Predictors of Response to Secukinumab in Patients with Psoriatic Arthritis and Axial Manifestations: A Post-Hoc Analysis of the MAXIMISE Trial

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ORIGINAL RESEARCH

Predictors of response to secukinumab in patients with psoriatic arthritis and axial manifestations: a post-hoc analysis of the MAXIMISE trial

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ABSTRACT

Objectives To investigate patient characteristics predictive of response to secukinumab in patients with psoriatic arthritis (PsA) with axial manifestations.

Methods In a post-hoc analysis from the MAXIMISE trial (NCT02721966) in patients with PsA and axial manifestations, we tested the hypothesis that the OR of the effect of treatment on the primary endpoint of the trial (Assessment of SpondyloArthritis international Society (ASAS) 20 responder status at week 12) would be different depending on 12 prespecified predictor variables. We applied a two-model logistic regression approach, a main effects and an interaction model.

Results The OR (95% CI) for ASAS20 response for the presence of nail dystrophy was 3.2 (95% CI 0.93 to 10.99) in the secukinumab 150 mg group and 5.0 (95% CI 1.47 to 17.19) in the secukinumab 300 mg group compared with the placebo group (p=0.029). Odds of being a responder were similar in men and women in the secukinumab groups, though men fared worse than women in the placebo group (p=0.039). Current smokers were less likely to be ASAS20 responders compared with never smokers regardless of the treatment group (p=0.589).

Conclusion Nail dystrophy was identified as a predictor of response to secukinumab in patients with PsA with axial manifestations in the MAXIMISE trial. These findings may be explained by the nail-entheseal concept as part of the axial phenotype in PsA .

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Secukinumab, a fully human monoclonal anti-interleukin-17A antibody was the first biologic to demonstrate efficacy in managing the axial manifestations of psoriatic arthritis (PsA).

WHAT THIS STUDY ADDS

⇒ Nail dystrophy was identified as a predictor of response to secukinumab in patients with PsA with axial manifestations in the MAXIMISE trial.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The nail-entheseal concept as part of axial phenotype in PsA is further substantiated, linking together the multiple manifestations of PsA and may inform treatment decision-making in managing this multifaceted condition.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory musculoskeletal disorder, remarkably heterogeneous in the extent and type of tissue involvement with a consequent adverse impact on the function and quality of life of affected individuals. Axial PsA (axPsA), that is, PsA involving the axial skeleton is the only one of six disease manifestations that is still not clearly defined, with no currently available or universally accepted clinical and imaging criteria.[1–4]

MAXIMISE (Managing AXIal Manifestations in psoriatic arthritis with Secukinumab; NCT02721966) was the first randomised controlled trial (RCT) to evaluate the efficacy and safety of a biologic in managing the axial manifestations in patients with PsA with an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).[5] In MAXIMISE, secukinumab 300 mg and 150 mg demonstrated significant improvements across the primary, key secondary and secondary clinical and imaging endpoints at week 12, which were sustained through week 52. Identifying potential demographic and disease characteristics as predictors of response to therapy could have considerable clinical relevance and applicability by defining optimal personalised treatment strategies and eventually paving the way towards precision medicine.[6–9] This post hoc exploratory analysis from the MAXIMISE trial aimed to

identify potential predictors of treatment response in patients with PsA with axial manifestations treated with secukinumab.

METHODS

Study design and patients

The details of the study design (online supplemental figure) and patient inclusion and exclusion criteria have been reported previously.[5] Briefly, MAXIMISE was a phase 3b, double-blind, placebo-controlled, multicentre 52-week trial which included patients (≥18 years) diagnosed with PsA and axial manifestations (spinal pain ≥40/100 Visual Analogue Scale (VAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4) despite use of at least two NSAIDs. Patients were randomised (1:1:1) to secukinumab 300 mg, secukinumab 150 mg or placebo; at week 12, placebo patients were re-randomised to secukinumab 300 mg or 150 mg. The primary endpoint was Assessment of SpondyloArthritis international Society (ASAS) 20 response with secukinumab 300 mg at week 12.

Statistical methods

The research hypothesis aimed to determine if the OR associated with the effect of treatment on ASAS20 responder status at week 12 would be different depending on baseline predictor variables. The differential treatment effects of demographics and baseline characteristics as predictive factors of response for each treatment group were modelled by applying inferential statistics. The main analysis set comprised all patients from the Full Analysis Set assigned to study treatment, fulfilling the predefined clinical criteria for active axial disease and for whom ASAS20 data were available at week 12. Patients for whom ASAS20 response status could not be calculated for week 12 due to missing data at one or more time points were excluded from the analysis. No imputation for missing data were performed.

The following 12 predictor variables at baseline were selected by the authors as potential candidates to examine the differential treatment effects: age, body mass index (BMI), smoking status (tobacco and e-cigarettes), sex, C-reactive protein (CRP), Berlin MRI score for the spine, Berlin MRI score for the sacroiliac joints (SIJ), total back pain score (BASDAI question 2), time since first axial signs and symptoms, number of swollen joints, psoriatic nail dystrophy and radiographic evidence of juxta-articular new bone formation (table 1). Although more predictors were initially selected and ranked by the clinical authors, top 12 predictors were selected based on limits on the number of predictors using the minimum of events/non-events in the data in order to develop a reliable regression model. Further details on the statistical methods and their justification are provided as online supplemental appendices 1 and 2.

A two-model approach was applied as follows:

Table 1 Predictors for the main analysis

Predictor number	Predictor	Number of parameters to estimate
1	Treatment (secukinumab 300 mg/secukinumab 150 mg/placebo)	2
2	Patient age (years)	1
3	BMI (**<25 kg/m² / 25 kg/m²≤ × <30 kg/m² / ≥30 kg/m²**)	2
4	Smoking status (never/former/current)	2
5	Sex (male/female)	1
6	CRP (mg/L)	1
7	Berlin MRI score for spine	1
8	Berlin MRI score for SIJ	1
9	Total back pain score, VAS	1
10	Time since first axial signs and symptoms	1
11	Number of swollen joints	1
12	Psoriatic nail dystrophy (yes/no)	1
13	Radiographic evidence of new bone formation (yes/no)	1

Model 1: total number of parameters=16; Model 2: total number of parameters=44.
CRP, C-reactive protein; SIJ, sacroiliac joint; VAS, Visual Analogue Scale.

Main effects model 1: A logistic regression model was fitted to the data, which included a term for treatment group as well as terms for each of the predictor variables mentioned above. This was a no-interaction logit-additive model that assumed constancy of treatment ORs.

Interaction model 2: A second logistic regression model was fitted to the data, which included all terms from model 1 and included interaction terms between treatment group and all other predictors.

The log-likelihood of the two models was compared using a χ^2 test to determine whether the effects of treatment depend on any of the other predictors in the model. If this test provided evidence against the null hypothesis of no interaction at an alpha level of 20% (ie, p value≤0.20), then we rejected model 1 and proceeded with model 2 because it was a better fit for the data. If the p value for this comparison was >0.20, we failed to reject the null hypothesis of no interaction and proceeded with model 1. The less stringent alpha level threshold of 20% allowed for the identification of true independent predictor effects at the expense of an increase in false positive findings. Only the model selected as best fit to the data by the likelihood ratio test was examined. A forest plot of the model coefficients was presented.

Table 2 Interaction model: hypothesis tests

Variable	df	χ^2	P value
(a) Main effects and interactions			
Patient age	3	1.0576	0.7873
BMI	6	10.5217	0.1043
Smoking status	**6**	**13.3249**	**0.0382**
Sex	**3**	**6.8315**	**0.0775**
CRP	3	4.1090	0.2499
Berlin MRI score for spine	3	3.0998	0.3765
Berlin MRI score for SIJ	3	2.2458	0.5230
Total back pain score (VAS)	3	0.9507	0.8132
Time since first axial signs and symptoms	3	5.0680	0.1669
Number of swollen joints	3	1.6316	0.6522
Psoriatic nail dystrophy: yes	**3**	**10.0831**	**0.0179**
Radiographic evidence of bone formation: yes	3	1.1512	0.7647
(b) Interactions only			
Treatment×patient age	2	1.0459	0.5928
Treatment×BMI	4	8.6836	0.0695
Treatment×smoking status	**4**	**2.8195**	**0.5885**
Treatment×sex	**2**	**6.4971**	**0.0388**
Treatment×C-reactive protein	2	1.6582	0.4364
Treatment×Berlin MRI score for spine	2	3.2052	0.2014
Treatment×Berlin MRI score for SIJ	2	1.2727	0.5292
Treatment×total back pain score (VAS)	2	0.2675	0.8748
Treatment×time since first axial signs and symptoms	2	1.0479	0.5922
Treatment×number of swollen joints	2	0.7589	0.6842
Treatment×psoriatic nail dystrophy: yes	**2**	**7.0720**	**0.0291**
Treatment×radiographic evidence of bone formation: yes	2	1.0288	0.5979

BMI, body mass index; CRP, C-reactive protein; SIJ, sacroiliac joint; VAS, Visual Analogue Scale.

The present analyses did not consider the presence of three-way interactions.

The same two-model approach was applied separately for the subsets of patients with radiographic data of SIJ (available X-rays of the SIJ) and human leucocyte antigen (HLA)-B27 status data at baseline. The main effects model included terms for treatment and either radiographic or HLA-B27 status only, while the interaction model included these terms along with the interaction term between the two. For a subset of patients with available radiographic and MRI data, a separate two-model approach was applied for the composite variable of radiographic and MRI status at baseline.

The effect of all variables was presented regardless of the magnitude of their individual p values. The lower the p value, the less likely it is that the apparent subgroup effect is based on chance. As the p value decreases, the subgroup effect becomes increasingly more credible.[10] Treatment contrast plots were generated for predictor variables found to significantly interact with treatment (table 2).

RESULTS

Main analysis set (N=473)

As the likelihood ratio test p value was ≤0.2 (p=0.0804), we proceeded with model 2 (interaction model). The main logistic regression analysis of baseline variables showed evidence of differential treatment effects for nail dystrophy and sex. The OR (95% CI) for ASAS20 response for presence versus absence of nail dystrophy was 3.2 (95% CI 0.93 to 10.99) in the secukinumab 150 mg group and 5.0 (95% CI 1.47 to 17.19) in the secukinumab 300 mg group compared with the placebo group (interaction alone p=0.029; figures 1 and 2A).

Smoking had a marked effect; current smokers were less likely to be ASAS20 responders compared with subjects who never smoked (main effect and interaction

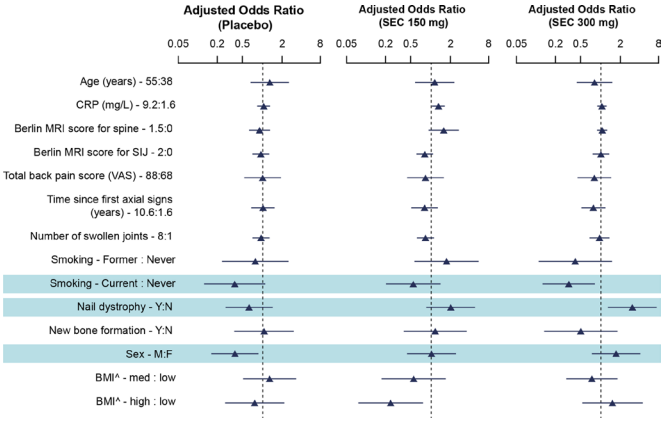

Figure 1 Interaction model: forest plots by treatment. The triangles denote adjusted OR point estimates and the bands denote 95% CIs. The vertical dashed line represents the null value, an OR of 1. An adjusted OR greater than 1 indicates a higher likelihood of being an Assessment of SpondyloArthritis international Society 20 responder. In case of continuous predictors, the IQR effect is presented, which is the average effect comparing two patients, one with a value equal to the lower quartile (25th percentile) and the other with a value equal to the upper quartile (75th percentile) of the continuous predictors distribution and who are identical in all the other predictors. Comparisons with the reference level are made for categorical factors. ^BMI categories: low: <25 kg/m^2; medium: 25 kg/m^2 to <30 kg/m^2; high: ≥30 kg/m^2. BMI, body mass index; CRP, C-reactive protein; F, female; M, male; N, no; SEC, secukinumab; SIJ, sacroiliac joint; VAS, Visual Analogue Scale; Y, Yes.

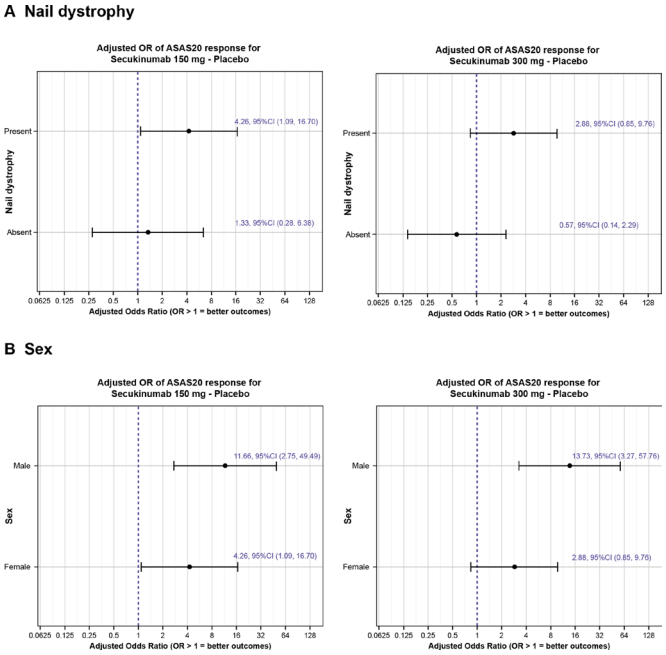

Figure 2 Treatment contrast plot (full analysis set). (A) Nail dystrophy. (B). Sex. The points denote adjusted OR point estimates and the bands denote 95% CIs. The vertical dashed line represents the null value, an OR of 1. An adjusted OR greater than 1 indicates a higher likelihood of being an ASAS20 responder. Treatment contrast point estimates and 95% CIs are presented in blue text. Other variables in the model are adjusted to the following values: age=47 years, BMI=medium, smoking status=never, sex=female for (A) and nail dystrophy at baseline=no for (B), CRP=4 mg/L, Berlin MRI score for SIJ=0.5, Berlin MRI score for spine=0.5, back pain score=78, time since first axial signs=4.1 years, number of swollen joints=4, new bone formation=no. The interaction p value from the ANOVA table is 0.029 for (A) and 0.039 for (B); this is the result of the hypothesis test assessing the interaction with treatment alone. ANOVA, analysis of variance; ASAS, Assessment of SpondyloArthritis international Society; BMI, body mass index; CRP, C-reactive protein; SIJ, sacroiliac joint.

p=0.038) irrespective of treatment group (interaction alone p=0.589).

In the secukinumab 150 mg and 300 mg treatment groups, the odds of being a responder were similar in men and women, though men fared worse than women in the placebo group (interaction alone p=0.039; figures 1 and 2B).

Baseline demographics and disease characteristics of patients stratified by nail dystrophy are shown in table 3. Mean CRP was higher in the subgroup of patients with versus without nail dystrophy (12.1 vs 7.8 mg/L), as was the proportion of patients with peripheral arthritis (86% vs 72%). Other baseline disease characteristics, including MRI positivity for the spine and SIJ, were similar across the subgroups of patients with or without nail dystrophy.

Radiographic analysis subset (N=351)

In the analyses of the radiographic subset, the log-likelihood ratio test result (p=0.69) failed to demonstrate a differential treatment effect. Subsequently, examination of the main effects-only model failed to demonstrate an effect of radiographic grade on ASAS20 response (figure 3).

HLA-B27 analysis subset (N=261)

In the HLA-B27 analysis subset, HLA-B27-positive patients in the placebo group fared worse than HLA-B27-negative patients. Similar odds of ASAS20 response were seen in the secukinumab 150 mg and 300 mg treatment groups irrespective of HLA-B27 status, with a likelihood ratio test p value of 0.13 (figure 4).

Composite radiographic and MRI status analysis subset (N=351)

In the composite radiographic and MRI status analysis subset, no differential treatment effect of the composite imaging status on ASAS20 response was observed, either using modified New York[11] or less stringent radiographic criteria (a score of ≥grade 1 on either the left or right side); all likelihood ratio test p values were >0.20 (figure 5).

DISCUSSION

In the current post hoc exploratory analysis comprising 473 patients with PsA with active axial manifestations from the MAXIMISE trial, there was evidence of a differential treatment effect in patients with nail dystrophy

Table 3 Baseline demographics and disease characteristics of patients, stratified by nail dystrophy

Variable	Total, N=498	
	Nail dystrophy present M=330	Nail dystrophy absent M=168
Demographics		
Age (years), mean (SD)	46.9 (11.6)	45.8 (12.1)
Female, n (%)	164 (49.7)	88 (52.4)
BMI (kg/m^2), mean (SD)	28.4 (5.82)	27.8 (5.24)
Smoking status		
Current	90 (27.3)	42 (25.0)
Former	50 (15.2)	26 (15.5)
Never	190 (57.6)	100 (59.5)
Disease characteristics		
CRP (mg/L), mean (SD)	12.1 (21.39)	7.8 (17.37)
Peripheral arthritis, n (%)	285 (86.4)	121 (72.0)
Spinal pain (VAS) at any time, mean (SD)	72.9 (14.05)	74.3 (14.67)
BASDAI score, mean (SD)	7.3 (1.22)	7.2 (1.31)
Positive MRI SIJ, n (%)	138 (41.8)	67 (39.9)
Positive MRI entire spine, n (%)	132 (40.0)	71 (42.3)
Positive MRI entire spine and/or SIJ, n (%)	195 (59.1)	95 (56.5)
HLA-B27 positive*, n (%)	53 (16.1)	32 (19.0)
Time since (years), mean (SD)		
First diagnosis of peripheral arthritis	5.2 (6.53)	4.7 (5.60)
First diagnosis of axPsA	3.1 (4.65)	2.9 (4.80)
Onset of back pain	7.4 (8.18)	7.7 (8.87)

N denotes the total number of patients in the randomised set and for each treatment group; n denotes the number of patients satisfying the criterion; M denotes the number of patients classified by nail dystrophy absent/present at baseline.
The BASDAI measures discomfort, pain and fatigue on a scale of 1–10 (0=no problem to 10=worst problem).
*HLA-B27 data were available only for 261/498 (52%) patients.
axPsA, axial psoriatic arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; HLA, human leucocyte antigen; SIJ, sacroiliac joint; VAS, Visual Analogue Scale.

suggesting that the presence of nail dystrophy may be a predictor of better response to secukinumab, especially for patients treated with secukinumab 300 mg.

MAXIMISE is the largest available cohort of patients with PsA and axial involvement and did not mandate MRI changes as an inclusion criterion. Therefore, this

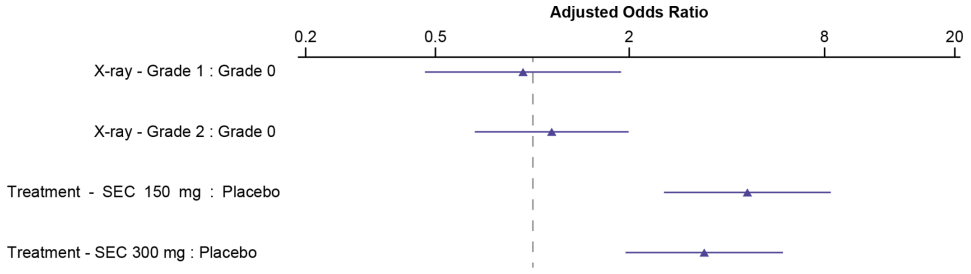

Figure 3 Model 1—radiographic subset—ASAS20 responses, week 12. Forest plot of the adjusted OR with associated 95% CI for each predictor in the model. Treatment=placebo and radiographic=grade 0 are the reference levels for the model predictors. The triangles denote adjusted OR point estimates and the bands denote 95% CIs. The vertical dashed line represents the null value, an OR of 1. An adjusted OR greater than 1 indicates a higher likelihood of being an ASAS20 responder. Comparisons with the reference level are made for categorical factors. X-ray data were categorised as follows: both 'sides' grade 0, left and/or right side ≥grade 1 and left and/or right side ≥grade 2. ASAS, Assessment of SpondyloArthritis international Society; SEC, secukinumab.

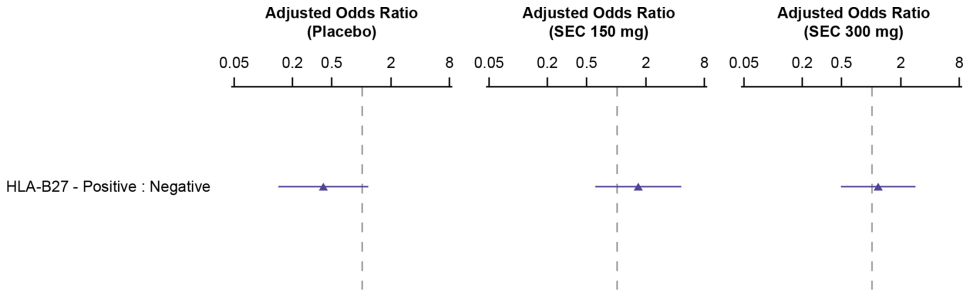

Figure 4 Model 2—HLA-B27 subset—ASAS20 responses, week 12. Forest plots of the adjusted OR with associated 95% CI. Treatment=placebo and HLA-B27=negative are the reference levels for the model predictors. The triangles denote adjusted OR point estimates and the bands denote 95% CIs. The vertical dashed line represents the null value, an OR of 1. An adjusted OR greater than 1 indicates a higher likelihood of being an ASAS20 responder. Comparisons with the reference level are made for categorical factors. ASAS, Assessment of SpondyloArthritis international Society; HLA, human leucocyte antigen; SEC, secukinumab.

is as close as possible to everyday clinical practice and, hence, is unique in providing valuable data to support deepening the clinical understanding of axPsA and identifying predictors of response to treatment. However, subgroup identification and analysis have a long and controversial history in the field of biostatistics, characterised by the issue of multiplicity and bias associated with the choice of covariates and appropriate analytical models.[10 12 13] Establishing the existence of differential treatment effects in RCTs is challenging because RCTs are typically sized just large enough to detect an overall average treatment effect, but the power is low for detecting true interactions. Although the two-model log-likelihood comparison approach used in the present study is the gold-standard frequentist method for multiplicity adjustment in subgroup analyses, caution is needed in the interpretation of the current findings[14] (online supplemental appendix 2).

The association of nail dystrophy with better treatment outcomes is clinically relevant as the nail is functionally integrated with the musculoskeletal system. Several imaging studies support the concept of the nail-enthesis unit in PsA through the attachment of the nail bed to the distal phalanx and related structures including extensor tensor and collateral ligaments with power doppler signal seen at the nail enthesis exclusively in patients with PsA,

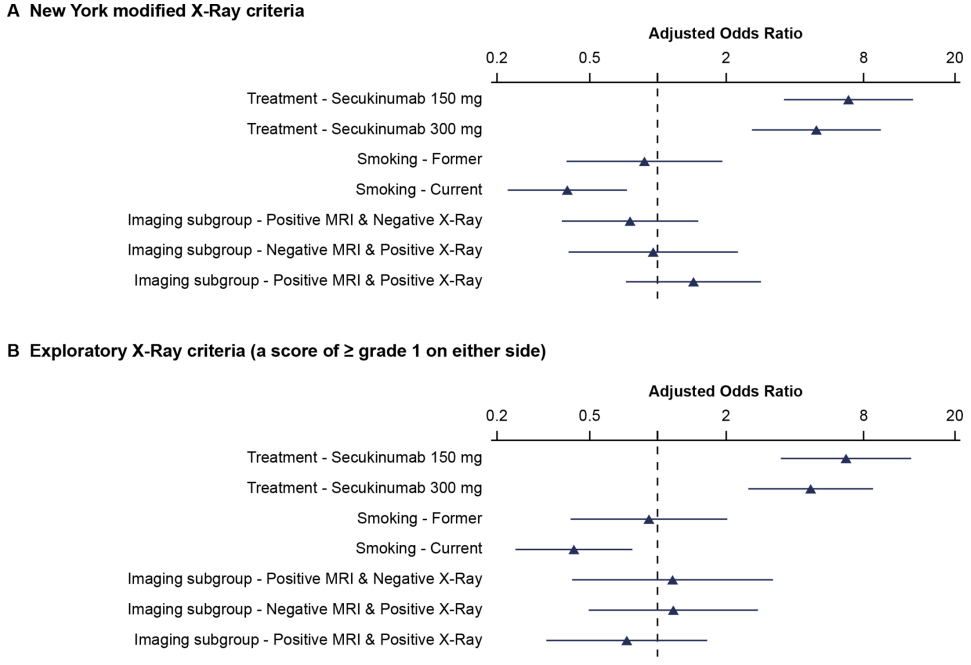

Figure 5 Forest plot of logistic regression coefficients predicting ASAS20 responders at week 12—imaging subgroup. Forest plots of the adjusted OR with associated 95% CI for each predictor in the model. Treatment=placebo, HLA–B27=negative, smoking never and imaging subgroup=negative MRI and negative X-ray are the reference levels for the model predictors. The triangles denote adjusted OR point estimates and the bands denote 95% CIs. The vertical dashed line represents the null value, an OR of 1. An adjusted OR greater than 1 indicates a higher likelihood of being an ASAS20 responder. Comparison with the reference level is made for categorical factors. The adjusted OR axis is plotted on the log scale but labelled with antilogs. ASAS, Assessment of SpondyloArthritis international Society; HLA, human leucocyte antigen.

when compared with other inflammatory or degenerative conditions.[6 15 16] In a high-resolution MRI and histological study of the nail in patients with PsA, the relationship between the extensor tendon enthesis as an integral supporting structure of the nail was confirmed with diffuse inflammation of the extensor tendon enthesis at the distal interphalangeal joint extending to the nail bed.[17] Furthermore, in a previous report with a follow-up of 10 years, nail dystrophy was found to increase the risk of developing axPsA, suggesting that the presence of nail dystrophy may point towards a primary nail-entheseal phenotype in patients with PsA with axial involvement.[18]

We did not find evidence that age, BMI, CRP, total back pain score, time since first axial signs and symptoms, number of swollen joints, radiographic evidence of juxta-articular bone formation, HLA-B27 status or objective signs of inflammation, such as Berlin MRI score for the spine or SIJ, positive X-ray at baseline or the composite radiographic and MRI status at baseline, had an effect on the achievement of the primary endpoint of ASAS20 response. The status of current smoker was associated with a poorer outcome across all treatment groups in agreement with previous reports that smoking may directly impact treatment response.[19] A potentially more severe disease in male patients might be related and explain the poorer outcomes for men only in the placebo group.

MAXIMISE was powered to detect a clinically meaningful average treatment effect and not to identify treatment effects in the subgroups. Therefore, the exploration of differential treatment effects was underpowered and hence this limitation should be taken into account when interpreting the results from a clinical perspective.

In conclusion, the presence of nail dystrophy was identified as a predictor of a better response to treatment in patients with PsA with axial manifestations. These results are consistent and support the emergent nail-entheseal concept as part of the axial phenotype in PsA.

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Contributors All authors were involved in the drafting and critical review of the manuscript and approved the final version for submission. EP was responsible for overall content as the guarantor. XB, LCC, LG and HM-O were involved in the acquisition of clinical data and participated as investigators in the clinical study. XB, EP, RW and EO were involved in the conception of the study. RW and EO were involved in the analysis of the data. All authors were involved with the interpretation of the results. All authors agreed to be accountable for all aspects of the work and attest to the accuracy and integrity of the work.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. The data sets 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 on the basis of scientific merit. All data provided is 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 by writing to the corresponding author.

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