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Effects of secukinumab on synovitis and enthesitis in patients with psoriatic arthritis: 52-week clinical and ultrasound results from the randomised, double-blind ULTIMATE trial with open label extension

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Keywords: Psoriatic arthritis, Power Doppler ultrasonography, OMERACT, Synovitis, Enthesitis, Clinical response

Statement of clinical significance

What was already known before the study was performed?

Secukinumab, a human monoclonal antibody that directly inhibits interleukin 17A, has previously demonstrated sustained efficacy on signs and symptoms, inhibition of structural damage progression, and a favourable long-term safety profile in patients with psoriatic arthritis (PsA) over 5 years. However, little is known on its direct effect on synovitis and enthesitis and the dynamics of such response measured by power Doppler ultrasound (PDUS).

What does this study add?

In PsA patients followed over 52 weeks, secukinumab led to stable improvement of clinical synovitis and enthesitis. PDUS confirmed improvements in synovitis at tissue-level, and PDUS-detected enthesitis showed a numerical improvement.

Abstract

Objectives: In the ULTIMATE study with open label extension, we assessed the long-term effect of secukinumab at tissue level on synovitis and enthesitis, and across all psoriatic arthritis (PsA) manifestations, using both clinical and power Doppler ultrasonography (PDUS) evaluations.

Methods: This randomised, placebo-controlled, Phase 3 study (ULTIMATE) included biologic-naïve patients with PsA with active PDUS synovitis and clinical enthesitis, and inadequate response to conventional synthetic disease-modifying antirheumatic drugs. The study consisted of 3 treatment periods; in the first (baseline to week 12) patients were randomised to receive subcutaneous secukinumab (150 mg or 300 mg according to severity of skin psoriasis) or placebo every week until week 4 and once every 4 weeks up to week 12. In the second period (weeks 12–24) all patients received open-label secukinumab with placebo patients switching to secukinumab (150 mg or 300 mg). The third period (weeks 24–52) extended open-label treatment. The long-term responsiveness of the Global EULAR-OMERACT Synovitis Score (GLOESS), clinical enthesitis and global PDUS-detected enthesitis score (using two candidate definitions of activity) at patient level, together with clinical efficacy across key manifestations of PsA and safety were assessed.

Results: Of the 166 patients enrolled, 144 completed week 52. A significant reduction in GLOESS was demonstrated in the secukinumab group vs placebo at week 12, followed by a stable reduction of synovitis until week 52 in the secukinumab group while placebo switchers from week 12 reached a similar level of reduction at week 24 with stability afterwards. Likewise, a significant reduction in the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index was shown in the secukinumab group vs placebo at week 12 with sustained

improvement to week 52. Global OMERACT PDUS enthesitis scores were numerically lower in secukinumab vs placebo switchers in the first two treatment periods, with some stability in the third period in both groups. Improvements in clinical responses were also observed across all key domains of PsA up to week 52 in both treatment groups with no new or unexpected safety signals.

Conclusions: ULTIMATE showed consistent improvements in clinically and ultrasound-assessed synovitis and enthesitis and sustained clinical efficacy through week 52 in patients with PsA treated with secukinumab and placebo switched to secukinumab.

Keywords: Psoriatic arthritis, Power Doppler ultrasonography, OMERACT, Synovitis, Enthesitis, Clinical response

Trial registration. ClinicalTrials.gov, NCT02662985. Registered on 26 January 2016.

Background

Psoriatic arthritis (PsA) is a chronic inflammatory disease of the joints leading to progressive damage of articular and periarticular structures, which can result in disability [1]. Synovitis is an important feature of PsA that impacts peripheral joints and may lead to structural damage and impairment of physical function. Enthesitis, the inflammation of the insertion of tendons, ligaments, aponeurosis and capsules into the bone, is considered a pathological hallmark of PsA [2].

Power Doppler ultrasonography (PDUS), a combination of ultrasonography (US) in B-mode and power Doppler (PD), permits visualisation of different forms of synovial and extrasynovial inflammation in PsA, such as synovitis, enthesitis, dactylitis, bursitis, and tenosynovitis, as well as structural lesions, such as bone proliferation and erosions [3-6]. The introduction of PD in addition to B-mode has provided greater details of synovial blood cell movements and increased sensitivity to low-volume and low-velocity blood flow at the microvascular level [7]. The European Alliance of Associations for Rheumatology (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have released treatment and management recommendations for predominant peripheral arthritis and entheseal disease in PsA that include US evaluation as an accepted method for detecting synovitis and enthesitis.

EULAR and the Outcome Measures in Rheumatology (OMERACT) initiative have recently standardised the use of PDUS for detecting synovitis and have developed a composite scoring system at joint and patient level, the global EULAR-OMERACT synovitis score (GLOESS), and have demonstrated its reliability, validity and feasibility to detect and score synovitis in rheumatoid arthritis and PsA [3,8]. PDUS is also a sensitive method for detecting enthesitis because it depicts the structural modifications and the increased vascularity of the enthesis once inflamed [9]. Within OMERACT, the development of a PDUS enthesitis score started with a Delphi exercise to define enthesitis and its core components [11]. The definitions include

hypoechogenicity, thickening, and Doppler signal as signs of inflammation, as well as erosions, enthesophytes, calcifications, and cortical irregularities as signs of structural changes [12,13]. In addition, a PDUS scoring system for enthesitis for use in clinical studies has been developed [2].

Secukinumab, a fully human monoclonal antibody that inhibits interleukin (IL)-17A has demonstrated sustained efficacy and safety in patients with PsA up to 5 years [14] and sustained inhibition of structural damage progression in PsA up to 3 years [15,16]. ULTIMATE (NCT02662985) was the first, large, randomised, double-blind, placebo-controlled, 52-week Phase 3 study that assessed the responsiveness of PDUS parameters to PsA treatment using GLOESS as the primary endpoint. It demonstrated that secukinumab rapidly and significantly decreased synovitis in PsA. All key secondary endpoints were also achieved, including the effect on clinical enthesitis as measured by the Spondyloarthritis Research Consortium of Canada (SPARCC) index, and the superior American College of Rheumatology (ACR) responses versus placebo at 12 weeks [8,9]. We report here the 52-week results of PDUS-assessed synovitis, clinical enthesitis, and of two “novel candidate” OMERACT enthesitis PDUS scores, as well as long-term clinical response across key manifestations of PsA.

Methods

Study design and patients

ULTIMATE is a multicentre, randomised, double-blind, placebo-controlled, 52-week Phase 3 study, conducted across 37 sites in 17 countries. Details of the study design have been published elsewhere [8]. The study consisted of 3 treatment periods (TPs) following a screening phase: Treatment period 1 (TP1 from baseline to week 12) which was a double-blind, placebo-controlled phase where patients were either randomly assigned to placebo or secukinumab 150 or 300 mg according to the severity of skin psoriasis; treatment period 2 (TP2 from week 12 to

week 24) which was an open-label phase where patients receiving placebo were switched to secukinumab similarly to the initial secukinumab group who continued on the same dose, and; treatment period 3 (TP3 from week 24 to week 52) which was an optional open-label extension period.

Detailed inclusion and exclusion criteria previously published [8] are provided in the **Supplementary Appendix**. The main inclusion criteria were adult patients with active PsA defined by at least 3 clinical tender joints and 3 swollen joints, active PDUS-detected synovitis according to a pre-defined cut-off, and at least one clinical enthesitis site, as defined by the SPARCC index. Importantly, there was no requirement for the presence of an active PDUS enthesitis. Patients had an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and were naïve to biologic (b)DMARDs.

Patients could receive a stable dose of background rheumatic therapy during the first 24 weeks and adjustments of these treatments were allowed afterwards from weeks 24 to 52.

Clinical evaluations

A detailed physical examination of joints and entheses was performed at each visit, blinded to the results of the other evaluations and of the responses to composite indexes. Clinical assessments across different manifestations of PsA were made on joints with ACR20/50/70 responses, on clinical enthesitis with SPARCC assessment, on dactylitis based on the Leeds Dactylitis Index (LDI), and on skin with the Psoriasis Area and Severity Index (PASI) score in patients with a psoriasis body surface area (BSA) >3%. All evaluations were performed from baseline to week 12 and in the open-label period of the study from week 12 to week 52. In addition, more stringent composite indices, i.e. disease activity in PsA (DAPSA) remission, and DAPSA low disease activity (LDA), minimal disease activity (MDA), and very low disease activity (VLDA) were assessed at weeks 24 and 52.

Safety assessments for the occurrence of adverse events (AEs), serious AEs (SAEs), and serious or other significant events were conducted for the entire TP of up to 52 weeks.

Details on clinical evaluations and of randomisation and drug administration are provided in the **Supplementary Appendix**.

The study protocol and its amendments were reviewed and approved by the respective independent ethics committee or institutional review board of each participating centre. The study was conducted according to the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) that has its origin in the Declaration of Helsinki [17]. Written informed consent was obtained from all enrolled patients. Data were collected in accordance with the GCP guidelines by the study investigators and analysed by the study sponsor.

Assessment of joints and enthesitis by ultrasound

PDUS evaluation of synovitis and enthesitis was performed at screening, baseline and weeks 1, 2, 4, 8, 12, 16, 20, 24, 36, and 52. A total of 24 pairs of joints were evaluated bilaterally [8]. The presence of synovitis according to EULAR-OMERACT definition [8] was scored on a PDUS composite semi-quantitative scale (range 0–3) [3-6] at joint level and its core components: hypoechoic synovial hypertrophy (SH) and PD synovial signals at each visit. The GLOESS at patient level was calculated as the sum of each PDUS composite score for 24 pairs of joints examined, with a score range of 0–144. Further details on PDUS measures of synovitis and grading of severity are provided in **Supplementary Table 1** and was reported in the primary manuscript [8].

Simultaneously, a total of 6 targeted pairs of entheses were examined bilaterally: common extensor tendon at the lateral humeral epicondyle insertion, quadriceps tendon at its insertion at the superior pole of the patella, patellar tendon at its proximal insertion at the inferior pole of the

patella, patellar tendon at its distal insertion at the tibial tuberosity, Achilles tendon at its insertion at the calcaneus, and plantar aponeurosis at its insertion at the calcaneus.

Each affected enthesis out of the 6 bilateral sites was scored in terms of inflammatory and morphological components according to the OMERACT enthesitis composite semi-quantitative scale (range 0–3). Two definitions of activity at site level were used to derive two OMERACT (PDUS) enthesitis scores (at patient level) for the first time in this study and are reported in **Table 1**. Definition 1 combines the rating of inflammatory abnormalities with B-mode (range 0–1) and inflammation activity with PD signal (range 0–3); Definition 2 only uses the PD signal rating (range 0–3) [8,18]. The severity was graded with the help of an atlas, available in each centre that had examples of B-mode and PD grading for each examined enthesis site (**Supplementary Table 2**).

The global OMERACT enthesitis score comprises the sum of each single abnormal site of the 6 bilateral targeted entheses, with a range of 0–48 using Definition 1 and a range of 0–36 using Definition 2. The total time required for each PDUS assessment of joint inflammation and enthesitis in the study was recorded in the electronic case report form (eCRF) to evaluate the variability of time spent by ultrasonographers to assess multiple joints and enthesitis across the sites.

All PDUS evaluations were performed at each site by an independent expert with more than 5 years of experience in musculoskeletal US and who was blinded to clinical evaluation. To ensure homogeneity of PDUS synovitis and enthesitis scoring, all US investigators were EULAR-certified and completed an extensive 2-day training session, including US examination of patients with PsA [8]. In addition, US settings were not changed during the study, standardised joint, enthesis, and probe positions were used, and software was not upgraded. Centres were advised to create a fixed study setting to be used at each evaluation. Moreover,

the quality and the Doppler capability of the ultrasound machines were verified prior to confirming site participation in the trial according to previous ultrasound studies [18].

All images for enthesitis and synovitis were also recorded, anonymised, and sent for central reading for the first patient enrolled at each centre to allow a verification of the consistent scoring across sites. Training session and central reading of images collected from the first patient enrolled in each site were considered adequate to ensure a homogeneous rating across sites. High-resolution PDUS machines (ESAOTE, Acuson, Logic Series 9, 7 and enext GE, Siemens or other, such as Toshiba Xario 200, Toshiba Aplio [300, 400], Aloka Arietta V70, and Samsung HS60) with high frequency transducers in the range of 12–18 MHz were used. B-mode and Doppler parameters were adjusted based on the device used (range of pulse repetition frequency 400–800 Hz; Doppler frequency 7–14.1 MHz). During follow-up, each patient was examined with the same PDUS machine.

Statistical analysis

The detailed primary analysis and key secondary analyses of the ULTIMATE study for the first 12 weeks have been published previously [8]. All efficacy analyses were performed based on the full analysis set that comprised all randomised patients to whom study treatment had been assigned. All safety analyses were performed based on the safety set which included all patients who took at least one dose of study treatment during the TP.

Inferential efficacy comparisons between the secukinumab and placebo groups were limited to the first 12 weeks of treatment before any treatment switch. After week 12, only descriptive summaries were provided by treatment sequences, which represent the treatment combinations the subjects experienced over the course of the entire trial: secukinumab (150 mg and 300 mg groups combined) and placebo to secukinumab (150 mg and 300 mg groups combined). The between-treatment differences at week 12 were compared with a mixed-effect repeated measures model that included treatment regimen, centre, and analysis visit as factors and

baseline weight and baseline score as continuous covariates. Treatment by analysis visit was also included as an interaction term in the model.

All descriptive summaries of efficacy variables up to week 52 were presented as observed. Safety analyses included all patients who received at least one dose of study medication. AEs were reported as absolute frequencies during the placebo-controlled period. All statistical analyses were performed by Novartis with SAS version 9.3 or higher.

Results

Demographics and baseline disease characteristics

Of the 166 patients randomised to secukinumab (N=83) or placebo (N=83), 144 patients completed 52 weeks (75 [90%] patients in the secukinumab group and 69 [83%] patients in the placebo to secukinumab [placebo switchers] group). Details on patient disposition across the 3 treatment periods are provided on **Supplementary Figure 1.** Seven patients (2 patients [2.4%] in the secukinumab group and 5 patients [6.0%] in the placebo switcher group) discontinued the study during TP3, mainly due to AEs (n=2, one in each treatment group) and patient/guardian decisions (n=2, one in each treatment group). Discontinuation rates were higher during TP3 than TP2 mainly due to the COVID-19 pandemic and not due to lack of treatment efficacy.

The proportion of patients with at least one protocol deviation was 41% in the secukinumab group and 39% in the placebo switcher group, with details presented in **Supplementary Table 3**. Ten patients (6%) received prohibited concomitant medication, of which 3 received an unstable and transient dose of non-steroidal anti-inflammatory drugs (NSAIDs) from week 16 to 20 (due to AE) and from week 20 to 24 (patient decision). Overall, 24 patients (14.5%) in the entire TP had ≥1 coronavirus disease 2019 (COVID-19) pandemic-related protocol deviation (secukinumab group: 11 patients [13.3%]; placebo switcher group: 13 patients [15.7%]), which was mainly due to lockdown/quarantine of patients due to the COVID-19 situation and drug supply issues.

Demographics and baseline clinical characteristics have been described previously [8] and were comparable between treatment groups (**Supplementary Table 4**). The mean tender joint count was 13 in the secukinumab group and 15 in the placebo group; the mean swollen joint count was 10 in the secukinumab group and 9 in the placebo group. Furthermore, the GLOESS scores were 24 in the secukinumab group and 27 in the placebo group (**Table 2**).

During the course of the trial, 59%, 42.8%, 22.3% and 13.3% of patients received NSAIDs, methotrexate, systemic corticosteroids and csDMARDs, respectively.

Efficacy on PDUS synovitis over time

In TP1 the secukinumab group showed a significant decrease in PDUS synovitis versus placebo (GLOESS −9 [0.9] versus −6 [0.9], difference [95% CI]: −3 [−6; −1]; one-sided *P*=0.004) as described previously [8]. In TP2 and TP3, PDUS synovitis remained stable up to week 52 in the secukinumab group, while it continued to gradually decrease in the placebo switcher group to reach levels similar to the secukinumab group from week 24 onwards (**Figure 1A–1C, Supplementary Table 6**). Among the two core components of GLOESS, PD signal showed smaller improvements than SH score throughout the trial. The distribution of synovitis by grade of severity at joint level showed that metatarsophalangeal joints, wrist, knee, and metacarpophalangeal 1 and 2 joints, which contributed to the severity at baseline, were the most responsive over time (**Figure 2**). Clinical synovitis as assessed by swollen joint counts also improved from baseline to week 52 (**Supplementary Table 7**).

Efficacy on clinical and PDUS enthesitis over time

In TP1 the secukinumab group showed a significant decrease in clinical enthesitis versus placebo (SPARCC, −2.2 [0.3] versus −1.6 [0.3], difference [95% CI]: 0.7 [−1.37, 0.04]; one-sided *P*=0.03). In TP2 enthesitis improved in both groups with the placebo switcher group catching up to reach levels similar improvement to secukinumab; these levels were sustained in

TP3 (**Figure 3**). Several Patients in both groups experienced sustained resolution of enthesitis at weeks 24 and 52 (**Supplementary Table 7**).

Compared to the mean number of tender entheses (4 in both groups) the mean global PDUS enthesitis scores (both Definition 1 and 2) were lower and imbalanced across the two treatment groups at baseline (**Table 2**), reflecting the lack of an ultrasound-detected enthesitis inclusion criterion. In addition, more patients with clinical enthesitis met PDUS enthesitis Definition 1 (B-mode and PD signal combined) than Definition 2 (PD signal only): 88% secukinumab vs 74% placebo; and 41% vs 24%, respectively. At baseline, PDUS enthesitis (Definition 1) was frequently found at the quadriceps tendon insertion, Achilles tendon and lateral epicondyle, consistent with clinical findings (medial epicondyle also clinically affected but not assessed by ultrasound) (**Figures 4** and **5**). The distribution of PDUS enthesitis as per Definition 2 was consistent with that of Definition 1 (**Figure 5**), but the prevalence was lower by this definition as some sites (especially the plantar fascia) were PD-negative.

In TP1 the secukinumab group showed a trend for more decrease in PDUS enthesitis versus placebo (see **Supplementary Table 5 and Figure 6A** and **6B**). Decreases were more profound for Definition 1 than for Definition 2. In TP2 PDUS enthesitis improved in both groups with the placebo switcher group catching up to reach levels similar to secukinumab; these levels were sustained in TP3, with some variability at the study end in the placebo switcher group related to a lower number of patients (**Figure 6A** and **6B, Supplementary Table 5**). This is also reflected in the mean number of PDUS-positive entheseal sites (score >0; **Supplementary Figure 2A** and **2B**). The most responsive enthesitis sites by PDUS were the lateral epicondyle, followed by the quadriceps tendon and patellar ligament (**Figure 5**).

No meaningful correlation was observed between global OMERACT enthesitis score and corresponding clinical enthesitis from total SPARCC scores with regards to change from baseline to week 24 (**Supplementary Table 8**).

Other clinical efficacy assessments

Sustained clinical improvements up to week 52 were observed in ACR responses (**Supplementary Figure 3**), dactylitis as assessed by LDI resolution and in the PASI 90 response in both treatment groups up to week 52 (**Supplementary Table 7**). An increasing proportion of patients met LDA or remission according to MDA, DAPSA LDA+ remission or VLDA and DAPSA remission between weeks 24 and 52 in both the secukinumab and placebo switcher groups.

No correlation was observed at any time point between changes from baseline in GLOESS versus any ACR core components.

The safety profile of secukinumab in the current study was consistent with the known safety profile of secukinumab in previously published studies [14, 20], with no new or unexpected safety signals (**Supplementary Table 9**). The open label extension phase overlapped with the beginning of the COVID-19 pandemic and one patient died owing to COVID-19 while receiving secukinumab 150 mg. Two other patients had confirmed COVID-19 infection; the events were not considered related to the study drug, and both resolved.

Discussion

ULTIMATE study was the first international multicentre long-term study to document the responsiveness of PDUS on synovitis and on enthesitis in patients with PsA with inadequate response to csDMARDs starting treatment with secukinumab. It showed that the IL-17A inhibition led to a rapid reduction of PDUS-detected synovitis (primary endpoint) through week 12 followed by a plateau effect up to week 52. A similar pattern was seen for the clinical enthesitis response (key secondary endpoint). Two new scoring systems have been proposed for the evaluation of ultrasound detected enthesitis to explore enthesitis activity, which showed similar trends, but the low prevalence of PDUS-positive enthesitis at baseline precluded a full assessment of the value of these scores. These data complement earlier studies showing

beneficial effects of secukinumab on signs and symptoms of PsA and suggest that this treatment approach has the potential to control the inflammation of joints and entheses in PsA. So far, only short-term effects of secukinumab in controlling synovitis were reported [8].

With respect to the PDUS synovitis response, a small decrease of synovitis was also observed in the placebo group over the first 12 weeks followed by a rapid reduction of synovitis, once placebo patients were switched to secukinumab similar to that of secukinumab group up to week 52 and was consistent with the long term response on clinical synovitis observed in FUTURE 2 and FUTURE 5 studies [20,21]. The composite score incorporates both PD and SH measures of synovitis, evaluating changes in both activity and morphology of synovitis. Of interest, it was the SH score but not PD signal that contributed predominantly to responsiveness in this trial. This may be explained by the high number of large joints evaluated in the study, which usually show lower Doppler signal. The distribution of synovitis included selected small (feet and hands) and large joints (wrists and knees), which were mostly responsive to secukinumab over time, and which is consistent with observations from clinical practice. Since SH score and PD signal are expressions of the same imaging inflammatory process (i.e., synovitis), it is worth remembering that the suppression of US synovitis inflammation by secukinumab in the PSARTROS study was associated with no radiographic progression of the joints in patients with PsA over 24 weeks [13].

The usefulness of PDUS evaluation of enthesitis has been reported in patients with PsA [22]. However, this is the first study using the validated OMERACT PDUS enthesitis score that combines B-mode morphologic inflammatory abnormalities and PD abnormal vascularisation at bony insertions at the enthesitis level [2,11]. In addition, two novel candidate OMERACT PDUS enthesitis scores were derived at the patient level, based on different standardized definitions of activity (the first combining B-mode and PD, and the second focusing on PD alone). They

demonstrated very good feasibility and numerical responsiveness, especially Definition 1, which covered a higher number of patients.

The clinical response on enthesitis in patients treated by secukinumab (150 mg and 300 mg) is consistent with the FUTURE 2 and FUTURE 5 studies, as well as the post hoc analysis of the EXCEED study, as assessed by Leeds Enthesitis Index and SPARCC [20,21,23]. Of note, the SPARCC clinical index and global OMERACT enthesitis scores are not correlated because they measure different aspects of enthesitis. The OMERACT PDUS enthesitis score measures inflammation based on morphological and functional tissue changes whereas the SPARCC index evaluates inflammation based on the clinical tenderness of the enthesis. Their effect size cannot be compared because of differences in number of enthesitis sites and ratings used in the two scores. Finally, our data showed that placebo responses in enthesitis indices can be substantial. This study illustrates the current challenges in assessing longitudinal responses in ultrasound enthesitis in PsA. In part, placebo responses may result from natural fluctuations in entheseal inflammation, which may be more pronounced than with synovitis and the potential effect of background therapy. On the other hand, placebo responses during the blinded 12-week phase were much higher for clinical response than for US enthesitis indices, indicating that ultrasound may also allow more objective assessment of enthesitis.

The ULTIMATE trial showed a sustained clinical benefit of secukinumab treatment across multiple domains of the disease up to 52 weeks with numerically higher response rates than previously published long-term efficacy data of secukinumab in patients with PsA. This observation may be related to the more specific additional inclusion criteria such as PDUS active synovitis and the presence of at least one clinical enthesitis at baseline compared to the FUTURE 1 through FUTURE 5 trials, as well as by the tight clinical and US monitoring of these patients during the trial [14,16,21,24,25]. The safety profile of secukinumab was also consistent with previous studies on PsA [15,16] with no new or unexpected safety findings to 52 weeks.

Some limitations related to the study design should be acknowledged: pooling of the two secukinumab doses in the same treatment group, inferential efficacy comparisons between the secukinumab and placebo groups limited to the first 12 weeks (TP1), ultrasound and clinical efficacy outcomes assessed as exploratory endpoints beyond week 12, and increased drop-out rates in the open label extension period related to the COVID pandemic.

In conclusion, the ULTIMATE study showed that IL-17A inhibition with secukinumab provided stable improvement of synovitis at tissue level and sustained clinical improvement in enthesitis up to week 52 in patients with PsA. PDUS-assessed enthesitis scores tended to be numerically improved with secukinumab and remained stable up to week 52. These results reinforce the evidence of responsiveness of inflammatory changes in joints and entheses in PsA clinical trials.

References

1. Schett G, Rahman P, Ritchlin C, McInnes IB, Elewaut D, Scher JU. Psoriatic arthritis from a mechanistic perspective. Nat Rev Rheumatol 2022;18(6):311–25.
2. Balint PV, Terslev L, Aegerter P, Bruyn GaW, Chary-Valckenaere I, Gandjbakhch F, et al. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: An OMERACT US initiative. Ann Rheum Dis 2018;77(12):1730–5.
3. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: A EULAR-OMERACT Ultrasound Taskforce-Part 1: Definition and development of a standardised, consensus-based scoring system. RMD Open 2017;3(1):e000428.
4. D'Agostino MA, Wakefield R, Hammer HB, Vittecoq O, Galeazzi M, Balint P, et al and OMERACT-Ultrasound Task Force. Assessment of OMERACT global power Doppler ultrasonography 44-joint scoring system and reduced joint scoring systems in rheumatoid arthritis patients treated with abatacept plus background methotrexate. Arthritis Rheum 2012;64:S352–S3.
5. Mandl P, Navarro-Compán V, Terslev L, Aegerter P, Van Der Heijde D, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015;74(7):1327-39.
6. Wakefield RJ, D'Agostino MA, Iagnocco A, Filippucci E, Backhaus M, Scheel AK, et al. The OMERACT ultrasound group: Status of current activities and research directions. J Rheumatol 2007;34(4):848–51.
7. Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H. Power Doppler ultrasonography and synovitis: Correlating ultrasound imaging with

histopathological findings and evaluating the performance of ultrasound equipments. Ann Rheum Dis 2006;65(12):1590–5.

8. D'Agostino MA, Schett G, López-Rdz A, Šenolt L, Fazekas K, Burgos-Vargas R, et al. Response to secukinumab on synovitis using power Doppler ultrasound in psoriatic arthritis: 12-week results from a phase III study, ULTIMATE. Rheumatology (Oxford) 2021;keab628

9. D'Agostino M, Schett G, López-Rdz A, Šenolt L, Maldonado-Cocco J, Burgos-Vargas R, Naredo E, Carron P, Boers M, Duggan A, Goyanka P, Gaillez C. Secukinumab Significantly Decreased Joint Synovitis Measured by Power Doppler Ultrasonography in Biologic-naïve Patients with Active Psoriatic Arthritis: Primary (12-Week) Results from a Randomized, Placebo-Controlled Phase III Study [abstract]. Arthritis Rheumatol. 2020; 72 (suppl 10). https://acrabstracts.org/abstract/secukinumab-significantly-decreased-joint-synovitis-measured-by-power-doppler-ultrasonography-in-biologic-naive-patients-with-active-psoriatic-arthritis-primary-12-week-results-from-a-randomized-p/. Accessed July 21, 2023.

10. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, Brasseur JL, Dougados M, Breban M. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: A cross-sectional study. Arthritis Rheum 2003;48(2):523–33.

11. Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, et al. Defining enthesitis in spondyloarthritis by ultrasound: Results of a delphi process and of a reliability reading exercise. Arthritis Care Res (Hoboken) 2014;66(5):741–8.

12. Polachek A, Cook R, Chandran V, Gladman DD, Eder L. The association between sonographic enthesitis and radiographic damage in psoriatic arthritis. Arthritis Res Ther 2017;19(1):1–8.

13. Kampylafka E, D'oliveira I, Linz C, Lerchen V, Stemmler F, Simon D, et al. Resolution of synovitis and arrest of catabolic and anabolic bone changes in patients with psoriatic arthritis by IL-17A blockade with secukinumab: Results from the prospective PSARTROS study. Arthritis Res Ther 2018;20(1):153.
14. Mease PJ, Kavanaugh A, Reimold A, Tahir H, Rech J, Hall S, et al. Secukinumab provides sustained improvements in the signs and symptoms of psoriatic arthritis: Final 5-year results from the phase 3 FUTURE 1 study. ACR Open Rheumatol 2020;2(1):18–25.
15. Mease PJ, Kavanaugh A, Reimold A, Tahir H, Rech J, Hall S, 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.
16. McInnes IB, Mease PJ, Kivitz AJ, Nash P, Rahman P, Rech J, et al. Long-term efficacy and safety of secukinumab in patients with psoriatic arthritis: 5-year (end-of-study) results from the phase 3 FUTURE 2 study. Lancet Rheumatol 2020;2(4):e227–e35.
17. World Medical Association. World Medical Association Declaration Of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191–4.
18. Boers M, Conaghan PG, Schett G, Mandl P, Naredo E, Van Den Bosch F, et al. POS0197 Responsiveness of ultrasound synovitis and clinical outcomes in psoriatic arthritis treated with secukinumab: Data from the ULTIMATE trial. Ann Rheum Dis 2021;80(314).
19. Torp-Pedersen S, Christensen R, Szkudlarek M, et al. Power and color Doppler ultrasound settings for inflammatory flow: impact on scoring of disease activity in patients with rheumatoid arthritis. Arthritis Rheumatol 2015;67(2):386-395.
20. Mease PJ, Landewé R, Rahman P, Tahir H, Singhal A, Boettcher E, et al. Secukinumab provides sustained improvement in signs and symptoms and low radiographic progression in patients with psoriatic arthritis: 2-year (end-of-study) results from the FUTURE 5 study. RMD Open 2021;7(2):e001600.

21. McInnes IB, Mease PJ, Ritchlin CT, Rahman P, Gottlieb AB, Kirkham B, et al. Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. Rheumatology (Oxford) 2017;56(11):1993–2003.
22. Molina Collada J, Macía-Villa C, Plasencia C, Álvaro-Gracia JM, De Miguel E. Doppler enthesitis: A potential useful outcome in the assessment of axial spondyloarthritis and psoriatic arthritis. Clin Rheumatol 2021;40(5):2013–20.
23. Kaeley GS, Schett G, Conaghan PG, Mcgonagle D, Behrens F, Goupille P, et al. POS0194 Enthesitis in patients with psoriatic arthritis treated with secukinumab or adalimumab: A post hoc analysis of EXCEED. Ann Rheum Dis 2021;80(Suppl 1):311–2.
24. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386(9999):1137–46.
25. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, Van Der Heijde D, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373(14):1329–39.

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Ethical approval and consent to participate

The study protocol was reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each participating centre. The study was conducted according to the ICH E6 guideline for Good Clinical Practice that has its origin in the Declaration of Helsinki. Written informed consent was obtained from all enrolled patients.

Data sharing statement

The datasets generated during and/or analyzed during the current study are not publicly available. Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved the basis of 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.

Authors' contributions

Study conception and design: MA D'Agostino, M Boers, G Schett

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version of the article to be submitted. All authors had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

MAD'A reports speaker or consultant fees from Sanofi, Novartis, BMS, Janssen, Celgene, Roche, AbbVie, UCB, and Eli Lilly. PC reports research grants from UCB, MSD and Pfizer;

speaker fees or consultant fees from Pfizer, MSD, Novartis, Bristol Myers Squibb, AbbVie, UCB, Eli Lilly, Gilead and Celgene Corporation. CG is a stockholder of Novartis and BMS and an employee of Novartis. PGC reports speaker fees or consultant fees from AbbVie, AstraZeneca, Eli Lilly, Galapagos, Merck, Novartis, Pfizer, Stryker and UCB. EN reports speaker fees from AbbVie, Roche, BMS, Pfizer, UCB, Lilly, Novartis, Janssen, and Celgene GmbH; honoraria for clinical trials from AbbVie, Novartis and BMS; research grants from Eli Lilly. AL reports speaker or consultant fees from Eli Lilly, Novartis, Janssen, Roche, all GSK and UCB. LS reports research grants, speaker fees, consultant fees and honoraria for clinical trials from AbbVie, Bristol-Myers Squibb, Celgene Corporation, Eli Lilly, Gilead, Merck Sharp and Dohme, Mylan, Novartis, Pfizer, Roche, Sanofi, Sandoz, Sobi, Takeda, and UCB. RB has received honoraria for speaking from Novartis. PH has nothing to disclose. IP has nothing to disclose. TC has nothing to disclose. MSS reports speaker or consultant fees or grants from AbbVie, MSD, Pfizer, Roche and UCB. MB reports speaker or consultant fees or grants from AbbVie, Amgen, BMS, Galapagos, Johnson, MSD, Novartis, Pfizer, Roche and UCB. GM reports speaker or consultant fees or grants from AbbVie, BMS, Celgene, Lilly, Novartis and Pfizer. WB and PG are employees of Novartis. MB is a consultant for Novartis, received speaker fees from Pfizer and provided expert testimony for Celltrion. GS reports speakers' honoraria from AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, Roche and UCB.

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Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Table 1. OMERACT Definitions for PDUS enthesitis: at enthesis level and at patient level

	Definition 1 (activity and structure)	**Definition 2 (activity only)**
OMERACT enthesitis score (at enthesis level)	PD signal (range 0–3) + Grey Scale (B-mode, range 0–1)	PD signal only
Score range	0–4	0–3
Global OMERACT enthesitis score (at patient level)	Sum over 6 sites scored bilaterally	Sum over 6 sites scored bilaterally
Score range	0–48	0–36

At each visit the inflammatory and structural components of all affected enthesis sites were scored. The sum of site scores comprises the global OMERACT enthesitis score at patient level.

OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; PD, power Doppler; PDUS, power Doppler ultrasonography

542 **Table 2. Baseline clinical and ultrasound synovitis and enthesitis**

Values, mean (SD)	Secukinumab (N=83)	Placebo (N=83)	Total (N=166)
Enthesitis			
Clinical (SPARCC index)	**n=83** 4 (3)	**n=81** 4 (3)	**n=164** 4 (3)
PDUS Global OMERACT Definition 1	**n=73** 6 (5)	**n=61** 5 (3)	**n=134** 6 (4)
PDUS Global OMERACT Definition 2	**n=34** 3 (3)	**n=20** 3 (2)	**n=54** 3 (3)
Synovitis			
Tender joint count (out of 78)	**n=83** 13 (8)	**n=83** 15 (12)	**n=166** 14 (10)
Swollen joint count (out of 76)	**n=83** 10 (8)	**n=83** 9 (9)	**n=166** 9 (8)
GLOESS	**n=83** 24 (16)	**n=83** 27 (17)	**n=166** 26 (16)
Synovial hypertrophy (SH)	**n=83** 24 (16)	**n=83** 27 (17)	**n=166** 25 (16)
Power Doppler (PD)	**n=83** 8 (8)	**n=83** 7 (7)	**n=166** 7 (7)

543
544 EULAR, European Alliance of Associations for Rheumatology; GLOESS, OMERACT-EULAR global
545 synovitis score; n, number of patients with complete assessment at BSL; OMERACT, Outcome Measures
546 in Rheumatology; PDUS, power Doppler ultrasonography
547

Figure legends

Figure 1. Mean change from baseline in GLOESS ultrasound synovitis score by treatment up to week 52 (A), and its components synovial hypertrophy (B) and power Doppler (C) from baseline up to week 52

Data presented as observed. Open-label period from week 12 to 52 (shaded area).

GLOESS=Global OMERACT-EULAR Synovitis Score using PDUS Composite score of 24 paired joints. The range for the GLOESS score is 0–144.

EULAR, European Alliance of Associations for Rheumatology; OMERACT, Outcome Measures in Rheumatology; PDUS, power Doppler ultrasonography

Figure 2. Distribution of PDUS-detected synovitis by grade of severity over time

*All placebo patients switched to active treatment at week 12. #Lower patient numbers due to delayed or missing efficacy assessments due to a confounding effect of the COVID-19 pandemic.

For each joint, sum of left and right side OMERACT-EULAR PDUS composite score. Data for top nine pairs of joints with most frequently detected PDUS synovitis are presented here.

EULAR, European Alliance of Associations for Rheumatology; N, total number of patients; OMERACT, Outcome Measures in Rheumatology; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PBO, placebo; PDUS, power Doppler ultrasonography; SEC, secukinumab

Figure 3. Mean change from baseline in SPARCC index clinical enthesitis score to week 52

Data presented as observed. Open-label period from week 12 to 52 (shaded area). The total score for the index ranges from 0–16.

SPARCC, Spondyloarthritis Research Consortium of Canada enthesitis index.

Figure 4. Baseline distribution of US enthesitis (Definition 1 [A] and Definition 2 [B]) and clinical enthesitis (C) in the secukinumab group

The numbers indicate the overall prevalence of enthesitis on either side (bilateral occurrence counted once).

Figure 5. Distribution of PDUS-detected enthesitis by grade of severity over time

*All placebo patients switched to active treatment at week 12. #Lower patient numbers due to delayed or missing efficacy assessments due to a confounding effect of the COVID-19 pandemic.

For each joint, sum of left and right side of OMERACT-EULAR PDUS composite score. Data for 6 bilateral sites are presented here.

EULAR, European Alliance of Associations for Rheumatology; N, total number of patients; OMERACT, Outcome Measures in Rheumatology; PBO, placebo; PDUS, power Doppler ultrasonography; SEC, secukinumab

Figure 6. Mean change from baseline global OMERACT enthesitis score at patient level (Definition 1) (A) and (Definition 2) (B) through week 52

Data presented as observed. Open-label period from week 12 to 52 (shaded area). Global OMERACT (PDUS) enthesitis score (Definition 1) ranges from 0–48 and is the sum of the B-mode (0=absence, 1=presence) and PD signal (score range: 0–48) across 12 enthesitis sites. At each time point, only patients with a value at both baseline and that time point were included. Only patients with positive values (>0 at baseline) were included. Definition 2: sum of the PD signal (score range: 0–36) across all sites. Score ranges from 0–36.

OMERACT, Outcome Measures in Rheumatology; PD, power Doppler; PDUS, power Doppler ultrasonography

Figure 1. Mean change from baseline in GLOESS ultrasound synovitis score by treatment up to week 52 (A), and its components synovial hypertrophy (B) and power Doppler (C) from baseline up to week 52

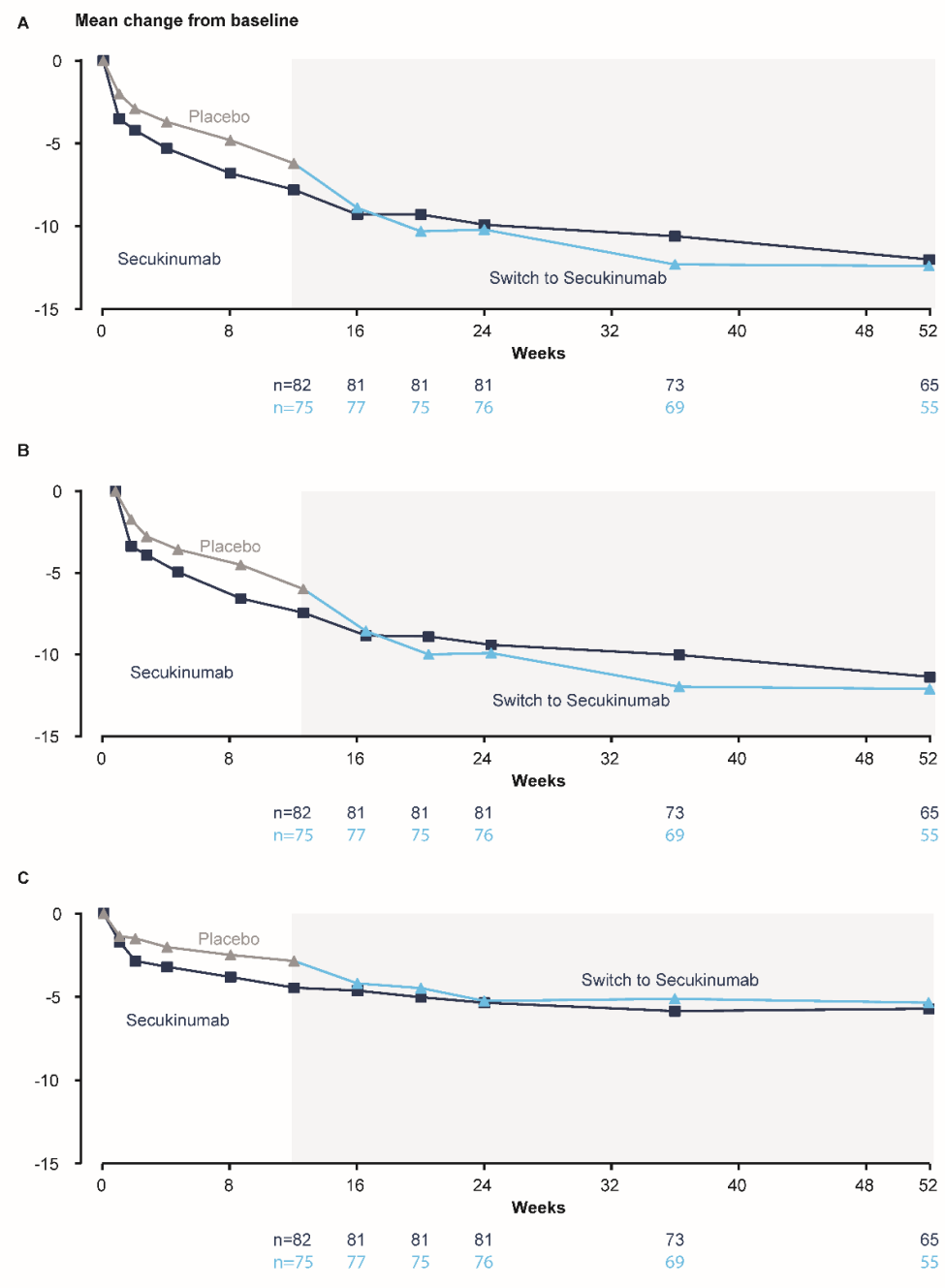

Figure 2. Distribution of PDUS-detected synovitis by grade of severity over time

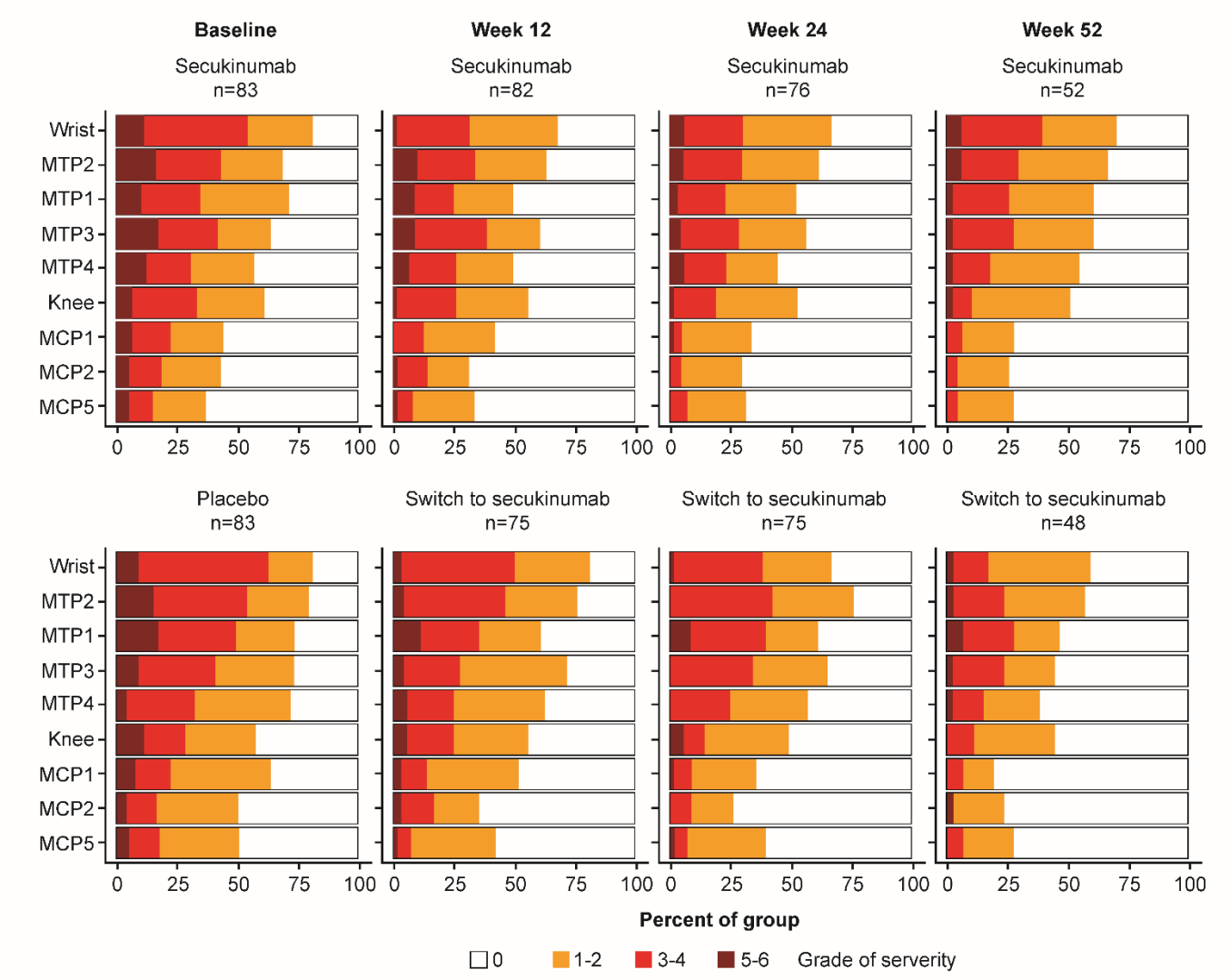

Figure 3. Mean change from baseline in SPARCC index clinical enthesitis score to week 52

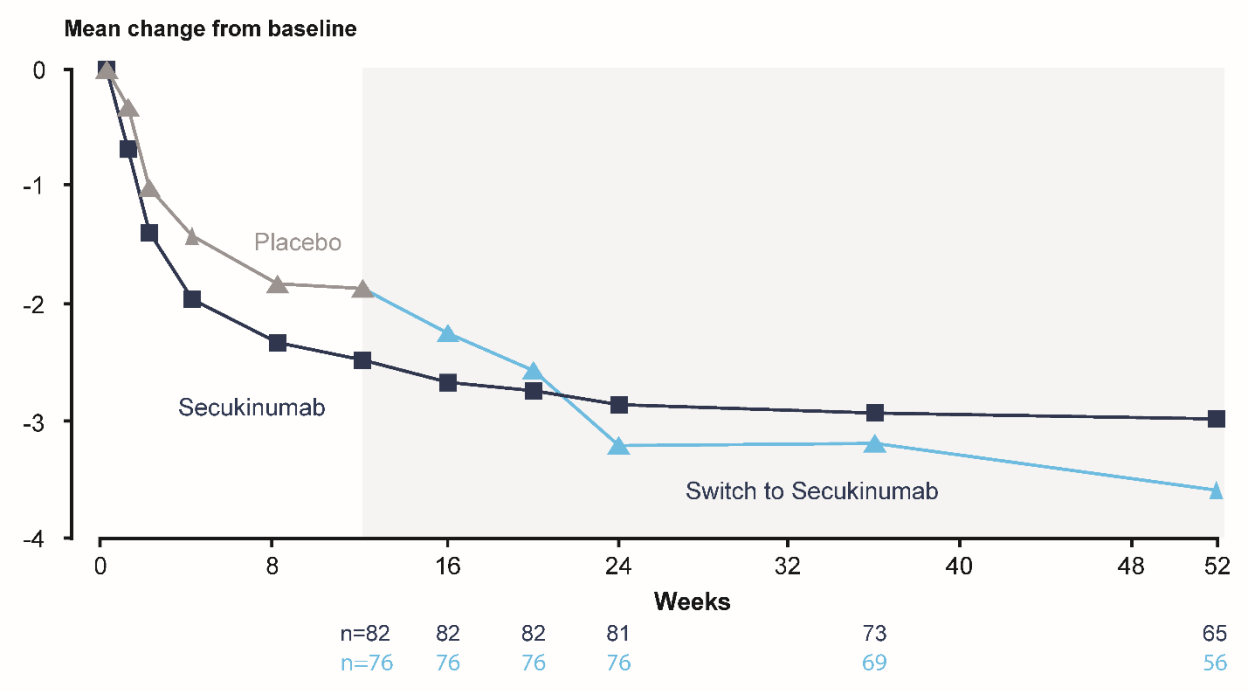

Figure 4. Baseline distribution of US enthesitis (Definition 1 [A] and Definition 2 [B]) and clinical enthesitis (C) in the secukinumab group

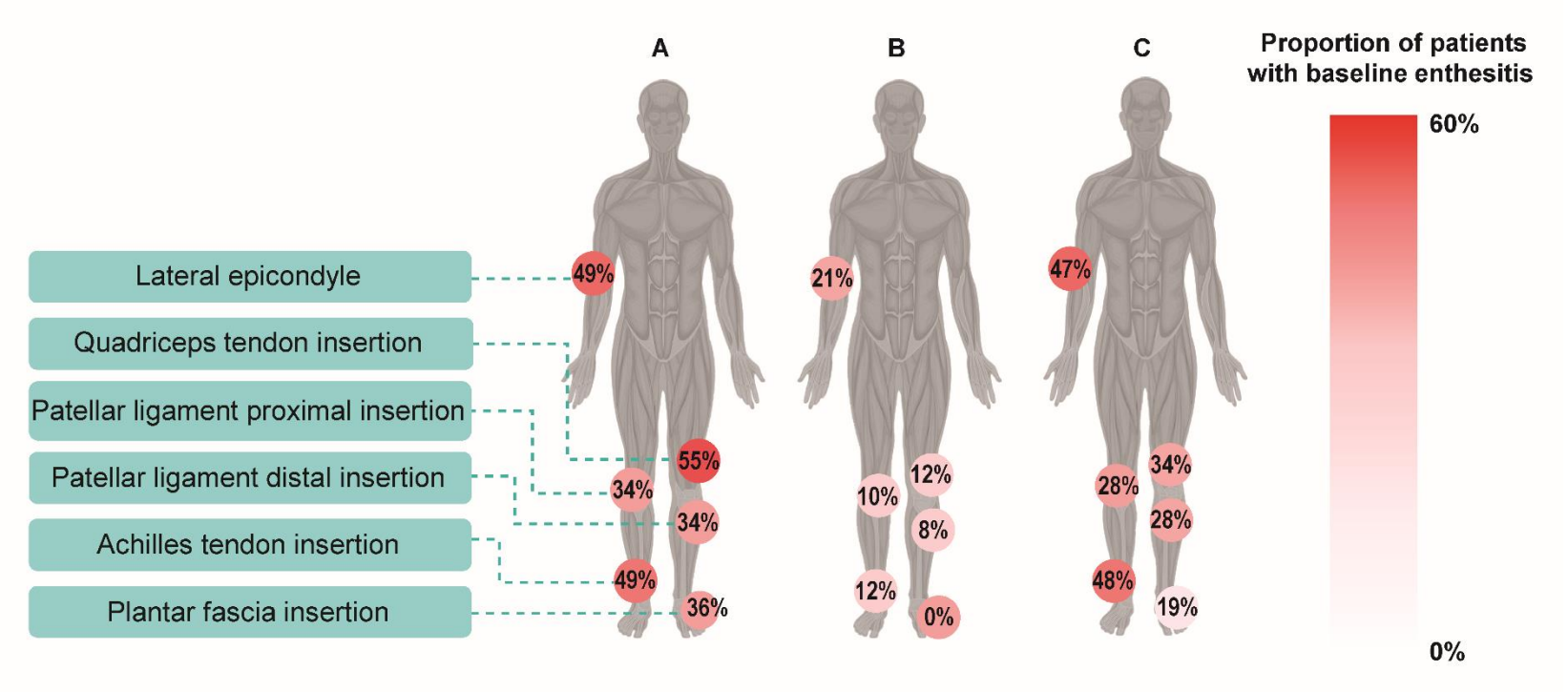

Figure 5. Distribution of PDUS-detected enthesitis by grade of severity over time

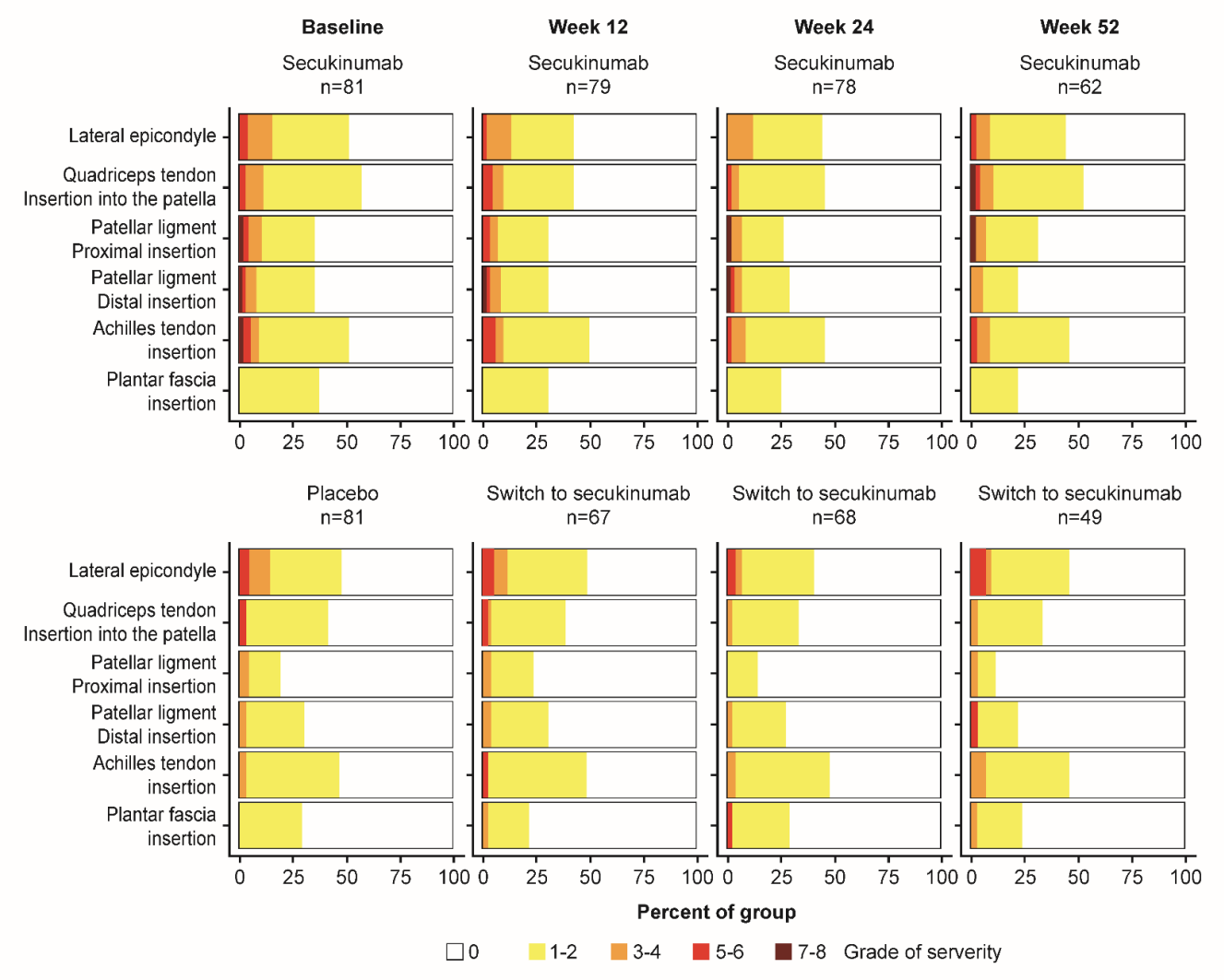

Figure 6. Mean change from baseline global OMERACT enthesitis score at patient level (Definition 1) (A) and (Definition 2) (B) through week 52