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ORIGINAL RESEARCH

Nipocalimab, an anti-FcRn monoclonal antibody, in participants with moderate to severe active rheumatoid arthritis and inadequate response or intolerance to anti-TNF therapy: results from the phase 2a IRIS-RA study

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ABSTRACT

Objectives To investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of nipocalimab in participants with moderate to severe active rheumatoid arthritis (RA) and inadequate response or intolerance to ≥1 antitumour necrosis factor agent.

Methods In this phase 2a study, participants with RA seropositive for anticitrullinated protein antibodies (ACPA) or rheumatoid factors were randomised 3:2 to nipocalimab (15 mg/kg intravenously every 2 weeks) or placebo from Weeks 0 to 10. Efficacy endpoints (primary endpoint: change from baseline in Disease Activity Score 28 using C reactive protein (DAS28-CRP) at Week 12) and patient-reported outcomes (PROs) were assessed through Week 12. Safety, pharmacokinetics and pharmacodynamics were assessed through Week 18.

Results 53 participants were enrolled (nipocalimab/placebo, n=33/20). Although the primary endpoint did not reach statistical significance for nipocalimab versus placebo, a numerically higher change from baseline in DAS28-CRP at Week 12 was observed (least squares mean (95% CI): −1.03 (−1.66 to −0.40) vs −0.58 (−1.24 to 0.07)), with numerically higher improvements in all secondary efficacy outcomes and PROs. Serious adverse events were reported in three participants (burn infection, infusion-related reaction and deep vein thrombosis). Nipocalimab significantly and reversibly reduced serum immunoglobulin G, ACPA and circulating immune complex levels but not serum inflammatory markers, including CRP. ACPA reduction was associated with DAS28-CRP remission and 50% response rate in American College of Rheumatology (ACR) criteria; participants with a higher baseline ACPA had greater clinical improvement.

Conclusions Despite not achieving statistical significance in the primary endpoint, nipocalimab showed consistent, numerical efficacy benefits in participants with moderate to severe active RA, with greater benefit observed for participants with a higher baseline ACPA.

Trial registration number NCT04991753.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ Anticitrullinated protein (commonly an immunoglobulin (Ig) G isotype) and rheumatoid factors (predominantly IgM autoantibodies reactive to the Fc domain of IgG) have been associated with more severe disease in patients with seropositive rheumatoid arthritis (RA) compared with patients with seronegative RA.

⇒ Nipocalimab is a fully human IgG monoclonal antibody that is designed to lower serum IgG levels by selectively blocking the neonatal Fc receptor (FcRn).

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory disease of unknown aetiology in which bone and cartilage erosion of synovial joints leads to irreversible joint damage.[1] RA affects an estimated 0.1%–1.1% of the population, with a higher prevalence reported in Northern European and North American countries.[2] Patients living with RA have been shown to have substantially reduced health-related quality of life compared with patients with other physical illnesses (ie, hypertension, type 2 diabetes, myocardial infarction and clinical depression) and the general population.[3–5] Furthermore, RA has been associated

WHAT THIS STUDY ADDS

⇒ This is the first study to evaluate the efficacy, safety, pharmacokinetics and pharmacodynamics of an anti-FcRn monoclonal antibody, nipocalimab, and its effect on disease-related biomarkers in patients with moderate to severe active seropositive RA with inadequate response or intolerance to antitumour necrosis factor (anti-TNF) agents.

⇒ Participants who received nipocalimab (15 mg/kg intravenously every 2 weeks for 10 weeks) showed numerically higher improvement in efficacy outcomes at Week 12 compared with placebo, with significant, reversible reductions in serum IgG, anticitrullinated protein antibody (ACPA) and circulating immune complex levels but not serum inflammatory markers (eg, C reactive protein). This is the first study to identify the association of ACPA reduction with clinical improvement in RA. Participants with higher baseline ACPA levels had a greater clinical response rate compared with the overall population. This study highlights the potential pathogenic role of IgG autoantibodies (eg, ACPA) in RA. No unexpected or new safety findings were identified.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings demonstrate the unique mechanism of nipocalimab in RA and its safety for patients with refractory RA who had inadequate responses to anti-TNF therapies.

with a 1.5-fold increased mortality risk compared with that of the general population, with increasing disease severity conferring a higher mortality risk.[6 7]

In recent years, real-world studies have confirmed that a higher remission rate and better health-related quality of life are achieved by patients with RA who follow a treat-to-target strategy compared with routine care.[8] However, many patients still fail to attain recommended treatment targets for low disease activity (LDA) or remission due to suboptimal treatment with available therapies and/or delay in initial treatment, with <50% remaining in remission after 1 year[9] and 20%–30% becoming refractory to current treatment options.[10] Treatment with biologic antitumour necrosis factor (anti-TNF) agents and other targeted therapies with different modes of action is often recommended for patients with moderate to severe RA and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs).[11] However, anti-TNF therapies have shown limited efficacy, as only 18%–55% of patients treated with anti-TNF agents achieve a ≥50% response rate in American College of Rheumatology (ACR) criteria (ACR50),[12–14] 27%–66% achieve Disease Activity Score 28 (DAS28) remission[15 16] and 4%–23% achieve Clinical Disease Activity Index (CDAI) or Simple Disease Activity Index remission.[17–19] Therapeutic options for patients who fail to respond to ≥1 anti-TNF agent remain an urgent unmet need in RA.

RA is associated with a variety of well-recognised pathogenic mechanisms. Autoantibodies are associated with a major subgroup of patients meeting classification criteria for RA and there has been debate as to whether these autoantibodies are pathogenic and play a role in driving the disease.[20] Anticitrullinated protein antibodies (ACPA; commonly an immunoglobulin (Ig)G isotype) are predictive of joint erosion progression.[21–23] Additionally, rheumatoid factors (RFs; predominantly IgM autoantibodies[24] reactive to the Fc domain of IgG) may stabilise IgG immune complexes (ICs), including ACPA-IgG ICs, and subsequently promote proinflammatory effector functions.[25] Both ACPA and RF have been associated with more severe disease, radiographic structural joint damage progression and fatigue in patients with seropositive RA compared with patients with seronegative RA.[26–28] Therefore, based on the hypothesis that these autoantibodies may be pathogenic, a targeted therapy capable of addressing the underlying IgG autoantibody-driven RA disease mechanism may provide benefits for patients with seropositive RA.

Nipocalimab is a high-affinity, fully human, effectorless IgG1 monoclonal antibody that is designed to selectively block the neonatal Fc receptor (FcRn), preventing IgG recycling and thereby lowering IgG levels.[29 30] Therefore, it potentially reduces levels of ACPA and other pathogenic antibodies involved in RA pathogenesis. As FcRn is involved in both cell-mediated and humoral immune functions through IgG trafficking and recycling, nipocalimab is selectively designed with an aglycosylated Fc domain to abrogate effector function, including when nipocalimab is presented in immune complexes.[31] Therefore, nipocalimab does not induce complement-mediated cytotoxicity or facilitate antibody-dependent cellular cytotoxicity/phagocytosis.[31] In addition to its role in IgG trafficking and recycling, FcRn may directly affect the functions of FcRn-expressing immune cells, such as monocytes and B cells, via a mechanism independent of IgG recycling.[32] However, nipocalimab has no impact on IgG production or on other Igs and does not completely deplete IgGs or perturb $CD4^+$/$CD8^+$ T cells, natural killer cells or innate cell functions of other Ig classes, thereby retaining the ability to respond to infectious agents.[31] In a phase 1 study, nipocalimab demonstrated a rapid, reversible reduction in serum IgG levels within 1 day of administration and reached nadir levels by 14 days, with a mean peak reduction of 85% from baseline observed after multiple administrations of the tested dose (15 and 30 mg/kg) in healthy volunteers.[29] Dose-dependent reductions in serum IgG and autoantibody levels were observed and correlated with clinical benefit in a phase 2 study of nipocalimab in participants with generalised myasthenia gravis (gMG).[30] Nipocalimab also demonstrated rapid, reversible reductions in serum IgG and alloantibody levels, as well as the ability to delay or reduce the risk of foetal anaemia and poor outcomes in pregnancies at high risk of alloantibody-driven haemolytic disease of the fetus and newborn (HDFN) in a phase 2 trial.[33]

In this phase 2a study (IRIS-RA; ClinicalTrials.gov Identifier: NCT04991753), we report the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of nipocalimab, as well as its effect on

disease-associated biomarkers in participants with moderate to severe active RA.

METHODS

Participants

Eligible participants were 18–75 years of age with moderate to severe active RA (≥6 swollen/tender joints of 66/68 joint counts), were positive for ACPA (≥17 U/mL) and/or RF (≥14 IU/mL), had C reactive protein (CRP) ≥0.3 mg/dL and had prior inadequate response or intolerance to ≥1 anti-TNF agent.

Study design and intervention

IRIS-RA was a randomised, double-blind, placebo-controlled, parallel-group study. The study included a screening period (Weeks –6 to 0), a double-blind treatment period (Weeks 0–12) and a safety/PD follow-up period (Weeks 12–18). Participants were randomised 3:2 to receive nipocalimab (15 mg/kg intravenously administered every 2 weeks) or placebo from Weeks 0 to 10. Participants were allowed to be on stable doses of non-steroidal anti-inflammatory drugs, oral corticosteroids or conventional synthetic DMARDs (online supplemental methods). At randomisation, participants were stratified based on baseline methotrexate (MTX) use (no use, >0 to <12.5 mg/week or ≥12.5 mg/week), anti-TNF inadequate response or intolerance and swollen/tender joint count levels using a covariate-adaptive randomisation algorithm.

The nipocalimab dose regimen of 15 mg/kg intravenously administered every 2 weeks was selected based on data from the phase 1 first-in-human study in healthy participants, where single doses of nipocalimab up to 60 mg/kg and multiple doses up to 30 mg/kg weekly were evaluated,[29] and the phase 2 gMG study, where dosages up to 60 mg/kg every 2 weeks were evaluated.[34] Mechanistic PK/PD simulations for the RA population were performed using a PK/receptor occupancy/PD model based on the first-in-human data and incorporating the typical RA population body weight. The 15 mg/kg intravenous dose regimen administered every 2 weeks was predicted to achieve a median of 71% IgG reduction on average (maximum: 77% and minimum (predose): 64%) for the RA population. Thus, the 15 mg/kg intravenous dose regimen administered every 2 weeks was selected to achieve the targeted IgG reduction for this study.

Study assessments

Efficacy, patient-reported outcomes (PROs), safety, PK, PD and immunogenicity of nipocalimab, as well as disease-associated biomarkers, were assessed at baseline and over time through Week 12 (for efficacy and PROs) or Week 18 (for safety, PK, PD and immunogenicity outcomes) of the follow-up period. The primary endpoint was the change from baseline in DAS28 using CRP (DAS28-CRP) at Week 12. Secondary endpoints included the proportions of participants who achieved a response rate in ACR criteria of ≥20% (ACR20), ≥50% (ACR50), ≥70% (ACR70) and ≥90% (ACR90); DAS28-CRP remission (defined as DAS28-CRP<2.6); DAS28-CRP LDA (defined as DAS28-CRP≤3.2) at Week 12 and change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 12. Other efficacy endpoints included changes from baseline in DAS28-CRP, CDAI, tender joint counts and swollen joint counts through Week 12. Additional PRO endpoints included the change from baseline in the Joint Pain Severity score, the 36-item Short Form Health Survey (SF-36), the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue), the patient's global assessment of disease activity and the patient's assessment of pain through Week 12.

Safety was evaluated based on treatment-emergent adverse events (TEAEs), adverse events (AEs) of special interest, clinical laboratory tests (including haematology and serum chemistry), vital signs and physical examination. AEs of special interest included infections that were severe or required intravenous anti-infective or operative/invasive intervention and hypoalbuminaemia with albumin <20 g/L.

Serum concentrations of nipocalimab and antibodies to nipocalimab (antidrug antibodies) were assessed and analysed using an electrochemiluminescent immunoassay and a highly sensitive drug-tolerant enzyme immunoassay (EIA) method. PD and disease-associated biomarker assessments included levels of serum total IgG and all IgG subclasses, ACPA IgG (measured by the Svar ACPA2 antibody assay), complement factor 3d-containing circulating ICs (C3d-CICs; measured by MicroVue CIC-Raji Cell Replacement Enzyme Immunoassay kit), complement activation markers and serum inflammatory markers. Associations between baseline (Week 0) and changes in biomarker levels with clinical responses at Week 12 were also assessed.

Statistical analysis

The sample size was determined based on the primary endpoint; a sample size of 20 participants in the placebo group and 30 participants in the nipocalimab group provided approximately 80% power to detect a significant treatment difference, assuming a difference of 1 in the change from baseline in DAS28-CRP between the nipocalimab and placebo groups and a pooled SD of 1.2 at a two-sided significance level of α=0.05 using a *t* test. The data were primarily summarised using descriptive statistics. Treatment failures due to any reason (ie, initiation of protocol-prohibited medication, adjusted study medication above the baseline dose for RA and/or discontinued study intervention) prior to the analysis time point were handled by a composite strategy, assuming a lack of response or improvement from baseline.

For all continuous endpoints of change from baseline score examined on scheduled visits, treatment

comparisons were performed using an analysis of covariance (ANCOVA) model adjusted for baseline scores and stratified by baseline MTX use. The treatment difference was reported as the least squares means (LS Means), with 95% CI and p values calculated based on the ANCOVA model adjusted for baseline DAS28-CRP and a randomised stratification factor (baseline MTX use) for the primary endpoint. For binary response efficacy endpoints, treatment comparisons were performed using a Cochran-Mantel-Haenszel (CMH) χ^2 test, stratified by baseline MTX use, when the Mantel-Fleiss criterion was met. If the Mantel-Fleiss criterion was not satisfied, Fisher's exact test was used instead of the CMH test. The treatment difference was estimated by the difference in response rates, with 95% CIs calculated based on Wald statistics.

For PD and disease-related biomarkers, if a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Participants with baseline levels below the lower limit of quantitation or above the upper limit of quantitation for a specific analyte were excluded. For changes in biomarkers between groups, comparisons were performed on the within-participant per cent change from baseline at the trough at the indicated visit and summarised as the median and IQR of the per cent change from baseline values for the indicated strata.

The statistical tests for all secondary endpoints and disease-related biomarkers were not controlled for multiplicity. All p values were considered nominal except for the primary endpoint.

Modelling and simulation

A population PK model with quasi-steady state target-mediated drug disposition was developed to characterise the relationship between the nipocalimab dose, PK and receptor occupancy following intravenous administrations. An indirect response model was used to describe the relationship between nipocalimab PK and serum total IgG levels. These two models were based on intravenous data from four completed phase 1 studies and the phase 2a IRIS-RA study, which adequately captured the available PK/PD data. Model-based simulations were performed to predict nipocalimab total IgG-time profiles following 15 mg/kg intravenous nipocalimab administered every 2 weeks in 1000 virtual participants using literature-reported baseline body weight and total IgG distributions. Simulated total IgG concentrations and per cent changes from baseline over time were summarised as the median and 90% prediction interval (5th and 95th percentiles).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines. Study protocols were reviewed and approved by an Independent Ethics Committee or Institutional Review Board. Participants or their legally acceptable representatives provided written informed consent to participate in the study.

RESULTS

Participants and treatment

A total of 53 participants were enrolled at 13 centres in Germany, Poland, Spain, the UK and the USA and included in the analyses (nipocalimab n=33 and placebo n=20). Demographic and baseline disease characteristics were generally comparable between groups (table 1). Most participants were female (67.9%) and white (90.6%); the median age was 59 (IQR 51–64) years; 90.6% of participants were positive for ACPA and the same percentage were positive for RF; 83% of participants were positive for both ACPA and RF. The median baseline DAS28-CRP was 5.6 (IQR 5.2–6.2). 40 participants (75.5%) had received 1 prior anti-TNF agent, 12 (22.6%) had received ≥2 prior anti-TNF agents and 1 (1.9%) had not received any prior anti-TNF agents.

32 (97%) of 33 participants in the nipocalimab group and all participants in the placebo group completed the study, with a median duration of treatment of 10.1 (range 0.1–11.9) and 10.1 (range 0.1–10.3) weeks, respectively (online supplemental figure 1).

Efficacy

At Week 12, participants in the nipocalimab group had a numerically greater LS Mean (95% CI) change in DAS28-CRP (–1.03 (95% CI –1.66 to –0.40)) compared with the placebo group (–0.58 (95% CI –1.24 to 0.07); LS Mean difference –0.45 (95% CI –1.17 to 0.28); p=0.224; figure 1). The effect of baseline medication use (ie, MTX, nonsteroidal anti-inflammatory drugs and corticosteroids) on the change in DAS28-CRP at Week 12 is shown in online supplemental table 1.

At Week 12, a numerically higher proportion of participants in the nipocalimab group achieved ACR20 (45.5%), ACR50 (15.2%) and ACR70 (12.1%) responses compared with placebo (20%, 5% and 0%, respectively; figure 2A). A numerically greater proportion of participants achieved DAS28-CRP remission and DAS28-CRP LDA (7 (21.2%)) compared with placebo (2 (10%) for both; treatment difference, 9.9% (95% CI –9.5 to 29.3); nominal p=0.456 based on Fisher's exact test). Similarly, participants in the nipocalimab group had a numerically greater LS Mean (95% CI) improvement in HAQ-DI score (–0.42 (95% CI –0.66 to –0.19) vs –0.21 (95% CI –0.45 to 0.04); treatment difference –0.22 (95% CI –0.49 to 0.05); nominal p=0.108) at Week 12 (figure 2B).

Through Week 12, a numerically greater improvement in DAS28-CRP and CDAI scores was observed as early as 6 weeks after the first dose in the nipocalimab group compared with the placebo group and increased over time (data not shown). At Week 12, LS Mean (95% CI) improvement in CDAI scores was –13.53 (95% CI –19.94 to –7.11) in the nipocalimab group versus –6.01 (95% CI

Table 1 Demographic and baseline characteristics

Characteristics	Nipocalimab (n=33)	Placebo (n=20)	Total (n=53)
Age, years, median (IQR)	59 (47, 65)	55.5 (52.5, 64)	59 (51, 64)
Sex, female, n (%)	24 (72.7)	12 (60)	36 (67.9)
Race, n (%)			
American Indian or Alaska Native	1 (3)	0	1 (1.9)
Asian	1 (3)	1 (5)	2 (3.8)
Black or African American	1 (3)	0	1 (1.9)
White	30 (90.9)	18 (90)	48 (90.6)
Not reported	0	1 (5)	1 (1.9)
Ethnicity, n (%)			
Hispanic or Latino	4 (12.1)	3 (15)	7 (13.2)
Not Hispanic or Latino	29 (87.9)	16 (80)	45 (84.9)
Unknown	0	1 (5)	1 (1.9)
BMI, kg/m^2, median (IQR)	27.4 (25.7–31.6)	26.9 (24.4–32)	27.3 (25.4–31.6)
Disease duration, years, median (IQR)	13 (7.8–18.3)	12.3 (7.5–17.9)	12.4 (7.8–18.3)
Swollen joint count (0–66), median (IQR)	11 (7.2–13.4)	14.1 (9.7–21.8)	11.3 (8.5–17)
Tender joint count (0–68), median (IQR)	18 (13–24)	22.3 (14.2–30.2)	18.6 (14–25)
DAS28-CRP, median (IQR)	5.6 (5.2–6)	5.8 (5.4–6.7)	5.6 (5.2–6.2)
Positive for ACPA,* n (%)	30 (90.9)	18 (90)	48 (90.6)
Positive for RF, n (%)	31 (93.9)	17 (85)	48 (90.6)
CRP, mg/dL, median (IQR)	0.80 (0.29–1.35)†	1.43 (0.68–3.78)†	0.89 (0.37–1.99)
≥1 Concomitant therapy, n (%)	31 (93.9)	20 (100)	51 (96.2)
csDMARDs	21 (63.6)	16 (80)	37 (69.8)
Oral corticosteroids	20 (60.6)	15 (75)	35 (66)
NSAIDs	21 (63.6)	15 (75)	36 (67.9)
Prior anti-TNF therapy, n (%)			
Adalimumab	19 (57.6)‡	12 (60.0)	31 (58.5)
Inadequate response to therapy	15 (45.5)	10 (50)	25 (47.2)
Intolerance to therapy	3 (9.1)	2 (10)	5 (9.4)
Certolizumab pegol	2 (6.1)	1 (5)	3 (5.7)
Inadequate response to therapy	2 (6.1)	1 (5)	3 (5.7)
Etanercept	17 (51.5)	7 (35)	24 (45.3)
Inadequate response to therapy	14 (42.4)	3 (15)	17 (32.1)
Intolerance to therapy	3 (9.1)	4 (20)	7 (13.2)
Golimumab	4 (12.1)	4 (20)	8 (15.1)
Inadequate response to therapy	3 (9.1)	4 (20)	7 (13.2)
Intolerance to therapy	1 (3)	0	1 (1.9)
Infliximab	3 (9.1)	2 (10)	5 (9.4)
Inadequate response to therapy	2 (6.1)	2 (10)	4 (7.5)
Other reason not specified	1 (3)	0	1 (1.9)

*ACPA IgG levels for inclusion were determined via the Roche assay performed at LabCorp.
†There was no statistically significant difference (p=0.077 using a Wilcoxon test) in baseline CRP values between the nipocalimab and placebo groups.
‡One participant discontinued adalimumab due to financial/insurance coverage.
ACPA, anticitrullinated protein autoantibody; BMI, body mass index; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP, Disease Activity Score 28 using C reactive protein; IgG, immunoglobulin G; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor; TNF, tumour necrosis factor.

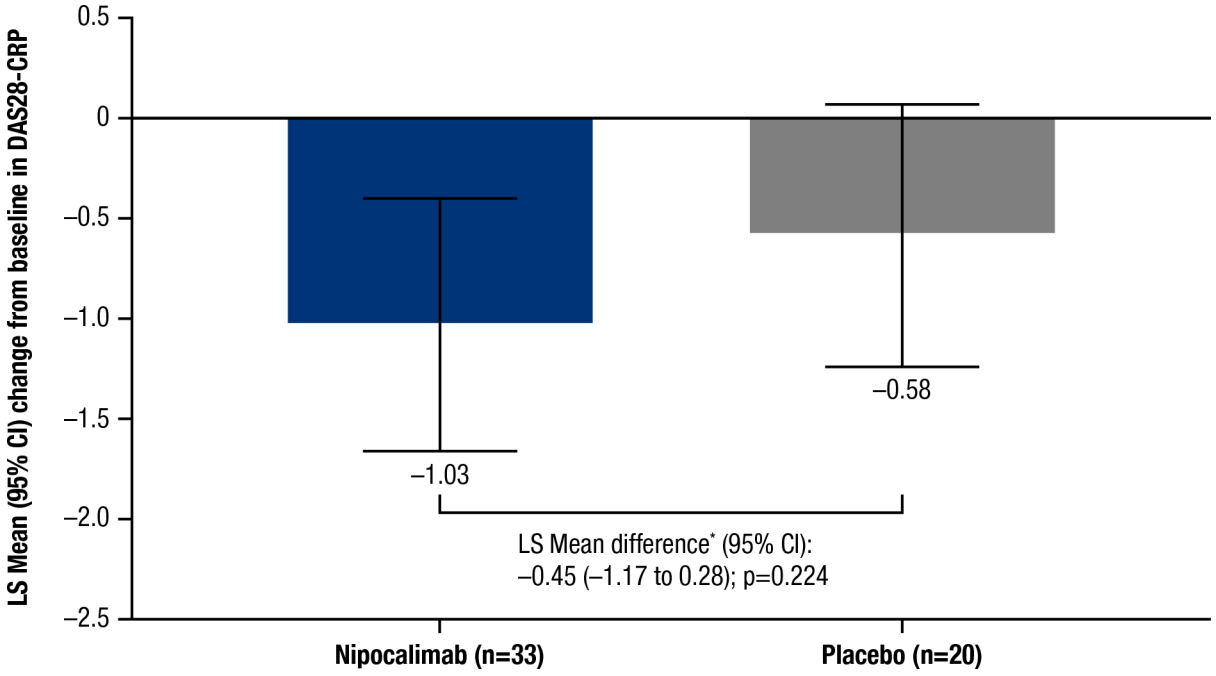

Figure 1 LS Mean (95% CI) change from baseline in DAS28-CRP at Week 12. ANCOVA, analysis of covariance; DAS28-CRP, Disease Activity Score 28 using C reactive protein; LS Mean, least squares mean; MTX, methotrexate. *The LS Mean difference between nipocalimab and placebo, the CIs and the p values were based on an ANCOVA model adjusted for baseline DAS28-CRP and randomised stratification factor (baseline MTX use).

–12.80 to 0.79) in the placebo group (treatment difference, –7.52 (95% CI –14.98 to –0.06); nominal p=0.048; figure 2C). Similarly, a numerically greater improvement in tender joint and swollen joint counts was observed as early as 4–6 weeks after the first dose in the nipocalimab group compared with the placebo group and increased over time (data not shown). At Week 12, mean (SD) per cent improvements in tender joint count (–42.77% (41.55) vs –24.14% (39.33)) and swollen joint count (–47.56% (38.74) vs –20.50% (35.70)) were observed in the nipocalimab group versus the placebo group (online supplemental table 2).

Patient-reported outcomes

At Week 12, participants in the nipocalimab group showed a greater decrease in Joint Pain Severity scores (LS Mean –1.58 (95% CI –2.76 to –0.41)) compared with the placebo group (LS Mean –0.25 (95% CI –1.48 to 0.99); treatment difference –1.34 (95% CI –2.67 to –0.01); nominal p=0.049). Numerically greater improvements in the mental and physical components of the SF-36 and FACIT-Fatigue scores, the patient's global assessment of disease activity and the patient's assessment of pain were observed as early as 6–8 weeks after the first dose in the nipocalimab group compared with the placebo group; these improvements appeared to increase over time.

Safety

Through Week 18, the proportion of participants with TEAEs was 81.8% versus 60% in the nipocalimab and placebo groups, respectively; the most common TEAEs were RA flares (27.3% vs 30%), headaches (12.1% vs 5%) and COVID-19 (12.1% vs 0; table 2). In the nipocalimab group, three (9.1%) serious TEAEs were reported, including burn infection, infusion-related reaction and deep vein thrombosis; the infusion-related reaction was related to nipocalimab, whereas burn infection and deep vein thrombosis were not considered related to nipocalimab.

Infusion reaction AEs (ie, headache, hypoglycaemia, chills, infusion-related reaction, muscle tightness, fever, rash and paraesthesia) were reported in four (12.1%) participants in the nipocalimab group and one (5.0%) participant in the placebo group (table 2). Infection AEs were reported in 13 (39.4%) participants in the nipocalimab group and five (25%) participants in the placebo group; the most frequently reported infection AE was COVID-19 (4 (12.1%)); all infection AEs were mild to moderate, except for the burn infection reported in the nipocalimab group, and all resolved within the study period.

There were no clinically meaningful differences in lipid profiles observed between the nipocalimab and placebo treatment groups (figure 3). The per cent change from baseline observed in serum albumin and total cholesterol with nipocalimab at Week 12 was –4% and 6%, respectively. There were no TEAEs that led to death or opportunistic infections, including pulmonary tuberculosis, anaphylactic reactions, major adverse cardiovascular events or malignancies.

PK and immunogenicity

Nipocalimab exhibited non-linear PK, with median post-infusion serum nipocalimab concentrations ranging

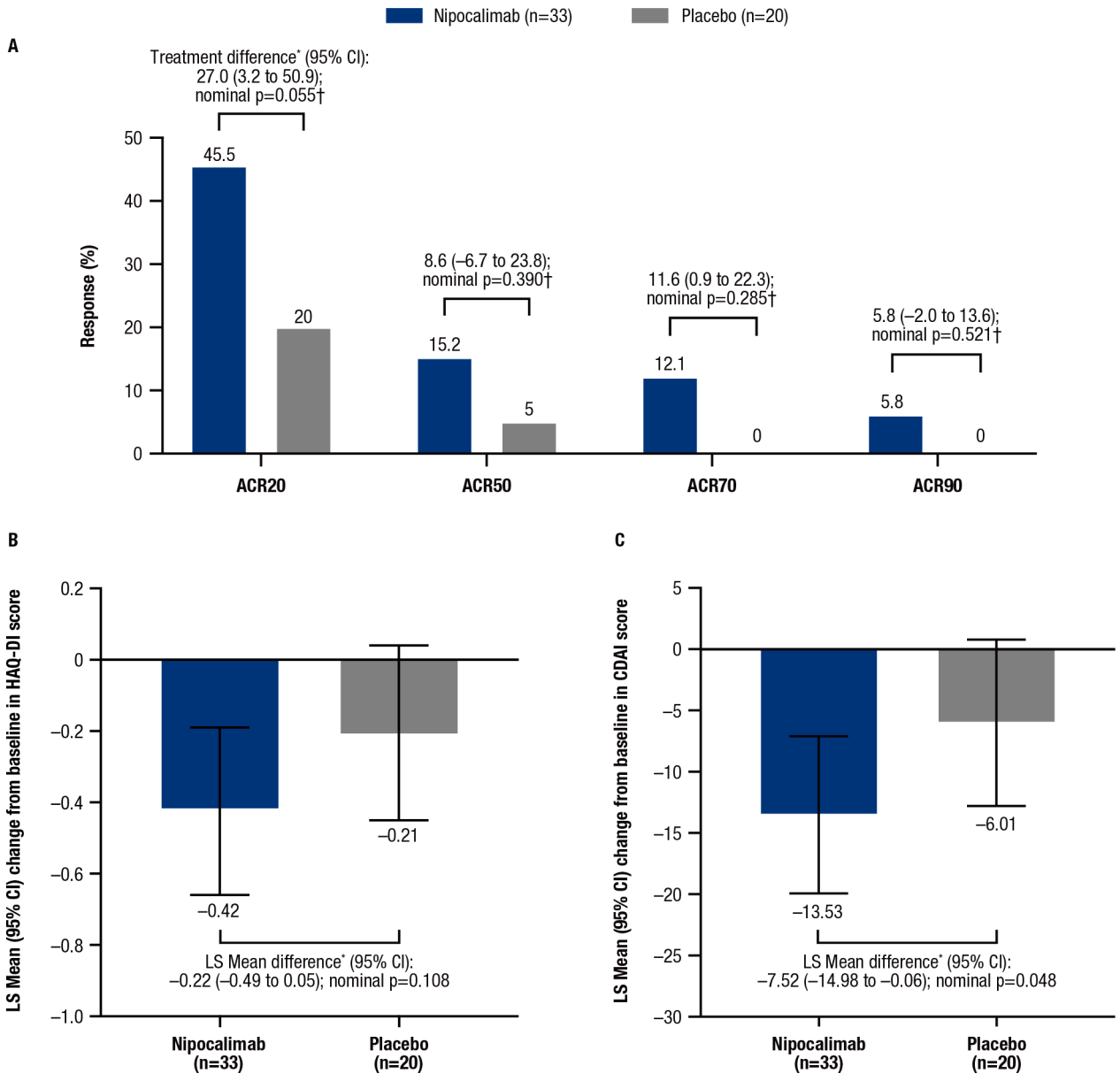

Figure 2 (A) Number of participants who achieved ACR20, ACR50, ACR70 and ACR90 responses at Week 12, (B) LS Mean (95% CI) change from baseline in HAQ-DI score at Week 12 and (C) LS Mean (95% CI) change from baseline in CDAI score at Week 12. ACR20, ≥20% response in American College of Rheumatology criteria; ACR50, ≥50% response in American College of Rheumatology criteria; ACR70, ≥70% response in American College of Rheumatology criteria; ACR90, ≥90% response in American College of Rheumatology criteria; ANCOVA, analysis of covariance; CDAI, Clinical Disease Activity Index; CMH, Cochran-Mantel-Haenszel; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS Mean, least squares mean; MTX, methotrexate. *The treatment difference between nipocalimab and placebo and the CIs for ACR was based on the Wald statistic with the CMH weight. The treatment difference between nipocalimab and placebo for HAQ-DI and CDAI scores were reported based on LS Means and p values calculated based on the ANCOVA model. †The p value was based on the CMH χ^2 test, stratified by randomised stratification factor (baseline MTX use). The Mantel-Fleiss criterion was not satisfied with the indicated p values and was therefore based on Fisher's exact test. The nominal p values presented for secondary and exploratory endpoints are for descriptive purposes only and do not represent statistical significance.

from 411 to 426 µg/mL across Weeks 0, 2 and 8 (online supplemental figure 2). Nipocalimab also exhibited accelerated clearance, with median preinfusion serum nipocalimab concentrations below the lower limit of quantitation across Weeks 2 and 8. Antibodies to nipocalimab were detected with a highly sensitive drug-tolerant EIA method in 21 (63.6%) participants with appropriate samples; most participants had low titre levels; all had peak titres <1:1000, except one who had a titre ratio of 1:2560. Overall, 7/33 (21.2%) participants were positive for neutralising antibodies. The presence of antibodies to nipocalimab was transient and did not impact PK or efficacy. Postinfusion serum nipocalimab concentrations were generally similar in participants who were positive for antibodies to nipocalimab and those who were negative for antibodies to nipocalimab (median Week

Table 2 Summary of TEAEs

Participants, n (%)	Nipocalimab (n=33)	Placebo (n=20)
≥1 TEAE	27 (81.8)	12 (60)
Related TEAEs*	12 (36.4)	3 (15)
Most common (≥10%) TEAEs		
Rheumatoid arthritis	9 (27.3)	6 (30)
Headache	4 (12.1)	1 (5)
COVID-19	4 (12.1)	0
Serious TEAEs	3 (9.1)	0
Related serious TEAEs	1 (3)	0
Reported serious TEAEs		
Burn infection	1 (3)	0
Infusion-related reaction	1 (3)	0
Deep vein thrombosis	1 (3)	0
TEAEs leading to treatment discontinuation	6 (18.2)	6 (30)
Related TEAEs leading to treatment discontinuation*	1 (3)	1 (5)
Infections and infestations	13 (39.4)	5 (25)
Related infection*	0	0
Burn infection	1 (3)	0
Infusion reaction†	4 (12.1)	1 (5)
Hypersensitivity‡	3 (9.1)	0
Hypoalbuminaemia (<20 g/L)	0	0

*Assessed by the investigator to be related to study treatment.
†Temporally associated with infusion (during or within 1 hour of infusion).
‡The MedDRA SMQ *Hypersensitivity reaction events* with a narrow and broad scope was used to identify AEs of hypersensitivity.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised MedDRA Queries; TEAE, treatment-emergent adverse event.

8 postinfusion nipocalimab concentration (range), 422 (263–537) µg/mL versus 387 (360–578) µg/mL). Four participants who were positive for antibodies to nipocalimab had an infusion-site reaction, of which one led to drug discontinuation.

PD and disease-related biomarkers

Serum total IgG levels were reduced in the nipocalimab group from Weeks 4 through 12 and returned to baseline levels at Week 18. At Week 12, the observed median predose (minimal) reduction in total IgG was 62.1% in the nipocalimab group compared with an observed median increase of 3.8% in the placebo group for participants who received all planned doses (figure 4A). At the same time, PK/PD model-based simulations using the ideal dosing (100% dosing compliance) resulted in a median steady-state predose (minimal) total IgG reduction of 64.5%, consistent with the observed reduction of 62.1% (online supplemental figure 3). Furthermore, the predicted median of the maximal total IgG reduction was 75% during a steady-state dosing interval. Decreases from baseline in all IgG subclasses were consistent with those observed for total IgG levels (online supplemental figure 4), and the observed median change in IgA, IgE and IgM was 3.2%, 1.6% and −10%, respectively, at Week 12 (online supplemental table 3).

For disease-related biomarkers, significant reductions in total C3d-CIC and ACPA IgG levels were observed in the nipocalimab group versus the placebo group, with a trajectory similar to that of total IgG reduction (figure 4B,C). The observed median trough reduction in ACPA IgGs (31.6%) at Week 12 was less than that of total IgGs (62.1%) and C3d-CICs (43.5%). RF IgM was reduced by a median of 26.3% in the nipocalimab group at Week 12, potentially attributed to the secondary effect of binding to IgG (RF IgM does not directly bind to FcRn), compared with a 5.5% increase in the placebo group (online supplemental table 3). No changes from baseline in complement activation markers (eg, Bb, C3a, C5a and Wieslab Alternative Pathway activity) or serum inflammatory markers (eg, CRP) were observed in either group (online supplemental tables 2 and 3).

Subgroup analyses

In the analyses among responders versus nonresponders, participants in the nipocalimab group who achieved DAS28-CRP remission or ACR50 response at Week 12 showed a 50.9% and 39% median of the observed predose (minimal) reduction in ACPA IgG, respectively, compared with 26.4% and 26.4% in nonresponders (figure 5). Additionally, greater proportions of placebo-adjusted DAS28-CRP remission rate (Δ23.3% vs Δ11.2%) or ACR50 response rate (Δ26.7% vs Δ10.2%) at Week 12 were observed among participants in the nipocalimab group who had baseline ACPA levels above the median of the overall study population compared with the overall population (figure 6).

DISCUSSION

This phase 2a study was the first to evaluate the efficacy, safety, PK and PD of an anti-FcRn monoclonal antibody, nipocalimab and its effect on disease-related biomarkers in participants with seropositive RA and an inadequate response or intolerance to anti-TNF agents. Despite not achieving statistical significance in the primary endpoint, nipocalimab treatment was associated with a numerically higher improvement in the primary endpoint of change from baseline in DAS28-CRP as well as all secondary endpoints and PROs (ie, ACR20, ACR50, ACR70 and ACR90 responses; DAS28-CRP remission and LDA; HAQ-DI scores; CDAI scores; Joint Pain Severity scores; SF-36 scores and FACIT-Fatigue scores) at Week 12 compared with placebo, with greater clinical benefit (ie, DAS28-CRP remission and ACR50 response) observed in participants with higher baseline ACPA levels. Nipocalimab was generally safe and well tolerated by participants,

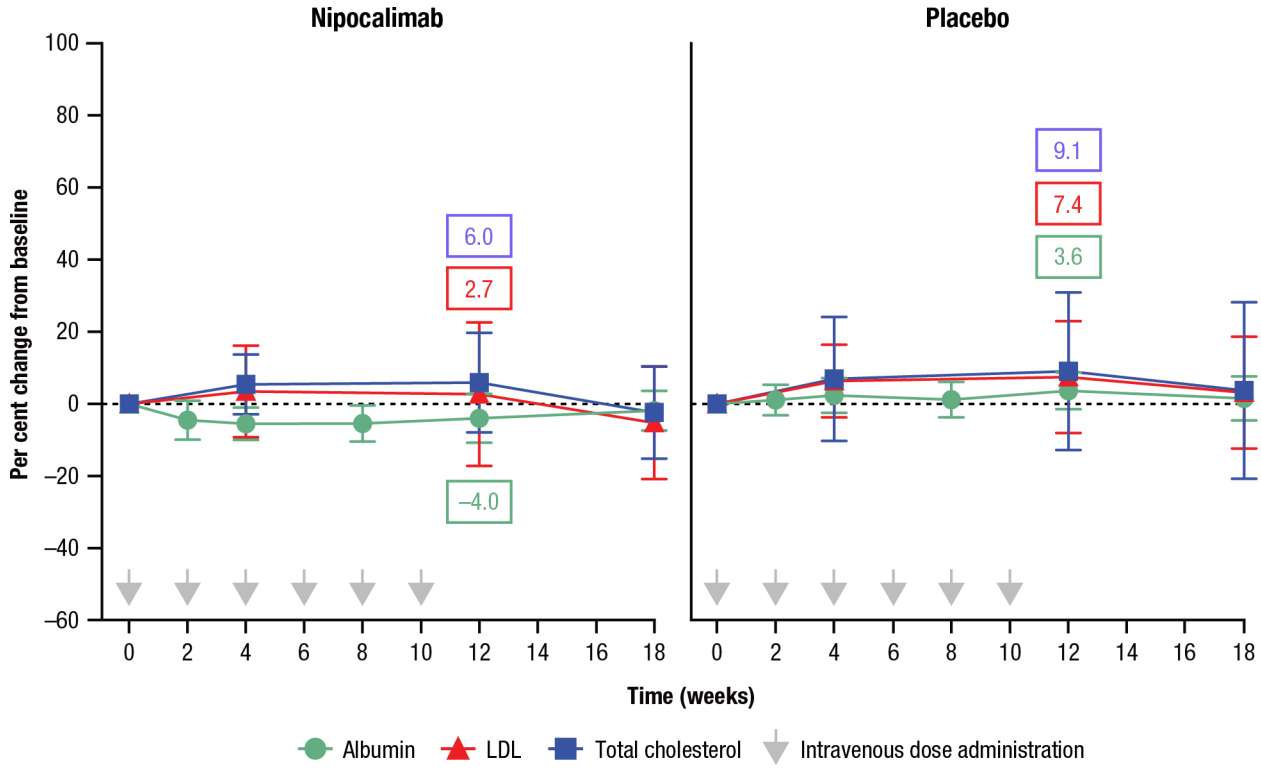

Figure 3 Mean (SD) per cent change from baseline in albumin, LDL and total cholesterol levels (safety population). LDL, low-density lipoprotein cholesterol.

with no new or unexpected safety findings, and provided consistent PK and PD profiles over the observation period.

Nipocalimab treatment significantly and reversibly reduced select biomarkers implicated in RA pathogenesis, including ACPA IgGs and CICs, with a similar trend for total IgG reduction, consistent with the mechanism of action of nipocalimab. Differences in reduction levels between total IgGs and ACPA IgGs were observed, which might have been due to differences in analytical assays, posttranslational modification of ACPA IgGs, distinctive unknown ACPA ICs that may alter its clearance mechanisms and/or compensatory ACPA-enhancing immune response. For example, ACPA IgG has been shown to be highly glycosylated in the Fab region compared with total IgGs, and the high levels of Fab glycosylation may hinder the interaction of ACPA IgGs with FcRn on the cell membrane.[35–37] The reduction in ACPA IgG was associated with DAS28-CRP remission and the ACR50 response. Furthermore, participants with higher baseline

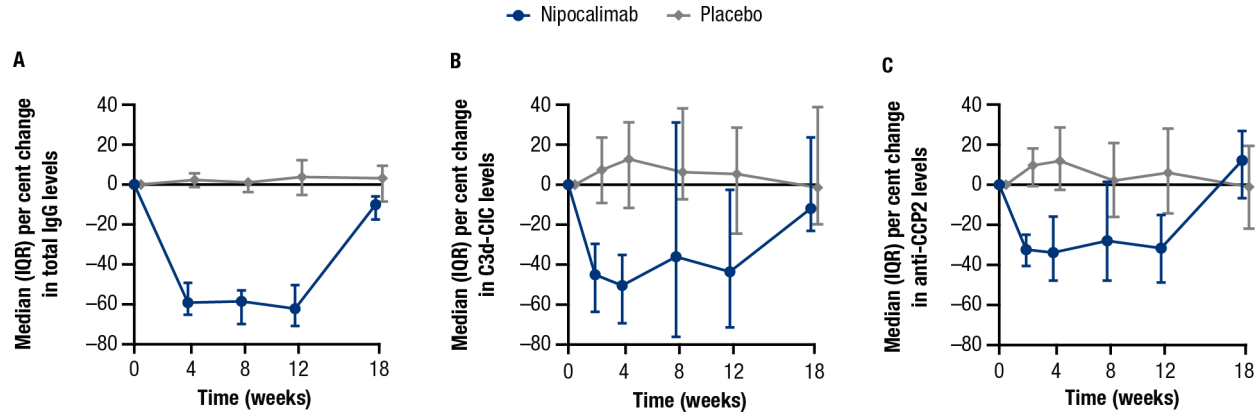

Figure 4 Median (IQR) per cent change from baseline at the trough in PD and disease-related biomarkers*: (A) total IgG, (B) C3d-CIC, and (C) ACPA IgG (anti-CCP2). ACPA, anticitrullinated protein autoantibody; anti-CCP2, anticyclic citrullinated peptide 2 antibody; C3d-CIC, complement factor 3d-containing circulating immune complex; IgG, immunoglobulin G; PD, pharmacodynamic. *The per cent change from baseline at the trough (y-axis) at the indicated visit week (x-axis) was stratified by treatment group for levels of (A) total IgG, (B) C3d-CIC and (C) ACPA IgG (anti-CCP2). If a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Participants with baseline levels of the indicated analyte below the lower limit of quantitation were excluded.

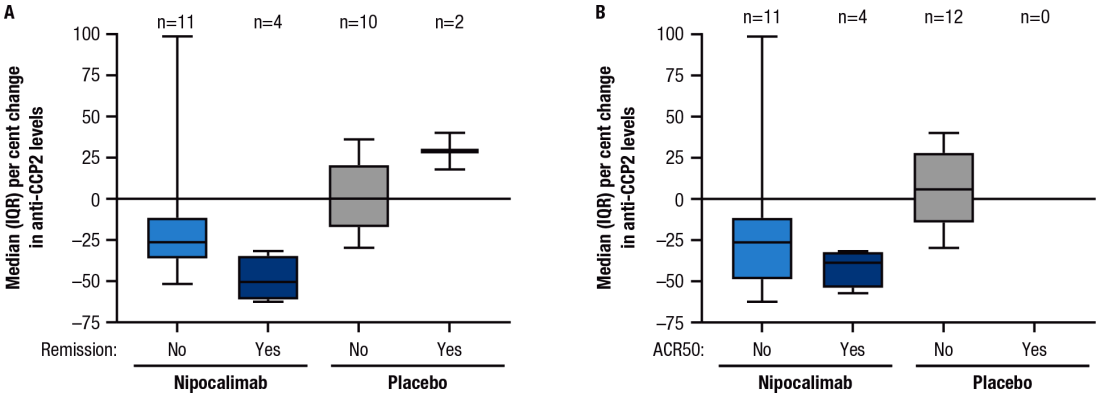

Figure 5 Median (IQR) per cent change from baseline at trough in ACPA IgG (anti-CCP2) levels versus (A) DAS28-CRP remission and (B) ACR50 response at Week 12.* ACPA, anticitrullinated protein autoantibody; ACR50, ≥50% response in American College of Rheumatology criteria; anti-CCP2, anticyclic citrullinated peptide 2 antibody; DAS28-CRP, Disease Activity Score 28 using C reactive protein; IgG, immunoglobulin G. *Per cent change in anti-CCP2 levels from baseline at Week 12 visit at the trough (y-axis) was stratified by (A) DAS28-CRP remission at Week 12, (B) ACR50 response at Week 12 and treatment group (x-axis). If a participant missed a planned dose of study intervention at any visit, their data were excluded from all subsequent visits after the first occurrence of a missed dose. Participants with baseline anti-CCP2 levels below the lower limit of quantitation were excluded. Data are presented as box (IQR) and whiskers (minimum and maximum values), with the median indicated by a bar.

ACPA levels, whose disease is presumably more autoantibody driven, preferentially benefitted from nipocalimab treatment. This greater clinical benefit was also observed with abatacept and rituximab.[38 39] To our knowledge, this is the first study to show a correlation between efficacy, PK, PD and the reduction of select disease-related biomarkers, suggesting that the observed clinical efficacy of nipocalimab may be driven by the reduction of ACPA IgGs.

Despite the substantial reduction in IgG, infection AEs with nipocalimab treatment were mild to moderate in severity (except for burn infection observed in one participant who had a history of thermal burn AE during screening) and resolved within the study period, similar to the phase 1 and phase 2 observations in healthy participants and patients with gMG.[29 34] Nipocalimab treatment is not expected to reduce immune or vaccine responses, as observed in a preclinical study and with another anti-FcRn agent.[31 40] However, further investigations are needed to better inform the risks of infections and immune responses associated with nipocalimab in the RA population. Additionally, the incidence of infusion reactions with nipocalimab treatment was low (12%) and consistent with the previous phase 1 and 2 observations

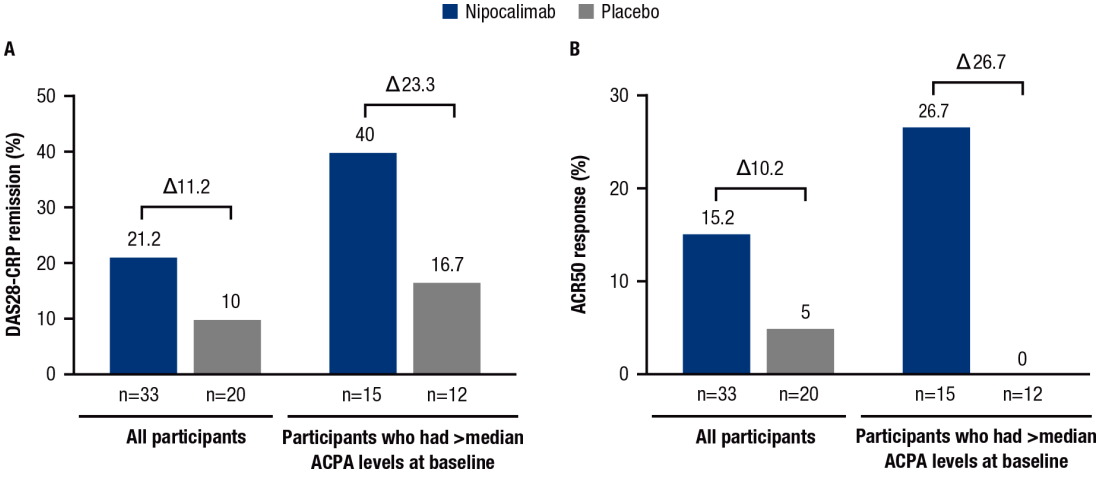

Figure 6 Associations of baseline ACPA IgG (anti-CCP2) levels and (A) DAS28-CRP remission and (B) ACR50 responses.* ACPA, anticitrullinated protein autoantibody; ACR50, ≥50% response in American College of Rheumatology criteria; anti-CCP2, anticyclic citrullinated peptide 2 antibody; DAS28-CRP, Disease Activity Score 28 using C reactive protein; IgG, immunoglobulin G. *Percentage of participants achieving (A) DAS28-CRP remission or (B) ACR50 response at Week 12 visit (y-axis) was stratified by treatment group and by either all participants or participants with baseline anti-CCP2 levels above the median value (x-axis). Participants with baseline anti-CCP2 levels below the lower limit of quantitation were excluded. The total number of participants in the strata is indicated below the x-axis, and the percentage of participants achieving responses is indicated above the respective bars.

with nipocalimab (6%–8%)[29 41–43] and with other anti-FcRn agents (8%–38%).[44 45] Overall, these safety findings support further evaluation of nipocalimab in RA.

Nipocalimab had no notable effect on systemic inflammatory markers. Despite that, nipocalimab treatment was associated with reductions in local inflammation in the joint tissue, as demonstrated by numerical improvements in swollen joint counts, tender joint counts, and decreases in Joint Pain Severity and HAQ-DI scores. This suggests a unique mechanism of action for nipocalimab in RA that can complement other biologic and targeted synthetic DMARDs that impact systemic inflammation markers, such as anti-TNF agents, but may not have an effect on ACPA levels.[46 47]

The similarity between the findings presented here and those of previous studies of nipocalimab in healthy volunteers and in patients with autoantibody/alloantibody-driven diseases (ie, gMG and HDFN)[29 30 33] indicates the potential of nipocalimab to address the underlying disease mechanism of seropositive RA and therefore support the further clinical development of nipocalimab in RA.

The limitations of this study include a relatively small sample size, a limited treatment period (10 weeks) and a single-dose regimen of nipocalimab (15 mg/kg intravenous every 2 weeks). Furthermore, this study was limited to patients with seropositive ACPA and/or RF; thus, the results cannot be generalised to patients with seronegative RA and may not be generalised to all patients with different ACPA and/or RF levels.

In summary, nipocalimab showed consistent efficacy benefits in participants with moderate to severe active RA who had shown an inadequate response or intolerance to anti-TNF agents, indicating proof of mechanism for FcRn blocking as a potential therapeutic pathway in RA. This study warrants further investigation to understand the mechanism of the nipocalimab response. Moreover, these findings generate the hypothesis that the combination of nipocalimab and therapy with a complementary mechanism of action, such as anti-TNF, may synergise to provide clinical benefits for patients with refractory RA. The efficacy and safety of nipocalimab in combination with an anti-TNF agent are currently being assessed in a proof-of-concept, phase 2a study in participants with active RA despite prior treatment with advanced therapies (DAISY-RA; ClinicalTrials.gov Identifier: NCT06028438).

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Competing interests PCT serves on a DSMB for Immunovant; serves as a consultant for AbbVie, Aqtual, Biogen, Eli Lilly, Fresenius, Galapagos, Gilead Sciences, GSK, Janssen, Nordic Pharma, Pfizer, Sanofi and UCB and receives grants/research support from Galapagos. GS has no conflict of interest. TWJH receives grants/research support from Janssen. QW, FI, BZ, SGL, JSBS, YX, JHL, RAP, MJL, KM, HD, RRC, CSK, CAC, SG and KF are employees of Janssen and may hold stock in Johnson & Johnson.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Independent Ethics Committees or Institutional Boards in Germany (Ethik-Kommission der Ärztekammer Nordrhein), Poland (Komisja Bioetyczna), Spain (CEIC HOSPITAL DE LA PRINCESA), the USA (Sterling Institutional Review Board and Oregon Health & Science University IRB) and the UK (North Tyneside General Hospital IRB/IEC, South Central Berkshire REC, Health Research Authority IRB/EC, Midlands Partnership NHS Foundation Trust, GBR-R&D-KINGS COLLEGE HOSPITAL NHS FOUNDATION TRUST and NHS Lothian Research & Development Office). Participants gave informed consent to participate in the study before taking part.

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