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Original Article

Clinical science

Association of the clinical components in the distal interphalangeal joint synovio-entheseal complex and subsequent response to ixekizumab or adalimumab in psoriatic arthritis

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Abstract

Objectives: To assess the frequency of simultaneous distal interphalangeal (DIP) joint disease and adjacent nail psoriasis (finger unit) among patients with psoriatic arthritis (PsA) and compare the efficacy of the IL-17A antagonist ixekizumab (IXE) and the TNF-α inhibitor adalimumab (ADA).

Methods: This *post hoc* analysis evaluated the simultaneous occurrence of DIP joint involvement (tenderness and/or swelling) and adjacent nail psoriasis among patients with PsA from the SPIRIT-H2H (NCT03151551) trial comparing IXE to ADA. Among patients with simultaneous DIP joint involvement and adjacent nail psoriasis in ≥1 digit at baseline, treatment effects were assessed through week 52 for each affected finger unit; 'finger unit' defines the connected DIP joint and adjacent nail of an individual digit.

Results: A total of 354 patients had simultaneous DIP joint involvement and adjacent nail psoriasis in ≥1 finger unit at baseline. Among them, 1309 (IXE: 639; ADA: 670) finger units had baseline DIP joint tenderness and/or swelling and adjacent nail psoriasis. Proportions of affected finger units achieving complete resolution were significantly higher with IXE *vs* ADA as early as week 12 (38.8% *vs* 28.4%, $P < 0.0001$) and at all post-baseline assessments through week 52 (64.9% *vs* 57.5%, $P = 0.0055$).

Conclusion: In this study cohort, patients with DIP joint involvement almost always had adjacent nail psoriasis. Greater resolution of DIP joint tenderness, swelling and adjacent nail psoriasis was achieved at all time points over 52 weeks through targeting IL-17A with IXE than TNF-α with ADA, which is noteworthy given prior comparable musculoskeletal outcomes for both drug classes.

Keywords: ixekizumab, psoriatic arthritis, nail psoriasis, distal interphalangeal joint, head-to-head.

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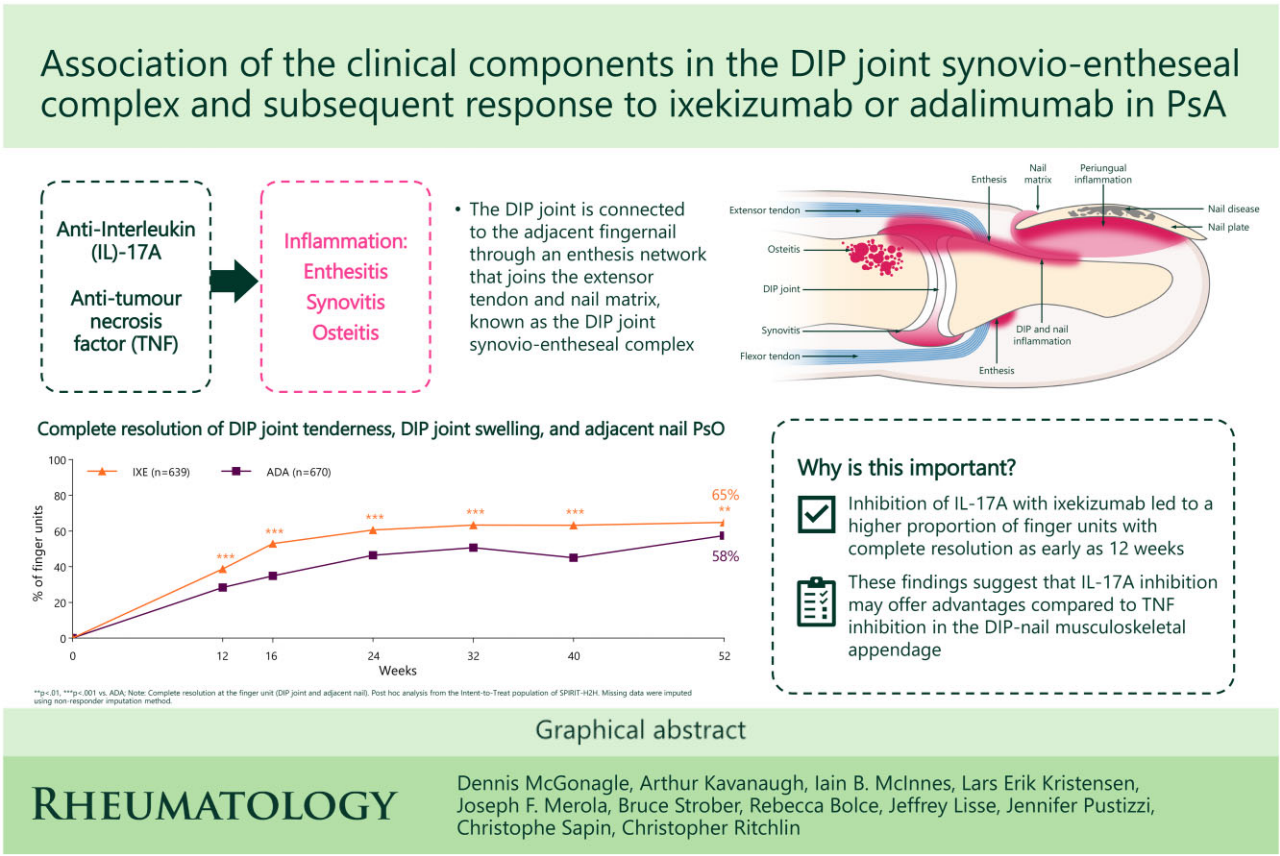
Graphical abstract



Rheumatology key messages

- The DIP joint and extensor tendon are physically integrated with the adjacent nail via entheses.
- In this PsA cohort, patients with DIP joint involvement almost always had adjacent nail psoriasis.
- IXE provided benefit over ADA in resolving DIP joint and nail disease over 52 weeks.

Introduction

Psoriatic arthritis (PsA) is an inflammatory rheumatic disorder usually associated with cutaneous psoriasis [1]. PsA commonly manifests in the peripheral joints, including the distal interphalangeal (DIP) joints of the hands [2]. DIP joint involvement is reported in up to one-third of patients with PsA [3–5].

Each DIP joint is connected to the adjacent fingernail through an enthesis network that joins the extensor tendon and nail matrix, known as the DIP joint synovio-entheseal complex (Supplementary Fig. S1, available at *Rheumatology* online) [6, 7]. As such, the DIP joint and adjacent nail may be considered a functional unit, the 'finger unit'. In patients with PsA, nail psoriasis is more common and tends to be more severe among those with DIP joint involvement *vs* those without [3, 4, 8–10]. The close association between DIP joint involvement and nail psoriasis in PsA suggests a common local inflammatory mechanism, or aetiopathogenetic localizing programme. A recent histochemical analysis of psoriatic nail beds found that the immunophenotype of psoriatic nail disease more closely resembled that of PsA than cutaneous psoriasis, although this immunophenotype was not shared with the adjacent DIP joints in patients with nail psoriasis and DIP PsA [11].

Nail psoriasis affects an estimated 63–83% of patients with PsA and is a strong predictor for future development of comorbid PsA when present in psoriasis patients [12, 13]. Nail psoriasis is highly visible, interferes with grip strength and fine motor skills, and causes pain in over 50% of affected patients [14, 15]. Patients with PsA and nail psoriasis experience increased disease activity and decreased quality of life compared with patients without nail involvement [16], while the converse is also reported [17]. The early and targeted treatment of nail psoriasis among patients with PsA is important to improve patient outcomes [18].

The pro-inflammatory IL-17 cytokines are key regulators of the pathogenesis of PsA and psoriasis [19–21]; ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets IL-17A and is approved to treat active PsA and moderate-to-severe psoriasis. In psoriasis, biologics targeting IL-17 cytokines provide more rapid skin clearance compared with other approved biologics, including those targeting

TNF-α, IL-23 p19 and IL-12/23 p40 [22–30]. The SPIRIT-H2H (NCT03151551) study was a Phase 3 b/4 clinical trial investigating the efficacy and safety of IXE *vs* the TNF-α inhibitor adalimumab (ADA) in biologic-naïve adults with active PsA and plaque psoriasis [31, 32]. A significantly higher proportion of SPIRIT-H2H patients treated with IXE *vs* ADA achieved the primary end point of simultaneous ACR50 and PASI100 response, and both drugs were comparable in respect to arthritis resolution, achieving similar ACR50, ACR20 and ACR70 response rates [31, 32]. In this study, IXE-treated patients also experienced significantly greater improvements in nail psoriasis compared with ADA-treated patients [31, 32].

The objective of this *post hoc* analysis was to investigate and confirm the association between DIP joint involvement and adjacent nail psoriasis expression. We thereafter compared the efficacy of IL-17A antagonist IXE and TNF-α inhibitor ADA specifically among the finger units affected by DIP involvement and adjacent nail disease in patients with PsA.

Methods

Clinical trial design

SPIRIT-H2H (NCT03151551) was a 52-week, multicentre, randomized, open-label, parallel-group, assessor-blinded study evaluating the efficacy and safety of IXE *vs* ADA in biologic-naïve patients with PsA. A detailed description of the study design has previously been published [31, 32]. Participants received approved-label dosing of the assigned treatment based on the presence or absence of moderate-to-severe psoriasis, as described in Supplementary Data S1 (available at *Rheumatology* online) [31, 32]. SPIRIT-H2H was conducted in accordance with the ethical principles of the Declaration of Helsinki of 1964 and its later amendments, and in compliance with local laws and regulations. All patients provided written informed consent for participation in the study. The study protocol was approved by the National Research Ethics Service Committee London (17/LO/0794) and the ethical review board of each investigative site prior to the start of study-related procedures. The full list of ethics committees has previously been published [33].

Post hoc analysis populations

Patient population

This *post hoc* study included patients from the intent-to-treat population of SPIRIT-H2H who had simultaneous DIP joint involvement (tenderness and/or swelling) and adjacent nail psoriasis (Nail Psoriasis Severity Index [NAPSI] total score >0) affecting the finger unit (DIP joint and adjacent nail) of at least one digit at baseline.

Finger unit analysis population

Each person from the patient analysis population could have between 1 and 10 finger units (DIP joint and adjacent nail) affected by simultaneous DIP joint involvement and adjacent nail psoriasis. The finger unit analysis population included all such affected finger units, where each was considered an individual entity.

Outcome measures

Joint outcome measures

SPIRIT-H2H patients were assessed for joint tenderness and for joint swelling at baseline and at weeks 4, 8, 12, 16, 24, 32, 40 and 52. Joint disease was measured by tender joint count (TJC68) and swollen joint count (SJC66) scores. The present analysis used the scores of the 10 joints adjacent to the fingernails, that is, the eight DIP joints of the fingers and the two interphalangeal joints of the thumbs, which we collectively refer to as the DIP joints. A patient was considered to have DIP joint involvement if the DIP joint was tender and/or swollen in the finger unit of at least one digit at baseline. A finger unit (DIP joint and adjacent nail) was considered to have DIP joint involvement if its DIP joint was tender and/or swollen.

Nail outcome measures

SPIRIT-H2H patients were assessed for fingernail psoriasis at baseline and at weeks 12, 16, 24, 32, 40 and 52. Nail psoriasis was measured using the NAPSI in the fingers of the hands only. NAPSI scores are calculated by dividing the fingernail into quadrants with imaginary longitudinal and horizontal lines. Each fingernail is then scored out of 8 for nail matrix psoriasis (0–4) and nail bed psoriasis (0–4), depending on the presence (1) or absence (0) of any associated psoriatic features per quadrant. Psoriatic nail matrix features include nail pitting, leukonychia, red spots in the lunula and crumbling. Psoriatic nail bed features include onycholysis, oil drop dyschromia, splinter haemorrhages and nail bed hyperkeratosis. Nail matrix psoriasis and nail bed psoriasis scores are combined for all fingers to give a total maximum score of 80 per patient. A patient was considered to have nail psoriasis if they had a NAPSI total score >0 in the finger unit of at least one digit at baseline. A finger unit (DIP joint and adjacent nail) was considered to have nail psoriasis if the nail had a NAPSI total score >0.

Combined outcome measure

This *post hoc* analysis used a combined outcome measure to assess the proportion of finger units with simultaneous resolution of DIP joint involvement and resolution of adjacent nail psoriasis at weeks 12, 16, 24, 32, 40 and 52.

Statistical analyses

Each finger unit (DIP joint and adjacent nail) affected by simultaneous DIP joint involvement and adjacent nail psoriasis was treated as an individual entity for these analyses. We evaluated the number of DIP joints affected by tenderness, swelling, or tenderness and/or swelling. We additionally evaluated the number of nails with nail matrix psoriasis, nail bed psoriasis or a NAPSI total score >0.

The χ^2 test was used to compare the proportions of finger units per treatment group that achieved resolution of DIP joint tenderness and/or swelling, resolution of nail matrix and/or nail bed psoriasis, and the combined outcome measure of simultaneous resolution of DIP involvement and adjacent nail psoriasis. The non-response imputation (NRI) method was used to handle missing data.

Results

Patient population

The present study focused on patients who had simultaneous DIP joint involvement (tenderness and/or swelling) and adjacent nail psoriasis (NAPSI total score >0) affecting the finger unit (DIP joint and adjacent nail) of at least one digit at baseline.

Figure 1 shows that among the 566 SPIRIT-H2H participants (1) 367 patients had DIP joint tenderness and/or swelling at baseline, (2) 368 patients had nail psoriasis defined by a NAPSI total score >0 at baseline, and (3) 354 patients had simultaneous DIP joint tenderness and/or swelling and adjacent nail psoriasis affecting the finger unit (DIP joint and adjacent nail) of at least one digit at baseline. The association between DIP joint involvement and nail psoriasis was very high in this study population. Among the patients with DIP joint tenderness and/or swelling at baseline, 96.5% ($n/N = 354/367$) had psoriasis of the adjacent nail in the finger unit of at least one digit (Fig. 1A). Among the patients with nail psoriasis at baseline, 96.2% ($n/N = 354/368$) had tenderness and/or swelling of the adjacent DIP joint in the finger unit of at least one digit (Fig. 1B).

Supplementary Table S1 (available at *Rheumatology* online) presents the baseline demographics and disease characteristics of the 354 patients with simultaneous DIP joint tenderness and/or swelling and adjacent nail psoriasis affecting the finger unit (DIP joint and adjacent nail) of at least one digit at baseline. Supplementary Table S2 (available at *Rheumatology* online) summarizes the distribution of affected digits among this patient population at baseline.

Finger unit population

Across the selected patient population ($N = 354$), a total of 1309 finger units (IXE: 639; ADA: 670) were affected by

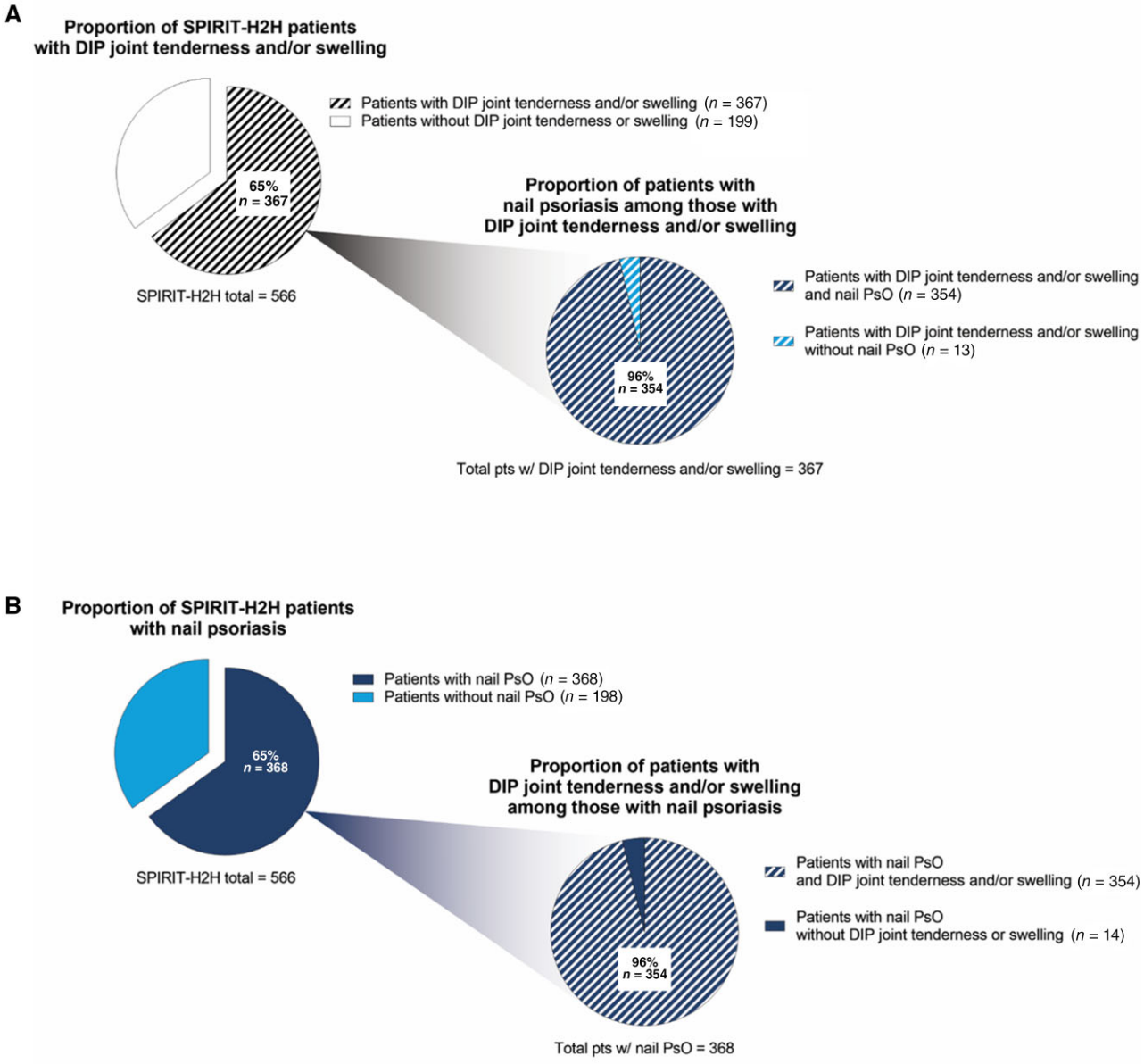


Figure 1. Proportions of patients with DIP involvement and/or nail psoriasis among different SPIRIT-H2H populations. (**A**) Sixty-five percent of SPIRIT-H2H patients had DIP tenderness and/or swelling (left), and of those, 96% had adjacent nail PsO (right). (**B**) Sixty-five percent of SPIRIT-H2H patients had nail PsO, and of those, 96% had adjacent DIP tenderness and/or swelling. Percentage values are rounded. DIP: distal interphalangeal joint; PsO: psoriasis; pts: patients; w/: with

simultaneous DIP joint involvement (tenderness and/or swelling) and adjacent nail psoriasis (NAPSI total score >0) at baseline. These 1309 affected finger units constitute the finger unit analysis population. The DIP joint was tender in 1217 (IXE: 594; ADA: 623) of these finger units, and swollen in 928 (IXE: 463; ADA: 465). The nail exhibited nail matrix psoriasis across 1033 (IXE: 516; ADA: 517) finger units, and nail bed psoriasis across 944 (IXE: 465; ADA: 479).

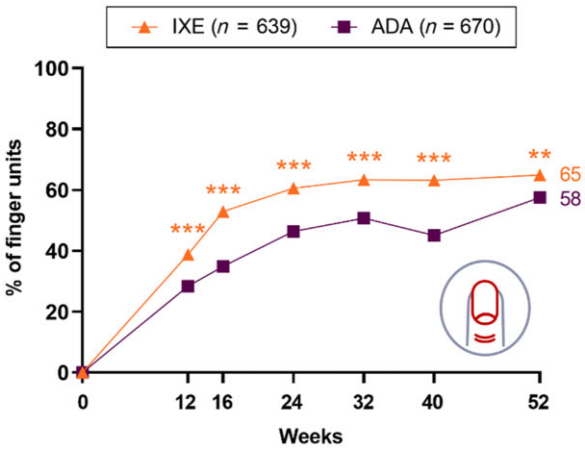


Figure 2. Proportion (%) of finger units (DIP joint and adjacent nail) with complete resolution of DIP joint tenderness, DIP joint swelling and nail psoriasis, among patients treated with IXE or ADA who had DIP joint disease and adjacent nail psoriasis at baseline. Finger unit refers to the DIP joint and adjacent nail of an individual digit. All finger units included in this analysis had DIP joint tenderness and/or swelling and adjacent nail psoriasis at baseline. The finger unit graphic signifies the simultaneous resolution of DIP joint disease and adjacent nail psoriasis. Missing data were imputed using the NRI method. Significant difference between IXE *vs* ADA treatment denoted by $^{**}P < 0.01$ and $^{***}P < 0.001$. ADA: adalimumab; DIP: distal interphalangeal joint; NRI, non-response imputation; IXE: ixekizumab

Treatment response among finger units

Resolution of DIP joint involvement and nail psoriasis

Approximately one-third of the total finger unit population had achieved complete resolution of DIP involvement and adjacent nail psoriasis at week 12. A statistically significantly larger proportion of IXE-treated finger units achieved this combined outcome at all post-baseline assessments over 52 weeks (Fig. 2). The difference between treatment arms was apparent by week 12 (38.8% *vs* 28.4%, $P < 0.0001$) and sustained out to week 52 (64.9% *vs* 57.5%, $P = 0.0055$).

Individually, DIP joint involvement (tenderness and/or swelling) was resolved in about two-thirds of finger units by week 12 (Fig. 3A). The proportion of finger units with resolution of DIP joint involvement (tenderness and/or swelling) was significantly higher with IXE at all post-baseline assessments over 52 weeks (Fig. 3A). The difference between treatments was apparent by week 12 (70.4% *vs* 63.1%, $P = 0.0016$) and sustained out to week 52 (87.9% *vs* 78.4%, $P < 0.0001$).

Separately, approximately half of the affected finger units had individually resolved nail psoriasis at week 12. The resolution response for nail psoriasis was significantly higher with IXE treatment at all post-baseline assessments over 52 weeks (Fig. 3B). The difference between treatment arms was apparent by week 12 (58.4% *vs* 48.8%, $P < 0.0002$) and sustained out to week 52 (85.1% *vs* 79.9%, $P = 0.04$).

Resolution of DIP joint tenderness and DIP joint swelling

DIP joint tenderness was the most common feature of the finger unit population, and it was resolved by week 12 in approximately two-thirds of affected finger units across both treatment arms (Fig. 4A). DIP joint tenderness was resolved in a significantly larger proportion of IXE-treated finger units at all post-baseline assessments over 52 weeks (Fig. 4A). The difference between treatment arms was apparent by week 12 (72.6% *vs* 64.5%, $P < 0.0001$) and sustained out to week 52 (89.4% *vs* 78.0%, $P < 0.0001$).

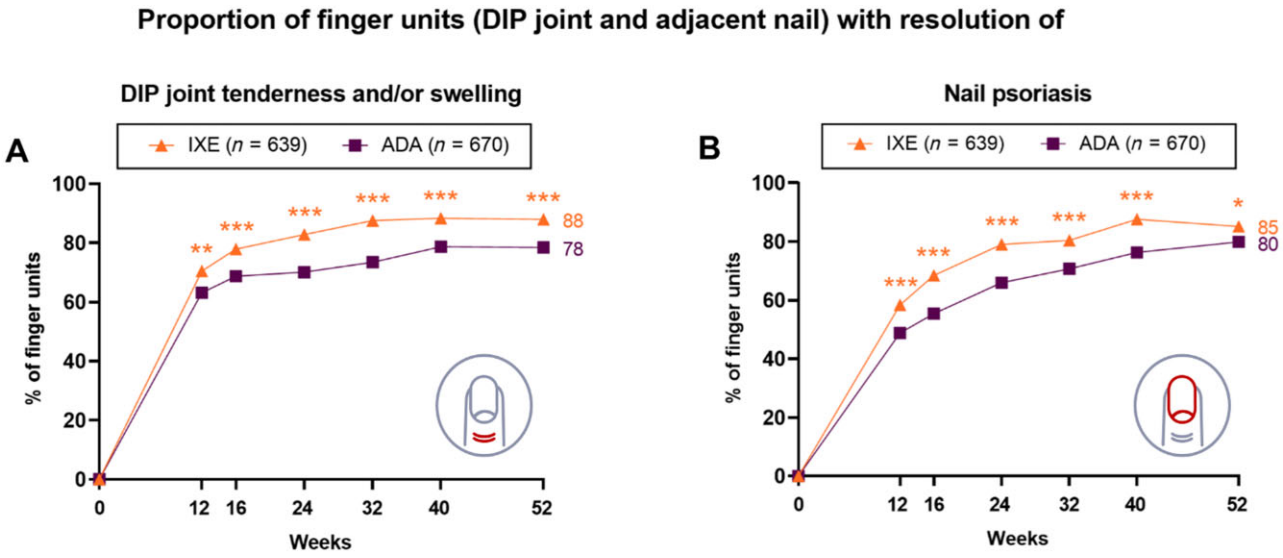


Figure 3. Proportion (%) of finger units (DIP joint and adjacent nail) with resolution of DIP joint tenderness and/or swelling (**A**), or resolution of nail psoriasis (**B**), among patients treated with IXE or ADA who had DIP joint disease and adjacent nail psoriasis at baseline. Finger unit refers to the DIP joint and adjacent nail of an individual digit. All finger units included in this analysis had DIP joint tenderness and/or swelling and adjacent nail psoriasis at baseline. The finger unit graphic signifies the resolution of DIP joint involvement (**A**) or the resolution of nail psoriasis (**B**). Missing data were imputed using the NRI method. Significant difference between IXE vs ADA treatment denoted by $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. ADA: adalimumab; DIP: distal interphalangeal joint; IXE: ixekizumab; NRI: non-response imputation

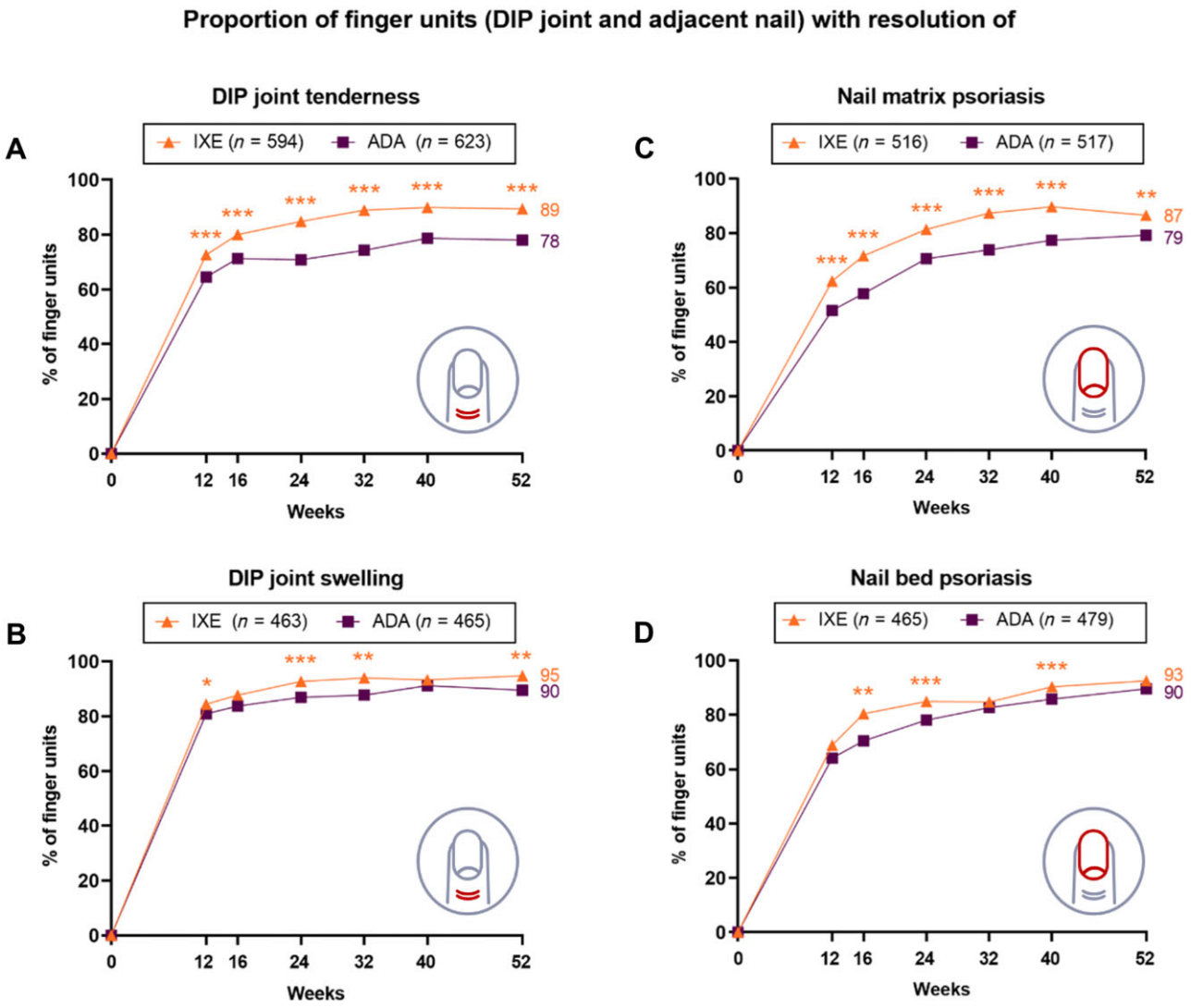


Figure 4. Proportion (%) of finger units (DIP joint and adjacent nail) with resolution of DIP joint tenderness (**A**), resolution of DIP joint swelling (**B**), resolution of nail matrix psoriasis (**C**), or resolution of nail bed psoriasis (**D**), among patients treated with IXE or ADA who had DIP joint disease and adjacent nail psoriasis at baseline. Finger unit refers to the DIP joint and adjacent nail of an individual digit. All finger units included in this analysis had DIP joint tenderness and/or swelling and adjacent nail psoriasis at baseline. The finger unit graphic signifies the resolution of a component of DIP joint involvement (**A**, **B**) or nail psoriasis (**C**, **D**). Missing data were imputed using the NRI method. Significant difference between IXE vs ADA treatment denoted by $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$. ADA: adalimumab; DIP: distal interphalangeal joint; IXE: ixekizumab; NRI: non-response imputation

DIP joint swelling was less frequent than DIP joint tenderness among the finger unit analysis population, but proportionally more finger units had resolved swelling compared with tenderness at earlier time points. With either IXE or ADA treatment, DIP joint swelling had resolved in over 80% of affected finger units by week 12 (Fig. 4B). This swelling was resolved in a larger proportion of IXE-treated finger units at all post-baseline assessments over 52 weeks. The difference between treatment arms ranged from 2.1% to 6.3% and reached statistical significance at all visits except week 16 and week 40 (Fig. 4B).

Resolution of nail matrix psoriasis and nail bed psoriasis

Nail matrix psoriasis affected over three-quarters of the total finger unit population, and with either IXE or ADA treatment it was resolved by week 12 in >50% of cases (Fig. 4C). Nail matrix psoriasis was resolved in a significantly larger proportion of IXE-treated finger units at all post-baseline assessments over 52 weeks (Fig. 4C). The difference between IXE and ADA treatment arms was apparent by week 12 (62.4% *vs* 51.6%, $P < 0.0002$) and sustained out to week 52 (86.6 *vs* 79.3%, $P = 0.0072$).

Nail bed psoriasis was less frequent among the finger unit population compared with nail matrix psoriasis, but proportionally more finger units had resolved nail bed psoriasis compared with nail matrix psoriasis at earlier time points. Across both treatment arms, nail bed psoriasis resolved in about two-thirds of affected finger units by week 12 (Fig. 4D). Nail bed psoriasis was resolved in a numerically larger proportion of IXE-treated finger units at all post-baseline assessments. The difference between treatment arms ranged from 2.0% to 10.0% and reached statistical significance at weeks 16, 24 and 40 (Fig. 4D).

Discussion

DIP joint arthritis is physically and pathophysiologically linked to nail psoriasis, and both can lead to severe functional impairment [14–17]. This *post hoc* analysis evidenced the association between DIP joint involvement and nail psoriasis at the individual digit level among a large cohort of patients with PsA. Specifically, in this study cohort at baseline, (i) 96.5% of patients with DIP joint involvement had at least one finger with psoriasis of the nail adjacent to an active (tender and/or swollen) DIP joint, and (ii) 96.2% of the patients with nail psoriasis had at least one finger with activity (tenderness and/or swelling) in the DIP joint adjacent to a psoriatic nail. Furthermore, across those patients, 1309 finger units were affected by simultaneous DIP joint involvement and adjacent nail psoriasis, where 'finger unit' defines the DIP joint and adjacent nail on an individual finger. Greater proportions of those affected finger units achieved complete resolution of DIP joint tenderness, swelling and nail psoriasis with the IL-17A antagonist IXE compared with the TNF inhibitor ADA. These data confirm and build on IXE's efficacy in nail psoriasis and provide evidence supporting the role of the IL-17A pathway in nail and periungual immunobiology.

This is the first report from a large, multicentre, prospective study to document the association between DIP joint involvement and nail psoriasis in individual digits at the finger unit level. Prior single-centre retrospective [34] and cross-sectional [5] studies of PsA have reported significant associations between nail disease and radiographic damage at the adjacent DIP joint. Radiographic damage of the DIP joint is a marker of relatively advanced DIP arthritis that may underestimate its prevalence compared with active joint tenderness or swelling, as used in the current analysis; this may in part explain why the percentage of adjacent DIP involvement is so high among PsA patients with nail psoriasis in the current study compared with previous reports [5, 16]. A recent retrospective study of patients with psoriasis [35] found that DIP joint pain was significantly more frequent in those with nail involvement *vs* those without, and that 100% of the patients with comorbid PsA had nail involvement. Overall, the present findings confirm the association between DIP joint disease and adjacent nail psoriasis and reinforce how frequently they manifest in patients with PsA.

Most prior studies that documented the relationship between DIP joint and nail involvement in PsA did not consider whether the affected DIP joints and nails were physically adjacent on the same digit; a strength of the current analysis is that it does. The finger unit approach utilized here further supports the association between DIP joint disease and nail psoriasis at the individual digit level.

Biologics targeting IL-17A have proven clinical efficacy [30, 36] and real-world effectiveness [22, 37] at achieving skin and difficult-to-treat areas clearance compared with biologics targeting TNF-α. At the finger unit level, the IL-17A antagonist IXE showed significant benefit over the TNF inhibitor ADA in achieving complete resolution of DIP joint tenderness, DIP joint swelling and adjacent nail psoriasis (Fig. 2). This is the first analysis to consider the simultaneous resolution of DIP joint disease and nail psoriasis in patients with PsA, despite their known association. Given the detrimental effects of DIP joint disease and nail psoriasis [14–17], their simultaneous resolution is a relevant outcome likely to reduce disease burden for patients with PsA.

The present analysis found that IXE still demonstrated a significant advantage over ADA when affected finger units were assessed for DIP joint disease resolution alone. This observation held true whether DIP joint disease was defined by tenderness and/or swelling (Fig. 3A), tenderness (Fig. 4A) or swelling (Fig. 4B), though the differential treatment effects were least pronounced for swelling. These are the first data reporting treatment effects of IXE on joint-specific tenderness and/or swelling. The results are notable given the previously reported parity between IXE and ADA in achieving ACR20, ACR50 and ACR70 response rates, which incorporate overall joint tenderness and swelling counts [31, 32]. Taken together, these data could be interpreted to suggest that PsA behaves differently in DIP joints with adjacent nail involvement *vs* other joints affected by PsA. A simple explanation for this could be that DIP region tenderness could actually be related to pain originating from the periungual non-DIP cavity tissue, such as the nail matrix region, with the resolution of this more cutaneous domain driven inflammation being more responsive to IXE therapy. More research is warranted to further investigate this phenomenon.

Across numerous clinical trials, IXE performed better than comparators at treating nail psoriasis [36]. The data presented here confirm the published finding that IXE provides greater therapeutic benefit for nail psoriasis in patients with PsA compared with ADA [32]; specifically extend it to finger units with adjacent DIP joint involvement (Fig. 3B); and provide additional detail at the level of the nail matrix (Fig. 4C) and nail bed (Fig. 4D). Among finger units with adjacent DIP involvement, IXE demonstrated a greater therapeutic advantage over ADA for nail matrix psoriasis compared with nail bed psoriasis.

ADA was previously shown to improve the signs and symptoms of nail psoriasis, including nail pain and quality of life [38]. Limitations of this *post hoc* analysis were the lack of nail psoriasis specific measures of pain and quality of life, as well as the lack of a comparison between patients with and without nail psoriasis. In addition, it is acknowledged that DIP region tenderness without swelling in subjects with nail psoriasis could represent matrix region or lateral anchorage region nail disease rather than DIP joint *per se*.

Overall, the results of this analysis show the specific association between DIP joint involvement and adjacent nail psoriasis in individual digits at the finger unit level and reinforce the importance of the IL-17A pathway in nail and periungual immunobiology. These findings support the idea of a greater impact of IL-17A inhibition compared with TNF inhibition in the DIP-nail musculoskeletal appendage [39].

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data may be obtained from a third party and are not publicly available. Eli Lilly and Company provides access to relevant anonymized patient-level data from studies on approved medicines and indications as defined by the sponsor-specific

information at www.clinicalstudydatarequest.com. Additional study-related documents will be made available, including the study protocol, statistical analysis plan, clinical study report and an annotated case report form. These materials will be available beginning 6 months after the publication is accepted, given approval of the indication in the USA and EU. These materials will be provided to achieve the aims in the provided proposal.

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Prior presentation: Parts of the analysis presented here have been presented as posters at the 2023 British Society of Rheumatology annual conference (Manchester, UK), the 2023 European Congress of Rheumatology (Milan, Italy), and the American College of Rheumatology Convergence 2023 (San Diego, CA, USA).

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Consistent safety profile with over 8 years of real-world evidence, across licensed indications[1–3]

Cosentyx® secukinumab

1,000,000 patients treated globally, and counting*[4]

100+ clinical trials*[5]

8+ years of real-world evidence[1–3]

8 indications[1–3]

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Real-world evidence shows a consistent safety profile over 6 years[6,7]

No trend toward increased AE rates over time (pooled PsA, AS, PsO):†[6]

AEs of select interest (EAIR per 100 PY)	1 year	2 years	3 years	4 years	5 years	6 years	Cumulative rate
Serious infections Cases	2.0 n=149	1.7 n=475	0.7 n=649	1.3 n=1,841	1.3 n=2,285	1.1 n=2,226	1.3 n=8,719
Malignant or unspecified tumours Cases	0.2 n=15	0.2 n=50	0.2 n=225	0.3 n=422	0.3 n=520	0.3 n=573	0.3 n=1,896
MACE Cases	0.2 n=15	0.1 n=39	0.2 n=151	0.2 n=238	0.2 n=264	0.1 n=287	0.2 n=1,031
Total IBD Cases	0.2 n=12	0.2 n=46	0.2 n=185	0.3 n=340	0.2 n=312	0.1 n=261	0.2 n=1,291
Exposure (PY)	7450	28,549	93,744	137,325	182,024	212,636	680,470

No trend towards increased rates of malignancy, MACE or IBD over time[6]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2] Refer to the prescribing information for a summary of adverse events.

Adapted from Novartis Data on File. 2021.[6]

Refer to the Cosentyx Summary of Product Characteristics for full details, dosing and administration, including special populations.

Cosentyx® (secukinumab) licensed indications in rheumatology: Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active **psoriatic arthritis** in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active **ankylosing spondylitis** in adults who have responded inadequately to conventional therapy; active **non-radiographic axial spondyloarthritis** with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active **enthesitis-related arthritis** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active **juvenile psoriatic arthritis** in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[1,2]

Prescribing information, adverse event reporting and full indication can be found on the next page.

*Patients prescribed Cosentyx for any indication since launch.

†Successive time periods of PSUR shown with cumulative rate: 26 Dec 2014 to 25 Dec 2015; 26 Dec 2015 to 25 Dec 2016; 26 Dec 2016 to 25 Dec 2017; 26 Dec 2017 to 25 Dec 2018: 26 Dec 2018 to 25 Dec 2019; 26 Dec 2019 to 25 Dec 2020.[6]

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; EIAR, exposure-adjusted incidence rate; HCP, healthcare professional; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; PsA, psoriatic arthritis; PsO, plaque psoriasis; PY, patient year.

References: 1. Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** European Medicines Agency. European public assessment report. Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed February 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** Novartis. Novartis Cosentyx® positive 16-week PREVENT results advance potential new indication for patients with axial spondyloarthritis. Available at: https://www.novartis.com/news/media-releases/novartis-cosentyx-positive-16-week-prevent-results-advance-potential-new-indication-patients-axial-spondyloarthritis [Accessed February 2024]; **6.** Novartis data on file. Cosentyx Periodic Safety Update Report (PSUR); 26 December 2019 – 25 December 2020. 22 February 2021; **7.** Deodhar A, et al. Arthritis Res Ther 2019;21(1):111.

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Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. 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If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com