SYNOPSIS

Study Title: A Phase 2a Multicenter, Randomized, Double Blind, Parallel, Proof of Concept Study Evaluating the Efficacy and Safety of Nipocalimab and Certolizumab Combination Therapy in Participants with Active Rheumatoid Arthritis Despite Prior Treatment with Advanced Therapies (bDMARD or tsDMARD)

Study Number: 80202135ARA2002

Study Phase: 2a

Name of Study Intervention: JNJ-80202135 (nipocalimab)

Name of Sponsor/Company: Janssen Research & Development*

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Status:	Approved
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Prepared by:	Janssen Research & Development, LLC

Study Name: DAISY

EudraCT Number: 2023-504045-31

NCT Number: NCT06028438

IND: 154384

Number of Study Centers and Countries/Territories: This study was conducted at 26 centers that enrolled participants across 6 countries (US, Argentina, Hungary, Poland, Germany, and Great Britain).

Publications: None

Study Period: 15 August 2023 to 29 October 2024

Rationale:

This was a multicenter, randomized, double blind, parallel, proof of concept study to assess the efficacy, safety, PK, immunogenicity, and biomarkers of combination therapy with nipocalimab and certolizumab in participants between 18 and 75 years old, with moderately to severely active RA despite ≥1 advanced therapies (bDMARDs or tsDMARDs) but were certolizumab naïve.

Nipocalimab (JNJ-80202135) is a fully human aglycosylated IgG1 monoclonal antibody designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor. Certolizumab is an anti-TNFα agent approved for active RA. The combination therapy of nipocalimab and certolizumab, based on mechanistic observations, was evaluated to address the unmet need in patients with moderately to severely active RA with inadequate responses to advanced therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy in participants with moderately to severely active RA despite ≥1 advanced therapy (bDMARDs or tsDMARDs).	• Change from baseline in DAS28-CRP at Week 12
Secondary	
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy in participants with moderately to severely active RA	• ACR20, ACR50, ACR70, and ACR90 responses at Week 12 • DAS28-CRP remission at Week 12 • DAS28-CRP LDA at Week 12 • Change from baseline in HAQ-DI score at Week 12 • Change from baseline in CDAI at Week 12
• To evaluate the safety and tolerability of combination therapy with nipocalimab and certolizumab	• Treatment-emergent AE • Treatment-emergent SAEs • Treatment-emergent AEs leading to discontinuation of study intervention • Treatment-emergent AESIs
Clinical Biomarkers • To evaluate the effect of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy on levels of serum biomarkers related to RA	• Change from baseline in biomarkers, including but not limited to: total IgG, IgG1, IgG2, IgG3, IgG4, and autoantibodies (anti-CCP2 and RF)

Hypothesis:

The primary hypothesis is that treatment with nipocalimab in combination with certolizumab is superior to certolizumab monotherapy in participants with moderately to severely active RA despite treatment with ≥1 advanced therapy (bDMARDs or tsDMARDs) as assessed by the mean change from baseline in DAS28-CRP at Week 12.

Statistical Analyses:

The planned analyses and determination of sample size are described in the final version of the SAP.

Following the decision to terminate the development of the program, it was decided that a summary of the primary endpoint (change from baseline in DAS28-CRP at Week 12), key secondary efficacy endpoints at Week 12, selected exploratory efficacy endpoints and some of the secondary endpoints (ACR50, DAS28-CRP remission and DAS28-CRP LDA, and change from baseline in HAQ-DI) through Week 24

and by visit in ACPA high subgroup (≥400 U/mL) will be presented. All safety data, pharmacodynamics, and selected PK will be presented in the abbreviated CSR.

Analysis Methods:

Descriptive statistics, such as mean, SD, median, IQ range, minimum and maximum for continuous variables; counts and percentages for discrete variables were used to summarize most data. For continuous efficacy endpoints, treatment comparisons were performed using ANCOVA. For binary response efficacy endpoints, treatment comparisons were performed using logistic regression.

The analysis of the primary efficacy endpoint included data from all randomized participants who received at least 1 administration (complete or partial) of study intervention based on their assigned intervention group, regardless of the actual intervention received (Full Analysis Set population).

For primary analysis, primary estimand (composite strategy - zero change from baseline) was applied to address the intercurrent events. Missing data were imputed using Multiple imputation under the assumption of missing at random. ANCOVA model, including treatment group, and randomization stratification factors (baseline csDMARDs use [yes or no], screening ACPA level [high ≥400 U/mL; low <400 U/mL], country, and continuous baseline DAS28-CRP) was used.

The assumptions for the sample size and power calculation were based on the primary endpoint, change from baseline in DAS28-CRP at Week 12 using data from the REALISTIC study for certolizumab monotherapy and GO-FORWARD study for the nipocalimab and certolizumab combination therapy.

85 participants were planned to be randomized in a 3:2 ratio either to combination therapy arm (N= 51) or the certolizumab monotherapy arm (N=34). The sample size provided the study a power of 80% to detect a difference of 0.67 in the change from baseline in DAS28-CRP at Week 12 with a pooled SD of 1.2 between the 2 study intervention arms and an alpha of 0.05 (1-sided).

No multiplicity control was planned for the study. All the p-values, reported in this document, are 2-sided nominal p-values. Nominal p-values do not constitute and may not be used to claim statistical significance.

Methods:

80202135ARA2002 was a Phase 2a, multicenter, randomized, double blinded, proof of concept, parallel study to evaluate the efficacy and safety of nipocalimab and certolizumab combination therapy in participants with moderately to severely active RA despite prior advanced treatment therapies (bDMARD or tsDMARD). Primary and key secondary endpoints were at Week 12. Additional efficacy endpoints were assessed through Week 24, while safety was assessed through the end of the study.

Participants were randomly assigned to 1 of 2 to the following treatment groups using 3:2 randomization ratio:

- **Combination Therapy**: nipocalimab CCI [redacted] and certolizumab CCI [redacted]
- **Certolizumab Monotherapy**: certolizumab CCI [redacted]

Number of Participants (Planned and Analyzed):

The planned sample size was 85 participants. A total of 103 participants were randomized. Of the 103 participants enrolled, 62 were randomized to combination therapy and 41 to certolizumab monotherapy.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The target population consisted of male or female participants between 18 and 75 years old (inclusive) diagnosed with moderately to severely active RA for at least 12 months prior to screening. Participants had to have active RA previously as defined by persistent disease activity with at least 6 swollen and 6 tender joints out of the 66/68-swollen and tender joint count at the time of screening and at baseline. Participants had to have inadequate response to at least 1 advanced therapy (bDMARDs or tsDMARDs) and were certolizumab naïve.

Study Interventions, Dose, Mode of Administration:

Nipocalimab was administered at CCI [redacted]

Duration of Study Intervention:

The total duration of the study was up to 36 weeks, consisting of 3 study periods: a ≤6-week screening period, a 24-week double-blind study period which includes 22 weeks of study treatment, and a 6-week safety follow-up (8 weeks after the last dose of study intervention administration). Both groups received their assigned treatment for 22 weeks (Week 0 through Week 22).

SUMMARY OF RESULTS AND CONCLUSIONS:

Disposition of Participants:

A total of 150 participants were screened and 103 participants were randomized into the study, of which 47 (31.3%) participants were screen failures, primarily due to failure to meet eligibility criteria. 62 participants received combination therapy and 41 participants received certolizumab monotherapy.

Demographic and Other Baseline Characteristics:

Of the 103 participants randomized, the majority of the participants were Female (91 [88.3%]) and White 93 (90.3%). The mean age (SD) of the participants was 53.8 (9.25) years (range: 26 to 72 years [inclusive]). Overall, the demographic characteristics were balanced across treatment groups.

Baseline Disease Characteristics

The baseline disease characteristics were comparable between combination therapy and certolizumab monotherapy.

The mean (SD) baseline for swollen joint counts (66) was 14.65 (9.38) and 24.94 (13.26) for tender joint counts (68).

The median baseline CRP (mg/dL) in combination therapy was 0.75 mg/dL (IQ range: 0.35 to 1.46). The median baseline CRP (mg/dL) in certolizumab monotherapy was 1.02 mg/dL (0.57 to 1.78).

The mean (SD) baseline DAS28-CRP score was 5.94 (0.90), ranging between 4 and 8.5, and the prevalence of positive anti-CCP antibody(U/mL) and positive rheumatoid factor (IU/mL) was 92.2% and 95.1%, respectively. 92.2% of participants had positive anti-CCP antibody, while 86.4% had baseline csDMARDS usage.

Exposure:

A total of 62 participants received combination therapy and 41 participants received certolizumab monotherapy. Mean exposure (SD) was CCI [redacted] over 28.92 (4.32) weeks for combination therapy and CCI [redacted] over 29.58 (2.97) weeks for certolizumab monotherapy.

Primary Efficacy Results: ***Change from Baseline in DAS-28 CRP at Week 12***

Based on the primary composite estimand, the primary endpoint, change from baseline in DAS28-CRP score at Week 12 did not reach statistical significance at 2-sided type-one error of 10%. The LS mean and associated 90% confidence intervals in combination therapy was: -1.92 (90% CI: -2.48, -1.36); certolizumab monotherapy: -1.86 (90% CI: -2.44, -1.28); LS Mean difference between combination therapy and certolizumab monotherapy was -0.06 (90% CI: -0.51, 0.39), p = 0.822.

Secondary Efficacy Endpoints:

Among the secondary endpoints, numerical improvements in combination therapy were observed in ACR50, ACR70, ACR90, DAS28-CRP remission, and DAS28-CRP LDA at Week 12 over certolizumab monotherapy. In contrast, certolizumab monotherapy achieved numerical improvement in ACR20, CDAI and HAQ-DI compared with combination therapy.

Summary of Response Rate (90% CI) [a], LS Mean and LS Mean Difference with 90% CI [b] for Secondary Endpoints Analysis at Week 12

	Certolizumab Monotherapy	Combination Therapy	Delta (90% CI)	P-value[c]
N	41	62		
ACR20 (Attachment TEFACR2001)	63.4% (49.4%; 75.9%)	62.9% (51.7%; 73.2%)	-0.5% (-16.5%; 16.4%)	0.818
ACR50 (Attachment TEFACR5001)	31.7% (19.9%; 45.6%)	40.3% (29.8%; 51.6%)	8.6% (-8.6%; 24.2%)	0.358
ACR70 (Attachment TEFACR7001)	12.2% (4.9%; 23.9%)	14.5% (7.8%; 24.0%)	2.3% (-10.6%; 13.7%)	0.675
ACR90 (Attachment TEFACR9001)	2.4% (0.1%; 11.1%)	3.2% (0.6%; 9.8%)	0.8% (-7.6%; 7.6%)	0.619
DAS28-CRP Remission (Attachment TEFDASCRP02)	14.6% (6.6%; 26.9%)	25.8% (16.9%; 36.5%)	11.2% (-3.1%; 24.0%)	0.231
DAS28-CRP LDA (Attachment TEFDASCRP03)	26.8% (15.8%; 40.5%)	43.5% (32.8%; 54.8%)	16.7% (-0.7%; 31.8%)	0.128
Change from Baseline in HAQ-DI (Attachment TEFHAQ01)	-0.33 (-0.57; -0.08)	-0.30 (-0.54; -0.06)	0.03 (-0.16; 0.22)	0.807
Change from Baseline in CDAI (Attachment TEFCDAI01)	-22.51 (-28.15; -16.86)	-21.36 (-26.84; -15.88)	1.14 (-3.21; 5.50)	0.666

[a]The response rates, response rate differences and 90% CI are without covariates adjustment; [b]LS mean differences and (90% CI); [c]p-values are either from an ANCOVA model or from Logistic model adjusting for randomization stratification factors.

Selected Exploratory Efficacy Endpoints

There were no consistent improvements in combination therapy compared with certolizumab monotherapy in change from baseline in DAS28-CRP, ACR50 response, DAS28-CRP remission, DAS28-CRP LDA, and change from baseline in HAQ-DI in the overall population and ACPA high (>400 U m/l) subgroup through Week 24.

Safety Results:

Overall, combination therapy with nipocalimab and certolizumab was generally well-tolerated with no unexpected findings from the known safety profile of the monotherapy components through the final safety visit.

The proportion of participants reporting 1 or more TEAE in combination therapy was numerically higher in the combination therapy than in certolizumab monotherapy (74.2% versus 56.1%, respectively). SAEs were reported for 7 (11.3%) participants in combination therapy and 1 (2.4%) participant in certolizumab monotherapy. The reported PTs were Myocardial infarction, Cellulitis, Influenza, Pneumonia, Pneumonia respiratory syncytial viral, Soft tissue infection, Rheumatoid arthritis, and Renal cell carcinoma.

The proportion of participants reporting infections was numerically higher in combination therapy (38.7%) than in certolizumab monotherapy (29.3%). One (1.6%) participant in combination therapy reported an Opportunistic infection (PT Herpes ophthalmic). There were 3 (4.8%) participants with serious treatment-emergent infections in combination therapy and 1 (2.4%) participant in certolizumab monotherapy.

Through the final safety visit, there were no events of death, anaphylactic reactions, venous thromboembolism, or hypoalbuminemia with albumin <20 g/L reported.

The percent mean change from baseline through Week 24 in lipid profiles for cholesterol, HDL cholesterol, and LDL cholesterol were numerically higher in combination therapy compared with certolizumab monotherapy (total cholesterol percent mean change of 10.10% versus -1.76%; HDL cholesterol percent mean change of 14.08% versus -0.35%; LDL cholesterol percent mean change of 10.40% versus -1.89%, respectively), whereas the percent mean change in triglycerides levels from baseline through Week 24 were similar between treatment groups (combination therapy [8.30%] versus certolizumab monotherapy [6.36%]).

Pharmacokinetic Results:

- Median pre-dose (trough) serum nipocalimab concentrations were below LLOQ or close to LLOQ as nipocalimab exhibits nonlinear PK and accelerated clearance due to its mechanism of action.
- Median post-dose serum nipocalimab concentrations after CCI ranged from 759 to 789 µg/mL across Weeks 0, 2, 8, and 12.
- The median post-dose serum nipocalimab concentrations across the body-weight quartiles ranged from 639 to 732 µg/mL (1st Quartile BW), 722 to 834 µg/mL (2nd Quartile BW), 761 to 848 µg/mL (3rd Quartile BW), and 875 to 1060 µg/mL (4th Quartile BW), respectively.

Biomarker Results:

Through Week 24, decreases in IgG levels from baseline were observed in combination therapy, whereas certolizumab monotherapy maintained IgG levels at baseline levels. The observed median percent change from baseline in pre-dose (minimally reduced) total IgG at Week 12 was -64.17% for combination therapy and 3.45% for certolizumab monotherapy, and at Week 24 was -60.45% for combination therapy and 8.37% for certolizumab monotherapy.

Changes from baseline for all IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were similar to the changes observed for total IgG values.

Through Week 24, the IgA observed median percent changes from baseline at Week 12 were 9.40% and -0.56%, and at Week 24 were 10.83% and 4.32% for combination therapy and certolizumab monotherapy, respectively. The IgE observed median percent changes from baseline at Week 12 were 0.00% and 0.00%, and at Week 24 were 0.00% and 20.65% for combination therapy and certolizumab monotherapy, respectively. The IgM observed median percent changes from baseline at Week 12 were -5.66% and 7.83%, and at Week 24 were -4.23% and 10.31% for combination therapy and certolizumab monotherapy, respectively.

Through Week 24, decreases in anti-CCP2 levels from baseline over time were observed in combination therapy, whereas certolizumab monotherapy maintained the anti-CCP2 levels from baseline over time. The

median percent change from baseline in total anti-CCP2 at Week 12 was -37.21% and 16.43%, and at Week 24 was -45.53% for combination therapy and -5.82% for certolizumab monotherapy.

Through Week 24, decreases from baseline in RF levels were observed in combination therapy, whereas certolizumab monotherapy maintained RF levels from baseline. The median percent change from baseline in RF levels at Week 12 was -46.83% and 0.46%, and at Week 24 was -48.34% for combination therapy and 4.44% for certolizumab monotherapy.

Conclusions:

Combination therapy, consisting of nipocalimab and certolizumab administered separately, did not achieve a statistically significant difference in the primary endpoint, change from baseline in DAS28-CRP compared with certolizumab monotherapy in participants with active RA who had an inadequate response to advanced therapy at Week 12. There were no consistent improvements in combination therapy in secondary endpoints over certolizumab monotherapy. Therefore, no benefit of combination therapy was established over certolizumab monotherapy in participants who failed advanced therapy. Nipocalimab was well-tolerated at CCI in combination with certolizumab, over a 24-week treatment period followed by a 6-week safety follow-up period. There were numerically higher proportions of participants who experienced more than 1 TEAEs in combination therapy over certolizumab monotherapy, including SAEs and infections.

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