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A Study to Evaluate the Safety, Tolerability, and Efficacy of Brodalumab in Subjects with Rheumatoid Arthritis and an Inadequate Response to Methotrexate

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of brodalumab, a human monoclonal antibody inhibitor of the interleukin 17 receptor, in subjects with rheumatoid arthritis (RA).

Methods. Patients (n = 252) with inadequate response to methotrexate (MTX) were randomized to receive subcutaneous injections of brodalumab (70 mg, 140 mg, or 210 mg) or placebo. The primary endpoint was the American College of Rheumatology 50% response (ACR50) at Week 12.

Results. Demographics and baseline characteristics were generally balanced among treatment groups. At Week 12, ACR50 occurred in 16% (70 mg), 16% (140 mg), 10% (210 mg), and 13% (placebo; all nonsignificant vs placebo) of subjects. No significant treatment effects were observed for the secondary endpoints, including ACR20, ACR70, and Disease Activity Score in 28 joints. Incidences of all adverse events (AE), including serious AE (SAE), were similar across treatment groups. A total of 7 subjects reported SAE during the study (2 in the placebo group and 5 in the brodalumab groups), none of which was treatment related. There was 1 death (cardiopulmonary failure) ~1 week after the last dose in the 140 mg group.

Conclusion. Our study failed to find evidence of meaningful clinical efficacy with brodalumab treatment in subjects with RA who had an inadequate response to MTX. These preliminary results do not support further evaluation of brodalumab as a treatment for RA. Clinicaltrials.gov number: NCT00950989. (First Release April 15 2015; J Rheumatol 2015;42:912–19; doi:10.3899/jrheum.141271)

Key Indexing Terms:
INTERLEUKIN 17 RANDOMIZED CONTROLLED TRIAL PHASE 2
RHEUMATOID ARTHRITIS BRODALUMAB

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease characterized by synovitis leading to cartilage and joint damage. Treatment with disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX), which can slow the progression of joint damage that leads to loss of function[1,2], may control established disease. More recently introduced targeted therapies, including biologics targeting tumor necrosis factor (TNF)-α and other immunologic pathways, are used in combination with MTX or as monotherapy in the treatment of RA[3,4,5,6]. The introduction of these biologics with structure-modifying effects has greatly increased the potential to suppress disease activity and inhibit joint destruction[7,8,9].

Although the efficacy of current treatments has been established, they often only partly control established disease. It is estimated that 30% to 40% of patients fail to respond to TNF-α antagonists[10,11,12] and the majority of those who initially respond do not achieve complete remission or lose response over time[13]. Thus, there remains an unmet need for the development of drugs that target new mechanisms of action in the treatment of RA.

Preclinical and early clinical studies have suggested that Th17 cells, a subset of helper T cells that preferentially produce interleukin 17 (IL-17), may play a role in orchestrating inflammation in RA[14,15]. Among the IL-17 cytokine family, which consists of 6 cytokines (IL-17A to 17F) and 5 receptors (IL-17 receptor types A to E), IL-17A signaling has emerged as a potential factor in the pathogenesis of RA. IL-17A can directly stimulate synoviocytes production of inflammatory mediators, including IL-6, granulocyte-macrophage colony-stimulating factor, and prostaglandin E2[16]. Increased levels of IL-17A have been detected in the synovial fluid (SF) of patients with RA[17,18,19]. Blockade of IL-17A signaling can inhibit osteoclast formation induced by culture

From the Institute of Rheumatology, Prague, Czech Republic; and Amgen Inc., Thousand Oaks, California, USA.

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K. Pavelka, MD, PhD, Institute of Rheumatology; Y. Chon, PhD; R. Newmark, PhD, Amgen Inc.; S.L. Lin, MD, PhD; S. Baumgartner, MD, formerly employed by Amgen Inc.; N. Erondu, MD, PhD, Amgen Inc.

Address correspondence to Dr. N. Erondu, 1 Amgen Center Drive, Thousand Oaks, California 91320, USA. E-mail: nerondu@amgen.com

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media of RA synovial tissues. In an *ex vivo* model using explanted synovial tissue from human patients with RA, blockade of IL-17A can reduce the spontaneous production of IL-6 and collagen breakdown products (C-telopeptide of type I collagen)[20]. In a prospective study, synovial membrane mRNA levels of IL-17A were predictive of damage progression, and the effects of IL-17A were shown to be synergistic with TNF[21]. In addition, clinical studies with anti-IL-17A antibodies have demonstrated some efficacy in patients with RA[22,23]. The IL-17A, 17F, and 17A/F heterodimer ligands share a common receptor subunit [IL-17 receptor type A] for signaling; thus, cytokine-targeted strategies aimed at blocking IL-17 receptor type A signaling may be beneficial in the treatment of RA. Preclinical studies have shown effectiveness of IL-17 receptor type A blockade in murine models of inflammatory arthritis[24].

Brodalumab is a human, anti–IL-17 receptor type A monoclonal antibody that binds with high affinity to the receptor, blocking the biologic activity of multiple IL-17 cytokines, including 17A, 17F, and 17A/F heterodimer. Brodalumab binds to IL-17 receptor type A with a dissociation equilibrium binding constant in the picomolar range and does not bind to other IL-17 receptor family members. Doses ranging from 140 mg to 280 mg every 2 weeks (Q2W) result in serum levels sufficient to inhibit over 90% of IL-17 and IL-25 receptor activity[25]. Pharmacokinetic modeling showing correlations with clinical activity in subjects with psoriasis[25] suggest that a 140-mg subcutaneous dose would be submaximally efficacious, and 210 mg and 280 mg subcutaneous doses would be expected to be near or at maximal efficacy when dosed every 2 weeks[26]. The primary objective of our study was to evaluate the short-term efficacy and safety of several brodalumab doses in subjects with RA.

MATERIALS AND METHODS

Patients. Patients aged 18 years to 70 years were eligible for the study if they had a diagnosis of RA [1987 American College of Rheumatology (ACR) classification criteria][27] for at least 6 months and active disease despite treatment with MTX for ≥ 12 weeks, and were naive to treatment with a biological DMARD. Active RA was defined as ≥ 6 swollen joints (out of 66 joints examined), ≥ 8 tender/painful joints (out of 68 joints examined), and either Westergren erythrocyte sedimentation rate (ESR) ≥ 28 mm or C-reactive protein (CRP) > 15 mg/l. Patients were required to have been receiving a stable dosage of MTX (15 mg/week to 25 mg/week) for at least 4 weeks prior to study enrollment. In addition, patients had to be positive at screening for either rheumatoid factor or anticyclic citrullinated peptide antibody. Patients were required to have negative test results for hepatitis B virus surface antigen, hepatitis C virus antibody, the human immunodeficiency virus, and tuberculosis (according to local guidelines: purified protein derivative tuberculin skin test + radiograph, history, or/and quantiferon test), and could not be pregnant or nursing. Treatment with stable doses of nonsteroidal antiinflammatory drugs or corticosteroids was allowed if patients were taking stable doses for at least 4 weeks prior to screening. Corticosteroid doses were not to exceed the equivalent of 10 mg of prednisone per day.

Patients were excluded if they had active infection based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (AE) grade 2 or higher within 30 days prior to or during screening, or if they had a serious infection requiring hospitalization or intravenous antibiotics within 8 weeks prior to screening, or if they had recurrent or chronic infections.

Study design. We conducted a randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of brodalumab in patients with RA. Subjects were enrolled at 64 sites in 9 countries (Bulgaria, Canada, Czech Republic, Latvia, Hungary, Mexico, Poland, United Kingdom, and United States), and were randomized 1:1:1:1 to receive brodalumab (70 mg, 140 mg, or 210 mg) or placebo subcutaneously at Day 1 and weeks 1, 2, 4, 6, 8, and 10 (Q2W). The study protocol was approved by the institutional review board or ethics committee at each participating site. The first subject was enrolled on December 30, 2009, and the last subject completed followup on February 11, 2011.

Efficacy and safety evaluations. The primary endpoint was the proportion of subjects achieving ACR response criteria[28] for 50% improvement (ACR50) at Week 12 compared with baseline. Secondary efficacy endpoints included the proportion of subjects with an ACR20 and 70 at Week 12 and Disease Activity Score at 28 joints (DAS28)[29] response at Week 12. Changes in CRP were assessed as an exploratory analysis. Other exploratory endpoints included the Medical Outcomes Study Short Form-36, the Medical Outcomes Study Sleep Scale, the Health Assessment Questionnaire–Disability Index, and patient global rating of change.

Safety was assessed by monitoring AE, serious AE, and routine hematologic and laboratory values. The NCI Common Terminology Criteria for AE, version 4.0, was used to grade the severity of AE.

Statistical analysis. Assuming ACR50 response rates at Week 12 of 10% and 40% (nonresponder analysis) for placebo and 210-mg brodalumab groups, respectively, a sample size of 60 patients per arm with a 1:1:1:1 randomization ratio was estimated to provide > 90% power at a 5% 2-sided significance level (chi-square test). The same sample size was also estimated to be sufficient to detect the efficacy for the secondary endpoint ACR20 with 90% power with response rates of 30% and 60% for placebo and highest dose brodalumab, respectively. Analyses of demographic and baseline characteristics and efficacy endpoints were performed on data from all subjects who were randomized, based on the intent-to-treat principle. Analyses of safety endpoints were performed on all subjects who were randomized and who received at least 1 dose of study drug. The primary endpoint (ACR50 at Week 12) and key secondary endpoints (ACR20 and 70 at Week 12) were analyzed by means of ANOVA or ANCOVA with the use of a Cochran-Mantel-Haenszel test, adjusting for sex. All the primary and secondary efficacy endpoints, except for DAS28, were tested sequentially in a prespecified order to control the overall family-wise type 1 error rate at 0.05 (2-sided). DAS28 was tested using a closed testing procedure with type 1 error rate of 0.025 (1-sided). Safety endpoints were summarized descriptively. Missing data were handled by means of the imputation of no response, except for change in DAS28, which was assessed by last observation carried forward (LOCF), and change in CRP, which was an observed analysis with no imputation for missing data.

RESULTS

Demographics and baseline characteristics. Of the 460 patients screened, 252 subjects were enrolled (189 to brodalumab and 63 to placebo), and 242 subjects [183 brodalumab (96.8%), 59 placebo (93.7%)] completed the study through Week 16 (Figure 1). Demographics and baseline characteristics were generally balanced among treatment groups (Table 1). The majority (> 75%) of subjects were female and white. The mean age for each treatment group ranged from 51 years (placebo) to 55 years (140 mg; Table 1). In subjects treated with placebo and brodalumab, respectively, the mean duration of RA was 8.1 years and 7.5

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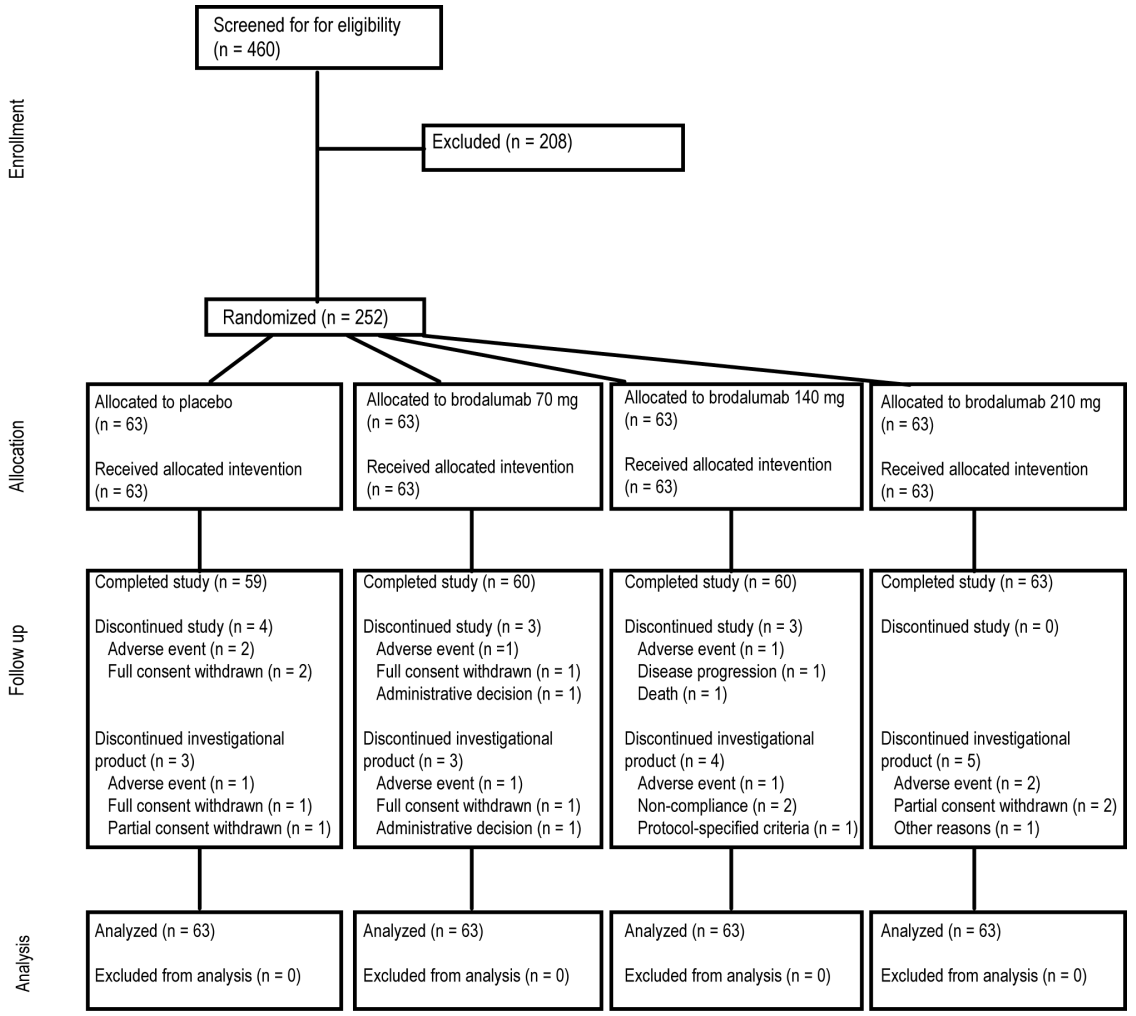

Figure 1. Patient disposition.

years, mean DAS28 was 6.5 and 6.4, mean (SD) CRP was 13 (12) mg/l and 15 (18) mg/l, and mean (SD) ESR was 48 (20) mm/h and 45 (20) mm/h.

Efficacy. At Week 12, ACR50 response criteria were met in 16% (70 mg), 16% (140 mg), 10% (210 mg), and 13% (placebo) of subjects; all nonsignificant versus placebo (Figure 2, Table 2). There were no significant differences in ACR50 responses at any timepoint among all treatment groups (Figure 2). Differences in ACR20 and 70 were also nonsignificant ($p > 0.05$) for any treatment group as compared with placebo (Table 2). Results from analyses of ACR20, 50, and 70 based on LOCF and observed data were consistent with the primary analysis using nonresponder imputation (data not shown). No differences in efficacy outcomes were observed for subgroup analyses based on sex, age, weight, or region (data not shown).

Mean (SD) change from baseline in DAS28 at Week 12 was –1.4 (1.3) for 70 mg, –1.3 (1.2) for 140 mg, –1.3 (1.2) for 210 mg, and –1.3 (1.2) for placebo (all nonsignificant vs placebo; Table 2). At Week 12, the mean (SD) percent change from baseline in CRP was 98 (345) for 70 mg, 51 (169) for 140 mg, 45 (159) for 210 mg, and 34 (170) for placebo (Table 3). There were no significant differences among treatment groups in other secondary and exploratory endpoints (data not shown).

Safety. During the study, 51% of the subjects in the 70-mg brodalumab, 210-mg brodalumab, and placebo groups and 63% of subjects in the 140-mg brodalumab group had at least 1 AE (Table 4). The most commonly reported AE (≥ 5% in brodalumab groups or placebo) were upper respiratory tract infection (6.3% brodalumab, 1.6% placebo), RA (5.8% brodalumab, 9.5% placebo), nasopharyngitis (5.8% brodalumab, 3.2% placebo), urinary tract infection (5.8% brodalumab, 1.6% placebo), injection site pain (3.2% brodalumab, 6.3% placebo), cough (2.6% brodalumab, 6.3% placebo), headache (3.7% brodalumab, 6.3% placebo), and hypertension (3.7% brodalumab, 6.3% placebo). Investigational product was discontinued in 5 subjects: 1 subject

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Table 1. Demographics and baseline characteristics. Values are mean (SD) unless otherwise specified.

Characteristic	Placebo, n = 63	Brodalumab		
		70 mg, n = 63	140 mg, n = 63	210 mg, n = 63
Male, n (%)	12 (19)	13 (21)	14 (22)	13 (21)
Race, n (%)				
White	48 (76)	53 (84)	50 (79)	56 (89)
African American	1 (2)	1 (2)	1 (2)	0 (0)
Hispanic or Latino	14 (22)	8 (13)	12 (19)	6 (10)
Asian	0 (0)	1 (2)	0 (0)	1 (2)
Age, yrs	51 (12)	53 (11)	55 (10)	52 (10)
Weight, kg	73 (15)	74 (15)	77 (17)	74 (17)
Height, cm	164 (8)	164 (8)	163 (10)	164 (9)
BMI, kg/m^2	27 (5)	27 (5)	29 (6)	28 (6)
RF, n (%)				
No	0 (0)	0 (0)	0 (0)	0 (0)
Yes	63 (100)	62 (98)	63 (100)	62 (98)
Unknown	0 (0)	1 (2)	0 (0)	1 (2)
Anti-CCP, n (%)				
Negative	8 (13)	6 (7)	8 (13)	8 (13)
Positive	55 (87)	58 (89)	55 (87)	55 (87)
Unknown	0 (0)	1 (2)	0 (0)	0 (0)
MTX weekly dose, mg	17 (3)	16 (3)	17 (6)	17 (4)
Corticosteroid use, n (%)	34 (54)	42 (67)	35 (56)	31 (49)
Duration of RA at baseline, yrs	8.1 (7.9)	7.2 (6.8)	7.6 (7.3)	7.6 (6.9)
DAS28	6.5 (0.8)	6.3 (0.8)	6.5 (0.8)	6.4 (0.7)
HAQ-DI	1.4 (0.6)	1.5 (0.6)	1.4 (0.6)	1.5 (0.6)
Swollen joint count	14 (7)	14 (6)	14 (6)	13 (5)
Tender joint count	27 (15)	25 (14)	25 (14)	23 (11)
Subject global assessment of disease activity	5.9 (1.9)	5.8 (1.8)	6.0 (2.0)	6.1 (1.9)
Physician global assessment of disease activity	6.3 (1.5)	6.4 (1.4)	6.1 (1.3)	6.3 (1.2)
Subject global assessment of pain	54 (21)	53 (22)	50 (25)	52 (22)
ESR, mm/h	48 (20)	45 (20)	44 (21)	45 (20)
CRP, mg/l	13 (12)	14 (17)	18 (23)	12 (11)

BMI: body mass index; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; MTX: methotrexate; RA: rheumatoid arthritis; DAS28: Disease Activity Score at 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

each in the placebo, 70 mg brodalumab, and 140 mg brodalumab treatment groups, and 2 in the 210 mg brodalumab treatment group, who reported AE of RA, osteomyelitis, upper respiratory tract infection, pleurisy, and laryngitis, respectively.

Seven serious AE were reported during the study: blepharitis in the 70-mg brodalumab group; death from cardiopulmonary failure about 1 week after the last dose in the 140-mg brodalumab group; lumbar vertebral fracture, thrombosis, and a suicide attempt in the 210-mg brodalumab group; and tibia fracture and RA in the placebo group (Table 4).

Four of the subjects (2.1%) treated with brodalumab tested positive for anti-brodalumab–binding antibodies at the end of the study; however, no neutralizing antibodies were detected by bioassay.

DISCUSSION

In the current study, there was no evidence of meaningful clinical efficacy with brodalumab treatment in subjects with RA who had an inadequate response to MTX. The proportion of subjects with an ACR50 response at Week 12 was no different in the brodalumab treatment groups as compared with the placebo group. Overall, the incidence of AE was similar in the brodalumab and placebo groups. Short-term treatment was well tolerated across a dose range of 70 mg to 210 mg and these analyses did not suggest any safety risks with brodalumab administration.

Studies with other biologic agents that target IL-17 signaling have shown modest improvements in ACR20 and DAS28 responses in patients with RA. In a phase 2 trial, treatment with ixekizumab, an anti-IL17A antibody, resulted in modestly increased ACR20 response and decreased DAS28 scores as compared with placebo[23]. In a separate trial of secukinumab, another anti-IL-17A antibody, there was no evidence of a significant treatment effect on the ACR20 response at the primary endpoint of Week 16[22]. However, there was some evidence of responses in the secondary endpoints, including DAS28, and in ACR20 at earlier timepoints[22]. In total, these data may suggest a difference in targeting IL-17 receptor type A versus the ligand in RA. The

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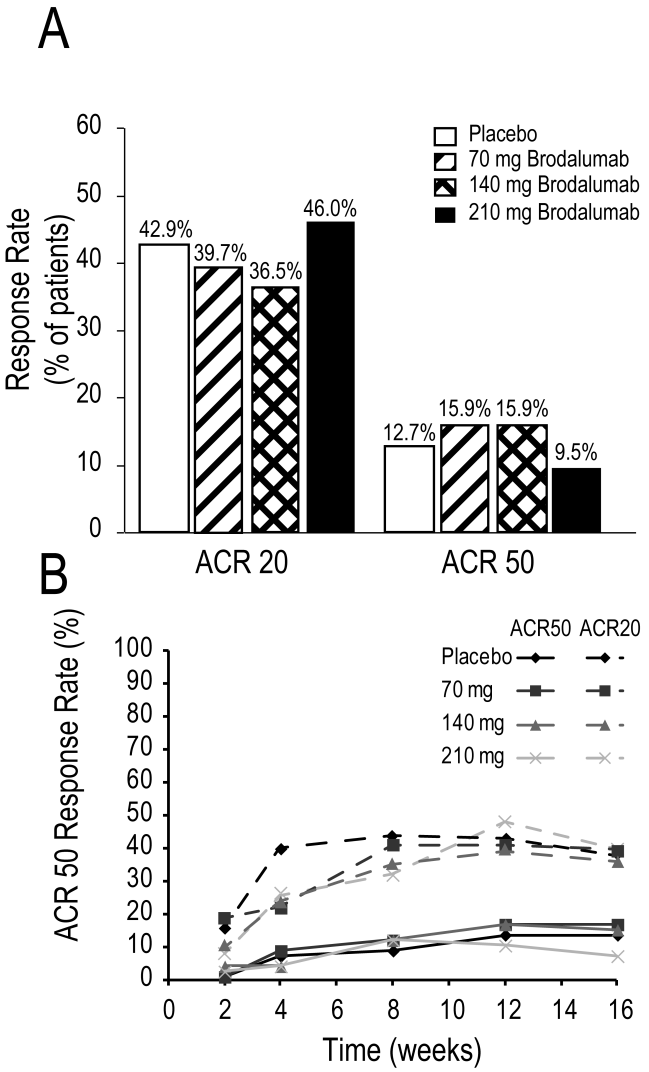

Figure 2. A. ACR50 (primary endpoint) and ACR20 responses at Week 12. n = 63 per group. Nonresponder imputation was used for the missing data. All comparisons between each brodalumab dose group and placebo were nonsignificant ($p > 0.05$; nominal p value without multiplicity adjustment based on Cochran-Mantel-Haenszel test adjusting for sex). B. ACR50 and ACR20 responses over time. ACR50: American College of Rheumatology 50% response; ACR20: ACR 20% response.

explanation for a difference is not clear. The modest responses seen with IL-17 ligand inhibitors, however, could suggest that IL-17 may not be as dominant a driver of inflammation in RA as was anticipated.

In contrast, blockade of IL-17 receptor A with brodalumab has demonstrated significant clinical improvement in a clinical trial of patients with psoriatic arthritis (PsA)[30]. The demonstrated clinical response to brodalumab in PsA and psoriasis, observed with doses as low as 140 mg Q2W, suggests that the inability to effectively block IL-17 receptor type A is not the explanation for the discrepant clinical effects of brodalumab in PsA versus RA. The more likely reason is the distinct nature of the 2 diseases, supported by clear differences in clinical, serological, and radiological features, as well as genetic associations[31].

Recent data have demonstrated that IL-17–producing lymphocytes in RA are from a different lineage than those in PsA. IL-17+CD4– T cells (predominantly CD8+ cells) are elevated in PsA SF, but are not detected in RA SF, and are correlated with disease activity, CRP levels, and bone erosion in PsA[32]. These data may suggest that a previously unrecognized IL-17–producing T cell population may be important in the immunopathogenesis of PsA and could account for the differences in clinical and radiographic manifestations of RA and PsA. The significant differences in these 2 diseases may likely account for differential responses to therapy as well.

As in any study, there are limitations in this phase 2 study. The high placebo response observed for the ACR20 endpoint may have partially limited the ability to detect a treatment response. However, the lack of clinical effect for the ACR50 and other endpoints strongly suggest a lack of clinically meaningful treatment response. The relatively small number of subjects per treatment arm in this dose-ranging study limited the ability to identify patient subgroups that might have benefited from treatment because the study was not powered to assess subgroup effects. We were unable to perform an exploratory analysis of efficacy by baseline disease severity because most subjects had high disease activity at baseline (DAS 28 > 5.1); only 2 subjects per treatment group had DAS 28 scores ≤ 5.1 at baseline. The duration of the study allowed for the analysis of safety data only to Week 12, limiting any conclusions on the longer-term safety of brodalumab.

There was no evidence of clinical efficacy with brodalumab in this phase 2 study in patients with RA who had an inadequate response to MTX. In addition, short-term treatment was well tolerated across a dose range of 70 mg to 210 mg, and no new safety risks were identified with brodalumab administration in the study. These preliminary results are not consistent with a role for blockade of IL-17 receptor type A in the treatment of RA, and thus our study does not support further evaluation of brodalumab for this indication.

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Table 2. Clinical responses at Week 12. The comparison is between each brodalumab dose group and placebo. Nonresponder imputation is used for the missing data.

Response	Placebo, n = 63	Brodalumab		
		70 mg, n = 63	140 mg, n = 63	210 mg, n = 63
ACR50				
Response rate, n/N1 (%)	8/63 (13)	10/63 (16)	10/63 (16)	6/63 (10)
Difference in response rate, %		3.2	3.2	–3.2
95% CI of difference		–9.0–15.4	–9.0–15.4	–14.1–7.9
p*		0.598	0.635	0.572
ACR20				
Response rate, n/N1 (%)	27/60 (45)	25/60 (42)	23/58 (40)	29/61 (48)
Difference in response rate, %		–3.3	–5.3	2.5
95% CI of difference		–21.1–14.4	23.1–12.5	–15.2–20.3
p*		0.727	0.539	0.794
ACR70				
Response rate, n/N1 (%)	2/63 (3)	2/63 (3)	2/63 (3)	0/63 (0)
Difference in response rate, %		0.0	0.0	–3.2
95% CI of difference		–6.1–6.1	–6.1–6.1	–7.5–1.2
p*		0.984	0.993	0.159
DAS28 change from baseline				
Mean (SD)	–1.3 (1.2)	–1.4 (1.3)	–1.3 (1.2)	–1.3 (1.2)
p**		0.459	0.906	0.849

* P value is nominal p value without multiplicity adjustment based on Cochran-Mantel-Haenszel test adjusting for sex. ** P value is nominal without multiplicity adjustment based on ANCOVA model adjusting for sex and baseline DAS28 score. ACR50: American College of Rheumatology 50% response; ACR20: ACR 20% response; ACR70: ACR 70% response; DAS28: Disease Activity Score at 28 joints.

Table 3. Percent change from baseline of ACR individual components at Week 12. As observed analysis with no imputation for missing data.

Response	Placebo, n = 63	Brodalumab		
		70 mg, n = 63	140 mg, n = 63	210 mg, n = 63
CRP				
n	60	59	58	61
Mean (SD)	34 (170)	98 (345)	51 (169)	45 (159)
ESR				
n	61	60	58	61
Mean (SD)	–20 (42)	–21 (44)	–12 (44)	–7 (61)
SJC				
n	61	60	58	61
Mean (SD)	–49 (46)	–52 (41)	–49 (47)	–46 (41)
TJC				
n	61	60	58	61
Mean (SD)	–42 (45)	–47 (41)	–45 (42)	–38 (45)
HAQ-DI				
n	61	60	58	59
Mean (SD)	–11 (45)	–13 (51)	1 (80)	9 (134)
PtGA of disease activity				
n	60	60	58	61
Mean (SD)	–12 (43)	–9 (53)	–14 (35)	–13 (47)
PGA of disease activity				
n	61	60	58	61
Mean (SD)	–36 (32)	–34 (28)	–31 (37)	–35 (29)
PtGA of pain				
n	61	60	58	61
Mean (SD)	–15 (49)	29 (323)	20 (160)	1 (93)

ACR: American College of Rheumatology; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; TJC: tender joint count; HAQ-DI: Health Assessment Questionnaire–Disability Index; PtGA: patient's global assessment; PGA: physician's global assessment.

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Table 4. Adverse events (AE). Values are n (%).

	Placebo, n = 63	Brodalumab			
		70 mg, n = 63	140 mg, n = 63	210 mg, n = 63	Total, n = 189
AE					
Any	32 (50.8)	32 (50.8)	40 (63.5)	32 (50.8)	104 (55.0)
Serious*	2 (3.2)	1 (1.6)	1 (1.6)	3 (4.8)	5 (2.6)
Fatal	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)
Leading to study discontinuation	2 (3.2)	1 (1.6)	2 (3.2)	0 (0.0)	3 (1.6)
Leading to investigational product discontinuation	1 (1.6)	1 (1.6)	1 (1.6)	2 (3.2)	4 (2.1)
CTCAE grade 3, 4, or 5**	4 (6.3)	3 (4.8)	2 (3.2)	4 (6.3)	9 (4.8)
Common AE***					
Upper respiratory tract infection	1 (1.6)	4 (6.3)	5 (7.9)	3 (4.8)	12 (6.3)
RA	6 (9.5)	4 (6.3)	7 (11.1)	0 (0.0)	11 (5.8)
Nasopharyngitis	2 (3.2)	3 (4.8)	4 (6.3)	4 (6.3)	11 (5.8)
Urinary tract infection	1 (1.6)	2 (3.2)	5 (7.9)	4 (6.3)	11 (5.8)
Injection site pain	4 (6.3)	2 (3.2)	2 (3.2)	2 (3.2)	6 (3.2)
Cough	4 (6.3)	2 (3.2)	2 (3.2)	1 (1.6)	5 (2.6)
Headache	4 (6.3)	3 (4.8)	3 (4.8)	1 (1.6)	7 (3.7)
Hypertension	4 (6.3)	2 (3.2)	3 (4.8)	2 (3.2)	7 (3.7)

* A serious AE was defined as an event that was fatal or life threatening, required or prolonged hospitalization, or caused persistent or substantial disability or incapacity or congenital anomaly or birth defect, or an event that was considered by the investigator to be a medically important event. ** The severity of AE was graded according to the National Cancer Institute CTCAE, version 4.0. *** Common adverse events were those that were reported in at least 5% of subjects in any treatment group. CTCAE: Common Terminology Criteria for Adverse Events; RA: rheumatoid arthritis.

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