Secukinumab Significantly Decreased Joint Synovitis Measured by Power Doppler Ultrasonography in Biologic-naïve Patients with Active Psoriatic Arthritis: Primary (12-week) Results from a Randomized, Placebo-controlled Phase III Study

MA D'Agostino[1,2], G Schett[3], A López-Rdz[4], L Šenolt[5], J Maldonado-Cocco[6], R Burgos-Vargas[7], E Naredo[8], P Carron[9], M Boers[10], AM Duggan[11], P Goyanka[12], C Gaillez[13]

[1]Université de Versailles-Saint Quentin en Yvelines, APHP-Paris Saclay, Boulogne-Billancourt, France; [2]Catholic University of Sacred Heart, Roma, Italy; [3]University of Erlangen-Nuremberg, Erlangen, Germany; [4]Dermatológico Country, PSOAPS Psoriasis Clinical and Research Center, Guadalajara, Mexico; [5]Institute of Rheumatology, Charles University, Prague, Czech Republic; [6]University of Buenos Aires, School of Medicine, Buenos Aires, Argentina; [7]Department of Rheumatology, Hospital General de Mexico, Mexico City, Mexico; [8]Department of Rheumatology and Joint and Bone Research Unit, Hospital Fundación Jiménez Díaz and Autónoma University, Madrid, Spain; [9]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium; [10]Department of Epidemiology & Data Science; Amsterdam Rheumatology and Immunology Center, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands; [11]Novartis Ireland Limited, Dublin, Ireland; [12]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [13]Novartis Pharma AG, Basel, Switzerland

INTRODUCTION

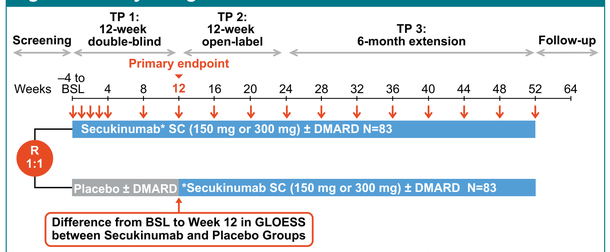
- Power Doppler (PD) ultrasonography (PDUS) is a sensitive non-invasive imaging technology used to assess synovitis and enthesitis of psoriatic arthritis (PsA) in clinical trials and in clinical practice[1,2]
- European League Against Rheumatism and Outcome Measures in Rheumatology (EULAR-OMERACT) developed a standardized and sensitive to change ultrasonography composite scoring system (global EULAR-OMERACT synovitis score [GLOESS]) to detect and score synovitis[3]
- Here we report primary (12-week) efficacy and safety results from the ULTIMATE study (NCT02662985), the first large, randomized, double-blind, placebo-controlled phase III study, primarily designed to assess the time course of response to subcutaneous secukinumab using ultrasound to assess the primary endpoint on synovitis

METHODS

Study Design and Patients

- This is a 52-week study with a 12-week double-blind treatment period (TP 1) followed by 12-week open-label (TP 2) and 6-month open-label extension (TP 3) (**Figure 1**)

Figure 1. Study design



*Secukinumab dosing based on severity of PsO through IRT (300 mg if BSA >10% or 150 mg (BSA ≤10%). BSA, body surface area; BSL, baseline; IRT, Interactive Response Technology; N, number of randomized patients; PsO, psoriasis; R, randomization; SC, subcutaneous

- **Main inclusion criteria:**
  - Biologic-naïve and inadequate response to conventional disease-modifying anti-rheumatic drugs (DMARDs)
  - Patients with active PsA:
    - Clinical assessment: tender joint count (TJC out of 78 joint count [JC]) and swollen joint count (SJC out of 76 JC) ≥3 at baseline
    - Ultrasound detected synovitis at screening and baseline with a total synovitis PDUS score ≥2 + PD signal >2 for ≥1 joint out of 48 JC or total synovitis PDUS score ≥2 + PD signal >1 for ≥2 joints out of 48 JC
    - ≥1 clinical enthesitis at screening and baseline

Assessment of joints by ultrasound

- PDUS evaluation was performed bilaterally for 24 pairs of joints at baseline and at Weeks 1, 2, 4, 6, 8, and 12 by an independent examiner, expert in musculoskeletal ultrasound, blinded from clinical evaluation
- The presence of synovitis (i.e. hypoechoic synovial hyperplasia [SH] and PD synovial signal) was scored according to the total OMERACT-EULAR synovitis score composite semi-quantitative scale (0 to 3)
- The GLOESS for the 24 paired joints was calculated as the sum of the total OMERACT-EULAR synovitis scores for all synovitis examined (range 0–144)
- The **primary endpoint** was the difference in mean change from baseline to Week 12 between secukinumab and placebo in terms of synovitis as measured by the **GLOESS**

Clinical and safety assessments

- Key secondary endpoints included:
  - Proportion of patients with American College of Rheumatology (ACR) 20 and ACR50 responses at Week 12
  - Change in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index score from baseline to Week 12
- Safety and tolerability up to Week 12

Statistical Analyses

- Primary analysis was done via a mixed-effect model repeated measures (MMRM) with treatment regimen, center 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
- Missing values were imputed as non-responders (non-responder imputation; NRI) for binary variables via logistic regression with study treatment as a factor and baseline weight as a covariate
- Odds ratios (for binary variables) or differences in adjusted mean change (for continuous variables) and 95% confidence interval (CI) are presented comparing secukinumab versus placebo
- Safety analyses included all patients who received at least 1 dose of study treatment

RESULTS

- Demographics and baseline clinical characteristics were comparable across treatment groups (**Table 1**). Almost all patients (96%, 160/166) completed the first 12 weeks (secukinumab: 99% [82/83] and placebo: 94% [78/83])

Efficacy

- The primary endpoint was met; adjusted mean change in GLOESS was significantly higher with secukinumab vs. placebo at Week 12, with statistical significance as early as Week 1 (**Figure 2A**)
- All key secondary endpoints were met (**Figure 2B–D**):
  - ACR20/50 responses and improvement in SPARCC enthesitis index were significantly higher with secukinumab at Week 12 vs. placebo

Safety

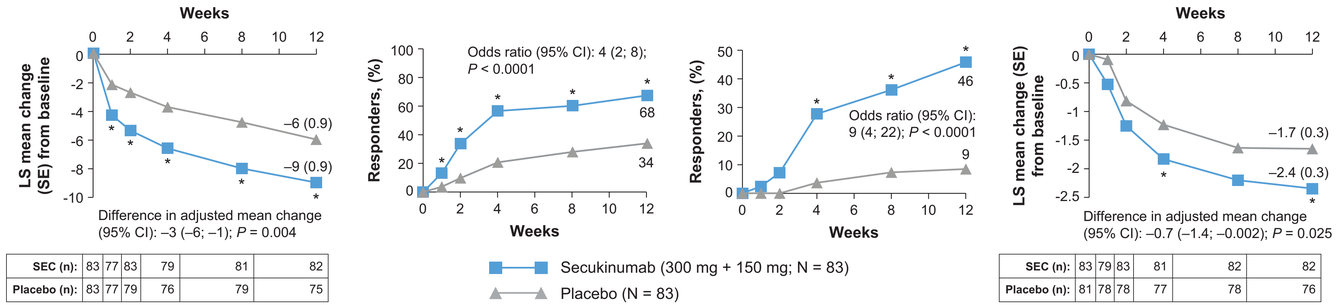
- The safety profile of secukinumab through 12 weeks was consistent with previous reports with no new or unexpected signals
  - Serious adverse events: secukinumab 0, placebo 2

Table 1. Baseline demographics and clinical characteristics

Characteristics, mean (SD) unless otherwise specified	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)
PsO (≥3% BSA), n (%)	36 (43)	33 (40)
PASI score (patients with BSA ≥3%)	9 (6)	11 (9)
SPARCC enthesitis index	4 (3)	4 (3)
Concomitant corticosteroids, n (%)	13 (16)	19 (23)
Concomitant methotrexate, n (%)	35 (42)	34 (41)
GLOESS	24 (16)	27 (17)
GLOESS synovial hypertrophy	24 (16)	27 (17)
GLOESS Power Doppler	8 (8)	7 (7)
Mean number of synovitis detected by ultrasound	9 (5)	10 (5)

BSA, body surface area; N, total number of randomized patients; PASI, Psoriasis Area and Severity Index; PsO, psoriasis; TJC, tenderness joint count; SJC, swollen joint count

Figure 2. Primary and key secondary endpoints through Week 12



SEC (n):	83	77	83	79	81	82	
Placebo (n):	83	77	79	76	79	75	

SEC (n):	83	79	83	81	82	82	
Placebo (n):	81	78	78	77	78	76	

*P < 0.05 versus placebo. Data presented as MMRM for GLOESS and SPARCC scores and NRI for ACR20/50 responses. LS, least squares; N, total number of randomized patients; n, number of evaluable patients; SEC, secukinumab

CONCLUSIONS

- ULTIMATE is the first randomized controlled trial in PsA using ultrasound to assess the time course of secukinumab on synovitis
- The use of GLOESS as the primary endpoint showed objectively significant benefit of secukinumab vs. placebo on synovitis at Week 12 with an early improvement from Week 1
- Secukinumab demonstrated superior clinical responses versus placebo on joints and enthesitis at Week 12 consistent with data from previous FUTURE and EXCEED studies[4-6]
- Safety profile of secukinumab was consistent with previous reports[7]

REFERENCES

1. D'Agostino MA *J Rheumatol* 2019;46:337–39.
2. Uson J, et al. *Rheumatol Clin* 2018;14:27–35.
3. D'Agostino MA, et al. *RMD Open* 2017;3:e000428.
4. McInnes IB, et al. *Lancet* 2015;386:1137–46.
5. Mease P, et al. *Ann Rheum Dis* 2018;77:890–97.
6. McInnes IB, et al. *Lancet* 2020;395:1496–505.
7. Deodhar A, et al. *Arthritis Res Ther* 2019;21:111.

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