Improvement in Psoriasis Signs and Symptoms Assessed by the Psoriasis Symptom Inventory with Brodalumab Treatment in Patients with Psoriatic Arthritis

Philip J. Mease, Mark C. Genovese, Alex Mutebi, Hema N. Viswanathan, Dina Chau, Jingyuan Feng, Ngozi Erondu, and Ajay Nirula

ABSTRACT. ***Objective.*** To evaluate the effect of brodalumab on psoriasis signs and symptoms assessed by the Psoriasis Symptom Inventory (PSI) in patients with psoriatic arthritis (PsA).

Methods. This prespecified analysis of a phase II study (NCT01516957) evaluated patients with active PsA and psoriasis-affected body surface area ≥ 3%, randomized to brodalumab (140 or 280 mg) or placebo every 2 weeks (Q2W) for 12 weeks with loading dose at Week 1. At Week 12, patients entering an open-label extension received brodalumab 280 mg Q2W. The PSI measures 8 psoriasis signs and symptoms: itch, redness, scaling, burning, stinging, cracking, flaking, and pain. PSI response is defined as total PSI ≤ 8 (range 0-32), each item ≤ 1 (range 0-4). PSI scores were assessed at weeks 12 and 24.

Results. There were 107 eligible patients. At Week 12, mean improvement in PSI scores was 7.8, 11.2, and 1.5 in brodalumab 140 mg, 280 mg, and placebo groups, respectively; by Week 24, improvement was 10.2, 12.4, and 11.7. At Week 12, 75.0%, 81.8%, and 16.7% of patients receiving brodalumab 140 mg, 280 mg, and placebo, respectively, achieved PSI response; improvement was sustained through Week 24, when 83.9% of prior placebo recipients achieved response. At Week 12, 25.0%, 36.4%, and 2.8% of patients receiving brodalumab 140 mg, 280 mg, and placebo, respectively, achieved PSI 0. Percentages improved through Week 24: 40.0% brodalumab 140 mg, 42.9% brodalumab 280 mg, and 48.4% placebo.

Conclusion. Significantly more brodalumab-treated patients with PsA achieved patient-reported improvements in psoriasis signs and symptoms than did those receiving placebo. Improvements were comparable between brodalumab groups. (J Rheumatol First Release January 15 2016; doi:10.3899/jrheum.150182)

Key Indexing Terms:
PSORIATIC ARTHRITIS
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Psoriatic arthritis (PsA) is an inflammatory disease that frequently presents with cutaneous symptoms associated with psoriasis and inflammatory joint disease[1,2,3]. Prevalence of PsA among patients with psoriasis varies widely and is estimated to be between 6% and 42%[1,2,4,5]. The clinical features of PsA include psoriasis, arthritis, dactylitis, enthesitis, spondylitis, and nail disease[6]. Most patients with PsA have active psoriasis or have had a history of psoriasis[7], and as PsA progresses, joint damage associated with arthritis increases[1,7,8,9]. Psoriasis symptoms in patients with PsA are likely to be associated with a greater effect on health-related quality of life (HRQOL)[10,11]: patients with psoriasis who also have PsA have worse health status and lower HRQOL than patients with psoriasis alone, as measured by the Health Assessment Questionnaire (HAQ), the Medical Outcomes Study Short Form-36 (SF-36) questionnaire, the Dermatology Life Quality Index (DLQI), and EQ-5D[12,13]. Patients with PsA with mild psoriasis are believed to experience minimal effect on quality of life, whereas patients with moderate to severe psoriasis experience a more than minimal effect on quality of life[14].

Interleukin (IL)-17 pathways may play a role in the patho-

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genesis of autoimmune diseases, including PsA, psoriasis, and ankylosing spondylitis[15,16,17,18,19,20,21]. This family of cytokines [including IL-17A, IL-17F, IL-17E (IL-25), and IL-22] is produced by Th17 and other immune cells, which are themselves induced by IL-23[22,23]. These proinflammatory cytokines then induce a cascade of downstream activities, including the production of additional proinflammatory cytokines and chemokines and antimicrobial peptides[24,25,26]. Patients with PsA have high expression of Th17 cells in peripheral blood and of IL-17 receptor antagonist (IL-17RA) in synovial fluid[27,28]. Brodalumab, a human monoclonal antibody against IL-17RA, blocks the signaling of multiple IL-17 cytokines including IL-17A, IL-17F, and the IL-17A/F heterodimer[29]. In a phase II, randomized controlled trial, patients with PsA treated with brodalumab experienced significant clinical benefit, as measured by 20% and 50% improvements in American College of Rheumatology response criteria (ACR20 and ACR50, respectively)[30].

Patient-reported outcomes (PRO) provide critical information about patient perception of treatment benefit and disease status that complements clinical assessments[31,32]. The Psoriasis Symptom Inventory (PSI) is a newly developed, 8-item PRO instrument of psoriasis signs and symptom severity assessing itch, redness, scaling, burning, stinging, cracking, flaking, and pain[31,33,34,35]. The development of the PSI was informed by a review of the literature, clinician input, and extensive involvement of patients with psoriasis, some of whom had PsA. Data from various analyses have shown the PSI to be a reliable and valid measure of psoriasis signs and symptom severity in patients with psoriasis and PsA[34,35,36]. In addition, the PSI is able to detect clinically meaningful change in psoriasis signs and symptom severity, because it closely correlates with improvements in Psoriasis Area and Severity Index (PASI) and static physician's global assessment (sPGA) of disease scores[33,35]. We sought to evaluate the effect of brodalumab on psoriasis symptoms as assessed by the PSI exclusively in patients with PsA.

MATERIALS AND METHODS

Patients. Patients were eligible to participate in our study if they were between the ages of 18 and 75 years with a diagnosis of PsA as defined by the Classification for Psoriatic Arthritis criteria (CASPAR), had at least 3 tender joints, and had at least 3 swollen joints for a minimum of 6 months. Patients were allowed to use methotrexate (≤ 25 mg/week), leflunomide (≤ 20 mg/day), corticosteroids (≤ 10 mg/day), or nonsteroidal antiinflammatory drugs if they had been on a stable dosage for at least 4 weeks before initiation of study drug. Patients with prior anti-tumor necrosis factor (anti-TNF) therapy and anti-IL-12/23 drug therapy were eligible for the study after washout periods of 2 months for anti-TNF therapy and 3 months for anti-IL-12/23 drug therapy.

Patients were excluded from the study if they had a recent infection (active infection within 28 days or serious infection within 8 weeks), recurrent infection, major chronic inflammatory or connective tissue disease, clinically significant systemic disease, or 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. Patients were required to have had a negative test result for tuberculosis or receipt of prophylactic treatment.

Study design. This was a prespecified analysis of a phase II, randomized, double-blind, placebo-controlled study (NCT01516957) of patients with PsA. The study design has been described[30] and is summarized in Figure 1. Patients were randomized 1:1:1 to receive brodalumab 140 mg, brodalumab 280 mg, or placebo at weeks 0, 1, 2, 4, 6, 8, and 10. At Week 12, patients had the option of entering the open-label extension (OLE) period, during which all patients received brodalumab 280 mg Q2W (patients initially randomized to placebo received a loading dose of brodalumab 280 mg at Week 13).

Outcome measures. The PSI measures patient-reported psoriasis signs and symptom severity on the basis of 8 items: itch, redness, scaling, burning, stinging, cracking, flaking, and pain[33,34,35]. Each item yields a severity score on a 5-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe), and the item scores are summed to yield a PSI total score ranging from 0 to 32. There are 2 recall versions of the PSI — 24-h recall and 7-day recall — that have been shown to yield comparable data[31]. This phase II study used the 7-day recall version. Patients are considered PSI responders if they achieve a PSI total score no higher than 8, with no item score above 1. Improvement in psoriasis symptoms was assessed by changes from baseline in PSI total and item scores at weeks 12 and 24, percentage of patients who achieved PSI responder status at weeks 12 and 24, and percentage of patients who achieved a PSI total score of 0 (i.e., not at all severe for all 8 signs and symptoms of the PSI) at weeks 12 and 24.

Statistical analyses. Analyses were based on observed PSI scores for patients with baseline affected body surface area (BSA) of at least 3%, without adjusting for multiple testing. For PSI total and item scores, an analysis of covariance model was used to assess the efficacy of brodalumab compared with placebo after adjusting for stratification factors (prior biologic use: yes vs no; baseline weight groups: > 100 kg vs ≤ 100 kg) and baseline values. For the percentage of patients who achieved PSI responder status and PSI total score of 0, the comparison between treatment arms and placebo was performed using a Cochran-Mantel-Haenszel test, which stratified results by prior biologic use and baseline weight.

RESULTS

Patients. The study population has been described in a separate publication[30]. Of the 168 patients who enrolled in the study, 107 had a baseline BSA involvement of at least 3% and were eligible for this analysis. Of these 107 patients, 99 entered the OLE period at Week 12 and 92 reached Week 24. Key demographics and baseline clinical characteristics are provided in Table 1.

Changes in PSI scores. Improvements in PSI score were observed as early as 2 weeks after the initiation of brodalumab treatment. At all timepoints measured from initiation of study drug to Week 12, patients in both brodalumab treatment groups had significantly greater mean change in PSI total score compared with patients receiving placebo ($p \leq 0.0001$ for all timepoints in both brodalumab treatment groups; Figure 2). At Week 12, the mean improvement in PSI total scores was 7.8 for brodalumab 140 mg Q2W and 11.2 for brodalumab 280 mg Q2W compared with 1.5 for placebo ($p < 0.0001$ for both brodalumab treatment groups; Figure 2). By Week 24, after initiation of the OLE period, during which all patients received brodalumab 280 mg Q2W, the mean improvement in PSI total scores was comparable between brodalumab-treated patients who were initially randomized to placebo and those who were initially randomized to brodalumab. Patients initially randomized to placebo experi-

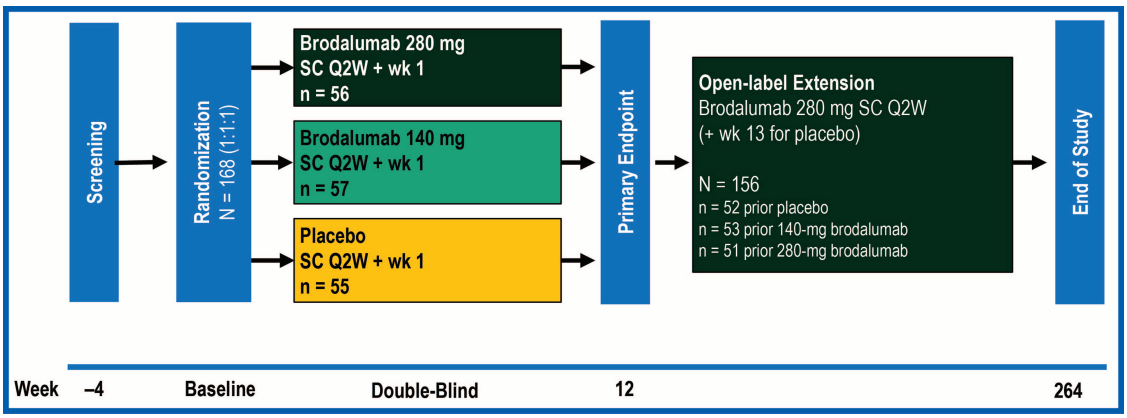

Figure 1. Study design. This was a prespecified analysis of a randomized, double-blind, placebo-controlled, phase II study. SC: subcutaneous; Q2W: every 2 weeks.

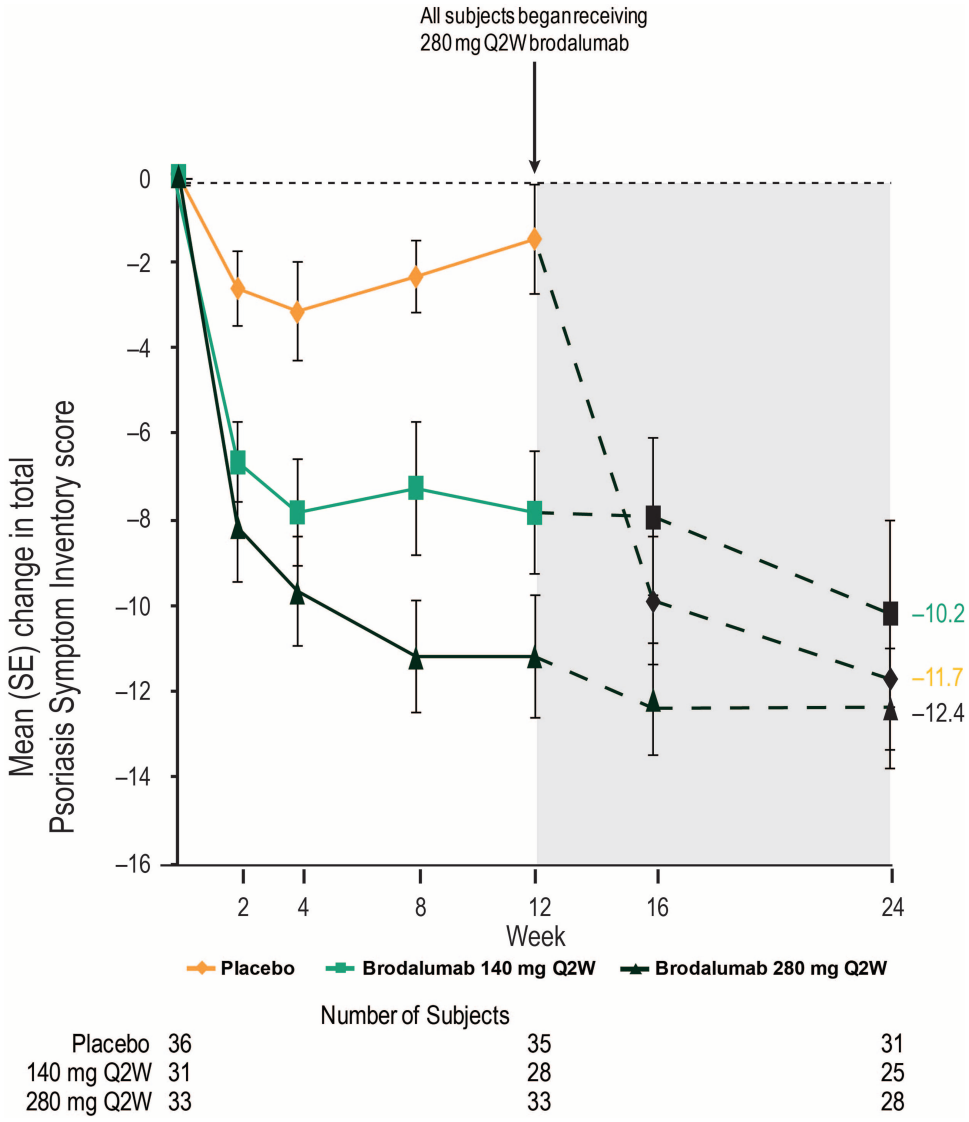

Figure 2. Changes in PSI total score at baseline, Week 12, and Week 24. Patients randomized to placebo (yellow diamond), brodalumab 140 mg Q2W (green square), and brodalumab 280 mg Q2W (black triangle) reported improvements in their psoriasis symptoms, as measured by the PSI, at the timepoints indicated. After Week 12, all patients initiated the OLE period, during which they received brodalumab 280 mg Q2W, indicated by the dotted line. Results shown are mean (SE) change in PSI total score. $P \leq 0.0001$ between brodalumab 140 mg and placebo, and brodalumab 280 mg and placebo at weeks 2, 4, 8, and 12. PSI: Psoriasis Symptom Inventory; Q2W: every 2 weeks; OLE: open-label extension; SE: standard error.

Table 1. Demographics and clinical characteristics at baseline. Data are mean (SD) unless otherwise indicated.

Baseline Characteristics	Placebo, n = 39	Brodalumab 140 mg Q2W, n = 31	Brodalumab 280 mg Q2W, n = 37
Female, n (%)	21 (53.8)	18 (58.1)	27 (73.0)
Age, yrs	54.0 (11.6)	52.6 (9.9)	50.4 (12.2)
Weight, kg	91.1 (20.6)	95.6 (24.1)	92.2 (23.9)
Duration of PsA, yrs	9.4 (8.0)	10.7 (8.4)	8.9 (8.4)
Affected BSA (%)	18.9 (20.9)	18.9 (17.8)	15.9 (19.2)
sPGA	6.2 (1.7)	6.6 (1.4)	6.1 (1.6)
SGA	6.6 (1.9)	7.3 (1.7)	6.5 (2.2)
HAQ	1.3 (0.6)	1.3 (0.7)	1.4 (0.7)
Prior biologic (yes), n (%)	20 (51.3)	18 (58.1)	25 (67.6)
PSI total score	16.0 (8.9)	14.5 (7.6)	15.1 (7.4)
PSI item score			
Itch	2.2 (1.2)	2.0 (1.1)	1.9 (1.1)
Redness	2.3 (1.0)	2.0 (1.1)	2.2 (1.2)
Scaling	2.2 (1.1)	2.3 (1.1)	2.1 (1.0)
Burning	1.8 (1.3)	1.6 (1.3)	1.7 (1.2)
Stinging	1.5 (1.5)	1.4 (1.2)	1.7 (1.1)
Cracking	1.9 (1.3)	1.7 (1.3)	1.7 (1.1)
Flaking	2.3 (1.1)	2.1 (1.1)	2.1 (1.0)
Pain	1.8 (1.3)	1.5 (1.1)	1.7 (1.2)

PsA: psoriatic arthritis; BSA: body surface area; sPGA: static physician's global assessment of disease activity; SGA: subject global assessment of disease activity; HAQ: Health Assessment Questionnaire; PSI: Psoriasis Symptom Inventory.

enced a mean improvement of 11.7 compared with 10.2 (brodalumab 140 mg Q2W) and 12.4 (brodalumab 280 mg Q2W).

Significant improvements were observed for individual items measured by the PSI. By Week 12, patients in both brodalumab treatment groups had significantly greater improvement in each of the PSI items when compared with patients in the placebo group ($p \leq 0.0031$ for all items in Table 2). Significant changes in mean item scores for all items were observed as early as 2 weeks in both treatment groups ($p \leq 0.04$ for all; data not shown).

PSI responders. Treatment with brodalumab resulted in a higher proportion of PSI responders compared with the placebo group at Week 12. The percentages of PSI responders were 75.0% and 81.8% in the brodalumab 140 mg Q2W and 280 mg Q2W treatment groups, respectively. Moreover, the percentages of PSI responders in the brodalumab groups were significantly higher than in the placebo group (16.7%; $p < 0.0001$ for both brodalumab treatment groups; Figure 3). During the OLE period, when all patients received brodalumab 280 mg Q2W, 83.9% of patients initially randomized to placebo, 80.0% of those initially randomized to brodalumab 140 mg Q2W, and 75.0% of those initially randomized to brodalumab 280 mg Q2W achieved a response by Week 24 (Figure 3). During the OLE, the percentage of PSI responders among patients who switched from placebo to brodalumab was comparable to the percentages of PSI

Table 2. Change in PSI item scores from baseline at weeks 12 and 24.

PSI Item		Placebo, n = 39		Brodalumab 140 mg Q2W, n = 31		Brodalumab 280 mg Q2W, n = 37	
		Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
Itch	Mean	−0.31	−1.48	−1.11	−1.20	−1.15	−1.36
	95% CI	(−0.66, 0.03)	(−1.90, −1.07)	(−1.59, −0.62)	(−1.87, −0.53)	(−1.62, −0.68)	(−1.77, −0.95)
	p*			< 0.0001		< 0.0001	
Redness	Mean	−0.29	−1.68	−1.00	−1.32	−1.64	−1.75
	95% CI	(−0.66, 0.09)	(−2.06, −1.29)	(−1.44, −0.56)	(−1.96, −0.68)	(−2.10, −1.18)	(−2.26, −1.24)
	p*			< 0.0001		< 0.0001	
Scaling	Mean	−0.17	−1.65	−1.39	−1.72	−1.55	−1.68
	95% CI	(−0.58, 0.23)	(−2.10, −1.19)	(−1.89, −0.89)	(−2.39, −1.05)	(−1.94, −1.15)	(−2.06, −1.30)
	p*			< 0.0001		< 0.0001	
Burning	Mean	−0.23	−1.35	−0.71	−1.00	−1.36	−1.50
	95% CI	(−0.60, 0.14)	(−1.85, −0.86)	(−1.17, −0.26)	(−1.68, −0.32)	(−1.78, −0.95)	(−2.03, −0.97)
	p*			0.0031		< 0.0001	
Stinging	Mean	0.06	−1.06	−0.68	−1.00	−1.21	−1.36
	95% CI	(−0.33, 0.45)	(−1.60, −0.53)	(−1.14, −0.22)	(−1.64, −0.36)	(−1.68, −0.75)	(−1.88, −0.84)
	p*			0.0006		< 0.0001	
Cracking	Mean	−0.03	−1.42	−0.82	−1.20	−1.27	−1.57
	95% CI	(−0.40, 0.34)	(−1.91, −0.93)	(−1.24, −0.40)	(−1.81, −0.59)	(−1.72, −0.83)	(−2.02, −1.12)
	p*			< 0.0001		< 0.0001	
Flaking	Mean	−0.31	−1.74	−1.25	−1.68	−1.67	−1.71
	95% CI	(−0.68, 0.05)	(−2.24, −1.24)	(−1.72, −0.78)	(−2.26, −1.10)	(−2.09, −1.24)	(−2.12, −1.31)
	p*			< 0.0001		< 0.0001	
Pain	Mean	−0.17	−1.29	−0.86	−1.04	−1.30	−1.43
	95% CI	(−0.54, 0.20)	(−1.79, −0.79)	(−1.25, −0.47)	(−1.58, −0.50)	(−1.71, −0.89)	(−1.92, −0.94)
	p*			< 0.0001		< 0.0001	

* Difference vs placebo at Week 12. PSI: Psoriasis Symptom Inventory.

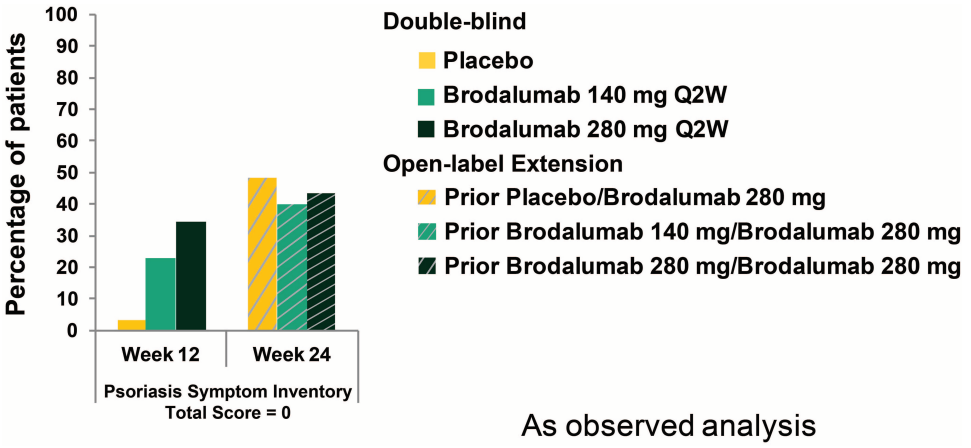

Figure 3. Percentages of patients who were PSI responders at weeks 12 and 24. The percentages of patients receiving placebo (yellow), brodalumab 140 mg Q2W (green), or brodalumab 280 mg Q2W (black) who were PSI responders at Week 12 are indicated by solid bars. During the OLE period, when all patients received brodalumab 280 mg Q2W, the percentages of patients who were PSI responders at Week 24 are indicated by hatched bars. PSI responders are defined as patients with a PSI total score ≤ 8 and each item score ≤ 1. PSI: Psoriasis Symptom Inventory; Q2W: every 2 weeks; OLE: open-label extension.

responders from either group of patients treated with brodalumab throughout the study. During the same period, the proportions of PSI responders were maintained among patients initially randomized to brodalumab 140 mg Q2W and 280 mg Q2W.

PSI score of 0. Within 12 weeks of brodalumab treatment, significantly higher percentages of patients receiving brodalumab 140 mg Q2W (25.0%) and 280 mg Q2W (36.4%) achieved a PSI total score of 0 than did patients receiving placebo (2.8%; $p < 0.01$ for both brodalumab treatment groups; Figure 4). After initiation of the OLE period, additional patients attained a PSI score of 0 at Week 24 in all groups (Figure 4): 48.4% of patients initially randomized to placebo, 40.0% of patients initially randomized to brodalumab 140 mg Q2W, and 42.9% of patients initially randomized to brodalumab 280 mg Q2W.

DISCUSSION

In our study, treatment with brodalumab resulted in improvement of psoriasis signs and symptoms in patients with PsA, as measured by the PSI. Improvements in PSI total and item scores were observed as early as Week 2; by Week 12, the majority of patients receiving brodalumab achieved PSI responder status and more than 25% of patients achieved a PSI total score of 0. These improvements in symptoms assessed by the PSI were similar between patients in the 2

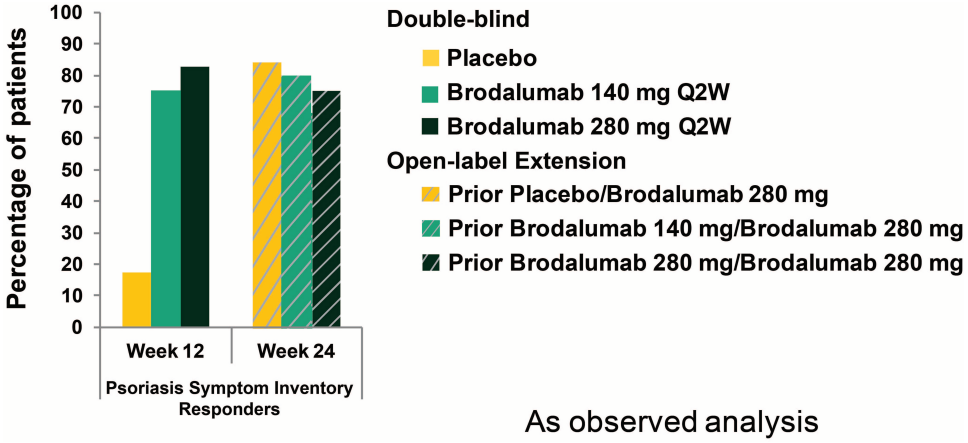

Figure 4. Percentages of patients with PSI total score of 0 at weeks 12 and 24. The percentages of patients receiving placebo (yellow), brodalumab 140 mg Q2W (green), or brodalumab 280 mg Q2W (black) who attained a PSI total score of 0 at Week 12 are indicated by solid bars. During the OLE period, when all patients received brodalumab 280 mg Q2W, the percentages of patients who attained a PSI total score of 0 at Week 24 are indicated by hatched bars. PSI: Psoriasis Symptom Inventory; Q2W: every 2 weeks; OLE: open-label extension.

brodalumab treatment groups. Improvements in psoriasis symptoms within 12 weeks for patients with PsA are similar to improvements found in previous studies of patients with moderate to severe psoriasis[33]. The percentage of placebo-treated patients who achieved PSI responder status in this study at Week 12 (16.7%) is comparable to that of a previous study reporting that 13.2% of placebo-treated patients with moderate to severe plaque psoriasis achieved PSI responder status[29].

Patients continued to experience improvements in psoriasis symptoms during the OLE period of the study. By Week 24, after switching to brodalumab 280 mg Q2W at Week 12, the majority of patients initially randomized to placebo attained improvements in PSI total score comparable to those achieved by patients initially randomized to brodalumab. The proportion of patients initially randomized to placebo who achieved PSI responder status and a PSI total score of 0 was similar to that of patients who received brodalumab throughout the study. Additional clinical benefit from treatment with brodalumab continued beyond Week 12, as shown by the additional patients in the brodalumab groups who achieved a PSI total score of 0 from Week 12 to Week 24.

PRO instruments are relevant and useful tools to measure patient-reported symptoms and treatment benefit. The use of both PRO and physician evaluations provides a complementary approach to evaluating treatment outcomes[32,37]. The PSI is a newly developed, psoriasis-specific PRO instrument that assesses the severity of psoriasis signs and symptoms. The PSI was developed in accordance with the recommendations set forth by the US Food and Drug Administration PRO Guidance[38] and has demonstrated excellent content and construct validity[34,35]. In addition to the PSI, several other PRO instruments have been used to evaluate patient-reported psoriasis signs and symptom experiences, albeit with limitations[32,39]. There is an increasing body of evidence to confirm the good measurement properties of the PSI in patients with psoriasis and PsA[31,33,34,35,36]. Collectively, these analyses support the use of the PSI to capture the severity of psoriasis-specific signs and symptoms and to evaluate treatment benefits as a complement to physician assessments both in clinical trials and clinical practice.

Published evidence supports the reliability and validity of the PSI to detect changes highly correlated with PASI and sPGA scores[35]. The findings from this analysis have further shown a significant therapeutic benefit of brodalumab treatment in patients with PsA. This therapeutic benefit of brodalumab as measured by the PSI mirrors improvements reported in other studies using clinical assessments such as PASI, sPGA, ACR20, Clinical Disease Activity Index, and 28-joint Disease Activity Score[30,31,33,35].

The present analysis is not without its limitations. First, this analysis was based on results from a single randomized controlled trial and may not be generalizable to broader populations. Second, the "as-observed" analysis may limit statistical interpretation of the findings. However, completion rates for the PSI were high, and the use of as-observed analyses informed a robust analysis of the data. Third, most of the currently published evidence supporting the good measurement properties of the PSI is based on analyses of data from patients with moderate to severe plaque psoriasis, with relatively less published evidence supporting the use of the PSI in PsA. Whereas the measurement properties of the PSI in PsA have not yet been extensively evaluated, data from our study have been analyzed to assess the reliability and construct validity of the PSI in PsA and will be published separately. This analysis included only patients with at least 3% psoriasis-affected BSA because the PASI does not perform well at that lower scale[40]; understanding the responsiveness of the PSI at a BSA below 3% will be worth exploring in future research. Finally, the effect of brodalumab on improvement of psoriasis signs and symptoms would have been better understood if additional skin-related assessments such as PASI had been included in this trial. Ongoing phase III trials include additional skin-related assessments, which are expected to provide a more complete evaluation of the effect of brodalumab in patients with PsA.

Brodalumab therapy improves psoriasis signs and symptoms in patients with PsA. Improvements in all signs and symptoms measured by the PSI were apparent as early as 2 weeks after initiation of treatment. Patients in the brodalumab treatment groups experienced significantly greater improvements in psoriasis signs and symptom severity than patients in the placebo group. A significantly higher proportion of patients treated with brodalumab compared with patients treated with placebo achieved PSI responder status and a PSI total score of 0, indicating no severe psoriasis signs and symptoms.

Treatment benefit from brodalumab was evident and maintained throughout the OLE period. This analysis further supports the use of brodalumab for the treatment of psoriasis signs and symptoms in patients with PsA.

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