PHARMACODYNAMIC EFFECTS OF NIPOCALIMAB IN PATIENTS WITH MODERATE TO SEVERE ACTIVE RHEUMATOID ARTHRITIS (RA): RESULTS FROM THE MULTICENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE 2A IRIS-RA STUDY

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BACKGROUND

- Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease with a multitude of pathogenic mechanisms[1]
- Anti-citrullinated protein autoantibody (ACPA) is one of the hallmark autoantibodies that may contribute to the pathogenesis of RA[2-4]
- Nipocalimab is a fully human, immunoglobulin G (IgG) 1 monoclonal antibody that blocks the neonatal Fc receptor responsible for IgG recycling, thereby lowering IgG levels[5,6]
- In a phase 1 study in healthy volunteers and a phase 2 study in adults with generalized myasthenia gravis (Vivacity-MG), nipocalimab has been shown to lower total IgG and disease-causing IgG autoantibody levels (anti-acetylcholine receptor antibody) with a favorable safety profile, suggesting that nipocalimab may be efficacious in autoantibody-mediated disorders, including RA[5,6]
- In a phase 2a proof-of-concept study (IRIS-RA; ClinicalTrials.gov Identifier: NCT04991753), nipocalimab demonstrated numerically greater improvements across different clinical endpoints and patient-reported outcomes in participants with moderate to severe, active RA with no new safety findings[7]
  - Participants who received nipocalimab showed numerically greater improvements in the primary efficacy endpoint, Disease Activity Score 28 using C-reactive protein (DAS28-CRP), compared to placebo
  - Participants who received nipocalimab also showed numerically higher changes in the secondary efficacy endpoints, including response rate in American College of Rheumatology response criteria ≥20% (ACR20), ≥50% (ACR50), ≥70% (ACR70), and ≥90% (ACR90); DAS28-CRP remission; and improvement in Clinical Disease Activity Index scores compared to placebo

OBJECTIVE

- To describe the pharmacodynamics of nipocalimab and associated disease biomarkers in the IRIS-RA study

METHODS

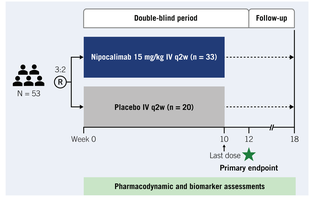
Participants

- Eligible participants were 18 to 75 years of age with moderate to severe RA (≥6 swollen and tender joints of 66/68 joint counts), were positive for ACPA (≥17.0 IU/mL) and/or rheumatoid factor (RF; ≥14.0 IU/mL), had C-reactive protein (CRP) ≥0.3 mg/dL, and had prior inadequate response or intolerance to ≥1 anti–tumor necrosis factor (TNF) agent

Study Design

- IRIS-RA was a phase 2a, multicenter, randomized, double-blinded, placebo-controlled study
- The study included a screening period (Weeks –6 to 0), a double-blind treatment period (Weeks 0 to 12), and a follow-up period (Weeks 12 to 18; **Figure 1**)
- Participants were randomized 3:2 to receive nipocalimab (15 mg/kg intravenous [IV] administered every 2 weeks) or placebo from Weeks 0 to 10

Figure 1. Study Design



IV, intravenous; q2w, every 2 weeks; R, randomization.

Pharmacodynamic and Biomarker Assessments

- The pharmacodynamics of nipocalimab and disease-associated biomarkers were assessed at baseline and over time through Week 18
- Blood samples were collected from all participants immediately prior to the administration of study intervention for the measurement of serum immunoglobulin levels, including total IgG and IgG subclasses
- Levels of serum ACPA IgG were measured using the Svar anti-cyclic citrullinated peptide 2 assay
- Circulating immune complexes (CICs), complement activation markers, and serum inflammatory markers, including cytokines and CRP, were also measured
- Associations of changes in biomarker levels with clinical responses at Week 12 were assessed

Statistical Analysis

- For the comparison of changes in biomarkers between groups, statistical analyses were performed on the $\log_2$-transformed ratio of the value at each visit over the respective baseline value for a given participant, with differences between groups evaluated using Welch's t-test
- For total IgG, ACPA IgG, and CIC, the geometric mean (GMean) and 95% confidence interval (CI) of the ratios of the value at each visit over the respective baseline value were derived from the exponentiation of the mean of the $\log_2$ ratios over baseline; results are reported as the corresponding percent change value (100% × (GMean ratio – 1))
  - The median percent change from baseline was also calculated for total IgG
- The statistical tests were not controlled for multiplicity, and all *P* values were considered nominal
- All pharmacodynamic and disease-related biomarker values after treatment failure (TF) were reported as missing (TF rule). Total IgG was also analyzed using the completer rule for pharmacokinetics and pharmacodynamics (PK/PD), where participants with missed doses of study intervention were excluded
- For ACPA IgG analyses, participants with baseline levels below the lower limit of quantitation were excluded

Modeling and Simulation

- A target-mediated drug disposition model was developed to characterize the relationship of PK/PD after IV nipocalimab administration based on data from phase 1 and phase 2 studies
- Simulations with 15 mg/kg IV nipocalimab administered every 2 weeks were performed in 1000 virtual subjects and summarized as the median and 90% prediction interval of percent change from baseline in total IgG over time

RESULTS

Participants

- There were 53 enrolled participants (nipocalimab, n = 33; placebo, n = 20), and demographic and baseline disease characteristics were generally comparable between groups (**Table 1**)
- At screening, 90.6% of participants were positive for ACPA and the same percentage was positive for RF
  - 83% of participants were positive for both ACPA and RF

Table 1. Demographic and Baseline Characteristics

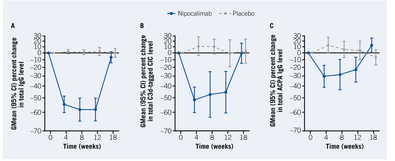
Characteristic	Nipocalimab (n = 33)	Placebo (n = 20)	Total (N = 53)
Age, years, median (IQR)	59.0 (47.0, 65.0)	55.5 (52.5, 64.0)	59.0 (51.0, 64.0)
Sex, female, n (%)	24 (72.7)	12 (60.0)	36 (67.9)
Race, n (%)			
White	30 (90.9)	18 (90.0)	48 (90.6)
Other[a]	3 (9.0)	1 (5.0)	4 (7.5)
Not reported	0	1 (5.0)	1 (1.9)
BMI, kg/m^2, median (IQR)	27.4 (25.7, 31.6)	26.9 (24.4, 32.0)	27.3 (25.4, 31.6)
Disease duration, years, median (IQR)	13.0 (7.8, 18.3)	12.3 (7.5, 17.9)	12.4 (7.8, 18.3)
Number of swollen joints (0-66), median (IQR)	11.0 (7.2, 13.4)	14.1 (9.7, 21.8)	11.3 (8.5, 17.0)
Number of tender joints (0-68), median (IQR)	18.0 (13.0, 24.0)	22.3 (14.2, 30.2)	18.6 (14.0, 25.0)
DAS28-CRP, median (IQR)	5.6 (5.2, 6.0)	5.8 (5.4, 6.7)	5.6 (5.2, 6.2)
Positive for ACPA, n (%)	30 (90.9)	18 (90.0)	48 (90.6)
Positive for RF, n (%)	31 (93.9)	17 (85.0)	48 (90.6)
CRP, mg/dL, median (IQR)	0.80 (0.29, 1.35)[b]	1.43 (0.68, 3.78)[b]	0.89 (0.37, 1.99)

ACPA, anti-citrullinated protein autoantibody; BMI, body mass index; CRP, C-reactive protein; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; IQR, interquartile range; RF, rheumatoid factor.
[a]Other includes American Indian or Alaska Native, Asian, or Black or African American.
[b]There was no statistically significant difference (*P* = 0.077 using a Wilcoxon test) in baseline CRP values between the nipocalimab and placebo groups.

Pharmacodynamics

- Serum total IgG levels were reduced in the nipocalimab group from Weeks 4 through 12 and returned to baseline levels at Week 18 (**Figure 2A**)
- At Week 12, there was a –58% GMean (–60% median) reduction at trough in the total IgG levels observed in the nipocalimab group compared to a 2.4% GMean increase in the placebo group (**Figure 2A** and **Table 2**)
- Significant reductions at trough for total CIC and ACPA IgG levels were also observed in the nipocalimab group versus placebo (**Figure 2B** and **2C**), with a trajectory similar to that of total IgG reduction
  - The magnitude of ACPA IgG reduction was approximately half of that of total IgG reduction

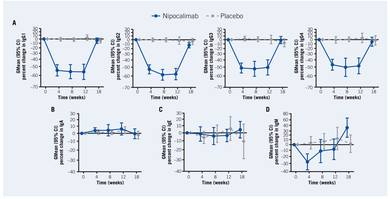
Figure 2. Percent Changes From Baseline at Trough in Pharmacodynamics and Disease-related Biomarkers: (A) Total IgG, (B) CIC, and (C) ACPA IgG (Anti-CCP2)



ACPA, anti-citrullinated protein autoantibody; anti-CCP2, anti-cyclic citrullinated peptide 2 antibody; C3d, complement 3d; CI, confidence interval; CIC, circulating immune complex; GMean, geometric mean; IgG, immunoglobulin G.

- Decreases from baseline at trough in all IgG subclasses were consistent with those observed for total IgG levels (**Figure 3**)
- Overall, no clinically meaningful changes from baseline in IgA, IgE, and IgM were observed in either group

Figure 3. Percent Changes From Baseline at Trough in (A) IgG Subclasses, (B) IgA, (C) IgE, and (D) IgM



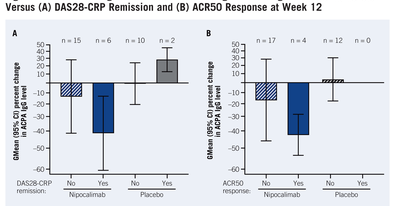
CI, confidence interval; Ig, immunoglobulin; GMean, geometric mean.

- Relative to baseline, no changes in complement activation markers (ie, Bb, C3a, C5a, soluble C5b-9, Wieslab Alternative pathway) or serum inflammatory markers (ie, CRP, annexin A, CXCL10, CXCL13, hepcidin, interleukin-6, matrix metalloproteinase-1, matrix metalloproteinase-3, serum amyloid A) were observed in either group

Association of Disease-related Biomarkers With Clinical Responses

- Numerical improvements in ACR components (eg, tender joint count, swollen joint count, and Health Assessment Questionnaire Disability Index score) were observed in the nipocalimab group
- In the nipocalimab group, responders who achieved DAS28-CRP remission or ACR50 response at Week 12 had numerically greater reductions in ACPA compared to nonresponders (**Figure 4**)

Figure 4. Percent Changes From Baseline at Trough in ACPA IgG (Anti-CCP2) Levels Versus (A) DAS28-CRP Remission and (B) ACR50 Response at Week 12



ACPA, anti-citrullinated protein autoantibody; ACR50, ≥50% response in American College of Rheumatology response criteria; anti-CCP2, anti-cyclic citrullinated peptide 2 antibody; CI, confidence interval; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; GMean, geometric mean; IgG, immunoglobulin G.

PK/PD Modeling–based Simulation

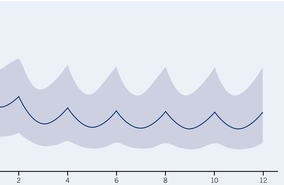
- PK/PD modeling–based simulations for nipocalimab treatment–mediated total IgG reduction at Week 12 are shown in **Table 2** and **Figure 5**; for 15 mg/kg IV nipocalimab administered every 2 weeks, median steady-state IgG reduction was predicted to be –76% at peak and –64% at trough
- Observed median steady-state trough IgG reduction at Week 12 for participants who received all doses of nipocalimab (completer rule) was consistent with the PK/PD modeling–based simulated values (–62% observed; –64% simulated)

Table 2. Observed and Simulated Values for Total IgG Reduction by Nipocalimab at Week 12

	Observed		Simulated	
Analysis rule	GMean at trough	Median at trough	Median at trough	Median at peak
TF rule[a]	–58%	–60%	–	–
Completer rule[b]	–60%	–62%	–64%	–76%

GMean, geometric mean; IgG, immunoglobulin G; TF, treatment failure.
[a]All observations in participants after TF were reported as missing for the analyses.
[b]Participants with missed doses of the study intervention were excluded from the analyses.

Figure 5. PK/PD Modeling–based Simulation for Percent Change From Baseline in Serum Total IgG Levels With 15 mg/kg IV Nipocalimab Administered Every 2 Weeks



IgG, immunoglobulin G; IV, intravenous; q2w, every 2 weeks; PI, prediction interval; PK/PD, pharmacokinetics and pharmacodynamics.
[a]Solid line represents median, and shaded area represents 90% PI (5th-95th percentile).

CONCLUSIONS

- **Nipocalimab significantly and reversibly reduced IgG, ACPA, and CIC levels, consistent with its mechanism of action**
- **Reduction in ACPA levels by nipocalimab was associated with DAS28-CRP remission and ACR50 responses**
- **These findings demonstrate the unique nipocalimab mechanism of action in RA, which appears to be independent of CRP and other inflammatory markers; thus, this generates the hypothesis that the combination of nipocalimab with complementary immune-modulating therapies may provide clinical benefits for patients with moderate to severe RA**
- **A study assessing the efficacy and safety of nipocalimab in combination with anti-TNF in RA is ongoing (NCT06028438)**

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