ORIGINAL ARTICLE

Brodalumab, an Anti-IL17RA Monoclonal Antibody, in Psoriatic Arthritis

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ABSTRACT

BACKGROUND

We assessed the efficacy and safety of brodalumab, a human monoclonal antibody against interleukin-17 receptor A (IL17RA), in a phase 2, randomized, double-blind, placebo-controlled study involving patients with psoriatic arthritis.

METHODS

We randomly assigned patients with active psoriatic arthritis to receive brodalumab (140 or 280 mg subcutaneously) or placebo on day 1 and at weeks 1, 2, 4, 6, 8, and 10. At week 12, patients who had not discontinued their participation in the study were offered open-label brodalumab (280 mg) every 2 weeks. The primary end point was 20% improvement in American College of Rheumatology response criteria (ACR 20) at week 12.

RESULTS

Of the 168 patients who underwent randomization (57 in the brodalumab 140-mg group, 56 in the brodalumab 280-mg group, and 55 in the placebo group), 159 completed the double-blind phase and 134 completed 40 weeks of the open-label extension. At week 12, the brodalumab 140-mg and 280-mg groups had higher rates of ACR 20 than the placebo group (37% [P=0.03] and 39% [P=0.02], respectively, vs. 18%); they also had higher rates of 50% improvement (ACR 50) (14% [P=0.05] and 14% [P=0.05] vs. 4%). Rates of 70% improvement were not significantly higher in the brodalumab groups. Similar degrees of improvement were noted among patients who had received previous biologic therapy and those who had not received such therapy. At week 24, ACR 20 response rates in the brodalumab 140-mg and 280-mg groups were 51% and 64%, respectively, as compared with 44% among patients who switched from placebo to open-label brodalumab; responses were sustained through week 52. At week 12, serious adverse events had occurred in 3% of patients in the brodalumab groups and in 2% of those in the placebo group.

CONCLUSIONS

Brodalumab significantly improved response rates among patients with psoriatic arthritis. Larger studies of longer duration are necessary to assess adverse events. (Funded by Amgen; ClinicalTrials.gov number, NCT01516957.)

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Psoriatic arthritis is a chronic inflammatory disorder involving joints, entheses, bone, axial skeleton, and skin, with heterogeneous clinical features associated with substantial disability and reduced life expectancy.[1-4] Psoriatic arthritis affects 0.3 to 1% of the global population and up to 30% of patients with psoriasis.[5,6] Despite improved therapeutic benefits with tumor necrosis factor (TNF) inhibitors, a need remains for patients who have poor disease control.[7-13]

Several lines of evidence suggest a role for interleukin-17 signaling in the pathogenesis of psoriatic arthritis. Polymorphisms associated with susceptibility to psoriatic arthritis are present in genetic loci involved in interleukin-17 signaling, such as *IL12B* and *TRAF3IP2*.[14] Levels of interleukin-17 receptor A (IL17RA) and interleukin-17–positive T cells are elevated in synovial fluid and psoriatic plaques of patients with psoriatic arthritis.[15,16] Levels of circulating type 17 helper T (Th17) cells are higher in patients with spondyloarthritides (psoriatic arthritis and ankylosing spondylitis) than in those with rheumatoid arthritis.[17] Interleukin-17 has been implicated mechanistically in both inflammation and bone remodeling in a murine model of spondyloarthritis.[18]

Multiple agents targeting interleukin-17 signaling, including the anti-IL17A monoclonal antibodies secukinumab and ixekizumab, are being evaluated for treatment of psoriatic arthritis, psoriasis, and other inflammatory diseases.[19-22] In contrast to anti-IL17A ligand antibodies, brodalumab, a human anti-IL17RA monoclonal antibody, inhibits the activity of interleukin-17A, interleukin-17F, interleukin-17A/F, and interleukin-17E (also called interleukin-25).[23] In a phase 2, placebo-controlled, dose-ranging trial involving patients with moderate-to-severe psoriasis, 77% and 82% of patients in the 140-mg and 210-mg brodalumab groups, respectively, had at least 75% improvement in the score on the psoriasis area-and-severity index (PASI 75) at week 12, as compared with no patients in the placebo group.[24] Complete skin clearance (PASI 100) occurred in 38% and 62% of patients in the respective brodalumab groups at week 12, as compared with no patients in the placebo group.[24] Here we report results from a 12-week, randomized, double-blind, placebo-controlled, phase 2 study of brodalumab in patients with psoriatic arthritis and from the first 40 weeks of the open-label extension of the study.

METHODS

PATIENTS

Patients between the ages of 18 and 75 years who were classified as having active psoriatic arthritis on the basis of the Classification Criteria for Psoriatic Arthritis (CASPAR)[25] with 3 or more tender joints and 3 or more swollen joints were eligible for the study. For 4 weeks or more before the initiation of a study drug, patients were required to receive stable doses of methotrexate (≤25 mg per week), leflunomide (≤20 mg per day), glucocorticoids (≤10 mg per day of prednisone equivalent), or nonsteroidal antiinflammatory drugs (NSAIDs). Anti-TNF and anti–interleukin-12/23 treatments required washout periods of 2 and 3 months, respectively.

Patients who had received rituximab or anti–interleukin-17 therapy were excluded. Other exclusion criteria included recent infection (active infection within 28 days or serious infection within 8 weeks), recurrent infections, major chronic inflammatory or connective-tissue disease, clinically significant systemic disease, or a history of cancer (other than in situ cervical cancer, in situ breast ductal cancer, or successfully treated nonmelanoma skin cancers) within the past 5 years. Negative test results for tuberculosis (or receipt of prophylactic treatment) were required. All patients provided written informed consent.

STUDY DESIGN

The study, which was conducted at 29 sites in the United States and Canada, was a randomized, double-blind, placebo-controlled, 12-week trial, which was followed by an open-label extension trial (up to 5 years). Patients were enrolled from October 17, 2011, to June 22, 2012. Patients were randomly assigned in a 1:1:1 ratio to receive brodalumab at doses of 140 mg or 280 mg or placebo by subcutaneous injection on day 1 and at weeks 1, 2, 4, 6, 8, and 10. Randomization was stratified according to previous biologic therapy (yes vs. no) and total body weight (≤100 kg vs. >100 kg). Randomization lists were generated by Amgen representatives with the use of a permuted-block design within each stratum. At the week 12 visit, patients who had not discontinued their

participation in the study were offered open-label brodalumab at a dose of 280 mg once every 2 weeks for the remainder of the study. Rescue medications for pain or other joint or skin symptoms were not allowed for patients who did not have a response until after week 24. However, NSAIDs could be used to treat flares. This report includes results for the placebo-controlled phase and an interim analysis for the initial 40 weeks of the ongoing open-label extension phase (i.e., week 52 overall).

STUDY OVERSIGHT

The study protocol was approved by the institutional review board or ethics committee at each participating center. The study protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. The study was funded by Amgen. Representatives of Amgen conducted the data analyses. All authors interpreted the data and collaborated in the preparation of the manuscript with support from professional medical writers funded by Amgen. All the authors made the decision to submit the manuscript for publication and vouch for the veracity and completeness of the data and analyses and for the fidelity of the study to the protocol.

EFFICACY AND SAFETY EVALUATIONS

The primary end point was the percentage of patients meeting the criteria for 20% improvement in American College of Rheumatology response criteria (ACR 20)[26] at week 12. Secondary efficacy measures included 50% and 70% improvement (ACR 50 and ACR 70), changes in individual ACR components, Clinical Disease Activity Index (CDAI),[27] Disease Activity Score for 28-joint counts (DAS28),[28] dactylitis (swelling of the whole digit, with assessment of the number of all 20 digits that are affected), and enthesitis (inflammation of tendon and ligament insertions, as assessed by the presence or absence of tenderness at the six sites of the Leeds Enthesitis Index).[29] Individual ACR components were the number of tender or painful joints, the number of swollen joints, the patient's global assessment of disease activity and joint pain, the physician's global assessment of disease activity, responses of the Health Assessment Questionnaire–Disability Index (HAQ-DI), C-reactive protein levels, and the erythrocyte sedimentation rate. Patient-reported outcome measures included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[30] version 2 of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36),[31,32] and the Psoriasis Symptom Inventory.[33,34] (See Table 1 for ranges of each scale.) Prespecified subgroup analyses on the basis of previous biologic therapy were performed for key efficacy end points.

Safety end points included adverse events (coded with the use of version 15.1 of the *Medical Dictionary for Regulatory Activities*),[35] serious adverse events (with severity grading based on the National Cancer Institute Terminology Criteria for Adverse Events [CTCAE], version 4.0[36]), adverse events of interest, laboratory assessments, vital signs, and antibodies to brodalumab.

STATISTICAL ANALYSIS

We determined that a sample size of 156 patients with a 1:1:1 randomization ratio would provide a power of more than 80% at a two-sided significance level of 0.05 (as calculated with the use of the chi-square test), assuming ACR 20 response rates of 50% in the brodalumab 280-mg group and 23% in the placebo group at week 12. Primary analyses were performed after all patients had completed week 12 visits, and interim analyses were performed after all patients had completed week 24 and week 52 visits. The ACR 20 response at week 12 was tested with the use of a stratified Cochran–Mantel–Haenszel test between the brodalumab groups and the placebo group, stratified according to total body weight and previous receipt of biologic therapy. Hypothesis testing followed a sequential testing procedure (brodalumab 280 mg vs. placebo, brodalumab 140 mg vs. placebo, and brodalumab 280 mg vs. brodalumab 140 mg) to preserve the two-sided family-wise type I error rate of 0.05.

In the analyses of secondary and exploratory end points, we used an analysis of covariance model with stratification variables and baseline values as covariates for continuous end points, the Quade test (rank analysis of covariance) for continuous end points that were not normally distributed, and the stratified Cochran–Mantel–Haenszel test for categorical end points. All P values in the nonprimary analyses were nominal and were not adjusted for multiple testing.

Missing data were imputed as no response for dichotomous end points and as last-observation-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

	Placebo (N=55)	Brodalumab		
		140 mg (N=57)	280 mg (N=56)	Combined Doses (N=113)
Female sex — no. (%)	30 (55)	37 (65)	40 (71)	77 (68)
White race — no. (%)†	51 (93)	54 (95)	52 (93)	106 (94)
Age — yr	53±13	53±10	51±12	52±11
Weight — kg	90±20	91±22	91±22	91±22
Body-mass index‡	31±6	33±7	33±8	33±7
Duration of psoriatic arthritis — yr	8.4±7.5	9.4±7.5	8.1±7.9	8.8±7.7
Use of methotrexate				
At the time of study entry — no. (%)	23 (42)	31 (54)	30 (54)	61 (54)
Weekly dose — mg	17.2±6.2	18.7±6.2	18.2±5.0	18.4±5.6
Use of biologic therapy — no. (%)§	25 (45)	30 (53)	31 (55)	61 (54)
Use of glucocorticoid — no. (%)	15 (27)	8 (14)	8 (14)	16 (14)
DAS28 score¶	5.5±1.1	5.7±1.2	5.5±1.2	5.6±1.2
CDAI score‖	31.3±11.3	34.0±13.1	30.0±12.7	32.0±13.0
HAQ-DI score**	1.3±0.6	1.2±0.7	1.4±0.6	1.3±0.6
BASDAI score††	6.2±1.8	5.9±2.1	6.2±1.8	6.1±1.9
Tender-joint count‡‡	25.0±16.2	27.0±16.4	20.8±15.3	24.0±16.1
Swollen-joint count§§	12.8±8.5	13.6±10.5	11.4±9.3	12.5±9.9
Enthesitis score >0 — no. (%)¶¶	45 (82)	41 (72)	32 (57)	73 (65)
Dactylitis score >0 — no. (%)‖‖	37 (67)	40 (70)	27 (48)	67 (59)
Median serum erythrocyte sedimentation rate (IQR) — mm/hr	20 (11–36)	26 (11–41)	26 (15–38)	26 (13–39)
Median serum C-reactive protein (IQR) — mg/liter	3.8 (1.4–10.1)	5.2 (1.6–9.5)	5.1 (2.9–13.4)	5.1 (2.3–10.2)

* Plus–minus values are means ±SD. There were no significant between-group differences except for enthesitis (P=0.01) and dactylitis (P=0.03). IQR denotes interquartile range.
† Race was self-reported. Hispanic or Latino patients were categorized as white, with proportions of 4% in the brodalumab 140-mg group, 5% in the brodalumab 280-mg group, and 9% in the placebo group.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Reasons for the discontinuation of previous biologic therapy were primary failure (in 45 patients), secondary failure (in 6), unacceptable side effects (in 8), and other reasons (in 27).
¶ The Disease Activity Score for 28-joint counts (DAS28) ranges from 2 to 10, with higher scores indicating more severe disease activity.
‖ Scores on the Clinical Disease Activity Index (CDAI) range from 0 to 76, with higher scores indicating more severe disease activity.
** Scores on the Health Assessment Questionnaire–Disability Index (HAQ-DI) range from 0 to 3, with higher scores indicating greater disability.
†† Scores on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) range from 0 to 10, with higher scores indicating more severe disease activity.
‡‡ The tender-joint count is the number of tender joints out of 68 joints assessed.
§§ The swollen-joint count is the number of swollen joints out of 66 joints assessed.
¶¶ The enthesitis score ranges from 0 to 6, with higher scores indicating more severe disease activity.
‖‖ The dactylitis score ranges from 0 to 20 digits (fingers and toes) as present or absent for each digit.

carried-forward for continuous measurements. Efficacy end points were analyzed according to the patients' assigned study group (full-analysis set). For the open-label extension, efficacy assessments were summarized as observed. The safety-analysis set included all patients who underwent randomization and received at least one dose of a study drug.

RESULTS

PATIENTS

Of 199 patients who were screened, 168 were enrolled in the study, with 57 assigned to receive 140 mg of brodalumab, 56 to receive 280 mg of brodalumab, and 55 to receive placebo. Of these patients, 159 completed the double-blind phase; 156 patients entered the open-label extension phase, and 22 patients discontinued their participation in the study by week 52. (Fig. S1 in the Supplementary Appendix, available at NEJM.org, includes reasons for discontinuation.)

Across treatment groups, the mean age was 52 years, 64% of patients were women, 94% were white (including Hispanic or Latino patients), and the mean duration of psoriatic arthritis was 9 years. Previous receipt of biologic therapies was reported by 51% of patients. Although baseline disease characteristics were balanced among the study groups, some imbalances in the combined brodalumab groups versus placebo at baseline were noted (Table 1, and Table S1 in the Supplementary Appendix). There was no evidence that these imbalances had an effect on the interpretation of treatment responses.

EFFICACY

The primary outcome, ACR 20 at week 12, occurred in 21 patients (37%) receiving 140 mg of brodalumab ($P=0.03$), in 22 patients (39%) receiving 280 mg of brodalumab ($P=0.02$), and in 10 patients (18%) receiving placebo (Table 2). At week 24, rates of ACR 20 response in the brodalumab 140-mg group and 280-mg group were 51% and 64%, respectively, as compared with 44% in patients who switched from placebo to brodalumab 280 mg during the extension phase (Fig. 1A). ACR 50 and ACR 70 response rates also continued to improve during the open-label extension and were sustained through week 52 for the brodalumab 140-mg group (Fig. 1B and 1C). ACR 70 response rates were not significantly different among treatment groups.

Scores for disease activity (CDAI and DAS28) showed significant improvement for patients receiving either dose of brodalumab, as compared with placebo, at week 12 (Table 2). For the CDAI, least-squares mean changes from baseline, as compared with placebo, were −6.6 for the 140-mg group ($P=0.001$) and −7.3 for the 280-mg group ($P<0.001$); for the DAS28, least-squares mean changes from baseline, as compared with placebo, were −0.7 ($P=0.002$) for both brodalumab groups. Least-squares mean DAS28 scores at week 12 were 4.5 in the two brodalumab groups and 5.2 in the placebo group. Among patients who had baseline scores of more than 0 for either dactylitis or enthesitis, there were no significant differences at week 12 between the group receiving 140 mg of brodalumab or the group receiving 280 mg of brodalumab, as compared with the placebo group, in improvement in dactylitis (−1.4 [$P=0.28$] and −2.0 [$P=0.11$] vs. −0.5) or in enthesitis (−0.7 [$P=0.84$] and −1.2 [$P=0.18$] vs. −0.6) (Table 2, and Table S2 in the Supplementary Appendix).

At week 12, individual ACR components, including tender-joint counts, swollen-joint counts, and patient's and physician's global assessments of disease activity, showed significant improvements in the brodalumab groups, as compared with the placebo group (Table S3 in the Supplementary Appendix). There were no significant differences in changes in the patient's global assessment of joint pain, the HAQ-DI, and the erythrocyte sedimentation rate (Table S3 in the Supplementary Appendix). Significant changes in C-reactive protein, as compared with placebo, were observed in the brodalumab 280-mg group but not in the brodalumab 140-mg group.

At week 12, significant improvements were observed in the physician's assessments of disease and patient-reported outcomes, as compared with placebo, including the Psoriasis Symptom Inventory (in both brodalumab groups), and in the BASDAI and SF-36 physical component scores (in the brodalumab 280-mg group) (Table 2). Approximately 94% of patients who had the ACR 20 response and 50% of those without such a response were classified as having a response on the Psoriasis Symptom Inventory (total score ≤8, with no item score of >1). There were no significant differences in changes in the SF-36 mental component score in the brodalumab groups, as compared with the placebo group (Table 2).

Clinical responses to brodalumab were similar among patients who had received previous biologic therapy and those who had not received such therapy. For patients without previous biologic therapy, ACR 20 response rates were 37% and 36% in the 140-mg and 280-mg brodalumab groups, respectively, versus 20% in the placebo group, as compared with 37% and 42% versus 16%, respectively, for patients who had received previous biologic therapy (Fig. S2 in the Supplementary Appendix). ACR 50 and ACR 70 re-

sponses were also observed in patients in the two brodalumab groups who had received previous biologic therapy (Fig. S2 in the Supplementary Appendix).

ACR response rates continued to improve during the open-label extension (Fig. 1). Additional improvements were observed among patients who had previously received 140 mg of brodalumab, and significant clinical responses were observed among patients who switched from placebo to brodalumab (Table S2 in the Supplementary Appendix). Secondary end points showed further improvement during the open-label extension portion of the trial, especially among patients from the original placebo group (Tables S2, S4, and S5 in the Supplementary Appendix).

SAFETY

During the double-blind phase, adverse events were reported in 62% of patients in the brodalumab 140-mg group, 71% of those in the brodalumab 280-mg group, and 65% of those in the placebo group (Table 3). The adverse events most commonly reported in the combined brodalumab groups were upper respiratory tract infection (12%, vs. 7% for placebo),

Table 2. Clinical Response at 12 Weeks.*

	Placebo (N=55)	Brodalumab	
		140 mg (N=57)	280 mg (N=56)
ACR 20†			
Response — no. (%)	10 (18)	21 (37)	22 (39)
Difference from placebo (95% CI) — %	NA	18.7 (2.5 to 34.8)‡	21.1 (4.7 to 37.5)‡
ACR 50†			
Response — no. (%)	2 (4)	8 (14)	8 (14)
Difference from placebo (95% CI) — %	NA	10.4 (0.1 to 20.7)	10.6 (0.2 to 21.1)‡
ACR 70†			
Response — no. (%)	0	3 (5)	3 (5)
Difference from placebo (95% CI) — %	NA	5.3 (–0.5 to 11.1)	5.4 (–0.5 to 11.3)
Clinical Disease Activity Index			
Change from baseline	–4.0	–10.6	–11.3
Difference from placebo (95% CI)	NA	–6.6 (–10.6 to –2.6)§	–7.3 (–11.3 to –3.2)¶
Disease Activity Score for 28-joint counts			
Change from baseline	–0.4	–1.1	–1.1
Difference from placebo (95% CI)	NA	–0.7 (–1.2 to –0.3)§	–0.7 (–1.2 to –0.3)§
Good response‖			
Patients — no. (%)	5 (9)	11 (20)	11 (20)
Difference from placebo (95% CI)	NA	10.6 (–2.6 to 23.7)	10.6 (–2.6 to 23.7)
Dactylitis**			
Change from baseline	–0.5	–1.4	–2.0
Difference from placebo (95% CI)	NA	–0.9 (–2.5 to 0.7)	–1.5 (–3.3 to 0.4)
Enthesitis**			
Change from baseline	–0.6	–0.7	–1.2
Difference from placebo (95% CI)	NA	–0.1 (–0.9 to 0.7)	–0.6 (–1.4 to 0.3)
Bath Ankylosing Spondylitis Disease Activity Index			
Change from baseline	–0.2	–0.8	–1.1
Difference from placebo (95% CI)	NA	–0.6 (–1.2 to 0.01)	–0.9 (–1.5 to –0.3)§

Table 2. (Continued.)

	Placebo (N=55)	Brodalumab	
		140 mg (N=57)	280 mg (N=56)
SF-36††			
Physical component			
Change from baseline	0.7	2.0	3.0
Difference from placebo (95% CI)	NA	1.4 (–0.8 to 3.6)	2.4 (0.1 to 4.6)‡
Mental component			
Change from baseline	–0.04	0.80	0.60
Difference from placebo (95% CI)	NA	0.8 (–1.6 to 3.3)	0.6 (–1.8 to 3.1)
Psoriasis Symptom Inventory‡‡			
Change from baseline	–1.3	–8.5	–10.9
Difference from placebo (95% CI)	NA	–7.2 (–10.1 to –4.3)¶	–9.6 (–12.4 to –6.7)¶

* Data are least-squares means unless otherwise indicated. NA denotes not applicable because the placebo group is the comparator.

† American College of Rheumatology (ACR) 20, ACR 50, and ACR 70 are defined as a reduction of at least 20%, 50%, and 70%, respectively, from baseline in the number of tender and swollen joints and in at least three of the five remaining ACR core set measures: patient's assessment of pain, level of disability, acute-phase reactant (C-reactive protein or erythrocyte sedimentation rate), patient's global assessment of disease, and physician's global assessment of disease. Missing data for ACR 20, ACR 50, and ACR 70 were imputed as no response.

‡ P<0.05 for the comparison with placebo.

§ P<0.01 for the comparison with placebo.

¶ P<0.001 for the comparison with placebo.

‖ A good response is defined as an improvement of more than 1.2 points in the DAS28 measurement based on the erythrocyte sedimentation rate (DAS28-ESR) and a current DAS28-ESR of 3.2 or less. Included in this analysis were 55 patients in the brodalumab 140-mg group, 55 patients in the brodalumab 280-mg group, and 53 patients in the placebo group.

** This category was measured only in patients with a baseline score of more than 0. Included in this analysis were 40 patients in the brodalumab 140-mg group, 27 in the brodalumab 280-mg group, and 37 in the placebo group in the dactylitis analysis and 40, 31, and 45 patients, respectively, in the enthesitis analysis.

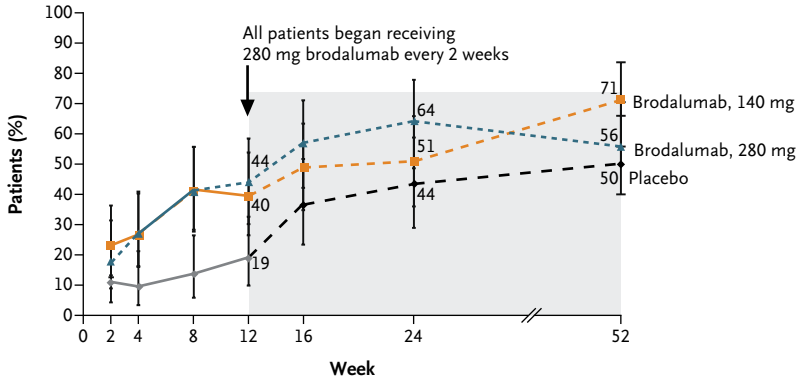
†† Version 2 of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) measures general health status and includes physical and mental component scores. The scores range from 0 to 100, with higher scores indicating better well-being.

‡‡ The Psoriasis Symptom Inventory consists of eight patient-reported outcomes assessing the severity of psoriasis symptoms. Scores range from 0 to 4; the total score ranges from 0 to 32, with higher scores indicating worse psoriasis symptoms. This assessment was performed only in patients with a baseline involvement of 3% or more of body-surface area, including 31 patients in the brodalumab 140-mg group, 36 in the brodalumab 280-mg group, and 38 in the placebo group.

fatigue (7% vs. 4%), diarrhea (6% vs. 4%), and headache (6% vs. 7%). A study drug was discontinued because of an adverse event in two patients (4%) in each of the three groups. There were no adverse events of neutropenia, but there were five laboratory reports of grade 1 neutropenia (one in the 140-mg group, three in the 280-mg group, and one in the placebo group). Serious adverse events were reported in four patients: one in the brodalumab 140-mg group (abdominal pain), two in the brodalumab 280-mg group (cholecystitis and cellulitis on the upper left chest), and one in the placebo group (cellulitis overlying the left knee). There were eight CTCAE grade 3 events overall and no grade 4 or 5 events.

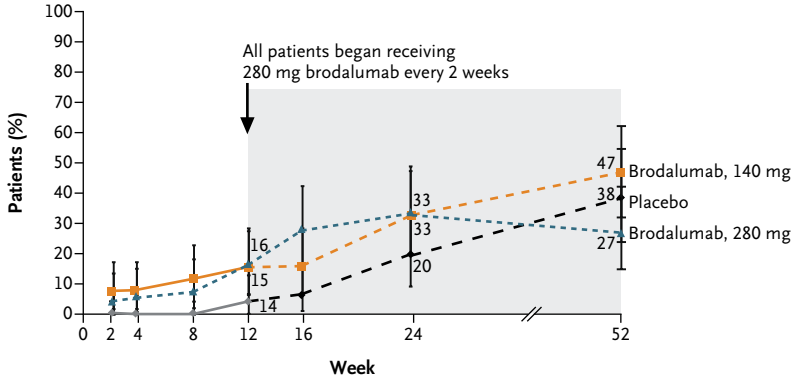
During the open-label extension phase (through week 52), patients were eligible to receive 280 mg of brodalumab once every 2 weeks. Adverse events occurred in 89% of patients in the original brodalumab 140-mg group, in 96% of patients in the original brodalumab 280-mg group, and in 89% of patients in the original placebo group (Table S6 in the Supplementary Appendix). Adverse events that were most commonly reported were nasopharyngitis, upper respiratory tract infection, psoriatic arthropathy (flare in underlying psoriatic

A ACR 20



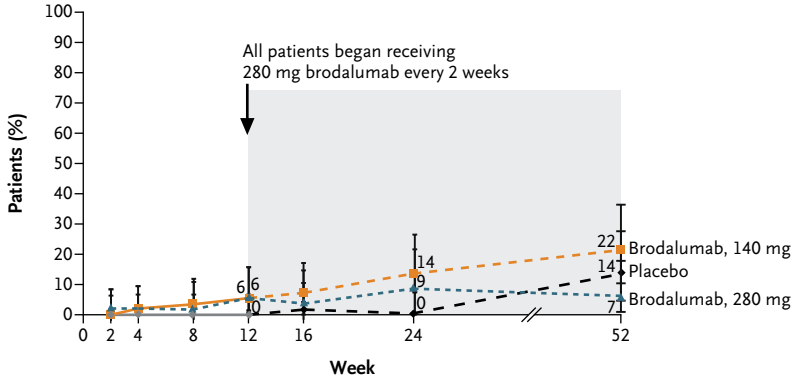
No. of Patients							
Placebo	54	52	51	52	49	46	42
Brodalumab, 140 mg	56	56	51	53	51	47	45
Brodalumab, 280 mg	50	55	53	50	49	45	45

B ACR 50



No. of Patients							
Placebo	54	53	51	52	50	46	42
Brodalumab, 140 mg	56	56	53	53	51	49	45
Brodalumab, 280 mg	50	55	53	51	50	45	45

C ACR 70



No. of Patients							
Placebo	54	53	52	53	50	47	43
Brodalumab, 140 mg	56	56	53	53	52	49	46
Brodalumab, 280 mg	50	55	53	51	50	45	45

Figure 1 (facing page). American College of Rheumatology (ACR) Response Rates during the Randomized 12-Week Trial and Subsequent Open-Label Extension Trial.

Shown are response rates for ACR 20 (Panel A), ACR 50 (Panel B), and ACR 70 (Panel C), which are defined as a reduction of at least 20%, 50%, and 70%, respectively, from baseline in the number of tender and swollen joints and in at least three of the five remaining ACR core set measures: patient's assessment of pain, level of disability, acute-phase reactant (C-reactive protein or erythrocyte sedimentation rate), patient's global assessment of disease, and physician's global assessment of disease. In the 12-week randomized trial, patients were assigned to receive brodalumab at doses of 140 or 280 mg or placebo on day 1 and at weeks 1, 2, 4, 6, 8, and 10. At the week 12 visit, patients who had not discontinued their participation in the study were offered open-label brodalumab at a dose of 280 mg once every 2 weeks for the remainder of the study (as indicated by shading). The I bars indicate standard errors.

arthritis or worsening of disease), arthralgia, bronchitis, nausea, oropharyngeal pain, and sinusitis. There were no adverse events of neutropenia, but there were eight laboratory reports (six reports of grade 1 neutropenia [three in the original brodalumab 140-mg group, one in the original brodalumab 280-mg group, and two in the original placebo group] and two reports of grade 2 neutropenia [one each in the original brodalumab 140-mg group and original placebo group]). Serious adverse events were reported in 10 patients: one case each of worsening of coronary artery disease, acute myocardial infarction (with coronary artery disease and thrombosis associated with a cardiac stent that was placed for treatment of acute myocardial infarction), invasive ductal breast carcinoma, and lower gastrointestinal hemorrhage in the original brodalumab 140-mg group; pyelonephritis, metastatic lung cancer, melanoma, septic arthritis from streptococcus, and aortic stenosis in the original brodalumab 280-mg group; and one case of cholelithiasis in the original placebo group. There were no deaths. Anti-brodalumab antibodies (non-neutralizing) were reported in 1 patient in the brodalumab 280-mg group at baseline and in 1 patient in the original placebo group during the extension trial at weeks 16 and 24.

DISCUSSION

This phase 2 study showed the efficacy of brodalumab blockade of IL17RA in patients with active psoriatic arthritis. There is accumulating evidence that interleukin-17 is central to the pathogenesis of psoriatic arthritis and other spondyloarthritides, such as ankylosing spondylitis. Inhibition of interleukin-17 signaling by brodalumab also induced significant clinical responses in patients with psoriasis.[23,24] By contrast, efficacy has not been observed for brodalumab in clinical trials involving patients with rheumatoid arthritis or Crohn's disease.[37,38] Differential responses in patients with rheumatoid arthritis versus those with psoriatic arthritis provide further evidence that these diseases have different causal mechanisms. The observed clinical response to brodalumab among patients with psoriatic arthritis in our study supports the concept that interleukin-17 pathways are critical in the pathogenesis of psoriatic skin and joint disease.

Significant improvements were observed at week 12 in the brodalumab groups, as compared with the placebo group, for most, but not all, efficacy outcomes that were measured, with significant improvement in the ACR 20 observed as early as week 4. Although the study was not adequately powered to formally differentiate between the two brodalumab doses, numeric trends favoring the brodalumab 280-mg group were observed for several outcomes at week 12.

During the first 40 weeks of the open-label extension, outcomes continued to improve except among patients in the original brodalumab 280-mg group, in whom responses were sustained or slightly declined between weeks 24 and 52. Although data from open-label trials need to be interpreted with caution, continued improvements beyond the primary end point suggest that a full clinical response among patients with psoriatic arthritis requires longer than 12 weeks, a hypothesis that must be evaluated in longer-term controlled studies.

The clinical response of psoriatic skin disease to brodalumab has been established in previous studies among patients with psoriasis, including approximately 20% who also had psoriatic arthritis.[24] Thus, skin assessments such as PASI and static physician's global assessment of psoriasis were not performed, since our study focused on musculoskeletal aspects of psoriatic arthritis. Instead, we used a validated patient-reported outcome measure, the Psoriasis Symptom Inventory, to assess skin. Larger phase 3 studies will better characterize relationships between skin and joint responses.

Table 3. Adverse Events at 12 Weeks.

Adverse Event	Placebo (N=55)	Brodalumab		
		140 mg (N=56)	280 mg (N=56)	Combined Doses (N=112)
	number of patients (percent)			
Any	36 (65)	35 (62)	40 (71)	75 (67)
Serious adverse event*	1 (2)	1 (2)	2 (4)	3 (3)
Death	0	0	0	0
Leading to study discontinuation	2 (4)	2 (4)	2 (4)	4 (4)
Leading to drug discontinuation	2 (4)	2 (4)	2 (4)	4 (4)
Grade 3†	1 (2)	3 (5)	4 (7)	7 (6)
Common adverse events‡				
Upper respiratory tract infection	4 (7)	5 (9)	8 (14)	13 (12)
Diarrhea	2 (4)	2 (4)	5 (9)	7 (6)
Nausea	2 (4)	4 (7)	1 (2)	5 (4)
Arthralgia	1 (2)	3 (5)	1 (2)	4 (4)
Psoriatic arthropathy	3 (5)	4 (7)	0	4 (4)
Fatigue	2 (4)	5 (9)	3 (5)	8 (7)
Injection-site erythema	3 (5)	2 (4)	1 (2)	3 (3)
Headache	4 (7)	2 (4)	5 (9)	7 (6)
Dizziness	0	3 (5)	1 (2)	4 (4)
Nasopharyngitis	3 (5)	0	0	0

* A serious adverse event was defined as an event that was fatal or life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, caused persistent or substantial disability or incapacity, caused congenital anomaly or birth defect, or was considered by the investigator to be medically important.
† The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. There were no grade 4 or 5 adverse events.
‡ Common adverse events were reported in at least 5% of patients in any study group.

In a subgroup analysis, similar improvements were found in ACR responses among patients who had received previous biologic therapy and those who had not received such therapy. Approximately 90% of patients who had received previous biologic therapies were treated with anti-TNF therapies.

Adverse events occurred with similar frequencies in the brodalumab and placebo groups, consistent with safety profiles observed for brodalumab in other patient populations.[23,24] Two patients tested positive for non-neutralizing anti-brodalumab antibodies. No significant neutropenic events were reported — an important safety outcome, since interleukin-17 is involved in neutrophil homeostasis.[39] Neutropenia and leukopenia have been noted in previous studies of anti–interleukin-17 treatments with a size and duration similar to those in our study.[21,24] No opportunistic infections (e.g., tuberculosis, fungal infection, or herpes zoster) were observed in either brodalumab group. No deaths occurred. The small size of the study population and short treatment duration limited our ability to detect infrequent adverse events, so larger studies are required to better characterize the safety profile.

In conclusion, our findings show that IL17RA is a potential target for the treatment of psoriatic arthritis, with the inhibition of downstream pathways associated with improvements in arthritis, psoriasis, and physical function in patients who had received previous biologic therapies and in those who had not received such therapies.

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