ORIGINAL ARTICLE

A Phase 2 Trial of Peresolimab for Adults with Rheumatoid Arthritis

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ABSTRACT

BACKGROUND

Peresolimab is a humanized IgG1 monoclonal antibody designed to stimulate the endogenous programmed cell death protein 1 (PD-1) inhibitory pathway. Stimulation of this pathway would be a novel approach to the treatment of patients with autoimmune or autoinflammatory diseases.

METHODS

In this phase 2a, double-blind, randomized, placebo-controlled trial, we assigned, in a 2:1:1 ratio, adult patients with moderate-to-severe rheumatoid arthritis who had had an inadequate response to, a loss of response to, or unacceptable side effects with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or to biologic or targeted synthetic DMARDs to receive 700 mg of peresolimab, 300 mg of peresolimab, or placebo intravenously once every 4 weeks. The primary outcome was the change from baseline to week 12 in the Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP). The DAS28-CRP ranges from 0 to 9.4, with higher scores indicating more severe disease. The primary comparison was between the 700-mg group and the placebo group. Secondary outcomes included the percentages of patients with American College of Rheumatology 20 (ACR20), ACR50, and ACR70 responses — defined as improvements from baseline of 20%, 50%, and 70% or more, respectively, in the numbers of tender and swollen joints and in at least three of five important domains — at week 12.

RESULTS

At week 12, the change from baseline in the DAS28-CRP was significantly greater in the 700-mg peresolimab group than in the placebo group (least-squares mean change [±SE], −2.09±0.18 vs. −0.99±0.26; difference in change, −1.09 [95% confidence interval, −1.73 to −0.46]; P<0.001). The results of the analyses of secondary outcomes favored the 700-mg dose over placebo with respect to the ACR20 response but not with respect to the ACR50 and ACR70 responses. Adverse events were similar in the peresolimab and placebo groups.

CONCLUSIONS

Peresolimab showed efficacy in a phase 2a trial in patients with rheumatoid arthritis. These results provide evidence that stimulation of the PD-1 receptor has potential efficacy in the treatment of rheumatoid arthritis. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT04634253.)

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A complete list of the trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on May 18, 2023, at NEJM.org.

N Engl J Med 2023;388:1853-62.
DOI: 10.1056/NEJMoa2209856

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Rheumatoid arthritis is a systemic, autoimmune, inflammatory disease that is characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Current treatment of patients with rheumatoid arthritis focuses on the timely initiation and modification of disease-modifying antirheumatic drug (DMARD) therapy to produce a sustained low level of disease activity or remission. Remission does not occur in most patients, and sustained remission (lasting at least 6 months) occurs in very few patients.[1] In addition, with multiple DMARDs, the response is lost over time in many patients. Taken together, these factors highlight the need for new, effective treatment options.

Programmed cell death protein 1 (PD-1) is an immune-checkpoint inhibitory receptor. Activation of PD-1 by its ligands, PD-L1 and PD-L2, can suppress lymphocyte activation[2] and is thought to have a pivotal role in peripheral immune tolerance.[3-5] The expression of PD-1 is regulated mainly by T-cell–receptor signaling and thus reflects T-cell activation.[6] T cells are thought to play pivotal roles in the chronic inflammation observed in rheumatoid arthritis and in supporting the production of antibodies by B cells.[7-9] Studies have shown that the expression of PD-1 is increased in the synovium of patients with rheumatoid arthritis,[10,11] with strong surface expression on CD4+ and CD8+ T cells that correlates with disease activity.[12,13] In addition, a subset of T cells — peripheral helper T cells — express high levels of PD-1.[14] These cells contribute to the formation of tertiary lymphoid structures alongside B cells and may be involved in the pathogenesis of various autoimmune diseases.

Immune dysfunction that encompasses the PD-1 pathway is thought to be involved in the pathogenesis of rheumatoid arthritis. While increased expression of PD-1 occurs on synovial T cells,[15] decreased binding of PD-1 by PD-L1 may cause inadequate down-regulation of pathogenic immune responses. Various studies have shown the potential for decreased interaction of PD-L1 with PD-1, either owing to low expression of PD-L1[13] or owing to the presence of competing or interacting molecules, such as CD80, soluble PD-1, soluble PD-L1, or autoantibodies to proteins in the PD-1 pathway.[10,11,14,16,17]

Immunotherapy targeting the PD-1–PD-L1 pathway has proved to be effective against various cancers, but it has also been associated with toxic effects collectively defined as immune-related adverse events.[18] One of these events, inflammatory arthritis, is associated with blockade of the PD-1 pathway, which further highlights the importance of the PD-1 pathway in synovial immune homeostasis.[18]

Peresolimab, a humanized IgG1 monoclonal antibody, binds and activates PD-1. Because PD-1 is expressed predominantly on activated T cells, the binding of peresolimab to PD-1 has the potential to restore immune homeostasis without affecting the remaining cells in the immune repertoire. We hypothesized that this novel approach to treating patients with autoimmune or autoinflammatory diseases would translate into an efficacious treatment. In this trial, we evaluated the efficacy and safety of peresolimab in adult patients with moderate-to-severe active rheumatoid arthritis who had had an inadequate response to, a loss of response to, or unacceptable side effects with either conventional synthetic DMARDs or biologic or targeted synthetic DMARDs.

METHODS

TRIAL DESIGN

This phase 2a, double-blind, randomized, placebo-controlled clinical trial of peresolimab in adult patients with moderate-to-severe active rheumatoid arthritis was the initial evaluation of the efficacy and safety of peresolimab in patients with rheumatoid arthritis. Patients who met the eligibility criteria were randomly assigned in a 2:1:1 ratio to receive 700 mg of peresolimab, 300 mg of peresolimab, or placebo intravenously once every 4 weeks. Patients were stratified according to the previous use of biologic or targeted synthetic DMARDs (yes or no). In the double-blind treatment period (period 1), the clinical efficacy and safety of peresolimab were evaluated through week 12.

All the patients who remained in the trial at the end of period 1 entered period 2. The patients in the peresolimab groups who had a low level of disease activity (Clinical Disease Activity Index [CDAI] low disease activity, defined as a CDAI score of ≤10; scores range from 0 to 76,

with higher scores indicating greater disease activity) at week 14 continued to receive the same dose of peresolimab during period 2, and safety and clinical disease activity were assessed through week 24. All other patients at week 14 received standard-of-care treatment regardless of their trial-group assignment at baseline. After the end of period 2, patients were monitored for 12 weeks for assessment of safety, pharmacokinetics, and measures of clinical disease activity.

PATIENT ELIGIBILITY

Patients were eligible for the trial if they were 18 years of age or older, had received a diagnosis of adult-onset rheumatoid arthritis (as defined by the 2010 American College of Rheumatology–European League against Rheumatism classification criteria[19]) at least 3 months before screening, had moderate-to-severe active rheumatoid arthritis (defined as ≥6 swollen joints out of a total of 66 joints and ≥6 tender joints out of a total of 68 joints) at screening and baseline, had active synovitis in 1 or more joints in the hands or wrists (as indicated by a Rheumatoid Arthritis Magnetic Resonance Imaging Score for synovitis[20] of ≥1 according to central assessment) at screening, and had had an inadequate response to, a loss of response to, or unacceptable side effects with at least one conventional synthetic DMARD or at least one biologic or targeted synthetic DMARD. Values for the Rheumatoid Arthritis Magnetic Resonance Imaging Score for synovitis range from 0 to 24, with a higher score indicating more severe synovitis. Patients with no response to more than two biologic or targeted synthetic DMARDs were ineligible for the trial. A full list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

CONCOMITANT THERAPIES

Concurrent treatment with stable doses of oral methotrexate (≤25 mg per week), parenteral methotrexate (≤20 mg per day), hydroxychloroquine (≤400 mg per day), oral sulfasalazine (≤3000 mg per day), nonsteroidal antiinflammatory drugs and oral glucocorticoids (≤10 mg per day of prednisone or equivalent), and leflunomide (20 mg per day) was permitted.

EFFICACY ASSESSMENTS

The primary outcome was the change from baseline at week 12 in the Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP), with the primary comparison being the difference in change between patients treated with 700 mg of peresolimab and those who received placebo. The components of the DAS28-CRP are the tender-joint count among 28 joints, the swollen-joint count among 28 joints, the patient's global assessment of disease activity (assessed on a visual analogue scale ranging from 0 to 100 mm, with higher scores indicating greater disease activity), and serum levels of high-sensitivity C-reactive protein. The formula we used is as follows:

$$\begin{aligned}\text{DAS28-CRP} = {} & 0.56 \times \sqrt{(\text{TJC28})} + 0.28 \\ & \times \sqrt{(\text{SJC28})} + 0.36 \times \ln(\text{hs-CRP} + 1) + 0.014 \\ & \times \text{PatGA} + 0.96,\end{aligned}$$

where √ is the square root, TJC28 is the tender-joint count among 28 joints, SJC28 is the swollen-joint count among 28 joints, ln is the natural log, hs-CRP is the high-sensitivity C-reactive protein level in serum, and PatGA is the patient's assessment of disease activity. The DAS28-CRP ranges from 0 to 9.4, with higher scores indicating more severe disease.[21]

The following key secondary outcomes were prespecified in the protocol (available at NEJM.org): American College of Rheumatology 20 (ACR20), ACR50, and ACR70 responses (defined as improvements from baseline of 20%, 50%, and 70% or more, respectively, in the numbers of tender and swollen joints and in at least three of five important domains) at week 12; improvements in individual domains of the ACR20, ACR50, and ACR70; and disease activity as assessed by the change from baseline in the CDAI score, the Simplified Disease Activity Index (SDAI) score (values range from 0 to 86, with higher values indicating greater disease activity), and the mental and physical component scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; scores range from 0 to 100, with higher scores indicating greater well-being). Exploratory and tertiary outcomes included a low level of disease activity or remission, as defined by the DAS28-CRP, the DAS28 based on the erythrocyte sedimentation rate

(DAS28-ESR; scores range from 0 to 9.4, with a higher score indicating greater disease activity), the SDAI, and the CDAI (Tables S6 through S8 in the Supplementary Appendix). A prespecified analysis of subgroups according to previous use of biologic or targeted synthetic DMARDs (yes or no) was also performed.

TRIAL OVERSIGHT

The sponsor, Eli Lilly, had a role in the design of the trial; the analysis, collection, and interpretation of the data; laboratory and site-monitoring services; and the writing of the manuscript. The last author had full access to all the data and made the final decision to submit the manuscript for publication. Three of the authors vouch for the accuracy and completeness of the data and the integrity of the analysis and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

We calculated that a sample size of 80 patients would provide the trial with more than 80% power to detect a significant difference between the 700-mg peresolimab group and the placebo group with respect to the primary outcome, with the assumption that the DAS28-CRP would change from baseline to week 12 by –1.80 in the 700-mg peresolimab group and by –0.75 in the placebo group, with a standard deviation of 1.25, on the basis of a two-sided t-test at an alpha level of 0.05. The comparison of the 300-mg peresolimab group with the placebo group was exploratory, and therefore no formal calculation of the target sample size for this comparison was performed. Because of the high number of persons being screened toward the end of the trial period, 98 patients received at least one dose of peresolimab or placebo and were included in the analysis.

We did not adjust for multiple comparisons in the analysis, and all secondary analyses are considered to be exploratory. Because the statistical analysis plan did not include a provision to correct for multiple comparisons in the analysis of secondary and other outcomes, the data for these outcomes are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test.

Efficacy and safety analyses were conducted in the modified intention-to-treat and safety populations, respectively; these analyses included all the patients who were randomly assigned to a trial group and received at least one dose of peresolimab or placebo. We analyzed efficacy during period 2 in the subgroup of patients who had a low level of disease activity as assessed with the CDAI at week 14 and who continued peresolimab treatment for up to 24 weeks. For analysis of dichotomous outcomes, we used a logistic-regression model, with trial group, baseline disease activity, and stratification factor (previous use of biologic or targeted synthetic DMARDs [yes or no]) as covariates. Missing data were imputed with use of the imputation method for nonresponse. For continuous efficacy outcomes, including the primary outcome, we used a mixed-effects model for repeated measures. This model included trial group, stratification factor, baseline disease activity, visit, and treatment-by-visit interaction as fixed factors; patients as a random factor; and an unstructured covariance matrix. A hypothetical estimand strategy was used to account for intercurrent events; a likelihood-based method was used to handle the missing data. All statistical tests of treatment effects were performed at a two-sided alpha level of 0.05 unless otherwise specified. Statistical analyses were performed with SAS software, version 9.4 or higher (SAS Institute).

RESULTS

PATIENTS

Between January 4, 2021, and January 10, 2022, we screened 172 patients for trial eligibility. A total of 98 patients were randomly assigned, in a 2:1:1 ratio, to receive 700 mg of peresolimab (49 patients), 300 mg of peresolimab (25 patients), or placebo (24 patients); all 98 patients received at least one dose of peresolimab or placebo and were included in the analysis (Fig. S1). Three patients who were eligible for the trial did not receive peresolimab or placebo: one patient underwent randomization inadvertently, and 2 patients withdrew from the trial before receiving the first dose. Two interim analyses were conducted — one when 100% of patients had either completed the trial through week 12 or discontinued peresolimab or placebo and one when 100% patients had either completed the

Table 1. Baseline Characteristics.*

Characteristic	Placebo (N=24)	Peresolimab, 300 mg (N=25)	Peresolimab, 700 mg (N=49)
Female sex — no. (%)	19 (79)	20 (80)	43 (88)
Age — yr	55.8±11.1	50.1±15.8	50.5±11.2
Body-mass index†	28.2±4.8	28.2±3.7	29.3±6.8
Race or ethnic group — no. (%)‡			
American Indian or Alaska Native	7 (29)	10 (40)	13 (27)
Black or African American	0	0	2 (4)
White	17 (71)	15 (60)	34 (69)
Seropositivity — no. (%)§			
For anti-CCP antibody or rheumatoid factor	20 (83)	22 (88)	45 (92)
For anti-CCP antibody	19 (79)	22 (88)	42 (86)
For rheumatoid factor	18 (75)	19 (76)	44 (90)
Use of glucocorticoids — no. (%)	14 (58)	15 (60)	30 (61)
Duration of rheumatoid arthritis — yr	10.9±8.4	9.8±8.9	9.7±7.5
DAS28-CRP¶	5.66±0.59	5.91±0.98	6.00±0.87
Tender-joint count among 68 joints — no. of joints	19.0±8.8	22.7±13.7	19.6±8.5
Swollen-joint count among 66 joints — no. of joints	13.7±5.2	18.7±13.3	14.6±5.6
Physician's global assessment of disease activity — mm‖	62.5±16.3	70.2±15.9	67.2±18.4
Patient's global assessment of disease activity — mm‖	69.0±15.8	69.5±15.5	70.8±17.4
Patient's assessment of arthritis pain — mm‖	67.3±18.0	70.4±14.3	72.2±18.1
HAQ-DI score**	1.55±0.56	1.63±0.57	1.66±0.54
High-sensitivity C-reactive protein level — mg/liter††	12.0±12.8	13.3±13.8	16.2±15.0
SF-36‡‡			
Mental component score	50.1±13.0	49.0±9.5	47.1±11.0
Physical component score	32.3±7.0	31.6±7.4	32.5±7.9
Clinical Disease Activity Index score§§	38.3±10.5	43.1±12.8	41.7±13.2
Simplified Disease Activity Index score¶¶	39.4±10.2	44.4±13.4	43.8±13.5
RAMRIS for synovitis‖‖	8.3±4.8	7.7±4.8	8.3±5.3

* Plus–minus values are mean ±SD. Additional information about the efficacy measures is provided in Table S12.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was reported by the patients.
§ Seropositivity for anti–cyclic citrullinated peptide (anti-CCP) was defined as a level of at least 17 IU per milliliter, and seropositivity for rheumatoid factor was defined as a level of at least 15 IU per milliliter.
¶ The Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP) ranges from 0 to 9.4, with higher scores indicating more severe disease.
‖ This evaluation was based on a visual analogue scale of 0 to 100 mm, with higher values indicating greater disease activity or pain.
** Heath Assessment Questionnaire–Disability Index (HAQ-DI) scores range from 0 to 3, with higher scores indicating greater disability.
†† The normal range of the high-sensitivity C-reactive protein level is 0 to 5 mg per liter.
‡‡ The mental and physical component scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating greater well-being.
§§ Clinical Disease Activity Index scores range from 0 to 76, with higher scores indicating more severe disease.
¶¶ Simplified Disease Activity Index scores range from 0 to 86, with higher scores indicating more severe disease.
‖‖ The Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) for synovitis ranges from 0 to 24, with higher scores indicating more severe synovitis.

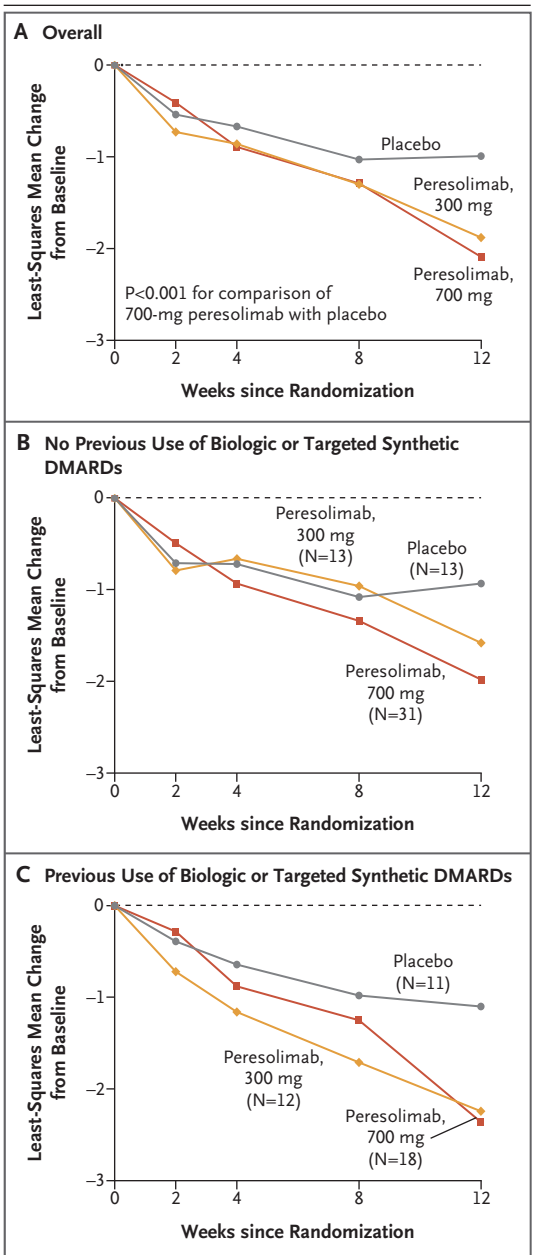

Figure 1. Change from Baseline in the DAS28-CRP Overall and According to DMARD Subgroup.

Shown is the change from baseline in the Disease Activity Score for 28 joints based on the C-reactive protein level (DAS28-CRP) at week 12 in the 700-mg and 300-mg peresolimab groups and the placebo group overall (Panel A) and according to whether there was no previous use of biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARDs; Panel B) or previous use of biologic or targeted synthetic DMARDs (Panel C). The primary outcome was the change from baseline in the DAS28-CRP at week 12. The DAS28-CRP ranges from 0 to 9.4, with higher scores indicating more severe disease.

trial through week 24 or discontinued peresolimab or placebo.

BASELINE CHARACTERISTICS

The baseline demographic characteristics and disease activity were similar across the trial groups (Table 1). The majority of the patients (84%) were women, and the mean (±SD) age at baseline was 51.7±12.6 years. At baseline, the mean duration of rheumatoid arthritis was 10.0±8.0 years, and the mean DAS28-CRP was 5.9±0.8, a level that corresponded to high disease activity.[22] A total of 42% of the patients had previously received biologic or targeted synthetic DMARDs (Fig. 1). Information about the broader population of patients with rheumatoid arthritis and the representativeness of the patients in this trial is provided in Table S11.

DISEASE ACTIVITY

The change from baseline in the DAS28-CRP at week 12 was significantly greater in the 700-mg peresolimab group than in the placebo group (between-group difference in the change from baseline, −1.09; 95% confidence interval, −1.73 to −0.46; P<0.001) (Table 2 and Fig. 1A). Post hoc analyses of the four components of the DAS28-CRP showed that for two components, the changes from baseline at week 12 in the tender-joint count among 28 joints and in the swollen-joint count among 28 joints, the results favored peresolimab over placebo; this effect was not seen for the other two components, serum levels of high-sensitivity C-reactive protein and patient's assessment of disease activity (Fig. S2B through S2E). The results of key secondary outcomes are shown in Table 2. The 700-mg dose of peresolimab appeared to result in a better ACR20 response than placebo, but not in a better ACR50 or ACR70 response (Table 2). Peresolimab had no beneficial effect as compared with placebo on the patient's global assessment of disease activity or the scores on the mental and physical components of the SF-36 (Table 2). The percentages of patients who had a low level of disease activity or remission at week 12 as assessed with the DAS28-CRP, DAS28-ESR, SDAI, and CDAI are shown in Table S7.

In prespecified subgroup analyses of the change in the DAS28-CRP from baseline to week 12 according to previous use of DMARDs, results were generally similar in the subgroup

Table 2. Primary and Secondary Efficacy Outcomes at Week 12.*

Outcome	Placebo (N=24)	Peresolimab, 300 mg (N=25)	Peresolimab, 700 mg (N=49)
Primary outcome			
DAS28-CRP			
Change from baseline	−0.99±0.26	−1.88±0.25	−2.09±0.18
Difference in change vs. placebo (95% CI)	—	−0.88 (−1.60 to −0.16)	−1.09 (−1.73 to −0.46)†
Secondary outcomes			
ACR20 response‡			
No. of patients (%)	10 (42)	11 (44)	35 (71)
Least-squares mean difference vs. placebo (95% CI)	—	2.3 (−25.4 to 30.0)	29.8 (6.3 to 53.2)
ACR50 response‡			
No. of patients (%)	5 (21)	5 (20)	19 (39)
Least-squares mean difference vs. placebo (95% CI)	—	−0.8 (−23.4 to 21.7)	17.9 (−3.3 to 39.2)
ACR70 response‡			
No. of patients (%)	4 (17)	1 (4)	10 (20)
Least-squares mean difference vs. placebo (95% CI)	—	−12.7 (−29.4 to 4.1)	3.7 (−15.0 to 22.4)
Tender-joint count for 68 joints			
Change from baseline	−6.89±1.85	−12.08±1.81	−12.33±1.29
Difference in change vs. placebo (95% CI)	—	−5.19 (−10.35 to −0.03)	−5.45 (−9.91 to −0.98)
Swollen-joint count for 66 joints — no. of joints			
Change from baseline	−6.18±1.09	−10.22±1.08	−10.49±0.76
Difference in change vs. placebo (95% CI)	—	−4.04 (−7.12 to −0.96)	−4.31 (−6.94 to −1.67)
Physician's global assessment of disease activity			
Change from baseline	−25.35±5.16	−39.07±5.13	−38.55±3.58
Difference in change vs. placebo (95% CI)	—	−13.72 (−28.23 to 0.80)	−13.20 (−25.68 to −0.72)
Patient's global assessment of disease activity			
Change from baseline	−21.66±5.39	−24.27±5.28	−29.67±3.74
Difference in change vs. placebo (95% CI)	—	−2.60 (−17.62 to 12.41)	−8.01 (−21.05 to 5.03)
Patient's assessment of arthritis pain			
Change from baseline	−17.94±5.10	−23.50±5.00	−31.55±3.54
Difference in change vs. placebo (95% CI)	—	−5.56 (−19.76 to 8.65)	−13.61 (−25.95 to −1.26)
HAQ-DI score			
Change from baseline	−0.41±0.11	−0.35±0.11	−0.42±0.08
Difference in change vs. placebo (95% CI)	—	0.06 (−0.24 to 0.36)	−0.01 (−0.27 to 0.26)
SF-36			
Mental component summary score			
Change from baseline	3.48±1.72	0.55±1.63	4.64±1.17
Difference in change vs. placebo (95% CI)	—	−2.93 (−7.63 to 1.77)	1.15 (−2.95 to 5.26)
Physical component summary score			
Change from baseline	5.01±1.71	7.03±1.63	6.43±1.16
Difference in change vs. placebo (95% CI)	—	2.02 (−2.69 to 6.73)	1.42 (−2.67 to 5.50)
High-sensitivity C-reactive protein level			
Change from baseline	1.34±3.72	−5.26±3.63	−0.66±2.57
Difference in change vs. placebo (95% CI)	—	−6.60 (−16.91 to 3.70)	−2.01 (−10.99 to 6.98)
Clinical Disease Activity Index score			
Change from baseline	−13.75±2.71	−24.06±2.63	−25.51±1.85
Difference in change vs. placebo (95% CI)	—	−10.30 (−17.83 to −2.77)	−11.76 (−18.29 to −5.22)
Simplified Disease Activity Index score			
Change from baseline	−13.80±2.66	−25.06±2.57	−26.90±1.88
Difference in change vs. placebo (95% CI)	—	−11.26 (−18.65 to −3.87)	−13.10 (−19.61 to −6.60)

* Plus–minus values are least-squares mean ±SE. The widths of the 95% confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used in place of hypothesis tests.
† P<0.001 for the difference in the change from baseline at week 12 in the DAS28-CRP between the 700-mg peresolimab group and the placebo group.
‡ American College of Rheumatology 20 (ACR20), ACR50, and ACR70 responses are defined as improvements from baseline of 20%, 50%, and 70% or more, respectively, in the numbers of tender and swollen joints and in at least three other important domains.

Table 3. Adverse Events between Baseline and Week 12 (Period 1).*

Event	Placebo (N=24)	Peresolimab, 300 mg (N=25)	Peresolimab, 700 mg (N=49)
		no. of patients (%)	
Adverse event during the treatment period			
Overall	9 (38)	8 (32)	14 (29)
According to severity†			
Mild	6 (25)	5 (20)	9 (18)
Moderate	3 (12)	3 (12)	5 (10)
Severe	0	0	0
Serious adverse event	0	0	1 (2)
Discontinuation of placebo or peresolimab because of adverse event	1 (4)	1 (4)	0
Infections and infestations‡	3 (12)	6 (24)	5 (10)
Nasopharyngitis	1 (4)	2 (8)	1 (2)
Coronavirus disease 2019	0	1 (4)	1 (2)
Vulvovaginal candidiasis	0	0	1 (2)§
Gastroenteritis	0	1 (4)	0
Helicobacter infections	0	1 (4)	0
Herpes simplex	1 (4)	0	0
Mastitis	0	1 (4)	0
Rhinitis	0	0	1 (2)
Sinusitis	0	1 (4)	0
Skin bacterial infection	0	1 (4)	0
Tooth abscess	1 (4)	0	0
Upper respiratory tract infection¶	0	0	1 (2)
Upper respiratory tract infection bacterial¶	0	0	1 (2)
Urinary tract infections	0	0	1 (2)
Neoplasma benign, malignant, and unspecified, including cysts and polyps: B-cell lymphoma‡	1 (4)	0	0
Skin and subcutaneous tissue disorders‡	2 (8)	0	2 (4)
Pruritus	1 (4)	0	1 (2)
Dermatitis atopic	0	0	1 (2)
Onycholysis	1 (4)	0	0

* There were no deaths, cases of herpes zoster, or thromboembolic events.
† For patients with multiple occurrences of the same event, the most severe event is reported.
‡ The headings and subheadings are the system organ classes and preferred terms, respectively, in the *Medical Dictionary for Regulatory Activities*, version 25.0.
§ The percentage was calculated with 43 female patients as the denominator.
¶ One patient had an adverse event that was coded as "upper respiratory tract infection," and another patient had an adverse event that was coded as "upper respiratory tract infection bacterial."

with no previous use of biologic or targeted synthetic DMARDs (Fig. 1B) and the subgroup with previous use of biologic or targeted synthetic DMARDs (Fig. 1C). The results of additional prespecified analyses are provided in the Supplementary Appendix.

A total of 27 patients (55%) receiving 700 mg of peresolimab and 11 (44%) receiving 300 mg of peresolimab had CDAI low disease activity at week 14 and were eligible to continue receiving peresolimab through week 24 (Fig. S3A). In contrast, 6 patients (25%) receiving placebo had CDAI low disease activity at week 14.

SAFETY

The safety profiles were similar in the three trial groups (Table 3). One serious adverse event — hypothyroidism — was reported in a patient treated with 700 mg of peresolimab; this event was assessed by an investigator as unrelated to the trial intervention. No deaths were reported in this trial. Two patients discontinued placebo or peresolimab because of adverse events (Table 3): one patient in the placebo group discontinued because of a low-grade B-cell lymphoma, and one patient in the 300-mg peresolimab group discontinued because of a mild bacterial skin infection on the foot. Safety profiles were similar in the trial groups in period 2 (weeks 14 through 24), with no severe or serious adverse events, deaths, or discontinuations of peresolimab or placebo in any group (Table S3). One serious adverse event — worsening of rheumatoid arthritis — was reported during the follow-up period (Table S5); the event occurred approximately 8 weeks after a patient in the 700-mg peresolimab group had received the final peresolimab dose. There were no clinically relevant differences in laboratory test results among the trial groups at week 12 (Table S4).

DISCUSSION

In this phase 2a trial, the improvement in the DAS28-CRP at week 12 was significantly greater — by about 1 point — in the 700-mg peresolimab group than in the placebo group. In larger clinical trials of treatments for rheumatoid arthritis, improvements in ACR criteria, assessed as the percentages of patients with ACR20, ACR50, and ACR70 responses, are often reported as the primary and key secondary outcomes.[23,24] For this smaller trial, treatment with 700 mg of peresolimab led to an ACR20 response in a higher percentage of patients than did placebo, but similar benefits were not shown for the ACR50 and ACR70 responses. Treatment with 300 mg of peresolimab did not result in higher percentages of patients with ACR20, ACR50, and ACR70 responses than placebo.

Clinical trials of treatments for rheumatoid arthritis have shown lower response rates among patients who had previously received biologic therapy than among patients who had not.[25] To evenly distribute the number of patients across the groups in this trial, we stratified patients according to the previous use of biologic or targeted synthetic DMARDs. Changes from baseline in the DAS28-CRP at week 12 were generally similar in the subgroup that did not receive biologic or targeted synthetic DMARDs and the subgroup that previously received biologic or targeted synthetic DMARDs, although larger studies are needed to confirm this observation.

There are some limitations to the design of this trial. Although it is notable that the efficacy at week 12 was significantly greater in the 700-mg peresolimab group than in the placebo group, the assessment of outcomes and safety is limited by the short time frame of the trial. The results at week 24 may be skewed because this period included patients with low disease activity, which may have resulted in selection bias, and because of the lack of a placebo control. The small sample size is also a limitation of this trial.

There were no obvious trends with respect to any type of adverse events. Longer and larger trials are needed to further assess the safety profile of peresolimab. Careful evaluation of the effect of peresolimab on the risk of cancer will be important given the efficacy of PD-1 inhibitors in oncologic disease.

In this phase 2a trial involving adults with moderate-to-severe rheumatoid arthritis, the PD-1 agonist monoclonal antibody peresolimab, at a dose of 700 mg, was superior to placebo with respect to the change from baseline in the DAS28-CRP at week 12. Longer and larger trials are needed to assess the efficacy and safety of peresolimab in rheumatoid arthritis.

Presented in part at the American College of Rheumatology Convergence, November 10–14, 2022, in Philadelphia.

Supported by Eli Lilly.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients for their participation and Conor McVeigh, Ph.D., for assistance with the writing of the manuscript.

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