Efficacy of secukinumab on dactylitis in patients with active psoriatic arthritis from the FUTURE 5 study

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Abstract

Objective

Dactylitis is an important clinical domain of psoriatic arthritis (PsA) associated with significant burden of disease and impaired function. Post-hoc analysis of the FUTURE 5 study was performed to evaluate the efficacy of secukinumab in patients with dactylitis at baseline over 2 years.

Methods

Randomised patients received secukinumab 300 mg with loading dose (LD)/150 mg LD/150 mg without loading dose/placebo. Assessment of dactylitis was based on Leeds Dactylitis Index. Exploratory analyses included resolution of dactylitis based on severity, time to first resolution of dactylitis (Kaplan-Meier estimate) and resolution of dactylitis (heatmap analysis). Clinical efficacy outcomes, composite domains of disease activity, health-related quality of life (HRQoL) and radiographic progression using van der Heijde-modified total Sharp score were assessed in patients with/without dactylitis at baseline.

Results

Overall, 389/996 (39%) patients presented with dactylitis at baseline, had more active clinical disease and greater disease activity than those without dactylitis at baseline. Resolution of dactylitis was observed across all treatment groups at Week 104. Improvement in joints, enthesitis, skin psoriasis, nail outcomes, physical function and HRQoL were sustained over 2 years in patients with dactylitis at baseline. With secukinumab treatment, >80% of patients did not show structural radiographic progression. The proportion of non-structural radiographic progressors were comparable across patients with/without dactylitis at baseline with secukinumab treatment over 2 years.

Conclusion

Patients with dactylitis at baseline were associated with higher burden of disease. Secukinumab provided sustained improvements across all clinical outcomes, QoL and inhibition of radiographic progression in PsA patients with dactylitis at baseline over 2 years.

Key words

psoriatic arthritis, dactylitis, burden of disease, quality of life, secukinumab, biologics

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Introduction

Psoriatic arthritis (PsA) is a multifaceted, chronic, inflammatory disease characterised by peripheral arthritis, dactylitis, enthesitis, axial disease, skin and nail psoriasis (PsO) (1, 2). Dactylitis is a characteristic musculoskeletal lesion of PsA. It is defined as a uniform swelling of the whole digit that results from inflammation in the soft tissues, tendon sheaths and joints (3, 4). Approximately, half of patients with PsA present with concomitant dactylitis. It usually involves several fingers and/or toes in an asymmetric manner, resulting in a sausage-like appearance of the affected digits (5). Dactylitis may occur as a tender swollen digit in the acute phase, or as a non-tender swollen digit in the chronic phase (6). Dactylitis is a marker of PsA disease severity (6, 7) more often associated with structural damage progression. Clinical outcome measures assessing dactylitis include Dactylitis count (DC) and Leeds Dactylitis Index (LDI). In addition, some composite indices targeting low disease activity or remission such as Composite Psoriatic Disease Activity Index and Psoriatic Arthritis Disease Activity Score (PASDAS) include dactylitis as one of the core components. PsA patients with dactylitis tend towards poor physical function and higher disease activity leading to greater burden of disease (8).

The recent GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) recommendations recognise dactylitis as a key domain that reflects higher disease burden and necessitates early diagnosis, assessment, and treatment in PsA (9). Most randomised controlled trials (RCTs) with biologics in PsA focus on peripheral arthritis, skin and enthesitis as key clinical domains and have used unvalidated measures of dactylitis to assess the impact.

Secukinumab (SEC), a fully human monoclonal antibody that selectively neutralises interleukin (IL)-17A, has provided significant and sustained improvement in PsO, PsA and axial spondyloarthritis, and has been approved for their treatment in many countries (10, 11).

In the FUTURE 5 study (NCT02404350), SEC with and without loading regimen provided sustained clinical efficacy and low radiographic progression over 2 years in patients with PsA (12).

Here, results from a comprehensive *post-hoc* analysis of the efficacy of SEC in the dactylitis subset (based on the presence or absence of clinical dactylitis at baseline) from FUTURE 5 are reported; it was evaluated whether the efficacy of SEC in this subset across all PsA domains, on structure and health-related quality of life (HRQoL), is consistent with that of patients without dactylitis at baseline.

Materials and methods

Patients and study design

FUTURE 5 is a randomised, double-blind, placebo (PBO)-controlled, parallel-group Phase 3 trial. Eligible patients were randomised (2:2:2:3) to receive subcutaneous (s.c.) SEC 300 mg with loading dose (300 mg LD), 150 mg with LD (150 mg LD), 150 mg without LD (150 mg NL) or PBO. All patients received s.c. SEC 300 mg, 150 mg, or PBO at baseline, at Weeks 1, 2, and 3, and every 4 weeks starting at Week 4. At Week 16, non-responders (<20% reduction in tender joint count [TJC] and/or swollen joint count [SJC]) in the PBO group were switched to s.c. SEC 300 mg or SEC 150 mg and all remaining patients (responders) on PBO were switched at Week 24. Patients, investigators, and assessors remained blinded to treatment assignment until all patients reached the Week 52 visit. Key exclusion criteria included active/history of ongoing infection, prior use of a biologic other than an anti-tumour necrosis factor (TNF) agent, use of ≥3 anti-TNF agents, and active inflammatory disease other than PsA. In this *post-hoc* analysis, patients were grouped based on the presence or absence of clinical dactylitis (as defined by LDI >0) at baseline. The baseline demographics and clinical characteristics were compared in patients with and without dactylitis at baseline. The study was conducted in accordance with the principles of the Declaration of Helsinki (13), International Conference of Harmonisation - Good Clinical Practice guidelines, and all applicable laws and regulations, with written informed con-

sent obtained from all enrolled patients. Data were collected in accordance with the GCP guidelines by the study investigators and analysed by the sponsor.

Efficacy assessments

- LDI for dactylitis assessment

Dactylitis was assessed based on the LDI basic and it measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit (14). The ratio of circumference is multiplied by a tenderness score, using a modification of the LDI, which is a binary score (1 for tender, 0 for non-tender). DC included total number of fingers and toes with dactylitis, with a range of 0-20 and if dactylitis was present in any finger or toe, the patient was counted as a patient with dactylitis.

- Time to first resolution of dactylitis

Among patients with dactylitis at baseline, the Kaplan-Meier analysis was employed to calculate the proportion of patients with resolution of dactylitis up to Week 104 and assess the median time to first resolution of dactylitis with DC=0.

- Shift analysis of DC from baseline to Weeks 16, 52, and 104

Shift analysis was performed to analyze the resolution of dactylitis at Weeks 16, 52, and 104 based on the number of DC at baseline (DC ≤2 and DC ≥3) representing severity of the disease.

Heat map analysis

Resolution of DC of each patient through Week 104 by treatment arms was developed using heat map analysis. All patients with dactylitis at baseline were followed until the end of the study or discontinuation. DC ≥ baseline was represented in red, partial resolution with a DC < baseline in yellow, while green shading for full resolution with a DC=0, and white corresponds to study discontinuation.

- Relationship between baseline dactylitis status and clinical outcomes

Efficacy outcomes in patients with or without dactylitis at baseline included the following: proportion of patients achieving American College of Rheumatology (ACR) 50 response rates, Psoriasis Area and Severity Index (PASI) 90 response rates, resolution of enthesitis. Involvement of psoriatic nail in patients with PsA was assessed based on, modified Nail Psoriasis Severity Index (mNAPSI) score.

The composite domains of disease activity in PsA included PsA disease activity score 28-C-reactive protein (PASDAS) and patient's assessment of PsA pain by visual analogue scale (VAS). The impact of PsA on various aspects of patients' HRQoL was assessed by mean change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI), Short Form 36 Physical Component Summary score (SF-36 PCS), and Dermatology Life Quality Index (DLQI) scores.

- Radiographic disease progression

Radiographic disease progression was evaluated as change from baseline in van der Heijde-modified total Sharp score (vdH-mTSS; sum of bone erosion [0–5 in the hands and 0–10 in the feet] and joint space narrowing [0–4] scores) for PsA (15). The scores were measured from three reading sessions: reading session 1: baseline, Weeks 16/24; and reading session 2: baseline, Weeks 16/24, and 52; session 3: baseline, Weeks 16/24, 52, 104/discontinuation. Images of earlier sessions were re-read at later sessions, *e.g.* baseline re-read at session 3 for all patients in the Week 104 analysis. Mean scores were assessed by two blinded readers independently (if there was an adjudicator involved, then three readers were used) who were blinded to all patient information, treatment allocation and order of radiographs. The total radiographic score (hands and feet combined) ranged from 0 to 528, with higher scores indicating more articular damage. Data are shown for Weeks 52 and 104. Patients achieving a change from baseline in vdHmTSS score ≤0.5 were defined as non-structural progressors at Week 52 and Week 104 (15).

Statistical analysis

The dactylitis subset included all full analysis set patients who had dactylitis at baseline. Data are presented for patients originally randomised to SEC and PBO. Clinical outcomes were evaluated by dactylitis status at baseline and data are presented as observed. The Kaplan-Meier estimate accounted for censoring, dropouts, and loss to follow-up. Patients randomised to the SEC arms were followed until their last visit or loss to follow-up. The survival function was calculated using the product-limit formula, which was the proportion (%) of patients who had not yet experienced resolution at a particular time multiplied by the percentage at all previous times when dactylitis occurred.

Heat map analysis used the last observation carried forward to impute status between scheduled visits with available data at baseline and Weeks 8, 16, 24, 52, and 104. Radiographic disease analysis was based on the patients with evaluable x-rays at both baseline and Weeks 24, 52 or 104. At each time point, only patients with a value at both baseline and that time point were included.

Baseline is defined as the last observation on the day of or before the first dose of study drug, or the first observation within 30 days post dosing when no observation is available prior to dosing. Week 24 missing radiographic values and values for PBO patients rescued at Week 16 were imputed via linear extrapolation (LE) if baseline and Week 16 values were available (LE 1).

Results

Patient disposition and baseline characteristics

A total of 389 (39%) patients in the trial had dactylitis at baseline and were randomised as follows: SEC 300 mg LD (n=82), SEC 150 mg LD (n=80), SEC 150 mg NL (n=103), or PBO (n=124). Overall, 78.4% (305/389) patients completed 104 weeks of treatment in the dactylitis subset with SEC 300 mg LD (82.9%; 68/82), 150 mg LD (83.8%; 67/80), 150 mg NL (73.8%; 76/103), and PBO (75.8%; 94/124) treatment groups. Patients in the dactylitis subset, had more active clinical disease with higher tender and swollen joints, more skin PsO, higher disease activity than those without dactylitis at baseline (Table I).

Table I. Demographics and baseline disease characteristics.

Characteristics, mean ± SD (unless otherwise stated)	With Dactylitis at baseline, total (N=389)	Without Dactylitis at baseline, total (N=607)
Age (years)	46.9 ± 12.24	50.0 ± 12.30
Female, n (%)	179 (46.0)	317 (52.2)
Weight (kg)	83.95 ± 20.18	83.12 ± 18.62
BMI (kg/m²)	29.40 ± 6.57	29.08 ± 5.92
Smoking status at baseline, n (%)	64 (16.5)	132 (21.7)
Presence of enthesitis, n (%)	261 (67.1)	341 (56.2)
MTX use at randomisation, n (%)	196 (50.4)	312 (51.4)
Adjusted tender joint total score for PsA (78 joints)	24.0 ± 16.98	19.1 ± 14.75
Adjusted swollen joint total score for PsA (76 joints)	14.5 ± 11.40	9.5 ± 8.53
Naïve to TNF-alpha inhibitors, n (%)	277 (71.2)	420 (69.2)
Time since first diagnosis of PsA (years)	7.19 ± 7.84	6.18 ± 6.98
Time since first PsO plaque (years)	14.47 ± 11.58	15.98 ± 14.06
Disability index score (HAQ-DI)	1.26 ± 0.65	1.26 ± 0.62
Subjects with psoriasis ≥3% of BSA, n (%)	224 (57.6)	290 (47.8)
PsA pain (VAS)	56.0 ± 23.81	53.1 ±23.83
SF-36 PCS	36.4 ± 8.41	36.6 ±8.28
DAS28-CRP	4.7 ± 1.11	4.5 ±1.028
PASDAS	6.45 ± 1.14	5.54 ± 0.87
PASI total score	8.73 ± 10.61	6.10 ± 8.43
Fingernails PsO count	6.8 ± 3.20	6.5 ± 3.22
mNAPSI total score	20.4 ± 19.70	17.1 ± 16.62
Dactylitis count	4.1 ± 4.16	0.0
DLQI total score	10.8 ± 7.87	10.3 ± 7.33
hsCRP	15.76 ± 28.74	10.95 ± 23.99
vdH-mTSS score	14.28 ± 32.14	12.12 ± 30.99

BMI: Body Mass Index; BSA: body surface area; CRP: C-reactive protein; DAS28: disease activity score 28; DLQI: Dermatology Life Quality index; HAQ-DI: Health Assessment Questionnaire Disability Index; hsCRP: high sensitivity CRP; mNAPSI: modified Nail Psoriasis Severity Index; MTX: methotrexate; n: number of patients; N: total number of randomised patients; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; PsO: psoriasis; TNF: tumour necrosis factor; SD: standard deviation; SF-36 PCS: Short Form 36 Physical Component Summary score; VAS: visual analogue scale; vdH-mTSS: van der Heijde modified total Sharp score.

Presence of enthesitis was higher in patients with dactylitis at baseline (67.1%) as compared to the subset without dactylitis (56.2%). At baseline, 199/389 patients had presented with mild dactylitis (DC ≤2) and 190/389 patients had moderate to severe dactylitis (DC ≥3). The mean dactylitis score with SEC 300 mg LD, 150 mg LD, 150 mg NL was 3.7, 4.3, 4.4, respectively and the total mean dactylitis count was 4 for the dactylitis subset.

Resolution of dactylitis

The Kaplan-Meier plots of time to first resolution of baseline dactylitis is presented in Figure 1A.

Median time to resolution of dactylitis was faster with SEC 300 mg LD group (57 days), SEC 150 mg LD (85 days), SEC 150 mg NL (85 days) than PBO (168 days) groups up to Week 104. The increasing proportion of patients that presented with resolution of dactylitis with SEC through Week 104 irrespective of the dose regimen is represented in Figure 1B.

In anti-TNF naive patients, the proportion of patients with resolution of dactylitis based on Kaplan-Meier estimates was higher with SEC than PBO

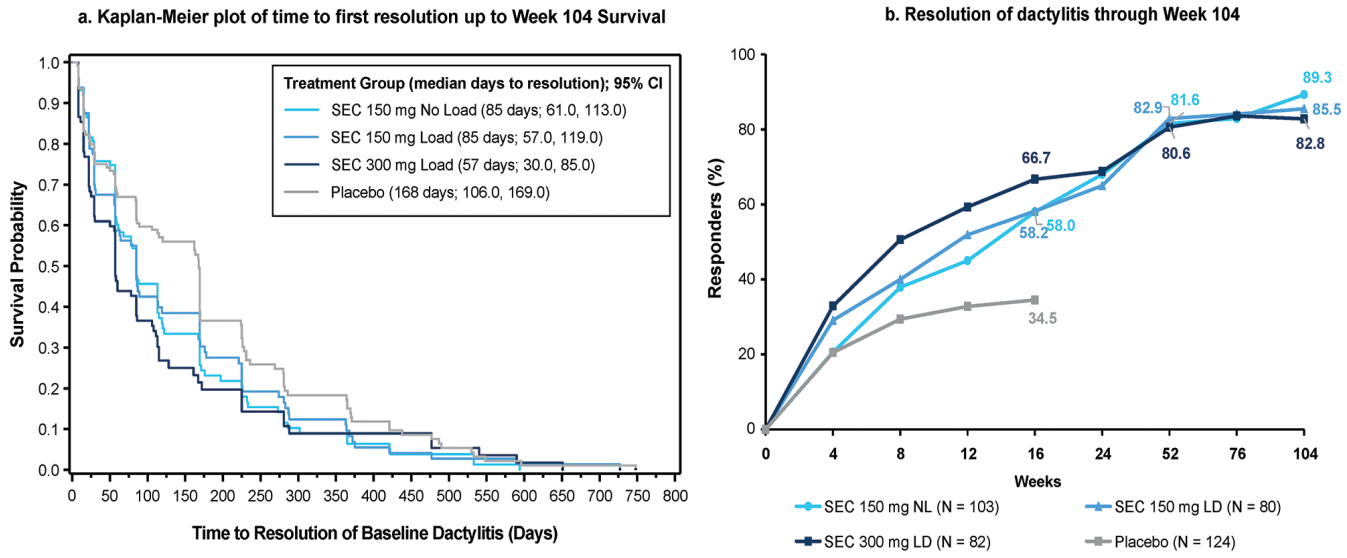

Fig. 1. Resolution of dactylitis in patients with baseline dactylitis.
A: Kaplan-Meier plot of time to first resolution up to Week 104 Survival. Percentages of patients with resolution at Weeks 16, 52, and 104 were derived as 1 minus the survival function at days 112, 365, and 729, respectively. Placebo patients were switched to SEC either at Week 16 or at 24. The Y-axis on the Kaplan-Meier plot represent the survival function.
B: Resolution of dactylitis to Week 104 in patients with dactylitis at baseline
Data presented as observed.
CI: confidence interval; LD: with loading dose; N: total number of patients with dactylitis at baseline; n: number of responders; NL: without loading dose; M: number of evaluable patients; SEC: secukinumab.

Table II. Resolution of dactylitis based on dactylitis count at baseline (≤2 and ≥3) through Week 104.

	SEC 300 mg LD (N=82)		SEC 150 mg LD (N=80)		SEC 150 mg NL (N=103)		PBO (N=124)	
Dactylitis count at baseline	≤2	≥3	≤2	≥3	≤2	≥3	≤2	≥3
N	47	34	34	46	48	52	64	53
Patients with dactylitis resolution, n/M (%)								
16 weeks	36/47 (76.6%)	18/34 (52.9%)	25/34 (73.5%)	22/46 (47.8%)	34/48 (70.8%)	24/52 (46.2%)	29/64 (45.3%)	12/53 (22.6%)
52 weeks	38/45 (84.4%)	22/29 (75.9%)	23/29 (79.3%)	35/41 (85.4%)	40/43 (93.0%)	33/46 (71.7%)	-	-
104 weeks	32/37 (86.5%)	23/29 (79.3%)	20/24 (83.3%)	36/41 (87.8%)	34/36 (94.4%)	35/41 (85.4%)	-	-

Data presented as observed.
LD: loading dose; M: number of evaluable patients; n: number of responders; N: total number of randomised patients; NL: without loading dose; PBO: placebo; SEC: secukinumab.

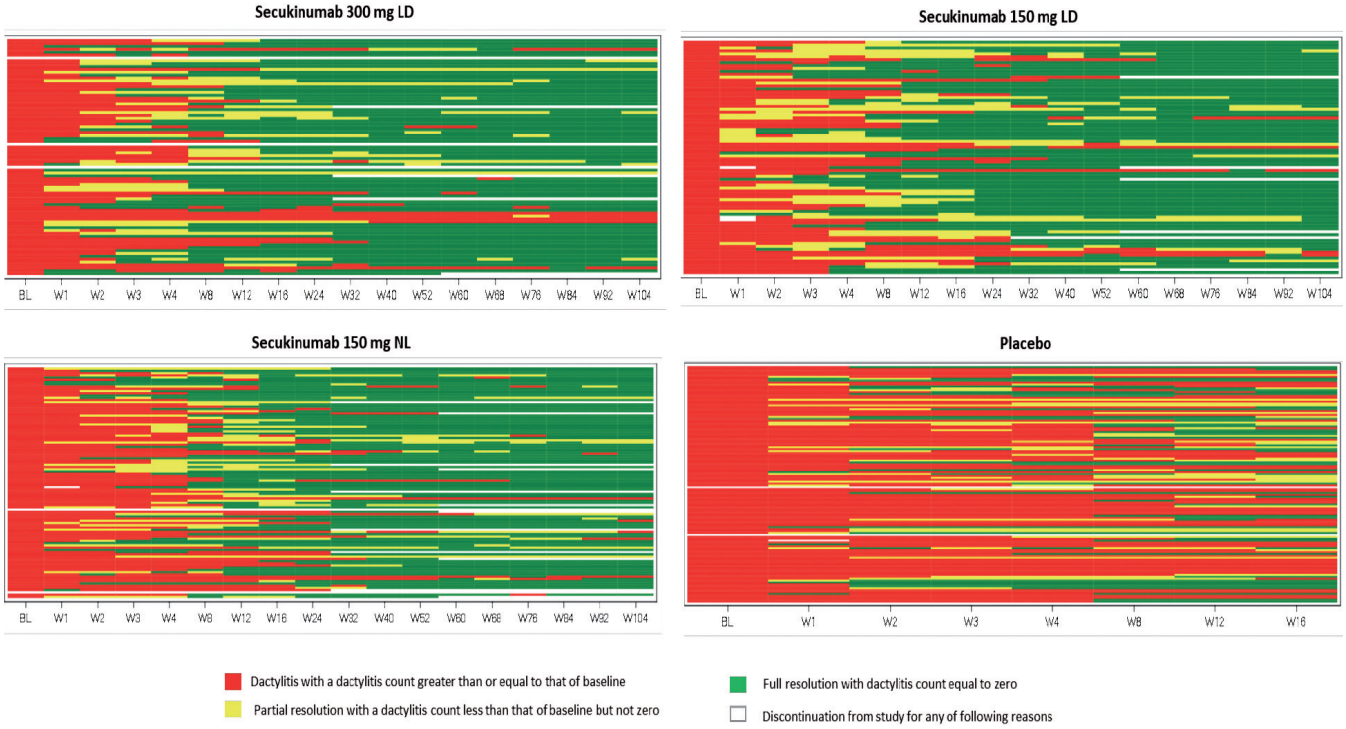

Fig. 2. Heat map of resolution of dactylitis by treatment group.
The discontinuation was due to following reasons: adverse events, death, lack of efficacy, lost to follow-up, non-compliance with study treatment, physician decision, pregnancy, patient/guardian decision, and withdrawal of informed consent. Placebo patients switched therapies at Week 16 or 24. All patients with enthesitis at baseline were followed until the end of study or discontinuation.
BL: baseline; LD: with loading dose; NL: without loading dose; W: week.

as reported in Supplementary Figure S1.

Resolution of dactylitis based on the dactylitis count (DC ≤2 and DC ≥3) at baseline through Week 16, 52 and 104 are shown in Table II. Median time to first resolution of baseline dactylitis in patients with DC ≤2 was 44 days with SEC 300 mg LD, 150 mg LD and 58 days for SEC 150 mg NL. While in patients with DC ≥3, 106 days for SEC 300 mg LD and 119 days for SEC 150 mg LD, 150 mg NL groups through Week 104.

Heat map analysis

Heat map analysis showed that SEC-treated patients at individual levels reported higher resolution of dactylitis than PBO treated patients at Week 16, which was sustained through Week 104 (Fig. 2).

Clinical efficacy

The improvements in efficacy outcomes with SEC 300 mg LD, SEC 150 mg LD and NL were sustained and further improved through Week 104 in joints, enthesitis, skin PsO and nail (mNAPSI) in patients with dactylitis at baseline (Fig. 3). The mean±SD nail PsO mNAPSI score was -16.2±11.8, -24.1±17.8, -20.1±25.3 with SEC 300 mg LD, 150 mg LD and NL, respectively at Week 104 (Suppl. Fig. S2). At Week 104, PASDAS score (mean±SD change from baseline) demonstrated decrease in disease activity with SEC treatment (300 mg LD, -3.44±1.57; 150 mg LD, -3.73±1.4; 150 mg NL, -3.8±1.4) in patients with dactylitis at baseline.

In the dactylitis subset, patient's assessment of PsA pain (VAS) decreased at Week 104 in all the SEC groups

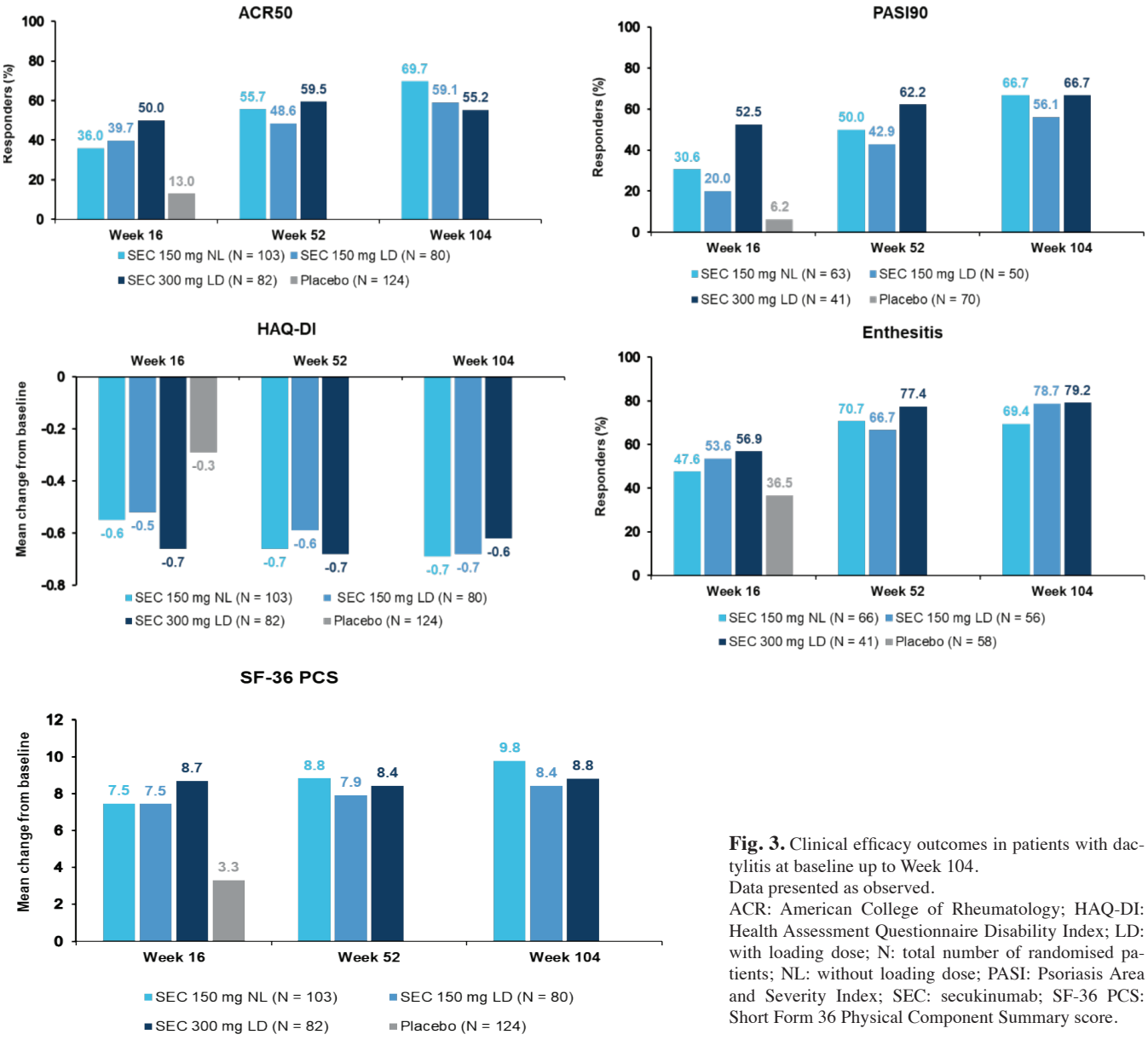

Fig. 3. Clinical efficacy outcomes in patients with dactylitis at baseline up to Week 104.
Data presented as observed.
ACR: American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire Disability Index; LD: with loading dose; N: total number of randomised patients; NL: without loading dose; PASI: Psoriasis Area and Severity Index; SEC: secukinumab; SF-36 PCS: Short Form 36 Physical Component Summary score.

(300 mg LD, -28.9±31.41;150 mg LD, -35.6±27.5; 150 mg NL, -33.4±29.9). Resolution of dactylitis was also associated with a sustained improvement in physical function and SF-36 PCS scores similar to patients without dactylitis at baseline as shown Fig. 3. Through Week 104, an improvement in HRQoL (DLQI scores) parameters was observed in patients with dactylitis at baseline as presented in Supplementary Figure S2.

Radiographic disease progression

The radiographic progression rate was low at Week 52 across all treatment groups in patients with and without dactylitis at baseline. Mean change from baseline in vdH-mTSS (≤0.5 change from baseline) using observed data at Week 52 and Week 104 are presented in Supplementary Table S1. At Week 104, 90%, 85.7%, and 86.8% patients were non-structural progressors in SEC 300 mg LD, 150 mg LD and 150 mg NL treatment groups, respectively as presented in Figure 4.

Discussion

The dactylitis subset of FUTURE 5 presented with more burden of disease and more severe disease activity at baseline than patients without dactylitis at baseline consistent with data reported in patients with dactylitis from observational and real-world evidence studies (16, 17). Diagnosis of dactylitis remains challenging as patients may present with swollen digits without any pain. LDI is an objective measure that uses assessment and a dactylometer, assessing tenderness and digit circumference between dactylitic and contralateral non-affected digits (18).

A recent study has shown that LDI is a reliable and responsive tool for assessment of PsA in patients with both skin and joint involvement (19). In a recent *post-hoc* analyses using pooled data from two Phase 3 studies with tofacitinib, patients with prior dactylitis de-

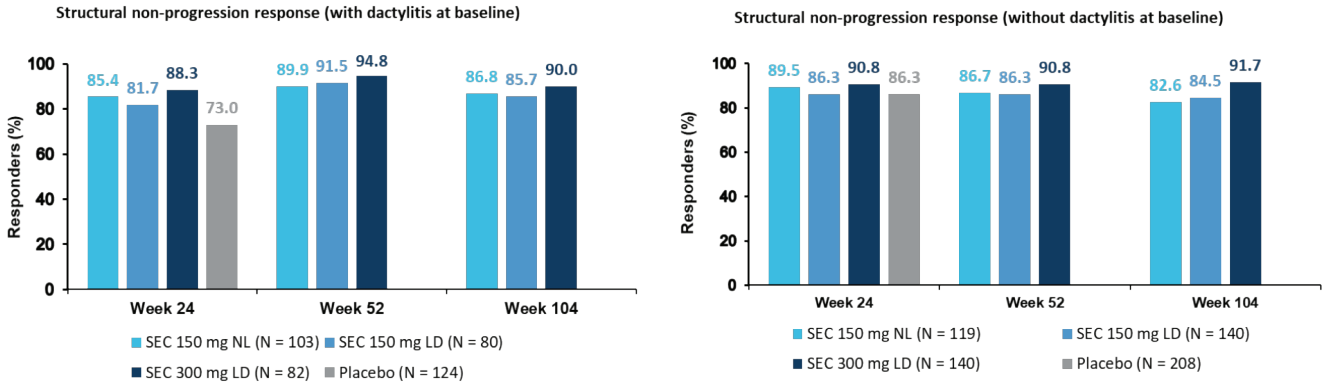

Fig. 4. Structural non-progression in patients with or without dactylitis at baseline through Week 104.
Analysis is based on the patients with evaluable x-rays at both baseline and at Weeks 24, 52 or 104. At each time point, only patients with a value at both baseline and that time point are included. Baseline is defined as the last observation on the day of or before the first dose of study drug, or the first observation within 30 days post dosing when no observation available prior to dosing.
LD: with loading dose; N: total number of patients randomised; NL: without loading dose; SEC: secukinumab.

monstrated improvements in dactylitis in hands, feet, or both, and in all digits based on Dactylitis Severity Score (20). There is limited scientific evidence of the efficacy of biologics on dactylitis mostly based on secondary or exploratory outcome measure. Only a small, randomised investigator-initiated trial (IITs) study: GO-DACT IIT showed superiority of golimumab plus methotrexate *versus* PBO for the treatment of dactylitis using a dactylitis severity score as a primary outcome (21). Substantial improvements in dactylitis have been noted in different RCTs including certolizumab pegol treatment in the RAPID-PsA trial, ustekinumab treatment in the PSUMMIT-1 and PSUMMIT-2 trials, golimumab in the GO-REVEAL trials, infliximab in the IMPACT1 and IMPACT2 trials and open label trials with infliximab and adalimumab and most of the studies have used unvalidated measures of dactylitis (21, 22).

EULAR (European League Against Rheumatism) (23) and GRAPPA (9) have identified dactylitis as one of the key clinical domains of PsA and have recommended targeting IL-17A as one of the potential biological options after failure to NSAIDs. Limited literature is available to characterise more in depth the time to response and breadth of efficacy (24, 25) on this key manifestation and its impact on other clinical PsA domains. Early and sustained resolution of dactylitis up to 2 years with SEC was previously reported in FUTURE 5 (12). The objectives of this exploratory analysis were to provide a more comprehensive analysis of the efficacy of SEC on dactylitis through 2 years.

We investigated the discriminatory dactylitis response to SEC *versus* PBO using DC and showed that a faster median time to resolution of dactylitis was observed with SEC than PBO with quicker response with SEC 300 mg. The heat map analysis confirmed the dactylitis response to SEC at individual level up to Week 104. Whether the response to SEC may vary according to the level of dactylitis severity was also explored. A faster and higher level of response to dactylitis was shown with SEC than PBO, irrespective of the level of severity with the fastest response with SEC 300 mg. However, both a lower magnitude of response and a slower response to SEC were observed in patients with more severe dactylitis. Experimental models and human studies indicate that dactylitis involves inflammation in multiple tissues including bone, periosteum, entheses, peri-entheseal and peritendinous soft tissue, tenosynovium and articular synovium. The inflammation is predominant in the vascular tissues adjacent to the relatively avascular tendons, pulleys and entheses which is different from rheumatoid arthritis (19).

These anatomical considerations around the extra-synovial structures may have a pivotal function in the pathogenesis of dactylitis which might be relevant for understanding why anti-IL-17A therapy is an effective therapy for synovitis and tenosynovitis in patients with PsA. In an integrated SPIRIT-P1 and SPIRIT-P2 analysis, ixekizumab-treated patients demonstrated a greater resolution in their baseline enthesitis or dactylitis symptoms compared to PBO at Week 24. Moreover, resolution of enthesitis was associated with improvements in patients' physical function, pain, and HRQoL (26).

The present study also showed sustained improvements with SEC across all PsA domains including peripheral arthritis, skin and nail PsO, enthesitis and composite measures of disease activity (PASDAS and PsA pain) in patients with dactylitis at baseline. We included an exploratory imaging evaluation. Evidence that biologics can reduce radiographic progression in PsA patients with dactylitis is lacking whereas this group is more at risk of progression. SEC prevented radiographic deterioration at group level and individual level in patients with and without dactylitis up to Week 104. It should be noted that the high mean (SD) values observed at Week 104 in SEC 300 mg LD group was due to an outlier with a very high mTSS change. PsA patients treated with SEC showed sustained improvement of physical function and HRQoL, regardless of dactylitis status at baseline in this study. The improvements across QoL indicators were consistent with the FUTURE 2 and 5 studies (12, 27).

A limitation of this study was its exploratory nature and dactylitis was a secondary endpoint, not the primary of the study. PBO-controlled period

was limited to Week 16/24, and there was no control group beyond Week 24; hence, no statistical comparisons were performed between treatment groups. Statistical method used for analysis was observed imputations so does not count for dropouts or missing data. The challenges in assessment of dactylitis included patients with chronic dactylitis, absence of pain and tenderness. In some cases of dactylitis, swelling was difficult to discern.

In conclusion, PsA patients with dactylitis presented with higher disease burden compared to patients without dactylitis at baseline. This granular analysis extends the evidence for the early and sustained efficacy of SEC on dactylitis domain irrespective of its severity and comprehensive efficacy across other PsA domains, low radiographic progression, improvement of function, and HRQoL to the same extent as patients without dactylitis.

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References

1. GLADMAN DD, ANTONI C, MEASE P, CLEGG DO, NASH P: Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; 64 (Suppl. 2): ii14-7. https://doi.org/10.1136/ard.2004.032482
2. TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54(8): 2665-73. https://doi.org/10.1002/art.21972
3. GLADMAN DD, ZIOUZINA O, THAVANESWARAN A, CHANDRAN V: Dactylitis in psoriatic arthritis: prevalence and response to therapy in the biologic era. *J Rheumatol* 2013; 40(8): 1357-9. https://doi.org/10.3899/jrheum.130163
4. COATES LC, HELLIWELL PS: Disease measurement – enthesitis, skin, nails, spine and dactylitis. *Best Pract Res Clin Rheumatol* 2010; 24(5): 659-70. https://doi.org/10.1016/j.berh.2010.05.004
5. LIU JT, YEH HM, LIU SY, CHEN KT: Psoriatic arthritis: Epidemiology, diagnosis, and treatment. *World J Orthop* 2014; 5(4): 537-43. https://doi.org/10.5312/wjo.v5.i4.537
6. HEALY PJ, HELLIWELL PS: Dactylitis: pathogenesis and clinical considerations. *Curr Rheumatol Rep* 2006; 8(5): 338-41. https://doi.org/10.1007/s11926-006-0062-y
7. BROCKBANK JE, STEIN M, SCHENTAG CT, GLADMAN DD: Dactylitis in psoriatic arthritis: a marker for disease severity? *Ann Rheum Dis* 2005; 64(2): 188-90. https://doi.org/10.1136/ard.2003.018184
8. MCHUGH NJ, BALACHRISHNAN C, JONES SM: Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology* (Oxford) 2003; 42(6): 778-83. https://doi.org/10.1093/rheumatology/keg217
9. COATES LC, KAVANAUGH A, MEASE PJ *et al.*: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol* 2016; 68(5): 1060-71. https://doi.org/10.1002/art.39573
10. HUEBER W, PATEL DD, DRYJA T *et al.*: Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med* 2010; 2(52): 52ra72. https://doi.org/10.1126/scitranslmed.3001107
11. GREGERSEN PK, OLSSON LM: Recent advances in the genetics of autoimmune disease. *Annu Rev Immunol* 2009; 27: 363-91. https://doi.org/10.1146/annurev.immunol.021908.132653
12. MEASE P, VAN DER HEIJDE D, LANDEWÉ R *et al.*: Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. *Ann Rheum Dis* 2018; 77(6): 890-7. https://doi.org/10.1136/annrheumdis-2017-212687
13. WORLD MEDICAL ASSOCIATION: World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310(20): 2191-4. https://doi.org/10.1001/jama.2013.281053
14. HELLIWELL PS, FIRTH J, IBRAHIM GH, MELSOM RD, SHAH I, TURNER DE: Development of an assessment tool for dactylitis in patients with psoriatic arthritis. *J Rheumatol* 2005; 32(9): 1745-50.
15. VAN DER HEIJDE D, LANDEWÉ R, KLARESKOG L *et al.*: Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. *Arthritis Rheum* 2005; 52(1): 49-60. https://doi.org/10.1002/art.20775
16. RAMIRO S, SMOLEN JS, LANDEWÉ R, VAN DER HEIJDE D, GOSSEC L: How are enthesitis, dactylitis and nail involvement measured and reported in recent clinical trials of psoriatic arthritis? A systematic literature review. *Ann Rheum Dis* 2018; 77(5): 782-3. https://doi.org/10.1136/annrheumdis-2017-211447
17. MEASE PJ, KARKI C, PALMER JB *et al.*: Clinical characteristics, disease activity, and patient-reported outcomes in psoriatic arthritis patients with dactylitis or enthesitis: results from the Corrona Psoriatic Arthritis/Spondyloarthritis Registry. *Arthritis Care Res* (Hoboken) 2017; 69(11): 1692-9. https://doi.org/10.1002/acr.23249
18. BAGEL J, SCHWARTZMAN S: Enthesitis and dactylitis in psoriatic disease: a guide for dermatologists. *Am J Clin Dermatol* 2018; 19(6): 839-52. https://doi.org/10.1007/s40257-018-0377-2
19. MCGONAGLE D, TAN AL, WATAD A, HELLIWELL P: Pathophysiology, assessment and treatment of psoriatic dactylitis. *Nat Rev Rheumatol* 2019; 15(2): 113-22. https://doi.org/10.1038/s41584-018-0147-9
20. ORBAI AM, MEASE PJ, HELLIWELL P *et al.*: Efficacy of tofacitinib on dactylitis in individual digits in patients with active psoriatic arthritis. EULAR 2021. http://dx.doi.org/10.1136/annrheumdis-2021-eular.73.
21. VIEIRA-SOUSA E, ALVES P, RODRIGUES AM *et al.*: GO-DACT: a phase 3b randomised, double-blind, placebo-controlled trial of GOlimumab plus methotrexate (MTX) versus placebo plus MTX in improving DACTylitis in MTX-naive patients with psoriatic arthritis. *Ann Rheum Dis* 2020; 79(4): 490-8. https://doi.org/10.1136/annrheumdis-2019-216500
22. RITCHLIN C, RAHMAN P, KAVANAUGH A *et al.*: Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014; 73(6): 990-9. https://doi.org/10.1136/annrheumdis-2013-204655
23. GOSSEC L, BARALIAKOS X, KERSCHBAUMER A *et al.*: EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020; 7989): 700-12. https://doi.org/10.1136/annrheumdis-2020-217159
24. SIMONS N, DEGBOE Y, BARNETCHE T, CANTAGREL A, RUYSSEN-WITRAND A, CONSTANTIN A: Biological DMARD efficacy in psoriatic arthritis: a systematic literature review and meta-analysis on articular, enthesitis, dactylitis, skin and functional outcomes. *Clin Exp Rheumatol* 2020; 38(3): 508-15.
25. COATES LC, WALLMAN JK, MCGONAGLE D *et al.*: Secukinumab efficacy on resolution of enthesitis in psoriatic arthritis: pooled analysis of two phase 3 studies. *Arthritis Res Ther* 2019; 21(1): 266. https://doi.org/10.1186/s13075-019-2055-z
26. GLADMAN DD, ORBAI AM, KLITZ U *et al.*: Ixekizumab and complete resolution of enthesitis and dactylitis: integrated analysis of two phase 3 randomized trials in psoriatic arthritis. *Arthritis Res Ther* 2019; 21(1): 38. https://doi.org/10.1186/s13075-019-1831-0
27. MEASE PJ, KAVANAUGH A, REIMOLD A *et al.*: Secukinumab in the treatment of psoriatic arthritis: efficacy and safety results through 3 years from the year 1 extension of the randomised phase III FUTURE 1 trial. *RMD Open* 2018; 4(2): e000723. https://doi.org/10.1136/rmdopen-2018-000723