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Efficacy of secukinumab and adalimumab in patients with psoriatic arthritis and concomitant moderate-to-severe plaque psoriasis: results from EXCEED, a randomized, double-blind head-to-head monotherapy study

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Summary

Background Secukinumab [an interleukin (IL)-17A inhibitor] has demonstrated significantly higher efficacy vs. etanercept (a tumour necrosis factor inhibitor) and ustekinumab (an IL-12/23 inhibitor) in patients with moderate-to-severe plaque psoriasis.
Objectives To report 52-week results from a prespecified analysis of patients with active psoriatic arthritis (PsA) having concomitant moderate-to-severe plaque psoriasis from the head-to-head EXCEED monotherapy study comparing secukinumab with adalimumab.
Methods Patients were randomized to receive secukinumab 300 mg via subcutaneous injection at baseline, week 1–4, and then every 4 weeks until week 48 or adalimumab 40 mg via subcutaneous injection every 2 weeks from baseline until week 50. Assessments in patients with concomitant moderate-to-severe psoriasis, defined as having affected body surface area > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10 at baseline, included musculoskeletal, skin and quality-of-life outcomes. Missing data were handled using multiple imputation.
Results Of the 853 patients [secukinumab (N = 426), adalimumab (N = 427)], 211 (24·7%) had concomitant moderate-to-severe psoriasis [secukinumab (N = 110, 25·8%), adalimumab (N = 101, 23·7%)]. Up to week 50, 5·5% of patients discontinued secukinumab vs.17·8% in the adalimumab group. The proportion of patients who achieved American College of Rheumatology (ACR) 20 response was 76·4% with secukinumab vs. 68·3% with adalimumab (P = 0·175), PASI 100 response was 39·1% vs. 23·8% (P = 0·013), and simultaneous improvement in ACR 50 and PASI 100 response at week 52 was 28·2% vs. 17·7%, respectively (P = 0·06). Secukinumab demonstrated consistently higher responses vs. adalimumab across skin endpoints.

Conclusions This prespecified analysis in PsA patients with concomitant moderate-to-severe plaque psoriasis in the EXCEED study provides further evidence that IL-17 inhibitors offer a comprehensive biological treatment to manage the concomitant features of psoriasis and PsA.

What is already known about this topic?

- Secukinumab, an interleukin-17A inhibitor, has previously been reported to have significantly higher efficacy in head-to-head trials vs. etanercept and ustekinumab in patients with moderate-to-severe plaque psoriasis.

What does this study add?

- The results of the study provide valuable head-to-head data on the efficacy of two biologics with different mechanisms of action (secukinumab and adalimumab) as first-line biological monotherapy for patients with psoriatic arthritis and concomitant moderate-to-severe plaque psoriasis.
- The findings of this study can further help physicians to make informed and evidence-based decisions for the treatment of patients with active psoriatic arthritis who have concomitant moderate-to-severe plaque psoriasis.

Psoriasis is an immune-mediated inflammatory disease with a prevalence varying from 0·14% [95% confidence interval (CI) 0·05–0·4%] in East Asia to 1·92% in Western Europe (1·1–3·5%) in the adult population.[1] Psoriatic arthritis (PsA) is a heterogeneous chronic disease that can affect peripheral and axial joints, and entheses.[2] PsA and psoriasis have related but different pathogenic mechanisms, with shared and unshared genetic factors and environmental stimuli contributing to the disease incidence and severity of both conditions.[3] Approximately 30% of patients with psoriasis develop PsA, often subsequent to the onset of skin disease. Hence, dermatologists have the opportunity to detect PsA before the patients are referred to rheumatologists.[4]

Recent European League Against Rheumatism 2019 recommendations suggest that the primary goal of treating patients with PsA should be to maximize health-related quality of life (HRQoL), through control of symptoms, prevention of structural damage, normalization of function and social participation. When evaluating whether a therapy is effective in PsA, it is vital to understand the efficacy in the context of active psoriasis and whether the therapy improves symptoms specifically associated with PsA. Patients with psoriasis, PsA, or both, generally have reduced HRQoL and productivity.[5]

Many patients with PsA who have concomitant psoriasis and musculoskeletal symptoms show inadequate clinical responses or intolerance to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate (MTX), both in musculoskeletal and nonmusculoskeletal manifestations in patients with PsA.[6] Similar to PsA, recent treatment recommendations for psoriasis suggest initiating biological therapy for patients if MTX or ciclosporin have failed, or considering biological therapy earlier in the treatment plan if MTX is not well tolerated.[7]

Adalimumab, a human monoclonal antibody against tumour necrosis factor (TNF), is widely used as a first-line biological disease-modifying antirheumatic drug (bDMARD) in the treatment of patients with PsA, with or without concomitant MTX, and in patients with psoriasis, particularly when psoriatic arthropathy is a major cause for concern.[7,8] Secukinumab, a human monoclonal antibody that directly inhibits interleukin (IL)-17A, has demonstrated sustained clinical efficacy in the key clinical manifestations of PsA, in addition to improvement in physical function, HRQoL and inhibition of radiographic progression. In the treatment of patients with moderate-to-severe plaque psoriasis, secukinumab has shown greater efficacy vs. etanercept (TNF inhibitor) and ustekinumab (IL-12/23 inhibitor).[9–13]

Both adalimumab and secukinumab have been proven to be effective options for the treatment of patients with active PsA with or without the use of concomitant MTX.[8,10,14] However, approximately 40% of patients treated with MTX stop treatment owing to poor tolerability and/or toxicity problems, or cannot be treated with MTX, because of hepatic abnormalities related to PsA or concomitant alcohol abuse.[6,15,16]

EXCEED is the first double-blind head-to-head study to evaluate the efficacy and safety of secukinumab vs. adalimumab as a first-line biological monotherapy in patients with active PsA who were naïve to bDMARDs for PsA and psoriasis, and who were intolerant or had an inadequate response to csDMARDs. The results of the study showed that secukinumab narrowly missed statistical significance for superiority vs. adalimumab in the primary endpoint of American College of Rheumatology (ACR) 20 response at week 52; ACR 20 responses at week 52 were 67·4% with secukinumab vs. 61·5% with adalimumab ($P = 0·071$).[17] Secukinumab provided numerically higher (not statistically significant) clinical responses across

musculoskeletal, skin and composite indices outcomes, with a higher retention rate than adalimumab at week 52.[17] Here, we report 52-week results from prespecified analyses in patients with PsA who had concomitant moderate-to-severe plaque psoriasis from the EXCEED study.

Materials and methods

Study design and participants

EXCEED is a 52-week phase IIIb randomized, double-blind, multicentre (168 sites in 26 countries), active-controlled, parallel-group monotherapy study (trial registration number NCT02745080). The detailed study design and the patient inclusion and exclusion criteria have been previously reported.[17]

Briefly, patients aged ≥ 18 years fulfilling the PsA classification criteria,[18] who had active PsA (defined as at least three tender joints and at least three swollen joints) and active plaque psoriasis, with at least one plaque with a diameter ≥ 2 cm or documented history of plaque psoriasis or nail changes that were consistent with psoriasis were included. Other inclusion criteria included patients who had received previous treatment with csDMARDs (included but not limited to MTX) and had an inadequate response or discontinued treatment owing to safety/tolerability problems, and had an inadequate response to nonsteroidal anti-inflammatory drugs for ≥ 4 weeks prior to randomization. Before randomization, patients were required to stop any csDMARD (including MTX) with a washout period of 4 weeks and 8 weeks for csDMARDs and leflunomide, respectively. Patients on concomitant corticosteroids were required to remain on a stable dose of ≤ 10 mg per day of prednisone for ≥ 2 weeks before randomization up to week 52. Key exclusion criteria were as follows: indication of ongoing infection or malignancy, pregnancy, former exposure to any biologics for PsA or psoriasis, intake of high-potency opioids, and ongoing use of oral/topical retinoids or skin treatment, or photochemotherapy.

Eligible patients were randomized (1 : 1) to receive secukinumab 300 mg or adalimumab 40 mg after a screening period of up to 8 weeks. Secukinumab was administered using subcutaneous injections (via a prefilled syringe) at baseline, weeks 1–4, and then every 4 weeks until week 48. Adalimumab was also administered via subcutaneous injection as 40 mg/0·4 mL citrate-free every 2 weeks from baseline until week 50. To ensure a consistent number of injections and to maintain allocation concealment, all groups received placebo injections at each visit.

The institutional review board at each participating centre approved the protocol. Data were collected in accordance with Good Clinical Practice guidelines by the study investigators and were analysed by the sponsor.

Outcome measures

The primary outcome in the EXCEED study was the proportion of patients with ≥ 20% improvement in the ACR response criteria (ACR 20) at week 52. The key secondary endpoints assessed at week 52 (in order of statistical hierarchy) were Psoriasis Area and Severity Index (PASI) 90 response, ACR 50 response, Health Assessment Questionnaire-Disability Index (HAQ-DI) score (mean change from baseline), and resolution of enthesitis [Leeds Enthesitis Index (LEI)].

In the present prespecified subgroup analyses, patients with active PsA who had concomitant moderate-to-severe plaque psoriasis defined as involvement of body surface area (BSA) > 10% or PASI ≥ 10 at baseline (henceforth, referred to as the psoriasis subset) were analysed.

The prespecified endpoints at week 52 evaluated in the psoriasis subset included ACR 20 response, PASI 90 response, ACR 50 response, mean change from baseline in HAQ-DI, resolution of enthesitis, the proportion of patients achieving PASI 75 and PASI 100 responses, and combined ACR 50 and PASI 100 response (defined as the proportion of patients who simultaneously achieved an ACR 50 and PASI 100 response).

In addition, composite indices outcomes often used in the management of PsA, such as the proportion of patients achieving low disease activity (LDA) and/or remission (REM) based on the Disease Activity index for PsA (DAPSA) and PsA Disease Activity Score (PASDAS) were also assessed. Quality of life was assessed using HAQ-DI response (≥ 0·35), Dermatology Life Quality Index (DLQI) 0/1 response, and mean change from baseline in DLQI. Mean change from baseline in the short form-36 survey – physical/mental component summary (SF-36 PCS/MCS) and Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) score were also evaluated.

In order to better understand the selection of certain outcome measures for clinical assessment of disease activity in patients with PsA adopted in the primary analysis, we have briefly summarized outcome measures in Appendix S1 (see Supporting Information).

Statistical analysis

The full analysis set (FAS) used for the primary efficacy analysis included all patients who were randomized and to whom study treatment was assigned.

The psoriasis subset considered in the present analysis included all patients with active PsA (FAS) with concomitant moderate-to-severe plaque psoriasis with BSA > 10% or PASI ≥ 10 at baseline.

It is important to note that the primary efficacy endpoint was defined as meeting all of the three following conditions: achieving an ACR 20 response, with no permanent termination of study treatment (secukinumab or adalimumab) before or at week 50 (the last dosing visit), and no concomitant use of csDMARDs (including but not limited to MTX) after week 36 (irrespective of the time initiation of csDMARDs).[17] There were only three patients who were taking csDMARDs while on study treatment (protocol deviators) but none of these patients were on csDMARDs after week 36. In the overall study and for the current prespecified analyses, all the

secondary and binary (exploratory) endpoints were defined in a similar fashion to that of the primary endpoint.

For binary endpoint analyses, odds ratios (ORs), 95% CIs and P-values were computed for comparative assessments of secukinumab vs. adalimumab from a logistic regression model with treatment as a factor and baseline weight as a covariate. Between-group differences in continuous endpoints were evaluated using a mixed-effect model with repeated measures approach, with treatment and assessment visit as factors, weight and baseline values of the endpoints as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms. For analyses of continuous efficacy endpoints, data for patients who discontinued study treatment before week 50 or who took csDMARDs after week 36 were considered as 'missing' for the visits after discontinuation of treatment or use of csDMARDs.

Although the analyses for the psoriasis subset were prespecified, the study was not prospectively powered for testing treatment difference. Thus, unadjusted nominal P-values (without adjusting for multiplicity) are presented.

Results

A total of 853 patients were randomized to receive secukinumab (N = 426) or adalimumab (N = 427) in the study; at baseline, there were 211 patients in the psoriasis subset [secukinumab (N = 110) and adalimumab (N = 101)]. Up to week 50, a total of six of 110 (5·5%) patients had discontinued treatment in the secukinumab group vs. 18 of 101 (17·8%) patients in the adalimumab group in the psoriasis subset. The major reasons for discontinuation of secukinumab vs. adalimumab treatment were lack of efficacy [one of 110 (0·9%) vs. seven of 101 (6·9%)] and patient/guardian decision [four of 110 (3·6%) vs. six of 101 (5·9%)] (Figure 1). The analysis of patients in the psoriasis subset for time to study treatment discontinuation (Kaplan–Meier curve) indicated that a higher proportion of patients were being retained for a longer period for secukinumab than adalimumab treatment until last dosing visit at week 50 (P = 0·0005) (Figure 2).

Demographics and disease characteristics at baseline were comparable in the secukinumab and adalimumab groups, except for the proportion of patients with enthesitis, which was higher in the adalimumab group [59 of 110 (53·6%) in secukinumab vs. 69 of 101 (68·3%) in the adalimumab groups] (Table 1). ACR 20 response rates at week 52 were 76·4% in the secukinumab group vs. 68·3% in the adalimumab group [OR (vs. adalimumab) 1·53, 95% CI 0·83–2·83; P = 0·175] (Figure 3a and Table 2). At week 52, PASI 90 responses in the secukinumab and the adalimumab groups were 68·6% and 41·7%, respectively (P < 0·001) (Figure 3b and Table 2). ACR 50 responses were 54·5% (secukinumab) vs. 49·3% (adalimumab) (P = 0·386) (Figure 3c and Table 2). A total of 74·5% of patients receiving secukinumab and 66·2% of patients receiving adalimumab achieved resolution of enthesitis at week 52 (P = 0·157) (Figure 3d and Table 2) and the mean (SE) change in HAQ-DI from baseline to week 52 in the secukinumab and the adalimumab groups was −0·60 (0·049) and −0·56 (0·053), respectively (P = 0·532) (Figure 3e and Table 2).

A total of 28·2% of patients achieved improvement in combined ACR 50 and PASI 100 response with secukinumab vs. 17·7% with adalimumab through week 52 (P = 0·06) (Figure 4 and Table 2). Other musculoskeletal outcomes such as ACR 70 response rate and the proportion of patients achieving resolution of dactylitis in the psoriasis subset are shown in Figure S1 (see Supporting Information). At week 52, PASI 100 responses in the secukinumab and the adalimumab groups were 39·1% and 23·8%, respectively (P = 0·013) (Figure 5a and Table 2). The additional skin-specific endpoints including PASI 75 (Figure 5b), quality of life (DLQI) (Figures 5c, d), and composite indices outcomes including achievement of LDA and/or REM responses/targets at week 52 in the secukinumab and the adalimumab groups (as assessed by minimal disease activity, very low disease activity, DAPSA and PASDAS) are shown in Table 2. The mean change from baseline in DLQI score in the secukinumab and the adalimumab groups was −10·27 [from the mean (SD) baseline score of 13.8] and −8·32 (from the mean baseline score of 13·3) at week 52, respectively; DLQI 0/1 response was 49·1% with secukinumab vs. 37·1% with adalimumab (P = 0·071) at week 52 (Figure 5c, d and Table 2). The mean change from baseline in SF-36 PCS/MCS and FACIT-F score in the psoriasis subset is presented Figure S2 (see Supporting Information).

Although the EXCEED study was designed to evaluate the efficacy of secukinumab vs. adalimumab at week 52, higher responses were observed with secukinumab from earlier timepoints. ACR 20 response rates at week 24 were 73·5% in the secukinumab group vs. 66·0% in the adalimumab group (Figure 3a). PASI 90 responses were 70·5% and 42·6% in the secukinumab and the adalimumab groups, respectively (Figure 3b). A total of 20·9% of patients achieved improvement in combined ACR 50 and PASI 100 response with secukinumab vs. 6·9% with adalimumab at week 24 (Figure 4).

The interaction testing for the efficacy outcomes between psoriasis status (stratified into 'active PsA with concomitant psoriasis' and 'nonpsoriasis subset of PsA') and the secukinumab treatment effect at week 52 was conducted and the results are shown in Table S1 (see Supporting Information).

Both secukinumab and adalimumab exhibited similar safety profiles in the overall population, which was consistent with previously published reports.[17] Separate safety analyses for this subset were not conducted.

Discussion

The results of the prespecified analyses in the subset of patients with active PsA and concomitant moderate-to-severe plaque psoriasis are consistent with the primary results of the head-to-head EXCEED monotherapy study.[17]

Psoriasis usually develops long before the symptoms and signs of PsA develop. Thus, it is more likely that patients will

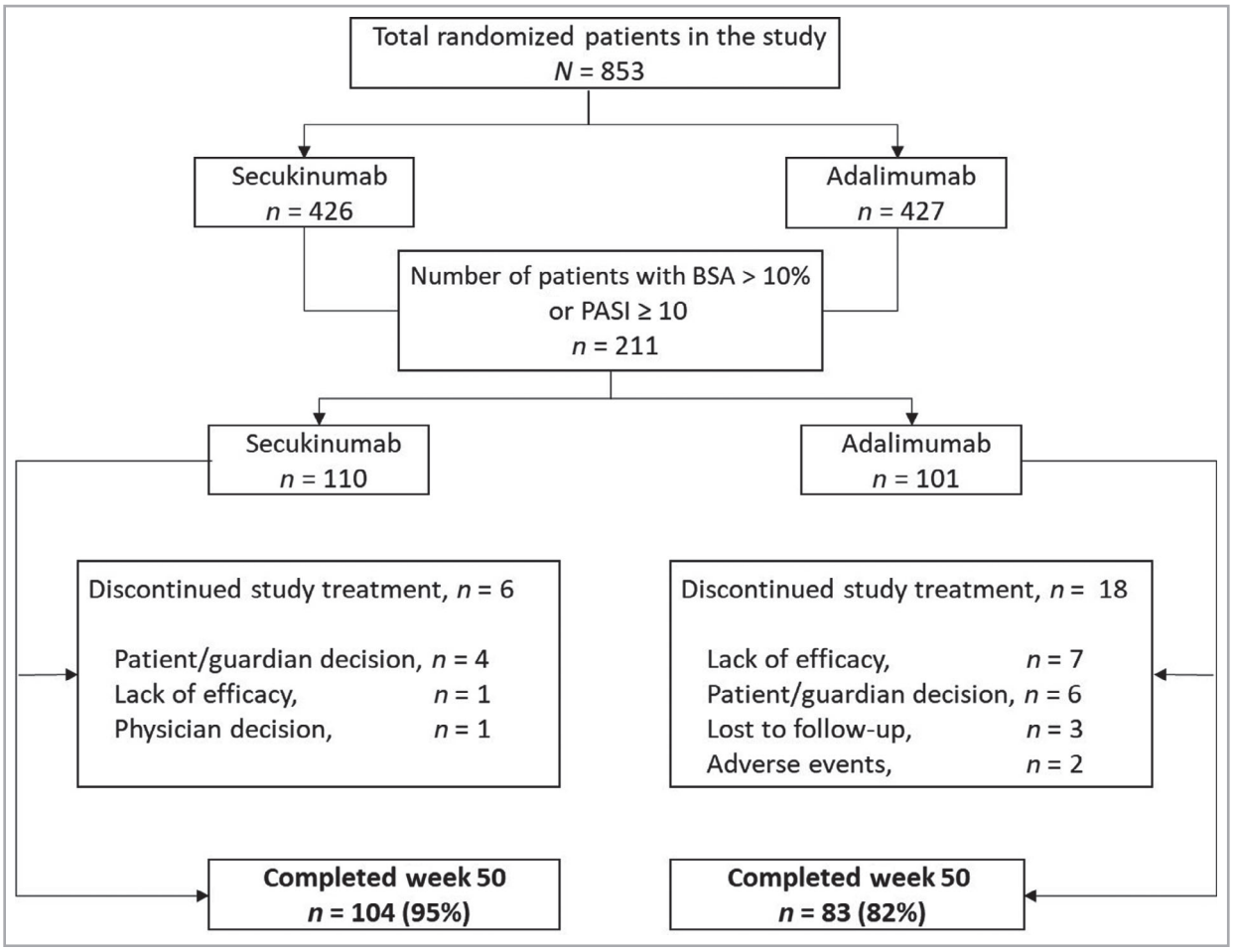

Figure 1 Patient study treatment disposition up to week 52 in the psoriasis subset of patients with psoriatic arthritis. N, number of randomized patients; n, number of available patients; BSA body surface area; PASI, Psoriasis Area and Severity Index.

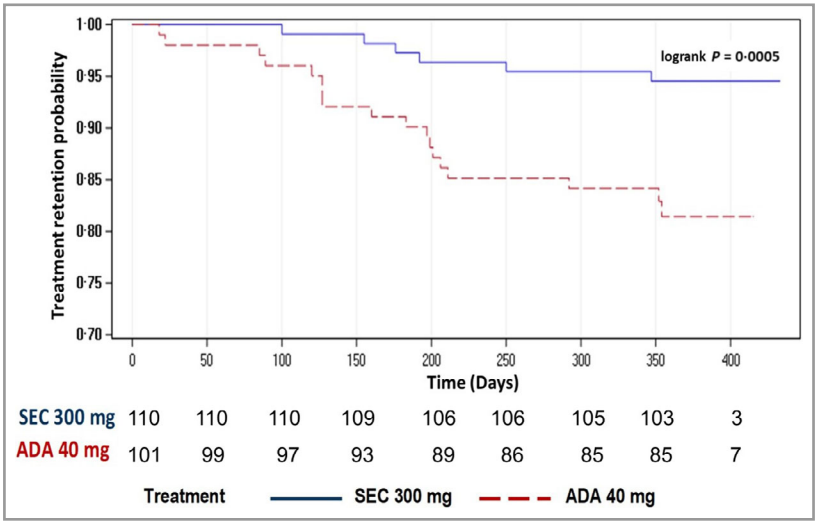

Figure 2 Kaplan–Meier time to study treatment discontinuation curve in the psoriasis subset of patients with psoriatic arthritis. ADA, adalimumab; SEC, secukinumab. P-value vs. adalimumab. Numbers of patients at risk are presented for SEC and ADA.

Table 1 Baseline demographic and disease characteristics in the psoriasis subset of patients with psoriatic arthritis

	SEC 300 mg (N = 110)	ADA 40 mg (N = 101)	Total (N = 211)
Age, years	48·9 (12·2)	46·9 (12·3)	47·9 (12·2)
Female sex, n (%)	44 (40·0)	44 (43·6)	88 (41·7)
White patients, n (%)[a]	108 (98·2)	90 (89·1)	198 (93·8)
Weight, kg	87·3 (20·4)	85·9 (16·6)	86·6 (18·6)
BMI, kg m^{-2}	29·5 (6·1)	29·6 (5·6)	29·5 (5·8)
Smoking status, yes, n (%)	29 (26·4)	25 (24·8)	54 (25·6)
Systemic glucocorticoids use at randomization, n (%)	8 (7·3)	5 (5·0)	13 (6·2)
Time since first diagnosis of psoriatic arthritis, years	6·1 (8·9)	6·7 (8·4)	6·4 (8·7)
Baseline PASI score	16·2 (9·6)	15·0 (8·9)	15·6 (9·2)
Patients with psoriasis of hands and feet, n (%)	73 (66·4)	73 (72·3)	146 (69·2)
Patients with psoriasis of nail, n (%)	77 (70·0)	74 (73·3)	151 (71·6)
Adjusted tender joint total score for psoriatic arthritis (78 joints)	17·4 (10·0)	19·7 (12·5)	18·5 (11·3)
Adjusted swollen joint total score for psoriatic arthritis (76 joints)	9·3 (6·5)	10·7 (8·2)	10·0 (7·4)
Patient's Global Assessment (0–100)	63·9 (21·3)	64·1 (20·6)	64·0 (20·9)
Physician's Global Assessment (0–100)	64·8 (15·1)	64·7 (13·9)	64·7 (14·5)
Psoriatic arthritis pain (0–100)	57·9 (25·0)	59·7 (24·0)	58·8 (24·5)
CRP $\geq$ 10 mg L^{-1}, n (%)	32 (29·1)	33 (32·7)	65 (30·8)
Disease Activity Score 28-CRP	4·7 (0·9)	4·8 (1·0)	4·7 (1·0)
Presence of enthesitis, n (%)[a]	59 (53·6)	69 (68·3)	128 (60·7)
Presence of dactylitis, n (%)	35 (31·8)	33 (32·7)	68 (32·2)
HAQ-DI score	1·3 (0·6)	1·3 (0·7)	1·3 (0·6)

ADA, adalimumab; BMI, basal metabolic index; BSA, body surface area; CRP, C-reactive protein; HAQ-DI, health assessment questionnaire-disability index; N, number of active PsA patients who had BSA involvement > 10% or PASI $\geq$ 10 affected by psoriasis at baseline; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SEC, secukinumab. [a]$P < 0·05$ using Fisher's exact test. Data are presented as mean (SD) unless otherwise stated.

visit a dermatologist prior to consulting with a rheumatologist. Furthermore, it is estimated that PsA in approximately 10–15% of patients with psoriasis remains undiagnosed or misdiagnosed.[19] Hence, it is vital to routinely screen patients with psoriasis for the diagnosis of PsA in a dermatology clinic.[20] Delay of PsA diagnosis can lead to irreversible joint damage, even if a significant improvement in psoriasis occurs.[5] Therefore, dermatologists have a pivotal role in early identification of patients with PsA and prevention of irreversible joint damage. This can be achieved by timely screening for PsA in patients with psoriasis and providing therapeutic options that are effective in treating both psoriasis and PsA.[21]

Head-to-head trials could play an important role in clinical decision making, given the increased availability of biologics with distinct modes of action, in the management of patients with active PsA who have concomitant skin disease after csDMARD failure, intolerance or contraindication (including MTX).

The study evaluated an important current gap in our understanding by examining the initiation of biological monotherapy in patients with active PsA. Combination therapy with MTX and biologics has not been shown to be superior to biological treatment alone[22,23] and many patients discontinue MTX as primary or combination therapy because of poor tolerability and/or toxicity, or cannot receive MTX owing to liver abnormalities.[6,15]

EXCEED is the first double-blind, randomized controlled head-to-head monotherapy study to compare secukinumab with adalimumab in patients with active PsA.[17] This study was primarily designed for rheumatologists to address a key question of whether secukinumab was superior to adalimumab for the treatment of patients with PsA as first-line bDMARD treatment after csDMARD failure, intolerance or contraindication.

In the primary analysis of the EXCEED study, secukinumab narrowly missed statistical significance for the primary endpoint of ACR 20 response at week 52; 67·4% with secukinumab vs. 61·5% with adalimumab ($P = 0·071$).[17]

In this prespecified analysis of patients with PsA who had moderate-to-severe psoriasis, secukinumab showed consistent improvements with respect to efficacy compared with adalimumab for musculoskeletal outcomes (ACR 20/50 responses, resolution of enthesitis and resolution of dactylitis), composite indices targeting remission or LDA, and physical function outcomes at week 52.

Secukinumab demonstrated consistently higher PASI responses vs. adalimumab across skin endpoints (PASI 75/90, $P < 0·001$; PASI 100, $P < 0·05$). These results are consistent with previous secukinumab studies (vs. placebo in the FIXTURE study, vs. etanercept and placebo in the ERASURE study, and vs. ustekinumab in the CLARITY study) in patients with PsA and psoriasis.[24–26]

A greater treatment retention rate was observed with secukinumab vs. adalimumab in patients with PsA who had

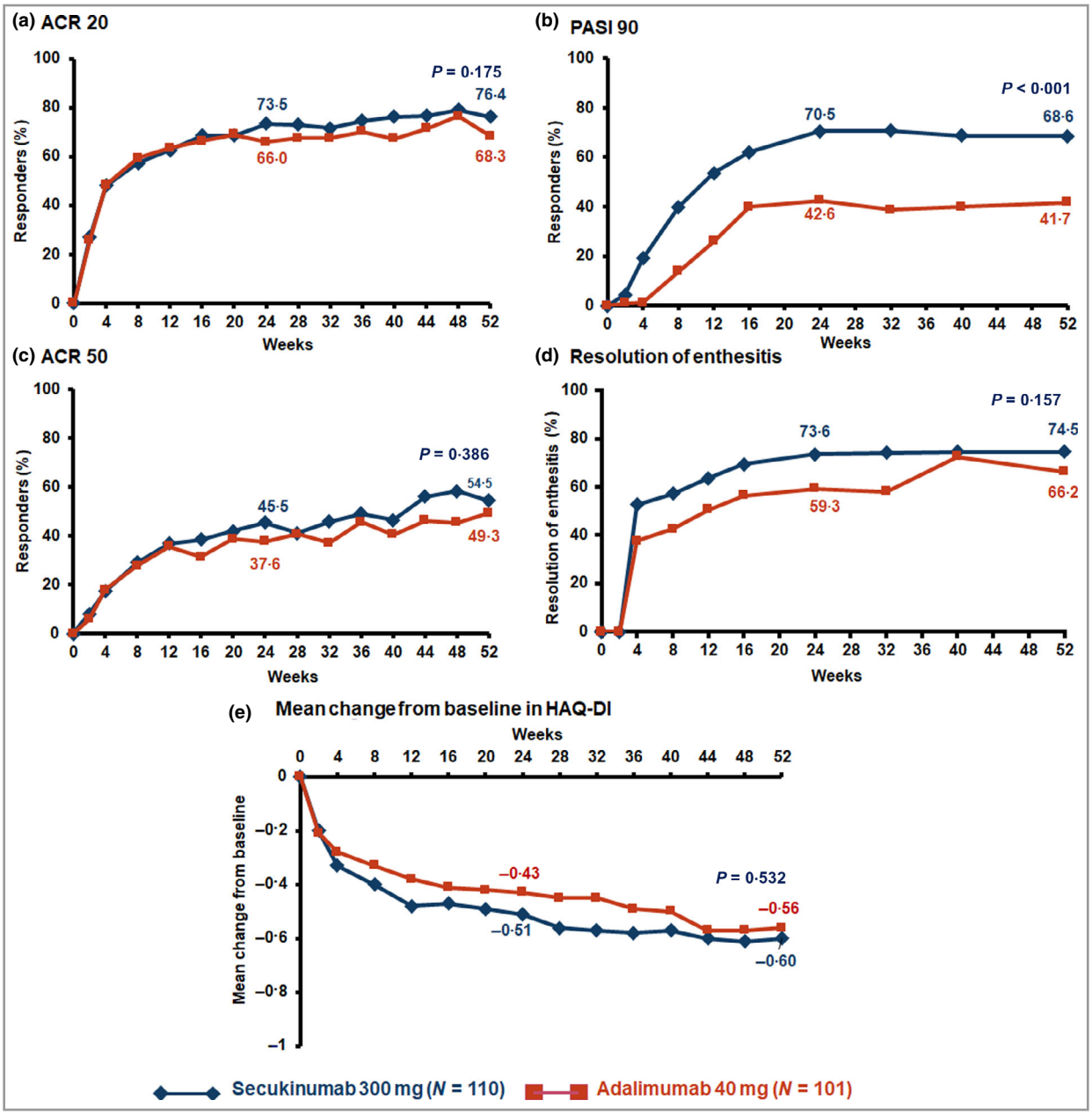

Figure 3 ACR 20/50, PASI 90 response rates, resolution of enthesitis, mean change from baseline in HAQ-DI through week 52 in the psoriasis subset of patients with psoriatic arthritis. N, number of active PsApatients who had body surface area (BSA) > 10% or PASI ≥ 10 affected by psoriasis at baseline. ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifyinganti-rheumatic drugs; HAQ-DI, health assessment questionnaire-disability index; PASI, psoriasis area severity index; PsA, psoriatic arthritis. P-value vs. adalimumab. Unadjusted P-values are reported at week 52. Binary outcomes (ACR 20, PASI 90, ACR 50 and resolution of enthesitis) were assessed using logistic regression; mean change from baseline in HAQ-DI was analysed using a mixed-effect model with repeated measures and HAQ-DI was analysed using logistic regression. Patients who discontinued study treatment before or at week 50 or took csDMARDs after week 36 are considered nonresponders for the visits after discontinuation or taking csDMARDs. Multiple imputation is used for all other missing data.

moderate-to-severe plaque psoriasis similar to that of the overall EXCEED study population.[17]

Owing to the diverse clinical manifestations of PsA, improvements in both musculoskeletal and skin outcomes (the combined effect) are considered essential for optimizing overall HRQoL in PsA.[27] Hence, the combination of two stringent endpoints; the musculoskeletal endpoint (ACR 50) and the skin endpoint (PASI 100) represent a treat-to-target endpoint to evaluate the response to active disease in patients with PsA, with both joint and skin components.[28] The combined ACR 50 and PASI 100 response at week 52 with secukinumab vs. adalimumab in the current analysis was 28·2% vs. 17·7%

Table 2 Efficacy outcomes at week 52 in the psoriasis subset of patients with psoriatic arthritis

Endpoints	SEC 300 mg (N = 110)	ADA 40 mg (N = 101)	Odds ratio	95% Confidence interval	P-values (unadjusted)
Musculoskeletal outcomes					
ACR 20	76·4	68·3	1·53	0·83–2·83	0·175
ACR 50	54·5	49·3	1·28	0·73–2·22	0·386
ACR 70	30·9	28·6	1·14	0·62–2·08	0·673
Resolution of enthesitis	74·5	66·2	1·54	0·85–2·82	0·157
Resolution of dactylitis	90·9	81·0	2·39	1·05–5·45	0·037
Combined outcome					
ACR 50 + PASI 100	28·2	17·7	1·92	0·97–3·79	0·06
Skin outcomes					
PASI 75	87·2	59·6	5·02	2·48–10·19	< 0·001
PASI 90	68·6	41·7	3·21	1·80–5·71	< 0·001
PASI 100	39·1	23·8	2·15	1·17–3·96	0·013
DLQI 0/1	49·1	37·1	1·67	0·96–2·93	0·071
Composite indices outcomes					
MDA	44·5	34·7	1·56	0·89–2·74	0·123
VLDA	14·5	14·9	0·98	0·45–2·13	0·968
DAS-28 CRP LDA	81·8	64·1	2·58	1·34–4·97	0·004
DAS28-CRP REM	58·2	50·5	1·34	0·76–2·38	0·309
DAPSA REM	25·5	24·9	1·00	0·53–1·89	0·992
DAPSA LDA + REM	73·6	59·9	1·74	0·95–3·21	0·073
PASDAS REM	19·1	14·6	1·41	0·66–3·02	0·374
PASDAS LDA + REM	52·0	44·1	1·37	0·78–2·39	0·273
QoL outcomes					
HAQ-DI score, change from baseline, mean (SE) (n)	−0·60 (0·049) (104)	−0·56 (0·053) (79)	−0·04[a]	−0·19–0·10	0·532
HAQ-DI (≥ 0·35)	57·3	55·1	1·2	0·67–2·14	0·532
DLQI score, change from baseline, mean (SE) (n)	−10·27 (0·526) (105)	−8·32 (0·580) (81)	−1·95[a]	−3·49 to −0·40	0·013
FACIT-F, change from baseline, mean (SE) (n)	8·78 (0·891) (105)	7·0 (0·977) (81)	1·78	−0·83–4·39	0·179

ACR, American college of Rheumatology; ADA, adalimumab; BSA, body surface area; CRP, C-reactive protein; DAPSA, Disease Activity index for PsA; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; MDA, minimal disease activity; PASDAS, PsA Disease Activity Score; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; QoL, quality of life; REM, remission; SE, standard error; SEC, secukinumab; VLDA, very low disease activity; N, number of active PsA patients who had BSA involvement > 10% or PASI ≥ 10 affected by psoriasis at baseline. P-value vs. adalimumab (unadjusted P-values at week 52 are presented). [a]Between-treatment difference in mean change from baseline for HAQ-DI, DLQI and FACIT-F is presented; n is the number of patients with values both at baseline and week 52. Binary and continuous variables were analysed using logistic regression model and mixed-effects model with repeated measures, respectively. Multiple imputation was used for handling missing data. Data are presented as percentage response unless otherwise stated.

(P = 0·06). This result is consistent with the results in the overall EXCEED study population and the results of the SPIRIT head-to-head study, which compared the IL-17 inhibitor ixekizumab with adalimumab in an open-label, assessor-blind study that recruited patients with PsA who had active plaque psoriasis affecting ≥ 3% of BSA at baseline.[17,28] However, it should be noted that the EXCEED study was a monotherapy study and concomitant csDMARDS were prohibited during the study, whereas in the SPIRIT study approximately 70% of patients were receiving concomitant csDMARDs.[17,28]

The interaction testing between psoriasis status (stratified as 'active PsA with concomitant psoriasis' and 'nonpsoriasis subset of PsA') and the secukinumab treatment effect showed no significant treatment by psoriasis status interaction for any of the four efficacy endpoints, i.e. ACR 20/50, resolution of enthesitis and change from baseline in HAQ-DI. This analysis reflects the lack of treatment heterogeneity in the psoriasis status.

A limitation of this psoriasis subset analysis is that the study was not designed or powered to compare efficacy responses between the two treatments in the mild-to-moderate psoriasis subset. The monotherapy design may also limit the generalization of its findings given that concomitant MTX is widely used in PsA. The lack of nail disease and X-ray assessments are further limitations of this study. It should also be noted that the recommended dose of adalimumab for patients with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg every other week. Therefore, the use of adalimumab 40 mg

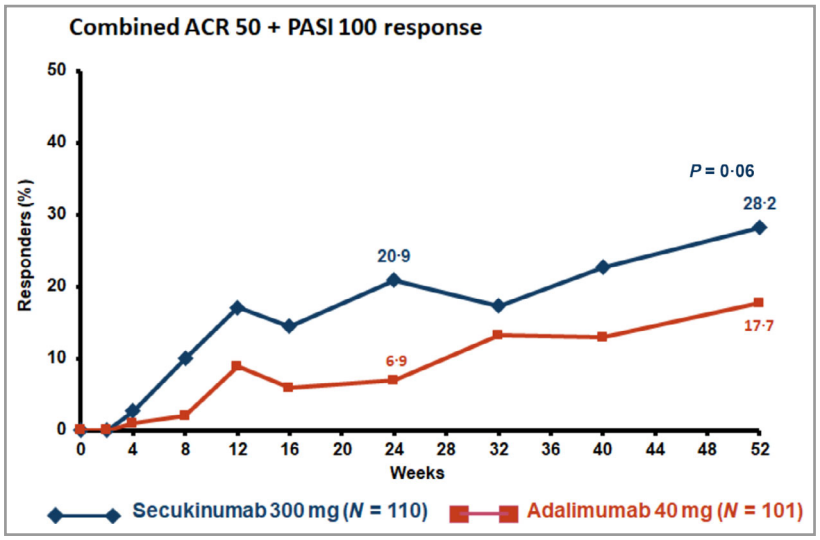

Figure 4 Combined ACR 50 + PASI 100 response rate through week 52 in the psoriasis subset of patients with psoriatic arthritis. N, number of active PsA patients who had body surface area (BSA) > 10% or PASI ≥ 10 affected by psoriasis at baseline. ACR, American College of Rheumatology; csDMARD, conventional synthetic disease modifyinganti-rheumatic drugs; PASI, psoriasis area severity index; PsA, psoriatic arthritis. P-value vs. adalimumab. Unadjusted P-values are reported at week 52. Patients who discontinued study treatment before or at week 50 or took csDMARDs after week 36 are considered nonresponders for the visits after discontinuation or taking csDMARDs. Multiple imputation is used for all other missing data.

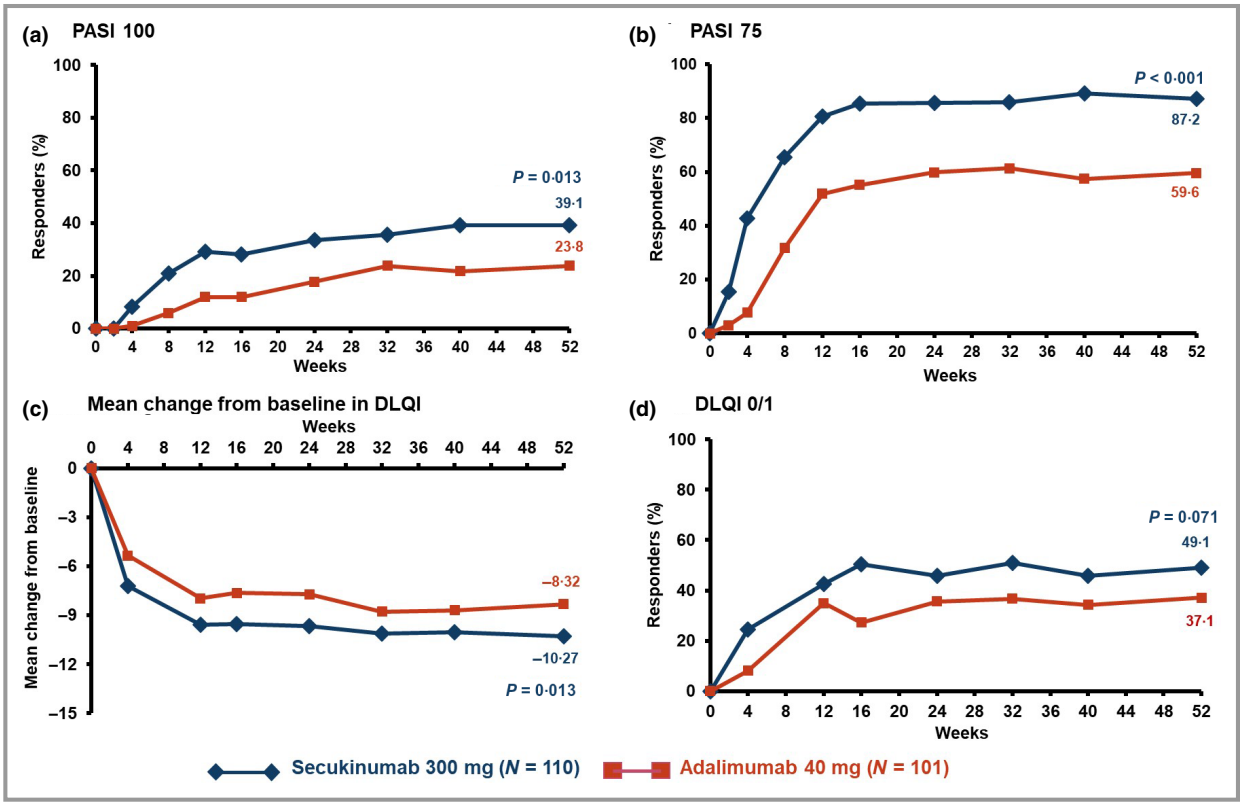

Figure 5 PASI 100 and PASI 75 response rates and mean change from baseline in DLQI and DLQI 0/1 response through week 52 in the psoriasis subset of patients with psoriatic arthritis. N, number of active PsA patients who had body surface area (BSA) > 10% or PASI ≥ 10 affected by psoriasis at baseline. csDMARD, conventional synthetic disease modifying anti-rheumatic drugs; DLQI, dermatology life quality index; PASI, Psoriasis Area Severity Index; PsA, psoriatic arthritis. P-value vs. adalimumab. Unadjusted P-values are reported at week 52. Patients who discontinued study treatment before or at week 50 or took (csDMARDs) after week 36 are considered nonresponders for the visits after discontinuation or taking csDMARDs. Multiple imputation is used for all other missing data. A mixed-effect model with repeated measures was used to assess mean change from baseline in DLQI.

throughout the study may have impacted skin outcomes during the first few weeks of the study.

In conclusion, the results of this prespecified analysis of the psoriasis subset of the EXCEED study provides further evidence that IL-17 inhibitors offer a comprehensive biological treatment profile to manage the concomitant features of psoriasis and PsA.[17]

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Appendix

Conflicts of interest

A.B.G. has received honoraria for acting as an advisory board member and for consulting from Anaptyps Bio, Avotres Therapeutics, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb Co., Incyte, Dermavant, Janssen Inc. LEO Pharma, Eli Lilly, Novartis, Sun Pharmaceutical Industries, UCB and Xbiotech (stock options). A.B.G. has received research/educational grants from Boehringer Ingelheim, Incyte, Janssen Inc., Novartis, UCB, Xbiotech and Sun Pharma (all educational and research grant income went to the Icahn School of Medicine at Mount Sinai). J.F.M. has acted as a consultant for Merck, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB Pharma, Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer, EMD Serono, Avotres and LEO Pharma. K.R. has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Centocor, Covagen, Dermira, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO, Lilly, Medac, Merck Sharp & Dohme, Novartis, Miltenyi Biotec, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant and Xenoport. F.B. has received research grants from Pfizer, Janssen, Chugai, Celgene and Roche. F.B. has also received consultancy/speaker fees from Pfizer, AbbVie, Amgen, Sanofi, Lilly, Novartis, Gilead, Genzyme, Boehringer, Janssen, MSD, Celgene, Roche and Chugai, BMS, UCB Pharma. P.N. has received grant/research support from AbbVie, BMS, Celgene, Eli Lilly, Gilead Sciences, Inc, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Amgen, Roche and Sanofi-Aventis. P.N. has been a consultant for AbbVie, BMS, Celgene, Eli Lilly, Gilead Sciences, Inc., Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Amgen, Roche and Sanofi-Aventis. P.N. has also participated in a speakers bureau for AbbVie, BMS, Celgene, Eli Lilly, Gilead Sciences, Inc, Janssen, MSD, Novartis, Pfizer Inc, Roche, Sanofi, UCB, Amgen, Roche and Sanofi-Aventis. C.E.M.G. has received honoraria and/or research support from AbbVie, Amgen, Almirall, BMS, Boehringer Ingelheim Celgene, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sun Pharma and UCB Pharma. W.B., P.P. and L.P. are shareholders of and employees of Novartis. I.B.M. has received grant/research support from AbbVie, Janssen, Novartis, Lilly, Celgene, UCB Pharma, BMS, Boehringer Ingelheim, AstraZeneca, Pfizer and has acted as a consultant for AbbVie, Janssen, Novartis, Lilly, Celgene, Compugen, UCB Pharma, BMS, Boehringer Ingelheim, AstraZeneca and Pfizer.

Ethics approval and consent to participate

All clinical studies were conducted in compliance with the Declaration of Helsinki, International Council for Harmonization Guidelines for Good Clinical Practice and local country regulations. All patients provided written informed consent to participate in the respective studies.

Data sharing statement

The datasets generated and/or analysed during the current study are not publicly available. Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Clinical assessments.

Figure S1 Other musculoskeletal outcomes (a) American College of Rheumatology 70 response and (b) resolution of dactylitis through week 52 in the psoriasis subset of patients with psoriatic arthritis.

Figure S2 (a) Short Form-36 survey – physical component summary, (b) Short Form-36 survey – mental component summary and (c) Functional Assessment of Chronic Illness Therapy –mean change from baseline through week 52 in the psoriasis subset of patients with psoriatic arthritis.

Table S1 Interaction testing between psoriasis status and the treatment effect at week 52.