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Secukinumab Efficacy on Enthesitis in Patients with Ankylosing Spondylitis: Pooled Analysis of Four Pivotal Phase 3 Studies

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Keywords

Ankylosing spondylitis, Biological therapy, Inflammation, Interleukins, Spondyloarthropathy

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Funding

This study was funded by Novartis Pharma AG, Basel, Switzerland.

Conflict of interest

G. Schett, Grant/research support from: BMS, Celgene, GSK, Lilly, Novartis, Consultant for: AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, UCB, Speakers bureau: AbbVie, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer

X. Baraliakos: Consultant for: AbbVie, BMS, Chugai, MSD, Novartis, Pfizer, UCB, Speakers bureau: AbbVie, BMS, Chugai, MSD, Novartis, Pfizer, UCB

F. Van Den Bosch: Consultant/speaker fees from: AbbVie, Bristol-Myers Squibb, Celgene, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Sanofi and UCB

A. Deodhar: Grant/research support from: AbbVie, Eli Lilly, GSK, Novartis, Pfizer and UCB, Consultant for: AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Gilead, Glaxo Smith Kline, Janssen, Novartis, Pfizer and UCB

L. Gensler: Grant/research support from: Novartis Pfizer and UCB, Consultant for: AbbVie, Gilead, GSK, Eli Lilly, Novartis, Pfizer and UCB

M Østergaard: Speaker/consultant fees from Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Gilead, Hospira, Janssen, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, and UCB, and research grants from Abbvie, Celgene, Centocor, Merck, and Novartis

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Short running head (maximum of 4 words):

Secukinumab in AS-related Enthesitis

Abstract**Objective**

To assess the efficacy of secukinumab on axial and peripheral enthesitis in patients with ankylosing spondylitis (AS) using pooled data from randomized controlled phase 3 studies.

Methods

In this post-hoc analysis, data were pooled from patients originally randomized to secukinumab 150 mg, 300 mg, or placebo from phase 3 MEASURE 1-4 studies (ClinicalTrials.gov identifiers: NCT01358175, NCT01649375, NCT02008916 and NCT02159053). Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was used for assessments of enthesitis through Week 52. Efficacy outcomes were mean change in MASES score and complete resolution (MASES=0) of enthesitis in patients with baseline MASES>0.

Results

A total of 693 (71.5%) patients had enthesitis at baseline in secukinumab 300 mg, 150 mg and placebo groups (58 [76.3%], 355 [70.4%] and 280 [72%]), respectively, out of 969 patients pooled in this analysis. At Week 16, mean change from baseline for overall MASES and enthesitis at axial MASES-sites was: secukinumab 300 mg (-2.9 [P<0.01] and -2.9 [P<0.01]); 150 mg (-2.4 [P<0.015] and -2.3 [P<0.05]), and placebo (-1.9 and -1.8), with improvements seen through Week 52. More than a third of secukinumab-treated patients (300 mg, 36.2% and 150 mg, 40.8%) achieved complete resolution of enthesitis at Week 16.

Conclusion

Secukinumab improved enthesitis at overall MASES and axial sites in patients with ankylosing spondylitis.

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Introduction

Enthesitis, inflammation of the entheses, is a hallmark feature of ankylosing spondylitis (AS, also termed as radiographic axial spondyloarthritis), a chronic and inflammatory form of arthritis. It is a distinctive pathological manifestation characterized by inflammation at the tendon, ligament, or joint capsule insertion sites to bones (1). Enthesitis is often associated with considerable pain, morning stiffness, fatigue, and impaired physical function, frequently leading to poor quality of life (2, 3).

The pathogenesis of enthesitis is not fully understood. Enthesitis is triggered by biomechanical stress or infection, which induces the activation of $\gamma\delta$ T cells and type 3 innate lymphoid cells at enthesal sites. This subsequently stimulates the production of tumor necrosis factor (TNF), interleukin (IL)-17A, and IL-23, leading to the influx and activation of neutrophils, which leads to enthesal inflammation (3, 4). This IL driven enthesitis may lead to irreversible structural damage in patients with AS (5, 6).

Enthesitis can encompass peripheral and/or axial manifestations. Peripheral enthesitis is frequently observed in the lower limbs, e.g., muscle attachments to the greater and lesser trochanters, the insertion of the quadriceps tendon at the upper patellar pole, the patellar tendon insertion on the tibial plateau and the Achilles tendon insertion into the calcaneus, while axial enthesitis sites mainly include the thoracic and lumbar spine and costosternal joints (7-9). Different indices have been developed for the clinical evaluation of enthesitis in AS, including the Mander Enthesitis Index, the Modified Mander Enthesitis Index (10), the Major Enthesitis Index (11), the Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES) (12), and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score (13).

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According to the CORRONA registry, patients with axial spondyloarthritis who suffer from enthesitis have a higher disease burden than those without enthesitis (14). Although, the prevalence of enthesitis among patients with AS ranged from 30-70%, enthesitis is often underdiagnosed in routine practice (15-17). In clinical practice, the aim of enthesitis treatment is to resolve enthesial related pain and inflammation (3). Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended first-line treatment for patients with AS and have been demonstrated to be effective in reducing inflammation and pain in peripheral enthesitis (18-21). However, as opposed to more recent onset, in patients with long-standing enthesitis NSAIDs may not adequately control the disease (3). In patients with axial spondyloarthritis who do not respond adequately or are intolerant to NSAIDs, treatment with TNF inhibitors (TNFi) is indicated and has been shown to be effective in the treatment of enthesitis. Although TNFi significantly improve the signs and symptoms in patients with AS (22-26), approximately 40-50% of patients experience either inadequate response, intolerance, or safety concerns with TNFi therapy (26-34).

Secukinumab, a human monoclonal IgG1 κ antibody that directly inhibits IL-17A, has been demonstrated to provide rapid and sustained improvement in the signs and symptoms of active AS (35-39). Secukinumab has been shown to provide rapid and sustained resolution of enthesitis in approximately 50-70% of patients with psoriatic arthritis (PsA) (40-42). However, data on the effect of secukinumab on improvement or resolution of enthesitis in patients with AS are limited. Herein, we present a *post hoc* analysis using data pooled from four phase 3 studies (MEASURE 1–4) through 52 weeks that had data available at the reporting cut-off date of 13 May 2018. The aim of

this post hoc analysis was to determine the efficacy of secukinumab versus placebo on mean change from baseline in MASES score and complete resolution of enthesitis (MASES=0) in AS patients with enthesitis at baseline.

Materials and Methods

Study design and patients

MEASURE 1 (NCT01358175) and MEASURE 4 (NCT02159053) were 2-year, while MEASURE 2 (NCT01649375) and MEASURE 3 (NCT02008916) were 5-year and 3-year, respectively, randomized, double blind, placebo-controlled phase 3 studies. The details of study designs, methods, and results have been reported previously (35-38). Detailed inclusion and exclusion criteria are listed in **supplementary table 1**. Briefly, in MEASURE 1 and MEASURE 3, patients were randomized to intravenous (IV) secukinumab 10 mg/kg or placebo at baseline, Weeks 2 and 4, followed by subcutaneous (s.c.) secukinumab 150 mg or 75 mg (MEASURE 1) or s.c. secukinumab 300 mg or 150 mg (MEASURE 3) versus matched placebo every 4 weeks (q4w) starting at Week 8. In MEASURE 2 and MEASURE 4, patients were randomized to s.c. secukinumab 150 mg or 75 mg (MEASURE 2) or s.c. secukinumab 150 mg with or without loading doses (MEASURE 4) versus matched placebo at baseline, Weeks 1, 2 and 3, and q4w starting at Week 4. In MEASURE 2–4, placebo-treated patients were re-randomized at Week 16 to s.c secukinumab q4w, regardless of clinical response, whereas in MEASURE 1, re-randomization from placebo to secukinumab occurred at Week 16 in non-responders failing to achieve ASAS20 and at Week 24 in responders (35-38). These multicenter randomized clinical trials (RCTs) were well designed and

fulfilled the CONSORT statement checklist, which comprises a minimum standard of recommendations for reporting RCTs (43).

The pooled patient population from MEASURE 1-4 studies were considered in this *post hoc* exploratory analysis. Data were pooled from patients originally randomized to secukinumab 150 mg, 300 mg (MEASURE 3 only), or placebo with enthesitis at baseline (defined as MASES >0). Patients on the same dose of secukinumab were pooled across studies, regardless of loading regimen (IV or s.c.). Analysis included all patients with baseline enthesal tenderness and/or swelling of at least 1 out of the 13 MASES sites [the bilateral first and seventh costochondral joints, the anterior and posterior superior iliac spines, the iliac crests, the proximal insertions of Achilles tendon, and the fifth lumbar spinous process (overall score range 0–13)], as well as subgroup analyses of the 11 axial enthesal sites (13 MASES sites minus 2 Achilles tendons), 6 peripheral enthesal sites (2 Achilles tendons + 4 lateral condyles of both humeri/femurs), and the 2 Achilles tendons separately (**FIGURE 1**).

All the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice guidelines. All patients signed an informed consent form that was reviewed and approved by an independent ethics committee or institutional review board (35-38). Ethics approval numbers for the main institutions are included in **supplementary table 2**.

In all the four studies, patients aged ≥ 18 years with active AS (assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 [range 0-10] at baseline) with prior documented radiological evidence (X-ray) fulfilling the modified New York

criteria for AS were included (44). Other inclusion criteria were a score of 4 or higher on the BASDAI (45), and a spinal pain score of ≥ 40 mm on a 100 mm visual analog scale (VAS), despite treatment with NSAIDs. Patients had either an inadequate response or were intolerant to not more than one TNFi agent (36, 46). Patients previously treated with not more than one TNFi were included if they had an inadequate response to an approved dosage for ≥ 3 months or were intolerant to at least one dose (hereafter collectively referred to as patients with an inadequate response to TNFi [TNFi-IR]).

Patients could continue to receive the following medications at a stable dose: sulfasalazine (≤ 3 g per day), methotrexate (7.5–25 mg per week), prednisone or equivalent (≤ 10 mg per day), and NSAIDs.

Key exclusion criteria were total spinal ankylosis, evidence of infection or cancer on chest radiography, active systemic infection within 2 weeks before the baseline visit, and previous treatment with cell-depleting therapies or biologics other than TNFi agents.

Efficacy Outcomes

In this *post hoc* analysis, the efficacy endpoints assessed at Week 52 were the mean change from baseline in MASES score and complete resolution (MASES=0) in patients with enthesitis at baseline.

Statistical analysis

A mixed-effect model for repeated measure (MMRM) analysis was done for change from baseline in MASES score for patients with enthesitis at baseline. Only patients with MASES > 0 at baseline were included in the analysis to avoid mis-representation of a potential treatment effect from the approximately 30% of patients with no enthesitis at baseline who would, therefore, be expected to have low enthesitis scores on treatment

as well. MMRM included treatment, TNFi Inadequate Responder status (Y/N), and scheduled visits as fixed effects, with baseline score and weight as co-variables. Treatment by visit and baseline by visit were included as interaction terms in the model. The effect of secukinumab 300 mg and 150 mg was analyzed using a logistic regression model for resolution of enthesitis through Week 16. Logistic regression used treatment as a factor, with baseline score and weight as covariates. These analyses were also performed for different enthesal sites (namely, overall MASES enthesal sites, at axial enthesal sites, at the Achilles tendons and at other peripheral enthesal sites). Missing values, including those due to discontinuation of study treatment, were imputed as non-response through Week 16. Data are reported as observed thereafter up to Week 52.

Results

Baseline characteristics and patient demographics

A total of 969 patients were included in this analysis, of which 693 (71.5%) patients had enthesitis at baseline (secukinumab 300 mg: 76.3% [58/76], 150 mg: 70.4% [355/504], and placebo: 72.0% [280/389]) (**FIGURE 2**). Baseline demographics were generally comparable across groups except for a higher proportion of females among the patients with enthesitis (39.7%, 39.2% and 39.6% in secukinumab 300 mg, 150 mg and placebo arms, respectively) versus patients without enthesitis (16.7%, 16.8% and 19.3% in secukinumab 300 mg, 150 mg and placebo arms, respectively). In line with the objective of this analysis, here we report data for patients with enthesitis at

baseline (**TABLE 1**). The baseline characteristics of patients without enthesitis have been presented in **supplementary table 3**.

Mean change from baseline in MASES score in patients with enthesitis at baseline

At Week 16, the mean change from baseline in MASES score for overall MASES and axial enthesal sites was higher for secukinumab 300 mg (-2.9 [95% CI: -1.84, -0.31; P <0.01] and -2.9 [95% CI: -1.76, -0.35; P <0.01]) and 150 mg (-2.4 [95% CI: -0.96, -0.11; P <0.05] and -2.3 [95% CI: -0.89, -0.10; P <0.05]) than placebo (-1.9 and -1.8), respectively. Reductions in MASES score at Achilles tendon and peripheral enthesal sites were -1.0 (95% CI: -0.61, 0.20; not significant [NS]) and -1.6 (95% CI: -0.85, 0.15; NS) for secukinumab 300 mg, -1.0 (95% CI: -0.34, 0.11; NS) and -1.3 (95% CI: -0.42, 0.15; NS) for 150 mg versus -0.8 and -1.2 for placebo. Improvements in MASES score were observed through 52 weeks, with the magnitude of response being numerically higher with secukinumab 300 mg (-3.9, -3.6, -1.3 and -2.1) than with secukinumab 150 mg (-3.5, -3.2, -1.2 and -1.9) for the overall MASES, axial enthesal sites, Achilles tendon and peripheral enthesal sites (**FIGURE 3**).

Complete resolution of enthesitis (MASES=0)

At Week 16, 36.2% (secukinumab 300 mg; 95% CI: 0.77, 2.77; NS) and 40.8% (secukinumab 150 mg; 95% CI: 1.27, 2.62; P <0.01 versus placebo) in the two secukinumab arms achieved complete resolution of enthesitis for overall MASES, with a corresponding placebo response of 28.9%. At axial enthesal sites, the response rates were 42.1% (secukinumab 300 mg; 95% CI: 0.95, 3.41; NS), 42.7% (150 mg; 95% CI: 1.29, 2.69; P <0.001) versus 30.1% (placebo). Response rates for Achilles and peripheral enthesal sites were variable and are shown in **figure 4**. At Week 52, 52.9%,

60.0%, 77.8% and 69.7% patients with secukinumab 300 mg and 56.4%, 58.6%, 78.4%^b and 65.5% patients with secukinumab 150 mg achieved complete resolution of enthesitis for the overall MASES, axial enthesal sites, Achilles tendon and peripheral enthesal sites, respectively (**FIGURE 4**).

Discussion

Biologics, such as TNFi and IL-17A inhibitors, have been shown to be effective in controlling AS-associated symptoms and are recommended by the Assessment of SpondyloArthritis international Society (ASAS) and European League Against Rheumatism (EULAR) for the management of AS (21). Enthesitis, a debilitating characteristic in patients with AS, has been associated with substantial axial and peripheral joint pain (47). Although the importance of enthesitis is acknowledged, the current knowledge on the pathogenesis and treatment of enthesitis is limited.

In various clinical trials, TNFi agents have been shown to improve enthesitis in patients with AS (22-26). However, there remains an unmet medical need for new therapeutic options, particularly in the patient population inadequately responding to TNFi therapy (26-34).

This pooled analysis from a large data set of patients from the MEASURE studies provides evidence for the efficacy of secukinumab on resolution of overall enthesitis and at axial enthesal sites in patients with AS through 52 weeks. The most commonly used clinically validated indices for the assessment of enthesitis include the MASES and SPARCC (48). In this analysis, we have used MASES to assess the resolution of enthesitis. Furthermore, to avoid diluting a treatment effect from including the approximately 30% of patients in the MEASURE studies with no enthesitis at

baseline who, therefore, cannot demonstrate improvement on treatment, only patients with MASES >0 at baseline were included in this analysis to assess for improvement over time.

Secukinumab-treated patients with enthesitis at baseline showed greater reductions in MASES, and a greater proportion of patients achieved complete resolution of enthesitis for overall MASES and at axial enthesal sites compared with placebo at Week 16, which improved through Week 52. However, the results for the Achilles tendon and other peripheral enthesal sites did not meet statistical significance for secukinumab versus placebo. Whether these results are due to ankylosing spondylitis being predominantly an axial disease, the limitations of assessments using MASES, and/or because of higher than expected placebo responses requires further research. Secukinumab has demonstrated significant and sustained resolution of enthesitis in patients with PsA (41). In addition, secukinumab has shown rapid and significant improvements in the axial manifestations of PsA (49).

The potential limitations of the current analysis include its *post hoc* nature, as well as the lack of a long-term comparator, since prolonged treatment with placebo is unethical in AS. In turn, the placebo-controlled period of the core MEASURE trials was, therefore, only up to Week 16. In addition, the number of patients and the mean disease duration were notably lower in the secukinumab 300 mg group than the 150 mg group, which limits any dose comparison. Further, the conduct of clinical trials is protocol-specified and hence subject to selection bias for inclusion/exclusion of the study population, which may not be fully reflective of real-world clinical experience for the study treatment outcomes. It also cannot be ruled-out that some of the patients who did

not have baseline enthesitis and were, therefore, excluded from the analysis could have developed enthesitis while on treatment, which would have lowered overall remission rates and increased enthesitis counts. The statistical model for this analysis did not adjust for potential confounding factors such as patient's sex which may limit the interpretation of results. In the current study, imaging confirmation of enthesitis was also not performed nor was this study designed to identify a difference between different regimens of secukinumab administration, which are additional limitations of the analysis.

In conclusion, this *post hoc* analysis demonstrated that secukinumab 300 mg and 150 mg improved enthesitis assessed by the overall MASES and at axial enthesal sites compared to placebo in patients with AS, extending the evidence for the clinical efficacy of secukinumab in patients with AS reported previously (35-38). Prospective controlled studies are needed to verify these findings. Also, the reasons for high placebo responses and variable efficacy at the assessed axial and peripheral enthesal sites warrants further research and highlights the need for a more objective assessment of enthesitis in patients with axial spondyloarthritis.

Acknowledgements

The authors thank the patients who participated in this study; the study investigators and John Gallagher, Novartis Pharmaceuticals UK Limited for valuable review. Manuscript writing support, under the guidance of all authors, was provided by Amit Agarwal and Priyanka Malla, Novartis Healthcare Pvt. Ltd, Hyderabad, India. The first draft of this manuscript was written by Priyanka Malla based on inputs from all the authors.

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Figure legends

FIGURE 1. Major enthesal sites

Overall MASES enthesal sites (13 sites), defined as: 1st costochondral (R, L) + 7th costochondral (R, L) + Posterior superior iliac spine (R, L) + Anterior superior iliac spine (R, L) + Iliac crest (R, L) + Proximal Achilles tendon (R, L) + 5th lumbar spinous process.

Achilles Tendon (2 sites), defined as: Proximal Achilles tendon (R, L)

Axial enthesal sites (11 sites), defined as: 1st costochondral (R,L) + 7th costochondral (R,L) + Posterior superior iliac spine (R, L) + Anterior superior iliac spine (R,L) + Iliac crest (R,L) + 5th lumbar spinous process.

Peripheral enthesal sites (6 sites), defined as: Proximal Achilles tendon (R, L) + Lateral epicondyle humerus (R, L) + Lateral condyle Femur (R, L).

L, left; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; N, total number of patients; R, right

FIGURE 2. Patient population of the pooled analysis from MEASURE 1-4 studies

FIGURE 3. Mean change from baseline in MASES score

§P <0.01; ‡P <0.05 versus placebo. LS Mean, and P value are from repeated measure mixed-effect model until Week 16. Observed data thereafter through Week 52 (shaded area).

LS, least squares; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; N, total number of patients; SD, standard deviation

FIGURE 4. Proportion of patients with complete resolution of enthesitis (MASES=0)

†P <0.001 ; §P <0.01; ‡P <0.05 versus placebo. P-values are from logistic regression model. NRI data were used for the analysis up to Week 16, thereafter observed data through Week 52 (shaded area).

MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; N, total number of patients; NRI, non-responder imputation

Declarations**Ethics approval and consent to participate**

This study was conducted in accordance with the principles of the Declaration of Helsinki, and all centers received approval from independent ethics committees or institutional review boards.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article, take responsibility for the integrity of the work as a whole, were involved in the drafting and critical review of the manuscript and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work.

Data Sharing Statement

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

Accepted Article

TABLE 1. Demographics and baseline patient characteristics

Variable	Secukinumab		Placebo N = 280
	300 mg N = 58	150 mg N = 355	
Female, n (%)	23 (39.7)	139 (39.2)	111 (39.6)
Age in years, mean (SD)	41.5 (11.3)	42.8 (12.1)	43.0 (12.7)
Age in years, n (%)			
<65	58 (100)	341 (96.1)	268 (95.7)
≥65	0	14 (3.9)	12 (4.3)
≥75	0	2 (0.6)	1 (0.4)
Time since AS diagnosis, years, mean (SD)	4.7 (6.6)	6.8 (8.6)	6.5 (8.1)
Total BASDAI score, mean (SD)	7.0 (1.4)	6.9 (1.4)	7.0 (1.3)
MASES, mean (SD)	5.3 (3.2)	5.1 (3.4)	5.1 (3.3)
HLA-B27, n (%)	42 (72.4)	271 (76.3)	205 (73.2)
hsCRP, median (min, max) mg/L	6.7 (0, 65)	6.7 (0, 237)	7.0 (0, 129)
Total BASMI (linear) score, mean (SD)	3.4 (1.4)	3.9 (1.7)	3.9 (1.5)
Total BASFI score, mean (SD)	6.4 (1.8)	6.3 (2.1)	6.3 (2.0)
Total ASDAS-CRP score, mean (SD)	3.6 (0.9)	3.7 (0.9)	3.8 (0.8)
Total ASDAS-ESR score, mean (SD)	3.9 (0.9)	3.9 (0.9)	3.9 (0.8)
Anti-TNF-naive, n (%)	44 (75.9)	247 (69.6)	198 (70.7)
N = total number of patients in the group with enthesitis at baseline AS, Ankylosing Spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ESR, erythrocyte sedimentation rate; hsCRP, high sensitivity C-reactive protein; HLA, human leukocyte antigen; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; max, maximum; min, minimum; SD, standard deviation; TNF, tumor necrosis factor			

Posterior superior
iliac spine

5th lumbar
spinous process

1st costochondral

7th costochondral

Lateral epicondyle Humerus

Iliac crest

Anterior superior
iliac spine

Lateral condyle Femur

Achilles tendon

B. At Achilles tendon sites

C. At axial enthesal sites

D. At peripheral enthesal sites

A. Overall MASES

■ Secukinumab 300 mg ■ Secukinumab 150 mg ■ Placebo

B. At Achilles tendon sites

■ Secukinumab 300 mg ■ Secukinumab 150 mg ■ Placebo

C. At axial entheses sites

■ Secukinumab 300 mg ■ Secukinumab 150 mg ■ Placebo

D. At peripheral entheses sites

■ Secukinumab 300 mg ■ Secukinumab 150 mg ■ Placebo