Short title: Secukinumab in PsA: PDUS assessment

Response to Secukinumab on Synovitis using Power Doppler Ultrasound in Psoriatic Arthritis: 12-week Results from a Phase III Study, ULTIMATE

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Abstract

Objectives. To investigate the dynamics of response of synovitis to interleukin (IL)-17A inhibition with secukinumab in patients with active psoriatic arthritis (PsA) using Power Doppler ultrasound.

Methods. The randomised, placebo-controlled, Phase III ULTIMATE study enrolled PsA patients with active ultrasound synovitis, and clinical synovitis and enthesitis having an inadequate response to conventional disease-modifying anti-rheumatic drugs (DMARDs) and naïve to biologic DMARDs. Patients were randomly assigned to receive either weekly subcutaneous secukinumab (300 or 150 mg according to the severity of psoriasis) or placebo followed by 4-weekly dosing thereafter. The primary outcome was the mean change in the ultrasound Global European League Against Rheumatism and Outcome Measures in Rheumatoid Arthritis Clinical Trials Synovitis Score (GLOESS) from baseline to Week 12. Key secondary endpoints included American College of Rheumatology 20 and 50 responses.

Results: Of the 166 patients enrolled, 97% completed 12 weeks of treatment (secukinumab, 99%; placebo, 95%). The primary endpoint was met, and the adjusted mean change in GLOESS was higher with secukinumab than placebo (−9 [0.9] vs −6 [0.9], difference [95% CI]: −3 [−6; −1]; one-sided P=0.004) at Week 12. The difference in GLOESS between secukinumab and placebo was significant as early as one week after initiation of treatment. All key secondary endpoints were met. No new or unexpected safety findings were reported.

Conclusion: This unique ultrasound study shows that apart from improving the signs and symptoms of PsA, IL-17A inhibition with secukinumab leads to a rapid and significant reduction of synovitis in PsA patients.

Trial registration: ClinicalTrials.gov; NCT02662985

Key messages:

- Importance of GLOESS using Power Doppler ultrasound (PDUS) for detecting synovitis in RA has been established.
- ULTIMATE is the first RCT to show the applicability of GLOESS using PDUS in PsA.
- The GLOESS results confirm rapid and early response to secukinumab on synovitis in PsA.

Key words: PsA, Power Doppler ultrasound, OMERACT, GLOESS, Clinical outcome, Responsiveness, Synovitis, Joints, Secukinumab, biological DMARDs.

Word count: 3054

Introduction

Psoriatic arthritis (PsA) is characterised by inflammation of synovial membranes and entheseal sites leading to pain, structural damage, impairment of physical function and quality of life [1–5]. Abrogation of inflammation in the joints is a central goal for the treatment of PsA, like in any other form of inflammatory arthritis. However, to date the effects of drug therapy on disease are usually measured indirectly, through assessing the impact on signs and symptoms of disease, rather than directly assessing inflammation at joint level. Hence, little is known about the dynamic effect of disease modifying anti-rheumatic drugs (DMARDs) on synovitis.

Ultrasound in B-mode combined with Power Doppler (PD; the association named PDUS), permits visualisation of both morphological and functional changes of synovium [6, 7]. The European League Against Rheumatism (EULAR) and the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) have recently standardised the use of PDUS for detecting synovitis and developed a composite scoring system at joint and patient level: the Global EULAR-OMERACT Synovitis Score (GLOESS), which has shown high responsiveness to treatment and excellent reliability in rheumatoid arthritis (RA) patients [8–11], suggesting the possibility to be used to monitor treatment response in inflammatory arthritis.

Secukinumab, a human monoclonal antibody that directly inhibits interleukin (IL)-17A, has demonstrated sustained efficacy on signs and symptoms, inhibition of structural damage progression, and a favourable long-term safety profile in patients with PsA over 5 years [12–14], however, little is known on its direct effect on synovitis (and enthesitis) and the dynamics of such response. To investigate this, we initiated the

ULTIMATE study, which is the first PDUS-based randomised placebo-controlled trial in PsA that primarily focussed on synovial responses rather than on signs and symptoms of disease. Hence, the primary aim of the ULTIMATE study was to evaluate whether treatment with secukinumab inhibits synovitis, as measured by PDUS, in patients with active PsA who failed conventional synthetic DMARDs (csDMARDs) therapy and were naïve to biological DMARDs (bDMARDs). Herein, we present the primary efficacy data of secukinumab on synovitis in patients with active PsA.

Methods

Patients and study design

Biologic-naïve patients (aged ≥18 years) with a diagnosis of PsA for at least 6 months, fulfilling the CASPAR criteria, and having an inadequate response to csDMARDs and an active disease based on tender joint count (TJC) ≥3 of 78 joints and swollen joint count (SJC) ≥3 of 76 joints were considered eligible for this study. In addition, patients had to present active PDUS synovitis according to a pre-defined cut-off (Supplementary Figure S1 and Table S1, available at *Rheumatology* online) at screening and baseline and at least one clinical enthesitis at screening and baseline. Patients could continue to receive methotrexate, glucocorticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs) at a stable standard dose from 1-month prior to screening to 24 weeks (Supplementary Figure S2, available at *Rheumatology* online).

Key exclusion criteria included evidence of an ongoing infection or malignant process; prior treatment with bDMARDs, including tumor necrosis factor inhibitors; active ongoing inflammatory conditions other than PsA; active systemic infection within

2 weeks before randomisation; history of ongoing, chronic, or recurrent infectious disease or evidence of tuberculosis infection; known infection with human immunodeficiency virus or hepatitis B or C at screening or randomisation; and history of lymphoproliferative disease, any known malignancy, or malignancy of any organ system within the past 5 years. Detailed inclusion and exclusion criteria are listed in the Supplementary Table S1, available at *Rheumatology* online.

ULTIMATE (NCT02662985) was a multicentre, randomised, double-blind, placebo-controlled, 52-week Phase III study (Supplementary Figure S2, available at *Rheumatology* online). The study was initiated on August 22, 2016 (first patient, first visit), and conducted across 37 active sites in 17 countries. This study consisted of a 1- to 4-week screening phase, followed by a 12-week, double-blind, placebo-controlled treatment period (TP 1; baseline to Week 12); a 12-week open-label period (TP 2; Week 12 to Week 24); a 6-month, open-label extension period (TP 3; Week 24 to Week 52); and a 12-week safety follow-up period (Week 52 to Week 64; Supplementary Figure S2, available at *Rheumatology* online).

Enrolled patients were randomised (1:1) using Interactive Response Technology (IRT) to receive either subcutaneous secukinumab (300 mg or 150 mg) or placebo weekly followed by 4-weekly dosing at Weeks 4 and 8 in a double-blind manner (Supplementary Figure S2, available at *Rheumatology* online). Patients received secukinumab 300 mg or 150 mg according to the severity of skin disease. The open-label phase started at Week 12 (TP 2), and all patients (including the placebo group) received secukinumab 300 mg or 150 mg depending on the skin severity through IRT every 4 weeks until Week 52 in an open-label manner. Patients, study centre personnel

(including ultrasound and clinical investigators), and data analysts were fully blinded to the treatment assigned to patients at randomisation for the first 12 weeks of the study (TP 1). The ultrasound and clinical investigators remained blinded from each other until the final database lock.

The study protocol and its amendments were reviewed and approved by the independent ethics committee or institutional review board for 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 [15]. 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 sponsor.

Assessment of joints by ultrasound

PDUS evaluation was performed at screening; baseline; and Weeks 1, 2, 4, 6, 8, and 12. The following 24 joints were evaluated bilaterally: metacarpophalangeal (MCP) joints 1 to 5, proximal interphalangeal (PIP) joints 1 to 5, metatarsophalangeal (MTP) joints 1 to 5, distal interphalangeal (DIP) joints 2 to 5, wrists, elbows, shoulders (glenohumeral), knees and ankles (tibiotalar). The joints were scanned at each visit from the dorsal aspect, with the joint in a neutral position, except for the knee, which was examined in a flexed position (30°). All recesses of each joint were scanned, and the detection of maximal grading of PDUS synovitis in one of these recesses determined the final grade of the joint.

All PDUS evaluations were performed at each site by an independent examiner, expert in musculoskeletal ultrasound, with more than 5 years of experience, and blinded

to the clinical evaluation. To ensure homogeneity of PDUS synovitis scoring, all ultrasound investigators completed an extensive 2-day training session, including examination of patients with PsA. In addition, ultrasound settings were not changed during the study, standardised joint 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.

Medium- to high-level ultrasound 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) were used, which employed high frequency (12–18 MHz) transducers. Doppler parameters were adjusted according to the device used (range of pulse repetition frequency 400–800 Hz; Doppler frequency 7–14.1 MHz).

PDUS synovitis was defined according to the EULAR-OMERACT definition as a hypoechoic synovial hypertrophy (SH) detected in B-mode, which may show PD signal. At each visit, PDUS synovitis was graded semi-quantitatively (0 to 3) according to the EULAR-OMERACT PDUS composite score (Table 1) [8, 11]. In addition, single components of this composite score (i.e. hypoechoic SH and PD synovial signal) were scored separately at each visit.

The GLOESS for the 24 paired joints was calculated as the sum of each PDUS composite score for all joints examined, giving a potential score ranging from 0 to 144. As previously reported, GLOESS incorporates both B-mode and PD measures of synovitis and allows to evaluate changes in the activity and morphology of synovitis. To help in grading severity, an atlas with examples of B-mode and PD grading for all joints examined was available in each centre.

All images were 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 the images collected from the first included patient enrolled in each site were considered adequate to ensure a homogeneous rating across sites.

Clinical and safety assessments

Joints were assessed clinically for tenderness and swelling to calculate the TJC and SJC. In addition, American College of Rheumatology 20, 50, and 70 (ACR20, 50, and 70) responses and their core components and the mean change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) were evaluated. Safety assessments, including adverse events (AEs), serious AEs, and AEs of special interest occurring during the first 12 weeks, were performed in all patients receiving at least one dose of study drug.

Statistical analysis

This study was designed to test the superiority of secukinumab compared with placebo at a 5% significance level with a two-sided test. No data applying the EULAR-OMERACT composite PDUS score at the joint or patient level (GLOESS) in PsA were previously reported; however, the mean change from baseline to Week 12 was assumed based on the abatacept treatment effect from a previous PDUS study in RA [16]. Assuming a difference in the mean change from baseline to Week 12 in GLOESS (primary objective) of −6 with a pooled standard deviation of 13.2, a total of 218 patients (109 patients per arm) were estimated to achieve a power of 90%.

Blinded sample size re-estimation (SSR) was performed after the completion of Week 12 for the first 60 patients and substantiated by data collection from the first 72 enrolled patients to reassess variability of the disease and adjust sample size calculation accordingly. A protocol amendment was introduced to reduce the study sample size from 218 patients to 164 patients (82 patients per arm) with the power relaxed to 80% and a one-sided (α=5%) superiority test versus placebo for the primary objective. The detailed SSR has been provided in Supplementary Table S2, available at *Rheumatology* online.

The efficacy analyses were performed on the full analysis set, which comprised all patients who were randomised and had study treatment assigned. The primary and key secondary endpoints were analysed according to a pre-defined statistical hierarchy (Supplementary Figure S3, available at *Rheumatology* online). The primary objective was to demonstrate a difference in mean change from baseline to Week 12 between secukinumab and placebo groups related to PDUS synovitis response using GLOESS (sum of the affected joints out of 48 joints). In addition, change between secukinumab and placebo from baseline to Week 12 in the core components (SH and PD signal) of GLOESS was analysed exploratory. The clinical exploratory outcome measures presented here include the proportion of patients achieving ACR70, the mean change from baseline in HAQ-DI score, and distribution of joints by ultrasound and clinical assessment at baseline.

Data presented for the secukinumab group were pooled data from 300 mg and 150 mg. The primary analysis was performed using a mixed-effect model repeated measures (MMRM; valid under the “missing at random” assumption), with treatment

regimen, centre, and analysis visit as factors and weight and baseline GLOESS as continuous covariates. Treatment by analysis visit was included as an interaction term in the model. An unstructured covariance structure was assumed for this model. The significance of the treatment effect for secukinumab was determined using the comparisons performed between the secukinumab and placebo arms at Week 12. Missing values were imputed as non-response (non-responder imputation [NRI]) for binary variables via logistic regression, with study treatment as a factor and baseline weight as a covariate. Odds ratio and relative risk (for binary variables) or differences in adjusted mean change (for continuous variables) and 95% confidence interval (CI) are presented comparing secukinumab versus placebo. A “null zone” derived from the CI around the difference, obtained from the MMRM analysis, was plotted for continuous variables [17]. It shows the area where the means are located when there is no significant difference between the groups at the $P<0.05$ level.

Safety analyses included all patients who received ≥1 dose of study medication. AEs were reported as absolute frequencies over the placebo-controlled period, referring to the cumulative treatment period (i.e. events started after the first dose of study treatment or events present before the first dose of study treatment but increased in severity based on preferred term and on or before the last dose plus 84 days). The clinical and ultrasound response on enthesitis which were secondary and exploratory objectives are not included in the present report.

RESULTS

Patient disposition and baseline characteristics

Overall, 258 patients were screened, of whom 82 were ineligible for the study and 10 were not included for other reasons (Figure 1). Out of 166 patients (64%) enrolled, 161 (97%) completed the first 12 weeks (secukinumab, 99%; placebo, 95%; Figure 1). The proportion of patients with at least one protocol deviation was 15% (secukinumab, 16%; placebo, 13%; Supplementary Table S3, available at *Rheumatology* online). Demographics and baseline clinical characteristics were comparable between the treatment groups (Table 2). The mean age was 47 years, median disease duration was 4 years, and 55% were women. Patients had active disease at baseline with a mean number of 14 tender joints, 9 swollen joints, and 4 clinically active enthesitis, as well as a mean Psoriasis Area and Severity Index score of 10.

The average time spent on PDUS assessments at baseline for the evaluation of the pre-specified set of 24 paired joints was 39 minutes, for both the secukinumab and placebo arms. The distribution of PDUS synovitis revealed that wrists, knees, MCPs, and MTPs were the more frequently affected joints. A similar distribution was observed on clinical examination of swollen or tender joints with lower frequency. These data are presented in a heat map in Figure 2 and Supplementary Figure S4, Tables S4 and S5 (available at *Rheumatology* online), respectively.

PDUS efficacy

The primary endpoint was met at Week 12 (Figure 3); the adjusted mean (SE) change in GLOESS was significantly higher in the secukinumab versus placebo (−9 [0.9] versus −6 [0.9], difference [95% CI]: −3 [−6; −1]; one-sided P=0.004). A markedly significant difference between secukinumab and placebo was observed as early as 1-week after treatment initiation. The mean (SE) change from baseline to Week 12 in SH

(secukinumab versus placebo) was −9 (0.9) versus −6 (0.9) and in PD was −4 (0.5) versus −2 (0.5), with significance as early as Week 1 for SH and Week 2 for PD signal (Figure 3).

Clinical efficacy

ACR20 and ACR50 responses were met and favored secukinumab-treated patients against placebo at Week 12, with significant improvements observed as early as Week 1 for ACR20 and Week 2 for ACR50 compared with placebo (Figure 4). Significantly higher responses were observed in secukinumab-treated patients for the exploratory endpoints (ACR70 response and HAQ-DI score) at Week 12 compared with placebo (Figure 4). The mean changes from baseline to Week 12 in ACR core components are presented in Supplementary Table S6, available at *Rheumatology* online.

Safety

Overall, the incidence of treatment-emergent AEs up to Week 12 was 58% for the secukinumab group and 57% for the placebo group. The most frequent treatment-emergent AEs in terms of crude incidence rates up to Week 12 were nasopharyngitis, hypertension, diarrhoea, headache, and latent tuberculosis in either secukinumab or placebo group. No serious AEs were reported in the secukinumab group. No deaths, serious infections, neutropaenia, major adverse cardiovascular events, inflammatory bowel disease, or malignancies were reported in either treatment group. Safety data are presented separately for individual treatment groups (secukinumab and placebo) in Supplementary Table S7, available at *Rheumatology* online.

DISCUSSION

ULTIMATE is the first randomised, placebo-controlled, PDUS Phase III study in PsA that primarily aimed to address the effects of biological DMARDs on synovitis detected by a validated ultrasound outcome measurement instrument as a primary endpoint. The primary efficacy data of the ULTIMATE study showed a significant effect of secukinumab treatment compared to placebo in reducing active synovitis in PsA. This effect was observed as early as 1-week after the initiation of treatment and continued to improve at each time point of evaluation until Week 12. The ultrasound approach also allowed assessment of which aspects of synovitis improved first. Thus, the SH component showed the response as early as 1-week and the PD component as early as 2 weeks after treatment initiation, highlighting a fast onset of efficacy of secukinumab in controlling inflammation in PsA.

To date, only one small observational study has suggested that DMARDs have an effect on synovitis in PsA. [18] Large controlled studies aiming to assess the direct effect of DMARDs on synovitis are lacking, despite the availability of objective instruments to measure such effects. ULTIMATE study revealed that the activity of synovitis in PsA, can be scored at patient level using a validated ultrasound scoring system (GLOESS). Moreover, the study showed that reliable assessment of synovitis in PsA is feasible across different centres. Thus, GLOESS was sensitive to detect decrease in synovitis across different ultrasound devices and examiners even without excluding patients with protocol deviations. The absence of a true reliability exercise among the examiners may be considered as a limitation. However, potential variability in ultrasound assessment related to expertise was minimised using a rigorous ultrasound training, an atlas with reference images and central reading of images of the

first patient enrolled across all sites. Possible remaining variability did not detract from the high sensitivity to change of GLOESS, which was developed to be sensitive across examiners and machines. Hence, these data suggest that assessment of synovitis by GLOESS is a reliable method to address the direct effect of DMARDs on synovitis in PsA.

The observed improvement in the signs and symptoms of PsA upon exposure to secukinumab confirmed its known clinical efficacy and was in accordance with earlier studies. Higher ACR responses were observed with secukinumab in the current study than in the secukinumab FUTURE 2 and FUTURE 5 studies [19, 20], possibly because of the uniquely rigorous combined clinical and ultrasound inclusion criteria on joints, and the stringent monitoring in this study over the initial 3 months. Treatment with secukinumab was well tolerated and the safety profile was consistent with the established safety profile across approved indications.[21]

In conclusion, ULTIMATE is the first randomised study that evaluated the effect of DMARDs on PDUS measured synovitis as the primary endpoint. It demonstrated that secukinumab rapidly and significantly decreased synovitis, indicating a direct effect of IL-17 inhibition on the synovium in patients with PsA. As synovitis is critical for cartilage and bone destruction in PsA [1, 3, 4], these data also provide the basis for the observed protection of joint structure by secukinumab in patients with PsA.

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Ethics Approval

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 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 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.

Disclosure of Interest

Maria Antonietta D'Agostino has received honoraria for consulting or speaking from Sanofi, Novartis, BMS, Janssen, Celgene, AbbVie, UCB pharma, and Eli Lilly.

Georg Schett has received honoraria for speaking from AbbVie, BMS, Celgene, Gilead, Janssen, Eli Lilly, Novartis, Roche, and UCB pharma.

Alejandra López-Rdz has received honoraria for consulting or speaking from Roche, Eli Lilly, Novartis, BMS, and Neovacs and research grant from those companies.

Ladislav Šenolt has received research grants from AbbVie; honoraria for speaking from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Gilead, MSD, Mylan, Novartis, Pfizer, Roche, Sanofi, Sandoz, and UCB pharma; expenses for attendance at advisory board meeting from AbbVie, BMS, Celgene, MSD, Novartis, Pfizer, Roche, and UCB pharma; and honoraria for clinical trials from AbbVie, Amgen, BMS, Celgene, Novartis, Pfizer, Takeda, and UCB.

Katalin Fazekas declares no competing interest.

Ruben Burgos-Vargas has received honoraria for speaking from Novartis.

Jose Maldonado-Cocco has received honoraria for speaking or consulting from Pfizer, MSD, Sanofi-Aventis, Novartis, BMS, Roche, Boehringer Ingelheim, Schering-Plough, Abbott, UCB, Eli Lilly, and Gilead and principal investigator in clinical trials for those companies.

Esperanza Naredo has received honoraria for speaking from AbbVie, Roche, BMS, Pfizer, UCB, Eli Lilly, Novartis, Janssen, and Celgene; honoraria for clinical trials from AbbVie, Novartis, and BMS; and research grants from Eli Lilly.

Philippe Carron has received research grants from UCB, MSD, and Pfizer; honoraria for speaking or consulting from Pfizer, MSD, Novartis, BMS, AbbVie, UCB, Eli Lilly, Gilead, and Celgene.

Anne-Marie Duggan and **Punit Goyanka** are employees of Novartis.

Maarten Boers has received honoraria for consulting from BMS, Novartis, Pfizer, and GSK.

Corine Gaillez an employee of Novartis and own stock from Novartis and BMS.

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Figure legends

Figure 1. Patient disposition through Week 12.

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N, total number of patients

Figure 2. Distribution of synovitis detected by ultrasound and, tender and swollen joints detected by clinical assessment at baseline.

The distribution of synovitis detected by ultrasound and distribution of tender and swollen joint detected by clinical examination at baseline side by side. Frequency of distribution varies from 0 to 80% (highest proportion of patients with ultrasound detected synovitis on wrist) and is visualised by a code of colour from yellow to red shown on the right bar. Grey colour means ultrasound did not assess synovitis of these joints.

CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal

Figure 3. PDUS efficacy outcomes through Week 12.

*P<0.05 versus placebo. (A) primary endpoint GLOESS (MMRM, difference [95% CI]: –3 [–6; –1], P=0.004) at Week 12; (B) GLOESS SH (MMRM, difference [95% CI]: –3 [–6; –1], P=0.004); and (C) GLOESS PD (MMRM, difference [95% CI]: –2 [–3; –1], P=0.001). The 'null zone' presented GLOESS scores was derived from the CI around the difference, which was obtained from the MMRM. It shows the area where the means

are located when there is no significant difference between the groups at the *P*<0.05 level.

EULAR, European League Against Rheumatism; GLOESS, Global OMERACT-EULAR Synovitis Score; LS, least squares; MMRM, mixed-effect model repeated measures; N, total number of randomised patients; n, number of evaluable patients; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; PD, Power Doppler; SEC, secukinumab; SH, synovial hypertrophy

Figure 4. Clinical efficacy outcomes through Week 12.

**P*<0.05 versus placebo. (A) ACR20 response (NRI, odds ratio [95% CI]: 5 [2; 9], *P*<0.0001, relative risk: 2); (B) ACR50 response (NRI, odds ratio [95% CI]: 10 [4; 24], *P*<0.0001, relative risk: 5); (C) ACR70 response (NRI, odds ratio [95% CI]: 23 [3; 178], *P*=0.0013, relative risk: 18); and (D) HAQ-DI score (MMRM, difference: –0.5 [–0.6; –0.3]; *P*<0.0001). The 'null zone' presented HAQ-DI score was derived from the CI around the difference, which was obtained from the MMRM. It shows the area where the means are located when there is no significant difference between the groups at the *P*<0.05 level.

ACR, American College of Rheumatology; HAQ-DI, Health Assessment Questioner Disability Index; LS, least squares; MMRM, mixed-effect model repeated measures; N, total number of randomised patients; NRI, non-responder imputation; n, number of evaluable patients; SEC, secukinumab

TABLES

Table 1. Ultrasound scoring system for B-mode and PD signal at joint level

B-mode: Inflammatory or active Synovial Hypertrophy	
Grade 0	No hypoechoic synovial thickening
Grade 1	Minimal hypoechoic synovial thickening filling the angle between the periarticular bones, without bulging over the line linking tops of the bones
Grade 2	Hypoechoic synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis
Grade 3	Hypoechoic synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphysis
PD signal	
Grade 0	No flow (PD signal) in the synovium
Grade 1	Up to three single spots signals or up to two confluent spots or one confluent spot plus up to two single spots
Grade 2	Vessel signals in less than half of the area of the synovium (<50%)

Grade 3	Vessel signals in more than half of the area of the synovium (>50%)

Grades: 0, normal joint; 1, minimal synovitis; 2, moderate synovitis; 3, severe synovitis.

EULAR, European League Against Rheumatism; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; PD, Power Doppler; PDUS, Power Doppler ultrasonography

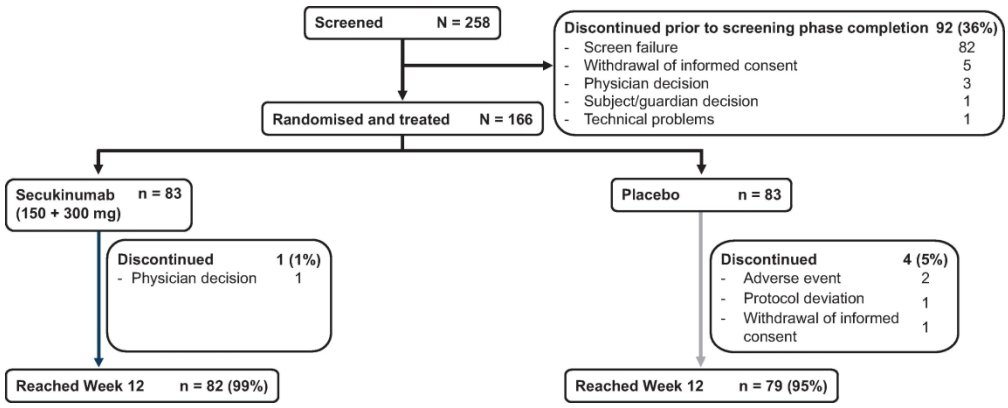
Table 2. Baseline demographic and clinical characteristics

Characteristics[§]	Secukinumab (300 mg + 150 mg) (N = 83)	Placebo (N = 83)
Age (years)	47 (12)	47 (12)
Female, n (%)	45 (54)	46 (55)
Caucasian, n (%)	75 (90)	75 (90)
Time since diagnosis of PsA (years)	6 (7)	7 (7)
TJC (78 joints)	13 (8)	15 (12)
SJC (76 joints)	10 (8)	9 (9)
Patient Pain (VAS)	59 (21)	59 (24)
Global assessment of disease activity (VAS)		
Patient	60 (23)	60 (23)
Physician	56 (18)	52 (22)
HAQ-DI score	1.3 (0.6)	1.2 (0.7)
hsCRP level (mg/L), median (min–max)	7 (1–77)	5 (0–102)
PsO[†], n (%)	36 (43)	33 (40)
PASI score[†]	9 (6)	11 (9)
GLOESS[‡]	24 (16)	27 (17)
SH	24 (16)	27 (17)
PD	8 (8)	7 (7)
Number of joints with PDUS synovitis	9 (5)	10 (5)
Concomitant corticosteroids, n (%)	13 (16)	19 (23)

Concomitant methotrexate, n (%)	35	(42)	34	(41)

§mean (SD) unless otherwise specified; †calculated only for patients with BSA ≥3%; ‡24 paired joints

BSA, body surface area; GLOESS, Global EULAR-OMERACT Synovitis Score; HAQ-DI, health assessment questionnaire disability index; hsCRP, high sensitivity C-reactive protein; N, total number of randomised patients; OMERACT, Outcome Measures in Rheumatoid Arthritis Clinical Trials; PASI, Psoriasis Area and Severity Index; PD, Power Doppler; PDUS, Power Doppler Ultrasonography; PsA, psoriatic arthritis; PsO, psoriasis; SJC, swollen joint count; SH, Synovial hypertrophy; TJC, tender joint count; VAS, visual analog scale (range, 0–100)



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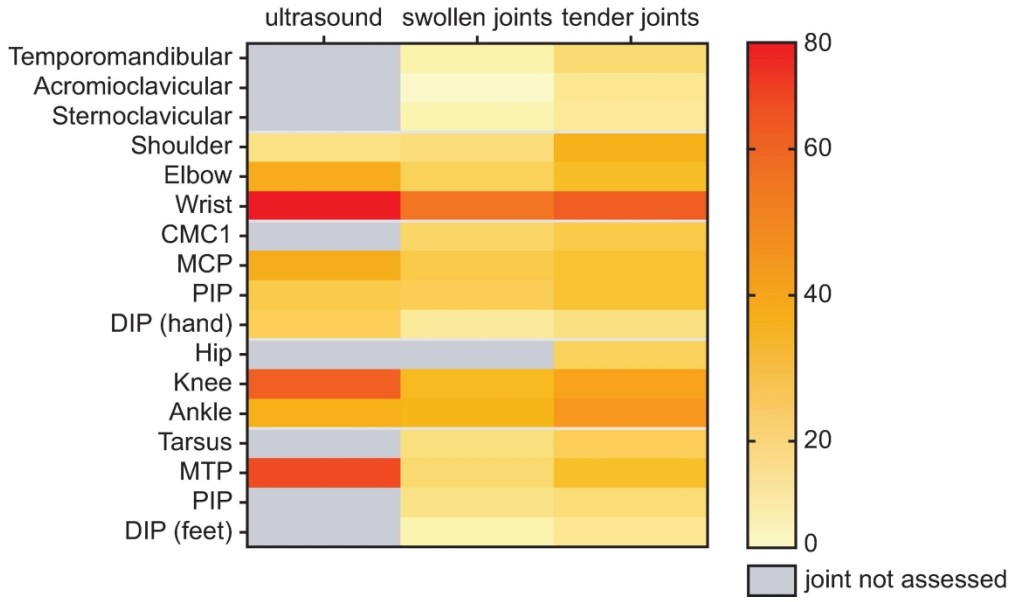

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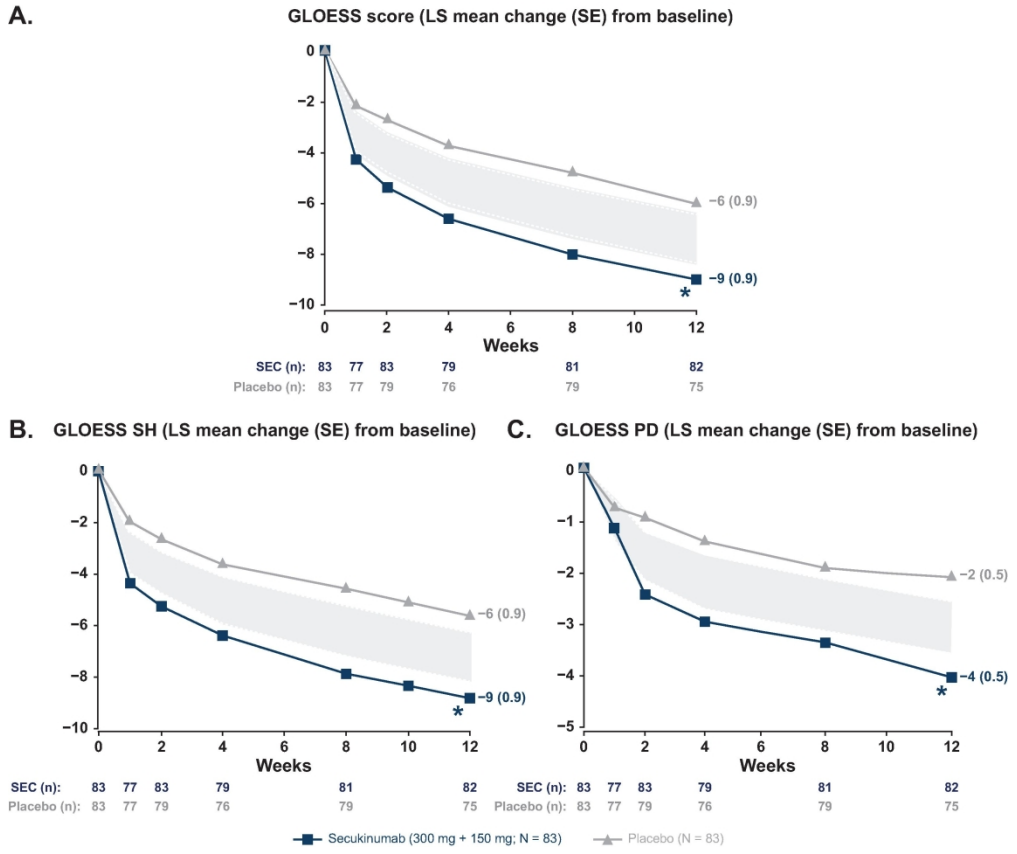

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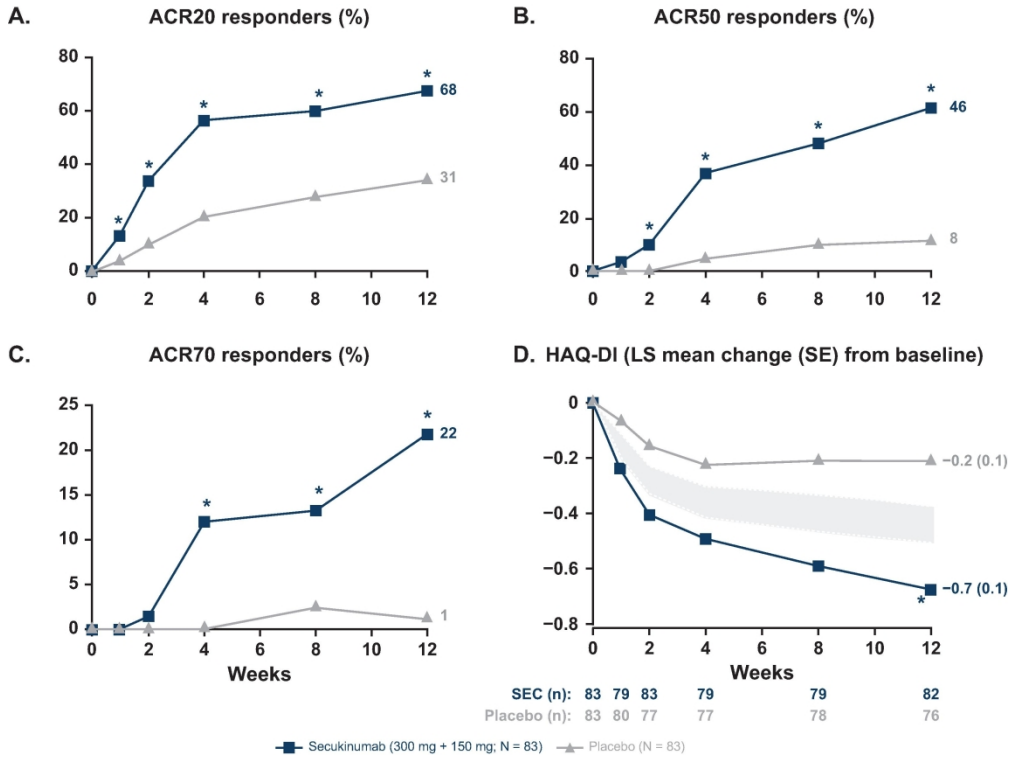

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