RHEUMATOLOGY

Rheumatology 2022;61:2856–2866
https://doi.org/10.1093/rheumatology/keab784
Advance Access publication 3 November 2021

Original article

Efficacy and safety of secukinumab in patients with spondyloarthritis and enthesitis at the Achilles tendon: results from a phase 3b trial

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Abstract

Objective. ACHILLES aimed to demonstrate efficacy of secukinumab on Achilles' tendon enthesitis in spondyloarthritis (SpA) patients.

Methods. Patients ≥18 years ($n = 204$) with active PsA or axial SpA and heel enthesitis were randomized 1:1 to secukinumab 150/300 mg or placebo up to week 24, and thereafter placebo patients were switched to secukinumab.

Results. At week 24, a higher, yet statistically non-significant ($P = 0.136$), proportion of patients in secukinumab *vs* placebo reported resolution of Achilles tendon enthesitis in affected foot (42.2% *vs* 31.4%; odds ratio [OR] = 1.63; 95% CI: 0.87, 3.08). Proportion of patients reporting resolution of enthesitis based on Leeds Enthesitis Index was higher with secukinumab *vs* placebo (33.3% *vs* 23.5%; OR = 1.65; 95% CI: 0.85, 3.25) at week 24. Mean change from baseline in heel pain at week 24 was higher in secukinumab patients *vs* placebo (−2.8 [3.0] *vs* −1.9 [2.7]). Greater improvements with secukinumab were observed in heel enthesopathy activity and global assessment of disease activity. Imaging evaluation by local reading confirmed heel enthesitis on MRI at screening for all patients. Based on central reading, 56% presented with bone marrow oedema and/or tendinitis; according to Heel Enthesitis MRI Scoring System (HEMRIS) *post hoc* analysis, 76% had signs of entheseal inflammation while 86% had entheseal inflammation and/or structural changes.

Conclusion. A substantial proportion of patients showed no signs of inflammation on the centrally read MRIs despite a clinical diagnosis of heel enthesitis, thus highlighting that the discrepancy between the clinical and imaging assessments of enthesitis requires further investigation. Although ACHILLES did not meet the primary end point, the study reported clinically meaningful improvements in patient-related outcomes.

Trial registration. clinicaltrials.gov, NCT02771210

Key words: spondyloarthritis, Achilles tendon enthesitis, heel enthesitis, pain, bone marrow oedema, biologics, IL-17 inhibitor, imaging outcomes

CLINICAL SCIENCE

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Submitted 19 April 2021; accepted 17 October 2021

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Rheumatology key messages

- ACHILLES is a randomized-controlled trial providing new clinical and imaging data on heel enthesitis across the spondyloarthritis spectrum.
- Secukinumab provides benefits on entheseal inflammation, disease burden and quality of life.
- ACHILLES reveals a discrepancy between the clinical and imaging assessment of heel enthesitis.

Introduction

Enthesitis is the hallmark feature of a broad spectrum of conditions termed spondyloarthritis (SpA) and can be the first clinical sign in this group of chronic progressive autoimmune disease [1–3]. The prevalence of enthesitis in patients with non-radiographic axial SpA (nr-axSpA) is 36% and ankylosing spondylitis (also termed radiographic axial SpA, r-axSpA) is 32–74%, with Achilles tendon, plantar fascia and lateral epicondyles presenting as the most common sites [4, 5]. The heel is frequently affected in patients with PsA [6] and axial SpA (axSpA) [7] at an estimated proportion of 35% and 8.5% for PsA and axSpA patients, respectively [8]. The two most common causes for posterior heel pain are plantar fasciitis and Achilles enthesitis [9].

The key symptom of entheseal involvement substantially contributing to the overall burden of disease in patients with PsA and axSpA is pain resulting in higher disease activity and lower quality of life (QoL) [10–12]. In patients with r-axSpA, QoL assessments, including physical function and general health, were related to entheseal involvement [13]. PsA patients with enthesitis also reported worse disease outcomes compared with those without [14].

IL-17, IL-23, and TNF are the effector cytokines of enthesitis, and their inhibition has proved effective in the management of PsA and axSpA [1, 15, 16]. Secukinumab, a fully human monoclonal antibody that directly inhibits IL-17A, has consistently demonstrated significant and sustained improvements in the signs and symptoms of PsA [16, 17] and axSpA [18–21]. Studies focusing on the underlying entheseal inflammation as a treatment target to relieve symptoms are limited [22].

ACHILLES (NCT02771210) investigated the efficacy and safety of secukinumab on the resolution of Achilles tendon enthesitis and the improvement of enthesitis-driven disease burden in patients with SpA and is so far the largest randomized controlled trial (RCT) that assessed clinical and imaging endpoints up to 52 weeks.

Methods

Study design and patients

ACHILLES is a randomized, parallel-group, double-blind, 52-week placebo-controlled study in patients with PsA and axSpA (Fig. 1). Patients were randomized 1:1 to receive either subcutaneous (s.c.) secukinumab 150 or 300 mg or placebo until week 24 (treatment period 1). At week 24, placebo patients were switched to s.c. secukinumab 150 or 300 mg (placebo–secukinumab group) up to week 52 without a loading phase (treatment period 2). The dose of secukinumab, 150 or 300 mg, was predetermined at baseline for both treatment groups to 300 mg for PsA patients with moderate-to-severe skin involvement or pre-treated with TNF-inhibitor (TNFi) and to 150 mg for PsA patients with none-to-mild psoriasis with no TNFi exposure and for all axSpA patients.

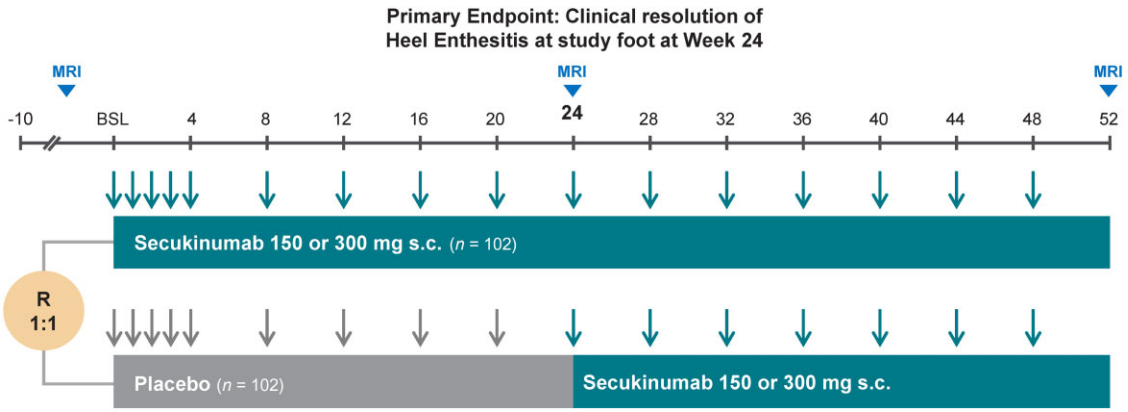
Patients (aged $\geq$18 years) with active PsA or axSpA were enrolled in the study. Patients were diagnosed with PsA with $\geq$1 tender joints out of 78 and $\geq$1 swollen joints out of 76 at baseline. Patients diagnosed with axSpA had to present with total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $\geq$4 (0–10) at baseline.

Patients should also have fulfilled the following inclusion criteria: clinical heel enthesitis, with onset of heel pain $\geq$1 month prior to inclusion, defined as swelling and tenderness at the insertional site of the Achilles tendon into the calcaneus (binary assessment rated as absent/present); and MRI-positive heel enthesitis, according to the investigator, defined as tendinitis and/or bone marrow oedema in the insertional area of the Achilles tendon and/or the plantar aponeurosis. Enthesitis of the heel must have been refractory to standard treatment defined as either NSAIDs or TNFi. Patients should have been on NSAIDs at the highest recommended dose for at least 1 month prior to randomization unless withdrawal was because of intolerance, toxicity or contraindications; patients who have been on TNFi (not more than two) were allowed to be enrolled but should have experienced an inadequate response or intolerance.

Key exclusion criteria included evidence of ongoing infection or malignancy, prior exposure to biologics directly targeting IL-17 or IL-17 receptors or ongoing use of high-potency opioid analgesics, oral or topical retinoids, photochemotherapy, phototherapy, or topical skin treatment. Concomitant use of NSAIDs, oral corticosteroids, methotrexate or sulfasalazine (only in case of axSpA) was allowed.

The study was carried out in accordance with the principles of the Declaration of Helsinki, International Conference of Harmonization Good Clinical Practice guidelines, and all applicable laws and regulations [23], with written informed consent obtained from all enrolled patients. The trial was submitted to several ethical committees, depending on country and district. Approvals

Fig. 1 Study design



Patients were stratified by underlying disease (PsA or axSpA) and randomized 1:1 to receive either secukinumab or matching placebo. The dosage of secukinumab/placebo (150 or 300 mg) was predetermined at baseline according to axSpA or PsA disease, extent of psoriasis and pretreatment with TNF-inhibitor. MRI assessments were performed at screening, week 24 and week 52. axSpA: axial spondyloarthritis; BSL: baseline; R: randomization.

were obtained from all relevant ethical committees as listed in the Supplementary Table S1, available at *Rheumatology* online.

Efficacy measures

The primary end point was superiority of secukinumab (any dose) over placebo based on the percentage of patients with clinical resolution of Achilles tendon enthesitis in the affected foot as assessed by the respective subcomponent of the Leeds Enthesitis Index (LEI) at week 24.

Enthesitis-related secondary endpoints at week 24 included the resolution of enthesitis based on LEI and the improvement of enthesitis-driven disease burden (heel pain, heel enthesopathy activity). A question on heel pain ('Please indicate with a cross (X) at the respective number the most pain you had from your heel today'; 0–10 numerical rating scale [NRS]) assessed the most pain a patient experienced on the respective day, and a question on heel enthesopathy ('How active was your heel enthesitis on average during the last week?'; 0–100 visual analogue scale [VAS]) assessed the activity of heel enthesitis on average during the last week, respectively.

Clinical efficacy and QoL were further assessed for the underlying condition with global disease activity (0–100 VAS) and Short Form-36 version 2 (SF-36 v2).

As previously described, PsAMRIS was adapted to assess MR images of the heel since there was no validated MRI scoring method to evaluate heel enthesitis available at the time of trial initiation [24]. Briefly, two blinded readers analysed the MR images in a consensus read fashion. The improvement of bone marrow oedema in the insertion of the Achilles tendon in the upper part of the calcaneus and/or in the insertion of the plantar aponeurosis in the lower part of the calcaneus as assessed by PsAMRIS was defined as the secondary imaging end point.

An additional *post hoc* analysis was conducted on all MRIs after re-evaluation by the central readers in a consensus read fashion for *a priori* defined MRI parameters based on the Heel Enthesitis MRI Scoring System (HEMRIS) [25].

Statistical analysis

The full analysis set used for efficacy analysis comprised all patients in the overall population (PsA and axSpA patients) who were randomized, to whom study treatment was assigned following an intent-to-treat principle, and who were evaluated according to the treatment assigned at randomization. For patients randomized erroneously into the wrong stratum (PsA or axSpA), the actual stratum was used for analyses.

The primary analysis was performed via a logistic regression model with the factors treatment, country and stratification factor diagnosis (PsA or axSpA); patients with a missing assessment at week 24 were considered as responders if they had already met the response criterion at the time of last assessment.

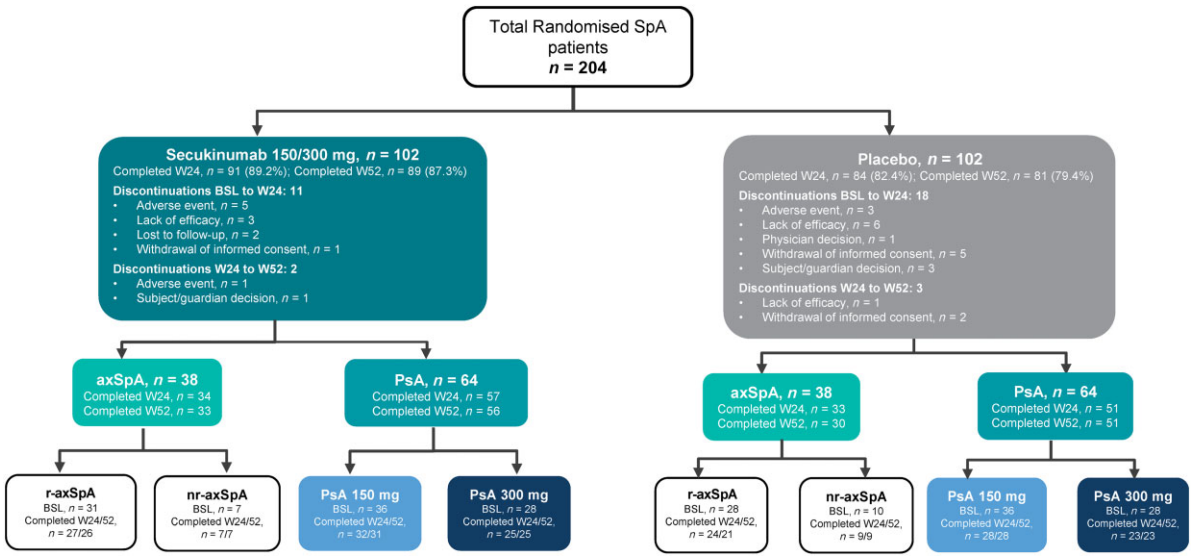
The secondary endpoints were reported as observed. *P*-values of secondary endpoints were exploratory and tested outside the confirmatory framework using an analysis of covariance model with missing data imputed by last observation carried forward (LOCF; Supplementary Table S2, available at *Rheumatology* online) or with mixed-effect model repeated measures (MMRM) as LOCF is considered methodologically inferior for continuous data [26]. Data from weeks 24–52 were reported as observed. Safety analyses included all patients who received at least one dose of study treatment.

Results

Patient characteristics

In total, 204 patients were randomized (102 patients in the secukinumab and 102 in the placebo group).

FIG. 2 Patient disposition to week 52



Of the overall population, 19/204 (9.3%) subjects had been pre-treated with TNF-inhibitors; no meaningful differences in week 24 outcome parameter could be observed between TNF-naïve and TNF-pretreated subjects. axSpA: axial spondyloarthritis; BSL: baseline; r-axSpA: radiographic axial spondyloarthritis; nr-axSpA: non-radiographic axial spondyloarthritis; W: week.

Overall, 89.2% (91/102) of patients in the secukinumab group and 82.4% (84/102) of patients in the placebo group completed week 24 (Fig. 2). At randomization, 90.2% of patients in the secukinumab group and 91.2% in the placebo group were TNFi-naïve, and concomitant use of NSAIDs and DMARDs was reported for 77.5% and 40.2% in the secukinumab *vs* 70.6% and 24.5% in the placebo groups, respectively (Table 1).

Baseline demographics and disease characteristics were comparable across the secukinumab and placebo treatment groups. The mean and median time since first diagnosis of PsA was higher in the placebo group (75.8 and 44.8 months, respectively) than in the secukinumab group (52.1 and 27.9 months, respectively) with a comparable time since onset of enthesitis. The mean and median time since first diagnosis of axSpA was comparable in the placebo (56.2 and 25.5 months, respectively) and the secukinumab group (49.7 and 28.5 months, respectively); however, the mean and median time since onset of enthesitis was higher in secukinumab group compared with placebo group (39.3 and 14.7 *vs* 28.9 and 8.9 months, respectively). The mean tender and swollen joint counts in the PsA subset were higher in the secukinumab *vs* the placebo group (16.2 and 7.8 *vs* 13.5 and 5.8, respectively).

The qualitative assessment of MRI parameters at screening based on central reading showed that 94/204 (46.1%) of all patients presented with tendinitis, 80/204 (39.2%) with bone marrow oedema and 78/204 (38.2%) with bursitis (Supplementary Table S3, available at *Rheumatology* online). Periarticular inflammation and bone erosion were less present. Compared with plantar fascia, the area of Achilles tendon is more frequently involved when analysing MRI parameter by location (Supplementary Table S4, available at *Rheumatology* online).

Based on the qualitative assessment of MRI parameters, 114/204 (56%) of all patients were classified as MRI-positive for heel enthesitis (presenting with tendinitis and/or bone marrow oedema), whereas 90/204 (44%) patients did not present with tendinitis nor oedema. An interesting question is whether the discrimination of MRI-positive and MRI-negative heel enthesitis on imaging is reflected by differences in the clinical characteristics of the two groups. However, the baseline and clinical characteristics were quite similar in the subgroups of MRI-positive and MRI-negative patients (Supplementary Table S5, available at *Rheumatology* online). An association was only observed for gender and HLA-B27 status in the axSpA subgroup: male gender is associated with MRI-positivity and patients with positive HLA-B27 status are more likely to present with bone marrow oedema.

In a *post hoc* analysis based on MRI central rereading by the HEMRIS scoring system, 156/204 (76%) of all patients presented with total entheseal inflammation score >0 at screening and 131/204 (64%) presented with total structural damage score >0 at screening. At least one parameter (inflammatory and/or structural, Achilles tendon and/or plantar fascia) was present in 171/204 (84%) of all patients at screening.

Efficacy outcomes

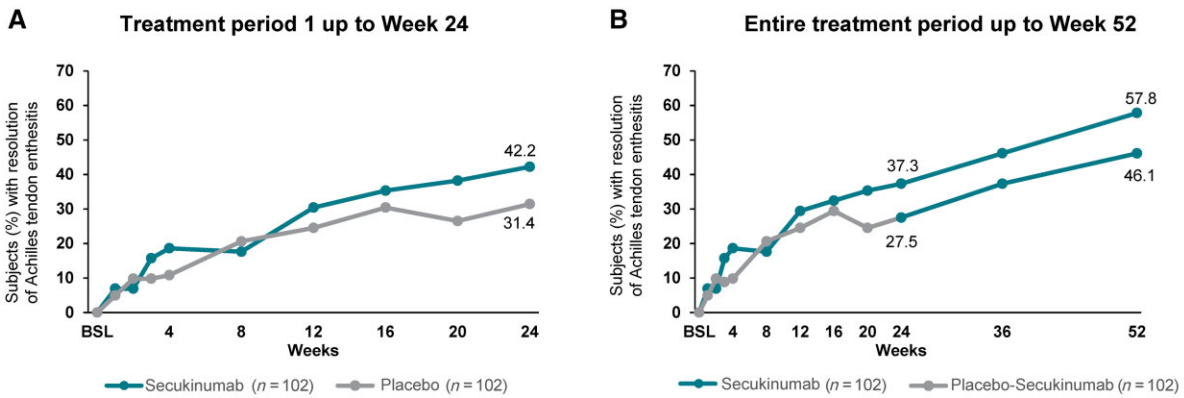
Although the primary end point was not met, a higher percentage of patients in the secukinumab group

Table 1 Demographics and baseline characteristics

Variable	Secukinumab 150/300 mg s.c. ($n = 102$)	Placebo ($n = 102$)
Age, mean (S.D.), years	47.8 (11.3)	47.7 (11.0)
Male, *n* (%)	44 (43.1)	47 (46.1)
Weight, mean (S.D.), kg	83.95 (18.61)	86.02 (18.63)
Height, mean (S.D.), m	1.70 (0.093)	1.70 (0.096)
BMI, mean (S.D.), kg/m^2	29.0 (6.3)	29.7 (6.3)
BMI <30 kg/m^2, *n* (%)	61 (59.8)	61 (59.8)
BMI ≥ 30 kg/m^2, *n* (%)	41 (40.2)	41 (40.2)
Time since diagnosis, mean (S.D.), months		
PsA	52.1 (58.6)	75.8 (92.1)
axSpA	49.7 (66.7)	56.2 (74.0)
Onset of enthesitis, mean (S.D.), months		
PsA	33.9 (51.8)	33.7 (62.2)
axSpA	39.3 (73.0)	28.9 (51.9)
TNF-naïve, *n* (%)	92 (90.2)	93 (91.2)
Number of LEI counts present, mean (S.D.)	2.6 (1.6)	2.5 (1.6)
Heel pain (0–10 NRS), mean (S.D.)	6.4 (2.3)	6.2 (2.1)
Physician's global assessment of heel enthesopathy (0–100 VAS), mean (S.D.)	63.3 (17.7)	62.9 (18.5)
Patient's global assessment of heel enthesopathy (0–100 VAS), mean (S.D.)	67.1 (22.1)	65.1 (21.0)
Physician's global assessments (0–100 VAS), mean (S.D.)	61.4 (18.8)	60.3 (19.4)
Patient's global assessment (0–100 VAS), mean (S.D.)	66.2 (20.8)	65.2 (19.6)
SF-36 v2 score, mean (S.D.)	33.1 (7.8)	34.5 (7.0)
TJC, PsA patients (78 joints), mean (S.D.)	16.2 (15.9)	13.5 (13.7)
SJC, PsA patients (76 joints), mean (S.D.)	7.8 (9.4)	5.8 (6.4)
BASDAI, axSpA patients, mean (S.D.)	7.1 (1.14)	7.1 (1.26)
NSAID use at randomization, *n* (%)	79 (77.5)	72 (70.6)
DMARD use at randomization, *n* (%)	41 (40.2)	25 (24.5)
Oral corticosteroid use at randomization, *n* (%)	14 (13.7)	17 (16.7)
hsCRP, mean (S.D.), mg/l	10.4 (17.8)	9.7 (18.3)
HLA-B27 positive, axSpA patients, *n* (%)	27 (71.1)	21 (55.3)

axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity CRP; LEI: Leeds Enthesitis Index; SF-36v2: Medical Outcome Short Form (36) Health Survey; SJC: swollen joint count score; TJC: tender joint count; VAS: visual analogue scale.

Fig. 3 Resolution of Achilles tendon enthesitis in affected foot



(**A**) data presented with imputed missing values; $n = 102$ in each group; $P = 0.136$ for secukinumab *vs* placebo at week 24. (**B**) Data presented as observed; number of patients with non-missing value: $n = 89$ at week 24 and $n = 84$ at week 52 in secukinumab group, $n = 86$ at week 24 and $n = 79$ at week 52 in placebo group. BSL: baseline.

compared with placebo (42.2% *vs* 31.4%) reported resolution of Achilles tendon enthesitis in the affected foot at week 24 (odds ratio [OR] = 1.63; 95% CI: 0.87, 3.08; $P = 0.136$) (Fig. 3A). It is worth noting that within the subgroup of patients with a BMI <30 kg/m^2, the resolution of Achilles tendon enthesitis (affected foot) at

week 24 was 49.2% in the secukinumab group and 24.6% in the placebo group (Supplementary Fig. S1, available at *Rheumatology* online). Up to week 52, a continuous improvement in the resolution of Achilles tendon enthesitis was observed in the secukinumab treatment group (57.8%) with notable improvement in placebo–secukinumab group (46.1%) after switching to active treatment at week 24 (Fig. 3B).

At week 24, the percentage of patients with resolution of enthesitis as assessed by LEI was 33.3% in the secukinumab group *vs* 23.5% in the placebo group; the mean (S.D.) improvement in LEI at week 24 was −1.1 (1.6) in the secukinumab group *vs* −0.6 (1.3) in the placebo group (Table 2). At week 52, 48.0% in the secukinumab group *vs* 34.3% in the placebo–secukinumab group reported resolution of enthesitis as assessed by LEI with a mean (S.D.) improvement in LEI of −1.6 (1.8) and −1.3 (1.4), respectively.

Heel pain, as reported by patients on a 0–10 NRS was notably reduced in the secukinumab-treated patients *vs* the placebo group with a mean (S.D.) change from baseline of −2.8 (3.0) *vs* −1.9 (2.7) at week 24. This improvement corresponds to a mean (median) reduction in heel pain of −41.4% (−42.9%) with secukinumab *vs* −19.0% (−28.6%) with placebo group (Supplementary Table S6, available at *Rheumatology* online). The improvement was sustained to week 52 with both the secukinumab group and the placebo–secukinumab group (Table 2).

Greater improvements in physician- and patient-reported heel enthesopathy activity reported on a 0–100 VAS were observed with secukinumab treatment at week 24. The decrease in heel enthesopathy activity reported by patients corresponds to a mean (median) reduction of −42.3% (−42.8%) in the secukinumab group *vs* −17.2% (−24.1%) in the placebo group (Supplementary Table S4, available at *Rheumatology* online). The improvements in physician- and patient-reported heel enthesopathy activity were sustained to week 52.

Secukinumab provided greater improvements *vs* placebo in physician's global assessment and patient's global assessment of disease activity at week 24 and week 52. Sustained improvements in SF-36 v2 scores were observed to week 52.

Although the study was not powered to investigate differences within the SpA indications, PsA or axSpA, nor to investigate a dose effect of secukinumab, an exploratory analysis was performed to describe differences by underlying disease as well as by secukinumab 150 mg and 300 mg in PsA population (Supplementary Tables S7 and S8, available at *Rheumatology* online).

Of the 80 subjects presenting with bone marrow oedema at baseline, 38.6% (17/44) in the secukinumab *vs* 33.3% (12/36) in the placebo group showed an improvement at week 24, as assessed by the PsAMRIS score.

Safety

The mean duration of exposure to study treatment was longer with secukinumab than with placebo group in treatment period 1 (up to week 24) and for the entire treatment period (up to week 52) (Table 3). The number of patients who experienced at least one adverse event (AE) to week 52 was slightly lower with secukinumab (64.7% [66/102]) than with placebo–secukinumab (67.6% [69/102]).

The proportion of patients with serious AEs (SAEs) was 2.9% for both the secukinumab group and placebo group to week 24. For the entire treatment period, 6.9% and 5.9% of patients reported SAEs in the secukinumab group and placebo–secukinumab group, respectively. No death was reported over the entire treatment period across all treatment groups.

Discussion

ACHILLES was the first large-scale double-blind, placebo-controlled RCT that investigated heel enthesitis by clinical and imaging endpoints.

The primary end point of resolution of Achilles tendon enthesitis at the affected foot at week 24 was not met; however, a numerically higher proportion of patients achieved resolution in the secukinumab treatment group *vs* placebo. It is worth noting that ACHILLES applied a high-hurdle primary end point, assessing the complete resolution of Achilles tendon enthesitis by using a single tender point out of the six-point LEI. This was a binary assessment with no gradual improvements; a complete resolution had to be achieved. Furthermore, the resolution of Achilles tendon enthesitis using the LEI subcomponent for the study foot assessed the change in 'tenderness' rather than 'inflammation', which is limited by the patient's subjectivity and variable sensitivity due to lack of standardization of the pressure on the Achilles tendon [27, 28]. The rationale for selecting a single tender point on the heel as the primary end point is to align clinical signs of heel enthesitis with the entheseal inflammation on MRI as LEI includes five additional tender points that are not investigated by MRI. In ACHILLES, only the heel of the affected foot was assessed by MRI to allow exploration of the relationship of clinical and imaging parameters. A *post hoc* analysis of the imaging data based on the recently developed HEMRIS score, including potential association of clinical and imaging parameters, will be presented in a dedicated imaging paper.

It should also be noted that spontaneous improvement and resolution of enthesitis at various time points might be part of the natural course of the disease resulting in the high placebo response [29]. A higher placebo response was observed in the 150 mg group, which had relatively less severe disease, whereas patients with more severe concomitant plaque psoriasis in the 300 mg group had a lower level of placebo response. As already shown in previous publications [14], secukinumab 300 mg exhibited better performance compared with 150 mg in all clinical outcome measures of ACHILLES. In addition, subgroup analyses suggest that a high BMI might have compromised the resolution of Achilles

Table 2 Clinical efficacy endpoints to week 52

Efficacy endpoint	Week 24			Week 52	
	Secukinumab 150/300 mg s.c. ($n = 102$)	Placebo ($n = 102$)	*P*-value *vs* placebo	Secukinumab 150/300 mg s.c. ($n = 102$)	Placebo- Secukinumab 150/300 mg s.c. ($n = 102$)
Resolution of enthesitis, responder *n* (%)					
Achilles tendon enthesitis (study foot)[a]	43 (42.2)	32 (31.4)	0.136	59 (57.8)	47 (46.1)
LEI	34 (33.3)	24 (23.5)	0.148	49 (48.0)	35 (34.3)
Disease activity: heel enthesitis, mean change (S.D.) (*n*)					
Heel pain (0–10 NRS)	−2.8 (3.0) (87)	−1.9 (2.7) (85)	0.027	−3.6 (3.1) (84)	−3.3 (2.8) (78)
Physician's heel enthesopathy (0–100 VAS)	−38.4 (24.2) (88)	−25.2 (25.3) (85)	<0.001	−49.0 (24.1) (84)	−44.0 (24.6) (78)
Patient's heel enthesopathy (0–100 VAS)	−31.1 (29.1) (86)	−20.8 (30.4) (84)	0.018	−38.9 (30.9) (84)	−35.9 (30.0) (76)
Disease activity: global, mean change (S.D.) (*n*)					
Physician's global assessment of disease activity (0–100 VAS)	−34.9 (25.9) (88)	−18.9 (26.3) (85)	<0.001	−45.4 (24.7) (84)	−37.8 (26.6) (78)
Patient's global assessment of disease activity (0–100 VAS)	−25.9 (31.1) (82)	−16.6 (29.2) (80)	0.005	−32.9 (32.0) (82)	−28.8 (30.9) (72)
SF-36 v2	8.3 (9.8) (87)	5.3 (7.3) (85)	0.005	8.9 (9.8) (84)	7.9 (7.5) (78)

Resolution of enthesitis: data presented based on LOCF at week 24; data presented as observed at week 52; disease activity: data presented as observed at week 24 and week 52. *P*-values were analysed exploratively outside the confirmatory framework with missing data imputed based on MMRM. [a]Single tender point out of the 6-point LEI. LEI: Leeds Enthesitis Index; LOCF: last observation carried forward; NRS: numerical rating scale; SF-36 v2: Short Form-36 version 2; VAS: visual analogue scale.

Table 3 Safety summary to week 52

Parameter	Treatment period 1		Entire treatment period	
	Secukinumab 150/300 mg s.c. (*n* = 102)	Placebo (*n* = 102)	Secukinumab 150/300 mg s.c. (*n* = 102)	Placebo–Secukinumab 150/300 mg s.c. (*n* = 102)
Duration of exposure, mean (S.D.), days	163.1 (26.6)	156.9 (35.1)	337.6 (89.2)	316.3 (111.8)
Any AE, *n* (%)	57 (55.9)	59 (57.8)	66 (64.7)	69 (67.6)
Any SAE, *n* (%)	3 (2.9)	3 (2.9)	7 (6.9)	6 (5.9)
AEs leading to study treatment discontinuation, *n* (%)	5 (4.9)	4 (3.9)	7 (6.9)	7 (6.9)
Death, *n*	0	0	0	0
n (%) or EAIR (95% CI)				
Common AEs[a]				
Nasopharyngitis	8 (7.8)	14 (13.7)	14.64 (7.79, 25.03)	28.46 (17.83, 43.08)
URTI	5 (4.9)	5 (4.9)	6.56 (2.41, 14.28)	5.72 (1.86, 13.36)
Diarrhoea	7 (6.9)	4 (3.9)	8.90 (3.84, 17.53)	5.82 (1.89, 13.58)
Nausea	5 (4.9)	1 (1.0)	5.48 (1.78, 12.78)	1.13 (0.03, 6.27)
Headache	5 (4.9)	8 (7.8)	6.51 (2.39, 14.16)	12.08 (5.79, 22.21)
Arthralgia	4 (3.9)	5 (4.9)	7.57 (3.04, 15.59)	5.79 (1.88, 13.52)
Back pain	1 (1.0)	3 (2.9)	2.11 (0.26, 7.64)	5.75 (1.87, 13.41)
Hypertension	1 (1.0)	4 (3.9)	2.11 (0.26, 7.62)	5.77 (1.87, 13.46)
AEs of special interest				
Candida infections				
Oral candidiasis	2 (2.0)	0	2.11 (0.26, 7.62)	0.00 (0.00, 4.11)
Oropharyngeal candidiasis	1 (1.0)	0	1.05 (0.03, 5.87)	0.00 (0.00, 4.11)
Vulvovaginal candidiasis	1 (1.0)	0	1.05 (0.03, 5.86)	0.00 (0.00, 4.11)
Malignancy				
Invasive breast carcinoma	—	—	1.05 (0.03, 5.83)	0.00 (0.00, 4.11)
Malignant melanoma	—	—	1.05 (0.03, 5.83)	0.00 (0.00, 4.11)
Uterine cancer	—	—	0.00 (0.00, 3.85)	1.11 (0.03, 6.21)
MACE	—	—	—	—
Inflammatory bowel disease	1 (1.0)	1 (1.0)	1.04 (0.03, 5.82)	1.13 (0.03, 6.27)
Oral herpes	1 (1.0)	1 (1.0)	2.12 (0.26, 7.66)	1.12 (0.03, 6.22)
Staphylococcal infections	0	1 (1.0)	0.00 (0.00, 3.85)	1.12 (0.03, 6.24)

[a]AEs with an EAIR ≥5 in either of the secukinumab treatment groups over the entire treatment period. AE: adverse event; EAIR: exposure-adjusted incidence rate; MACE: major adverse cardiovascular event; SAE: serious AE; URTI: upper respiratory tract infection.

tendon enthesitis, presumably due to constantly higher mechanical stress [30].

Improvements in the placebo group were also observed when analysing the questionnaires related to disease activity. However, higher improvements in heel pain (NRS) and physician's and patient's heel enthesopathy activity (VAS) were observed with secukinumab treatment at week 24. The improvements of enthesitis-driven disease burden by heel pain and heel enthesopathy activity suggest a clinically meaningful improvement in the burden of disease for patients treated with secukinumab [31, 32]. Notable improvements in physician's and patient's global assessment of disease activity (reduction in VAS) and QoL (SF-36 v2) were also observed with secukinumab treatment at week 24, confirming the positive outcomes of secukinumab in previous trials [14, 19].

From week 24 to week 52, a continuous improvement in response rates for resolution of Achilles tendon enthesitis and for all secondary outcomes was observed in secukinumab-treated patients. Improvements in all outcome measures related to enthesitis as well as the global disease condition were observed for placebo

patients who switched to active treatment at week 24, indicating the clinical benefits for the patients.

Imaging examination was performed complementary to the clinical assessment at three different time points. Although detailed results on the imaging data are not part of the objectives of the current paper, baseline imaging characteristics should be taken into account when interpreting the clinical data. According to the local reading by investigators at site, all enrolled patients had a positive MRI for heel enthesitis at screening. However, based on central reading, there was a substantial proportion of patients without objective signs of inflammation by imaging. Some of the clinical diagnoses might have therefore been driven by other pain-related features not caused by enthesitis, as the entheseal sites may also serve as tender points due to mechanical stress or even fibromyalgia [33].

As per central reading, about 60% of the subjects presented without bone marrow oedema at screening; hence, it was not possible to assess improvement of oedema in the majority of patients, although a higher percentage of patients in the secukinumab group compared with the placebo group had a bone marrow oedema improvement based on PsAMRIS. Similar findings were reported in the HEEL trial with a positive trend although not statistically significant for etanercept *vs* placebo in oedema extension from baseline to week 12 [22]. The high placebo response rates in bone marrow improvement may be attributed to the natural course of the disease and the spontaneous improvement of enthesitis lesions.

Furthermore, the PsAMRIS score was originally developed for the hand and the HEMRIS score specifically developed for Achilles tendon has been published long after the time of the ACHILLES trial design [25]. Based on HEMRIS *post hoc* analysis, 84% of the overall trial population presented with inflammatory and/or structural pathologies on MRI.

ACHILLES enrolled a heterogeneous patient population including PsA, r-axSpA and nr-axSpA patients, focusing on heel enthesitis and its higher disease burden assuming enthesitis is similar across the SpA spectrum and has the same responsiveness to treatment. Although the heterogeneity of the study population can be considered as a strength, it might also be a limitation as responses to treatment vary depending on the underlying condition. In addition, LEI is a validated enthesitis measure that is mainly used for PsA patients as this index does not include axial tender points [28]. As recent analysis from pooled r-axSpA trials (MEASURE 1–4) revealed, the axial entheseal sites of r-axSpA patients showed a better response to secukinumab treatment compared with peripheral sites; therefore, LEI might not be the most appropriate measurement to assess enthesitis in axSpA [34]. Furthermore, the inclusion criterion of MRI-positive heel enthesitis based on the investigators' judgement and not on central reading and the discordance between the local and central reading may suggest that a substantial proportion of patients might have been potentially misdiagnosed for enthesitis.

In conclusion, although secukinumab did not achieve statistical significance *vs* placebo on the resolution of Achilles tendon enthesitis at week 24, it improved the burden of heel enthesitis as assessed by patient and physician reported outcomes in patients with active SpA refractory to standard treatment. Notable improvements in global disease activity and QoL were also observed as assessed by patient and physician reported outcomes in secukinumab treatment. The clinical improvements were maintained up to week 52 and also observed for the placebo patients switching to active treatment. MRI analysis revealed that clinical and imaging assessments for the diagnosis of heel enthesitis remain a challenge for the treating rheumatologist. The substantial proportion of patients without signs of inflammation on the centrally read MRIs despite a clinical diagnosis of heel enthesitis indicates that the discrepancy between the clinical and imaging assessments of enthesitis remains an unmet need and therefore ACHILLES sheds light into the understanding of the clinical and imaging assessments of enthesitis.

Acknowledgements

The authors thank the patients who participated in this study and the study investigators for their contributions. Kamalakkannan Narasimha Naidu and Tanya Debnath, medical writers (Novartis Healthcare Private Ltd, Hyderabad, India) provided medical writing support and John Gallagher (Novartis Pharmaceuticals Ltd, UK) provided medical and editorial guidance. The trial was designed by the sponsor, Novartis, in collaboration with the authors. The institutional review board at each participating centre approved the protocol. Data were collected in accordance with Good Clinical Practice guidelines by the study investigators and were analysed by the sponsor. All the authors contributed to the interpretation of the data and had access to the full data sets. Statistical analyses were performed by statisticians employed by the sponsor and were reviewed by all authors. Agreements between the sponsor and the investigators included provisions relating to confidentiality of the trial data. The writing support for the manuscript was provided by a medical writer from Novartis, India, and funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and analyses, as well as for the fidelity of this report to the trial protocol, which are available from the funder.

Funding: The study was funded by Novartis Pharma AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Disclosure statement: F.B. received grant/research support from AbbVie, Pfizer, Roche, Chugai, Janssen, Novartis; and consultancy/speaker fees from AbbVie, Pfizer, Roche, Chugai, UCB, BMS, Celgene, MSD, Novartis, Biotest, Janssen, Sanofi, Genzyme, Lilly, Boehringer, Galapagos. P.S. received grant/research support from AbbVie, Celgene, Chugai, Janssen-Cilag, Lilly, Novartis, Pfizer,

UCB; was a consultant for AbbVie, Biogen, BMS, Celgene, Chugai, Hexal, Janssen-Cilag, Lilly, Novartis, Pfizer, Roche, Sanofi-Genzyme, Swedish Orphan Biovitrum, UCB; and on the speaker's bureau of AbbVie, Biogen, BMS, Celgene, Chugai, Hexal, Janssen-Cilag, Lilly, Novartis, Pfizer, Roche, Sanofi-Genzyme, Swedish Orphan Biovitrum, UCB. E.D.M. received grant/research support from AbbVie, Novartis, Pfizer; was a consultant for for AbbVie, Novartis, Pfizer; and on the speaker's bureau of AbbVie, BMS, MSD, Novartis, Pfizer, UCB, Roche. A.B. received consultancy fees from AbbVie, Amgen, MSD, Myland, Novartis, Pfizer, Roche, Sandoz and UCB. E.D. received grant/research support from Samsung Bioepis. C.K. is an employee of ClinProject GmbH, Eurasburg, Germany and consultant for Novartis. E.P., A.S., C.J. and A.W. are employees of Novartis. X.B. received grant/research support from AbbVie, BMS, Celgene, Chugai, Merck, Novartis, Pfizer, UCB, Werfen; was a consultant for AbbVie, BMS, Celgene, Chugai, Merck, Novartis, Pfizer, UCB, Werfen; and on the speaker's bureau of AbbVie, BMS, Celgene, Chugai, Merck, Novartis, Pfizer, UCB, Werfen. Y.P. has nothing to declare.

Data availability statement

The datasets generated and/or analysed 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 based on scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the manuscript. The protocol would be made available on request by contacting the journal or the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Schett G, Lories RJ, D'Agostino MA *et al.* Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731–41.

2 Godfrin B, Zabraniecki L, Lamboley V *et al.* Spondyloarthropathy with entheseal pain. A prospective study in 33 patients. Joint Bone Spine 2004;71:557–62.

3 Scarpa R, Cuocolo A, Peluso R *et al.* Early psoriatic arthritis: the clinical spectrum. J Rheumatol 2008;35:137–41.

4 de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis Res Ther 2016;18:196.

5 Ciurea A, Scherer A, Exer P *et al.*; Rheumatologists of the Swiss Clinical Quality Management Program for Axial Spondyloarthritis. Tumor necrosis factor α inhibition in radiographic and nonradiographic axial spondyloarthritis: results from a large observational cohort. Arthritis Rheum 2013;65:3096–106.

6 Morales Ivorra I, Juárez López P, López de Recalde M, Carvalho PD, Rodriguez Moreno J. Heel pain in psoriatic arthropathy: analysis of a series of 291 patients. Reumatol Clin 2018;14:290–3.

7 D'Agostino MA, Enthesitis OI. Best practice and research. Clin Rheumatol 2006;20:473–86.

8 Koumakis E, Gossec L, Elhai M *et al.* Heel pain in spondyloarthritis: results of a cross-sectional study of 275 patients. Clin Exp Rheumatol 2012;30:487–91.

9 Williams SK, Brage M. Heel pain-plantar fasciitis and Achilles enthesopathy. Clin Sports Med 2004;23:123–44.

10 McInnes IB, Puig L, Gottlieb AB *et al.*; PSUMMIT 1 and 2 Study Groups. Association between enthesitis and health-related quality of life in psoriatic arthritis in biologic-naive patients from 2 phase III ustekinumab trials. J Rheumatol 2019;46:1458–61.

11 Rezvani A, Bodur H, Ataman S *et al.* Correlations among enthesitis, clinical, radiographic and quality of life parameters in patients with ankylosing spondylitis. Mod Rheumatol 2014;24:651–6.

12 Sunar I, Ataman S, Nas K *et al.* Enthesitis and its relationship with disease activity, functional status, and quality of life in psoriatic arthritis: a multi-center study. Rheumatol Int 2020;40:283–94.

13 Turan Y, Duruöz MT, Cerrahoglu L. Quality of life in patients with ankylosing spondylitis: a pilot study. Rheumatol Int 2007;27:895–9.

14 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;21:266.

15 Marzo-Ortega H, Sieper J, Kivitz A *et al.*; Measure 2 Study Group. Secukinumab and sustained improvement in signs and symptoms of patients with active ankylosing spondylitis through two years: results from a phase III study. Arthritis Care Res 2017;69:1020–9.

16 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;77:890–97.

17 McInnes IB, Mease PJ, Ritchlin CT *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;56:1993–2003.

18 Baeten D, Sieper J, Braun J *et al.* Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. New Engl J Med 2015;373:2534–48.

19 Baraliakos X, Braun J, Deodhar A *et al.* Long-term efficacy and safety of secukinumab 150 mg in

ankylosing spondylitis: 5-year results from the phase III MEASURE 1 extension study. RMD Open 2019;5: e001005.

20 Marzo-Ortega H, Sieper J, Kivitz AJ *et al.* 5-year efficacy and safety of secukinumab in patients with ankylosing spondylitis: end-of-study results from the phase 3 MEASURE 2 trial. Lancet Rheumatol 2020;2:e339–e46.

21 Deodhar A, Blanco R, Dokoupilová E *et al.* Secukinumab improves signs and symptoms of non-radiographic axial spondyloarthritis: primary results of a randomized controlled phase III study. Arthritis Rheumatol 2021;73: 110–20.

22 Dougados M, Combe B, Braun J *et al.* A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitis in spondyloarthritis: the HEEL trial. Ann Rheum Dis 2010;69: 1430–5.

23 World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4. https://jamanetwork.com/journals/jama/fullarticle/1760318.

24 Baraliakos X, Sewerin P, de Miguel E *et al.* Achilles tendon enthesitis evaluated by MRI assessments in patients with axial spondyloarthritis and psoriatic arthritis: a report of the methodology of the ACHILLES trial. BMC Musculoskelet Disord 2020;21:767.

25 Mathew AJ, Krabbe S, Eshed I *et al.* The OMERACT MRI in enthesitis initiative: definitions of key pathologies, suggested MRI sequences, and a novel heel enthesitis scoring system. J Rheumatol 2019;46:1232–8.

26 Lane P. Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. Pharm Stat 2008;7:93–106.

27 Mease PJ. Measures of psoriatic arthritis: tender and swollen joint assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res 2011;63(Suppl 11): S64–85.

28 Mease PJ, Van den Bosch F, Sieper J *et al.* Performance of 3 enthesitis indices in patients with peripheral spondyloarthritis during treatment with adalimumab. J Rheumatol 2017;44:599–608.

29 Kivitz AJ, Wagner U, Dokoupilova E *et al.* Efficacy and safety of secukinumab 150 mg with and without loading regimen in ankylosing spondylitis: 104-week results from MEASURE 4 study. Rheumatol Ther 2018; 5:447–62.

30 Abate M, Di Carlo L, Salini V, Schiavone C. Metabolic syndrome associated to non-inflammatory Achilles enthesopathy. Clin Rheumatol 2014;33:1517–22.

31 Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs 2005;14: 798–804.

32 Busse JW, Bartlett SJ, Dougados M *et al.* Optimal strategies for reporting pain in clinical trials and systematic reviews: recommendations from an OMERACT 12 workshop. J Rheumatol 2015;42: 1962–70.

33 Kristensen S, Christensen JH, Schmidt EB *et al.* Assessment of enthesitis in patients with psoriatic arthritis using clinical examination and ultrasound. Muscles Ligaments Tendons J 2016;6:241–7.

34 Schett G, Baraliakos X, Bosch FVD *et al.* FRI0380 Secukinumab provides sustained improvement of enthesitis in patients with ankylosing spondylitis: pooled analysis of four pivotal phase 3 studies. Ann Rheum Dis 2019;78:873–4.