-SLE study of participants with moderate-to-severe systemic lupus erythematosus (SLE), treatment with nipocalimab (5 mg/kg or 15 mg/kg intravenous [IV] every 2 weeks [Q2W]) in addition to standard-of-care therapy resulted in predose median IgG reductions of 38.8% or 54.6%, respectively, at Week 52; treatment with nipocalimab 15 mg/kg IV Q2W was associated with reduced disease activity through Week 52 and an acceptable safety profile
- In JASMINE-SLE, the overall rates of infections, as well as opportunistic and serious infections, were similar across treatment groups:
  - Infections/infestations: 5 mg/kg, 58.4% (45/77); 15 mg/kg, 60.5% (46/76); placebo, 56.0% (42/75) (herpes zoster: 2.6% [2/77]; 1.3% [1/76]; 2.7% [2/75], respectively)
  - Opportunistic infections: 5 mg/kg, 0% (0/77); 15 mg/kg, 1.3% (1/76); placebo, 0% (0/75)
  - Serious infections/infestations: 5 mg/kg, 5.2% (4/77); 15 mg/kg, 3.9% (3/76); placebo, 4.0% (3/75)

Objective

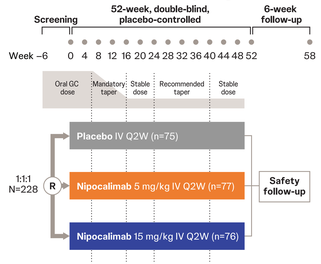
To explore the potential association of IgG reduction with infection rates in participants with moderate-to-severe SLE from the phase 2 JASMINE-SLE study

Methods

Study Design

- JASMINE-SLE was a global, multicenter, randomized, double-blind, placebo-controlled, phase 2 study that enrolled individuals with moderate-to-severe SLE
- Eligible participants were required to:
  - Be 18 to 65 years of age and positive for antinuclear antibodies (ANA) and/or anti–double-stranded DNA (dsDNA) and/or anti-Smith
  - Have SLE Disease Activity Index 2000 (SLEDAI-2K) scores ≥6 and clinical SLEDAI-2K (excluding headache and serologies) scores ≥4
  - Have ≥1 British Isles Lupus Assessment Group (BILAG) A or ≥2 BILAG B domain scores, a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score ≥6, and/or ≥4 active joints (joints with pain, tenderness, and swelling/effusion)
  - Have not adequately responded to ≥1 standard-of-care treatment
- Participants were randomized (1:1:1) to receive IV nipocalimab 5 mg/kg, nipocalimab 15 mg/kg, or placebo Q2W (**Figure 1**)

FIGURE 1: The JASMINE-SLE study design



GC=glucocorticoid, IV=intravenous, Q2W=every 2 weeks, R=randomization.

Analysis Population

- Analyses included all randomly assigned participants who received ≥1 dose (partial or complete) of study intervention according to the actual intervention received

Assessments

- Receiver operating characteristic (ROC) analysis was conducted to assess whether IgG levels (evaluated as a continuous variable) were associated with infection rates
- Area-under-the-curve (AUC) values for maximum change from baseline in IgG (as well as length of follow-up) and subsequent infection rates were calculated using logistic regression ROC analysis with treatment group (combined nipocalimab and placebo groups), maximum change from baseline in IgG, and baseline IgG as covariates
  - Infections were defined as those occurring after the time point when maximum change from baseline in IgG occurred
  - AUC values range from 0 to 1, with 0.5 to ≤0.7 indicating no/poor discrimination and higher values indicating predictive association (**Table 1**)[4]

TABLE 1: Interpretation of AUC values[4]

AUC value	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 (≤5, ≤4, ≤3, and ≤2 g/L)
- The proportion of participants with adverse events (AEs) of infection that followed the nadir IgG time point was evaluated at each nadir IgG threshold
- Participants were stratified as those with low IgG (below nadir IgG threshold) versus those with IgG levels above that nadir threshold, and incidence of infection AEs was compared between nipocalimab and placebo groups

Results

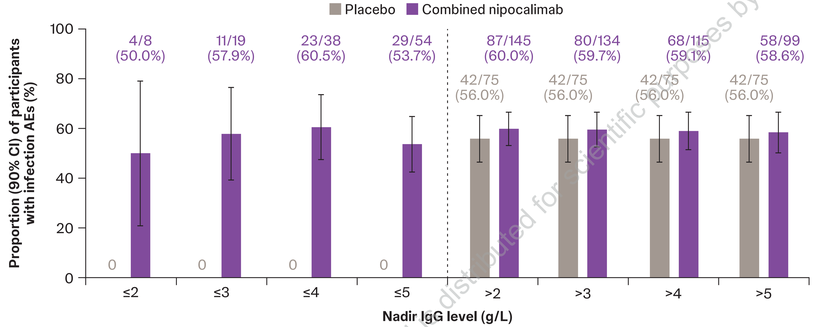
Participants

- A total of 228 participants were randomized and received ≥1 IV dose of study intervention (nipocalimab 5 mg/kg, n=77; nipocalimab 15 mg/kg, n=76; placebo, n=75) and were included in the analysis

Proportion of Participants With Infection

- The threshold-based infection results among nipocalimab-treated participants showed that the proportion with infection AEs was 53.7% at ≤5 g/L, 60.5% at ≤4 g/L, 57.9% at ≤3 g/L, and 50.0% at ≤2 g/L (**Figure 2**)
- Overall infection incidence was similar between nipocalimab and placebo groups (59.5% vs 56.0%)

FIGURE 2: Proportion (90% CI) of participants with infection AEs[a] by nadir IgG level



[a]Infections occurred after the time point when the nadir IgG level occurred.
AE=adverse event, **CI**=confidence interval, **IgG**=immunoglobulin G.

AUC Analysis

- The calculated AUC scores were in the 0.4 to 0.6 range (**Table 2**)
  - The predictive power of IgG levels on infection occurrence was generally equivalent to chance, even at IgG levels ≤3 g/L
- The predictability of infection did not meaningfully change by a nadir IgG level between ≤5 g/L and ≤3 g/L

Summary of Serious AEs in Participants With ≤1 g/L of IgG

- While sustained IgG levels <1 g/L is associated with increased risk of infection,[5] nadir IgG ≤1 g/L was observed in only 1 participant treated with nipocalimab and no serious AEs (including serious infections) were reported through Week 58

TABLE 2: ROC analysis of predictability of infection rate with maximum change in IgG and length of follow-up by nadir IgG level

Nadir IgG, g/L	n	P-Y exposure	AUC (SE) for maximum change from baseline in IgG and infection[a]	AUC (SE) for length of follow-up and infection
≤1	1	0.27	NE	NE
≤2	8	2.37	NR[b]	NR[b]
≤3	19	12.96	0.544 (0.142)	0.622 (0.142)
≤4	38	26.05	0.484 (0.100)	0.611 (0.094)
≤5	54	37.97	0.527 (0.082)	0.621 (0.079)

[a]Infection occurred after the time point when maximum change from baseline in IgG occurred.
[b]NR due to an exceedingly small sample size, which can result in unreliable estimates and higher variability.
AUC=area-under-the-curve, **IgG**=immunoglobulin G, **NE**=not estimable, **NR**=not reported, **P-Y**=patient-years, **ROC**=receiver operating characteristic, **SE**=standard error.

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