Machine Learning and Meta-analysis of Four Phase 3 Trials

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Background: Using a machine learning approach, the study investigated if specific baseline characteristics could predict which psoriatic arthritis (PsA) patients may gain additional benefit from a starting dose of secukinumab 300 mg over 150 mg. We also report results from individual patient efficacy meta-analysis (IPM) in 2049 PsA patients from the FUTURE 2 to 5 studies to evaluate the efficacy of secukinumab 300 mg, 150 mg with and without loading regimen versus placebo at week 16 on achievement of several clinically relevant difficult-to-achieve (higher hurdle) endpoints.

Methods: Machine learning employed Bayesian elastic net to analyze baseline data of 2148 PsA patients investigating 275 predictors. For IPM, results were presented as difference in response rates versus placebo at week 16.

Results: Machine learning showed secukinumab 300 mg has additional benefits in patients who are anti–tumor necrosis factor–naïve, treated with 1 prior anti–tumor necrosis factor agent, not receiving methotrexate, with enthesitis at baseline, and with shorter PsA disease duration. For IPM, at week 16, all secukinumab doses had greater treatment effect (%) versus placebo for higher hurdle endpoints in the overall population and in all subgroups; 300-mg dose had greater treatment effect than 150 mg for all endpoints in overall population and most subgroups.

Conclusions: Machine learning identified predictors for additional benefit of secukinumab 300 mg compared with 150 mg dose. Individual patient efficacy meta-analysis showed that secukinumab 300 mg provided greater improvements compared with 150 mg in higher hurdle efficacy endpoints in patients with active PsA in the overall population and most subgroups with various levels of baseline disease activity and psoriasis.

Key Words: biologics, efficacy, interleukin, machine learning, TNF inhibitors

Secukinumab, a human immunoglobulin G1c monoclonal antibody that directly inhibits interleukin 17A, inhibits radiographic analysis and interpretation of the data. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. A.B.G. receives consulting and/or other fees from Novartis, Janssen, Eli Lilly, Beiersdorf, Abbvie, Amgen, Pfizer, BMS, UCB, Sun, Xbiotech, Leo, and Aventes. P.J.M. receives grant/research support from Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, and UCB; is a consultant to Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB; and is on speakers' bureaus of Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, and Roche. B.K. receives research grants, consultation fees, or speaker honoraria from Abbvie, BMS, Celgene, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, and UCB. P.J.M. receives grant/research support for clinical trials and honoraria for lectures and advice from Novartis, Abbvie, Roche, Pfizer, BMS, Janssen, and Celgene. A.B.C. receives research grants, consultation fees, or speaker honoraria for lectures from: Abbvie, Pfizer, MSD, Roche, UCB, Celltrion, Novartis, Sandoz, Nordic, and Lilly. B.C.C. receives consulting fee and/or is on speakers' bureaus' of BMS, AbbVie, Gilead, Janssen, Lilly, Pfizer, MSD, Novartis, Roche-Chugai, Sanofi UCB and receives research grant from Pfizer, MSD, and Roche. J.R. receives research grant from BMS, Celgene, and Novartis; is on speakers' bureau of Abbvie, BMS, Celgene, Fresenius, Medicap, MSD Novartis, Pfizer, and Roche. X.Z. is an employee of Novartis. D.J., R.M., G.L., K.A., and L.P. are shareholders and employees of Novartis.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal’s Web site (www.jclinrheum.com).

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ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000001302

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The study was sponsored by Novartis Pharma AG, Basel, Switzerland, and designed by the scientific steering committee and Novartis personnel. Medical writing support was funded by Novartis. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The data sets generated during and/or analyzed during the current study are not publicly available. Novartis is committed to sharing with qualified external researcher 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 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.

Medical writing support was provided by Suchita Dubey, scientific writer, and review support was provided by Santoshkumar Tata, senior scientific writer, Novartis, India, which was funded by Novartis in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

All authors were involved in the drafting and critical review of the manuscript and approved the final version for submission. A.B.G., P.J.M., B.K., P.N., A.B.C., B.C., and J.R. were involved in the acquisition of clinical data and participated as investigators in the clinical studies from which data are reported in the article. L.P. and K.A. were involved in the conception and design of the study. R.M., G.L., D.J., and X.Z. were involved in the statistical

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progression and has demonstrated long-term improvements in the signs and symptoms of patients with active PsA in several phase 3 trials. Subcutaneous secukinumab 150 mg and 300 mg are approved doses for the treatment of PsA worldwide, with the 300 mg starting dose recommended for patients with prior anti-tumor necrosis factor (TNF) inadequate responders (IRs) or those having moderate to severe psoriasis. For other patients, based on clinical response, the dose can be increased from 150 mg to 300 mg.

The clinical response in patients with PsA is variable because of the heterogeneous manifestations of the disease, and therefore, a better understanding of the disease characteristics of patients who would benefit from a starting dose of secukinumab 300 mg is warranted. In addition to traditionally reported high-efficacy endpoints such as American College of Rheumatology (ACR) 50, ACR70, and Psoriasis Area Severity Index (PASI) 90, several other composite clinical outcomes such as Psoriatic Arthritis Disease Activity Score—low disease activity/remission (PASDAS-LDA/REM) and minimal disease activity (MDA) are considered clinically important and patient-relevant treatment targets, which are more difficult to achieve (higher hurdle) in patients with PsA.

To simplify and substantiate the decision-making process for the clinicians in choosing the starting dose of secukinumab 300 or 150 mg, we report the results obtained through a machine learning approach in which we investigated if specific baseline clinical characteristics could predict which patients with PsA may show additional benefit with a starting dose of secukinumab 300 mg compared with 150 mg.

Because machine learning is a novel and complicated approach, therefore, to further validate results, we identified baseline variables for subgroup efficacy for secukinumab 300 mg, 150 mg load, and 150 mg without load (no-load) in achieving higher hurdle endpoints versus placebo at week 16 in patients with active PsA from four phase 3 studies: FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5. Additionally, efficacy results for secukinumab 300 mg, 150 mg load, and 150 mg no-load were evaluated in patients stratified by several baseline characteristics, such as prior anti-TNF use, use of concomitant methotrexate (MTX), baseline Disease Activity Score (DAS) 28 C-reactive protein (CRP), baseline CRP, and baseline body surface area (BSA) with psoriasis. Data from FUTURE 1 study were excluded from the present post hoc analyses specifically because present analyses were designed and conducted to demonstrate the efficacy of subcutaneously administered secukinumab.

**METHODS**

For this study, a machine learning exploratory approach was used to screen a more comprehensive set of baseline patient characteristics. Unlike traditional multivariate statistical regression methods that tend to break down when the number of predictors is relatively large or the predictors are highly correlated, machine learning techniques allow us to evaluate much larger numbers of potential highly correlated predictors. One such machine learning method is the Bayesian elastic net that extends traditional regression method by including large numbers of patient characteristics together with constraints on the magnitude of their associations with the response. These constraints effectively remove all those predictors with little or no association with the response, and by selecting the appropriate constraints, a parsimonious yet complete set of baseline characteristics associated with the response can be identified. One additional advantage of the Bayesian elastic net over other machine learning methods is that it supports statistical inferences (e.g., confidence intervals) on the coefficients of the identified predictors.

We investigated a total of 275 predictors (based on disease characteristics and interaction terms) for association with the improvement of disease signs and symptoms, and the Bayesian elastic net algorithm identified predictors for enhanced benefit of secukinumab 300 mg as a starting dose versus 150 mg from the data of 2148 patients.

The predictors thus identified were further subjected to evaluation of the treatment effect of secukinumab 300 versus 150 mg using individual patient efficacy meta-analysis (IPEM).

Individual patient efficacy meta-analysis aims to summarize the evidence on a specific clinical question from multiple related studies. The statistical implementation of an IPEM fundamentally retains the clustering of patients within studies. It facilitates standardization of analyses across studies and direct derivation of the information desired, independent of significance or how it was reported.

The IPEM included 2049 patients with PsA from four phase 3 studies; FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5. The designs and patient inclusion and exclusion criteria of the individual studies have been reported previously. Patients in each study were randomized to secukinumab and placebo at baseline. Secukinumab doses included subcutaneous 300 and 150 mg administered at baseline with loading dose at weeks 1, 2, and 3, followed by maintenance dose every 4 weeks starting at week 4; placebo group was treated similarly. For secukinumab no-load regimen (in FUTURE 4 and 5), secukinumab 150 mg was administered at baseline, with placebo at weeks 1, 2, and 3 followed by secukinumab 150 mg every 4 weeks starting at week 4. For IPEM, from a total of 2148 patients with active PsA who were originally randomized in 4 phase 3 studies (397, 414, 341, and 996 patients in FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5, respectively), data from 2049 patients receiving secukinumab 300 mg, 150 mg load, and 150 mg no-load were included in the efficacy pool for subgroup analysis. A total of 99 patients who received secukinumab 75 mg were excluded. Achievement of several clinically relevant higher hurdle endpoints with secukinumab versus placebo at week 16 was assessed in the overall population and in a subgroup analysis by prior anti-TNF use (naive and IR), concomitant MTX use (with and without MTX), baseline DAS28-CRP levels (≤5.1 [LDA and/or REM] and >5.1 [active disease]), baseline CRP levels (≤10 and >10 mg/L), and baseline BSA with psoriasis (≥23%, <10%, and ≥10%).

**Outcome Measures**

Efficacy endpoints analyzed at week 16 using machine learning included ACR20/50 response, ACR-n score (an extension of the ACR response criteria defined as the lowest of the following three values: percentage change in the number of swollen joints, percentage change in the number of tender joints, and the median of the percentage change in the other five measures, which are part of the ACR criteria), PASI 75/90 response, PASDAS (change from baseline), resolution of dactylitis and enthesitis, improvement in MDA, and Health Assessment Questionnaire–Disability Index (HAQ-DI) response and HAQ-DI score.

Individual patient efficacy meta-analysis was performed in outcomes including ACR50/70, PASI 90, PASDAS-LDA, and MDA at week 16 (placebo-controlled period) in the overall population. The ACR50, ACR70, and PASI 90 responses were also assessed in patients stratified by prior anti-TNF use, concomitant MTX use, baseline DAS28-CRP, baseline CRP, and baseline BSA with psoriasis.

**Statistical Analysis**

For analyses involving machine learning, a Bayesian elastic net algorithm was used to predict each endpoint from a set of ~40 of 275 covariates, and their interactions with treatment were
identified to form subgroups of covariates with substantial predictive power. A heatmap was used to display common predictors’ magnitude across efficacy endpoints at week 16. Missing values for binary endpoints were imputed as nonresponders.

To assess the performance of the Bayesian elastic net model, receiver operating characteristic curves were produced to quantify the trade-off between sensitivity and specificity for each modeled endpoint. The area under each receiver operating characteristic curve (AUC) was computed to summarize the overall model discriminating ability to identify subgroups (0/1) of patients for each outcome. In particular, the AUC scores at week 16 used 5-fold cross validation within FUTURE 2 to FUTURE 5 studies that randomly selected 4-fold of the entire patients to predict the fifth fold. This step was iterated 5 times to get the average. The scores ranged from 0.75 for dactylitis to a high score of 0.81 corresponding to PASI 90. The AUC scores observed with Bayesian elastic net model were higher than those observed with multivariate logistic regression (0.45 for enthesitis to 0.58 for PASI 90) (Supplementary Table 1, http://links.lww.com/RHU/A174).

For IPEM, model-based treatment effects versus placebo (%) for the meta-analysis of binary endpoints are expressed as least-squares means from logistic regression, with study, treatment, and anti-TNF status (removed when the subgroup is stratified by prior anti-TNF use) as factors and body weight as a covariate. Missing values were imputed as nonresponders.

RESULTS

For machine learning analysis, the patient population was distributed almost equally in three groups for time since diagnosis of PsA (33% patients each with time since diagnosis between 0 and 2 years, 2–7 years, and >7 years).

Of the 2049 PsA patients included in the IPEM, 461, 572, 335, and 681 patients received secukinumab 300 mg, 150 mg, 150 mg no-load, and placebo, respectively. The majority of patients completed week 24 in all treatment groups (95.7%, 94.8%, 94.0%, and 93.0% patients in secukinumab 300 mg, 150 mg load, 150 mg no-load, and placebo, respectively). Demographic and baseline characteristics were comparable across the treatment groups (Supplementary Table 2, http://links.lww.com/RHU/A174). Approximately two-thirds of patients were anti-TNF–naive (68.5%–72.8%), and approximately half (47.4%–51.9%) were receiving concomitant MTX at baseline.

Predictor Outcome Analyses by Machine Learning

No single predictor alone could identify patients who would benefit from a starting dose of secukinumab 300 versus 150 mg for the endpoints assessed. Heat map analysis showed that of 275 predictors, several predictors jointly produced adequate predictions for achieving better treatment response with secukinumab 300 versus 150 mg (Fig. 1). This figure includes only baseline predictors that were found to be associated with 2 or more endpoints (these predictors suggest a treatment difference between 300 and 150 mg among subgroups of patients). Rows depict patients’ baseline predictors (e.g., MTX use), and columns depict endpoints (e.g., ACR20). The color of each cell depicts the association between the dose-response differences (300 vs 150 mg) for each endpoint (column) among patient subgroups defined by the predictors (row) (e.g., patients with or without dactylitis at randomization). Green color depicts greater efficacy response of secukinumab 300 versus 150 mg among patients in the mentioned subgroup (e.g., patients without concomitant MTX use) than their counter subgroup (e.g., patients with concomitant MTX), red color depicts greater efficacy of secukinumab 300 versus 150 mg.

FIGURE 1. Heat map showing common predictors of response to secukinumab 300 versus 150 mg across endpoints at week 16.
150 mg among patients in the counter subgroup, and no color exhibits almost equal difference in efficacy responses of secukinumab 300 and 150 mg in the mentioned subgroup and its counter subgroup. Intensity of the color depicts the degree of association between the subgroup of patients and the efficacy outcome and is in no way related to the inefficacy of any dose.

Patients without concomitant MTX use were estimated to have better responses with secukinumab 300-mg than 150-mg dose regimens for several endpoints. The patients treated prior with one anti-TNF agent were predicted to show better improvement in HAQ-DI and PASDAS scores and ACR-n responses and higher resolution of enthesitis with secukinumab 300 mg compared with 150 mg. Similarly, the presence of enthesitis at baseline was a strong predictor of greater reduction in PASDAS score with secukinumab 300 versus 150 mg. Patients who did not use any systemic glucocorticoid achieved better PASI 90 responses with secukinumab 300 mg than 150 mg.

Covariates that demonstrated greater response for secukinumab 300 versus 150 mg in terms of improvement of disease symptoms at week 16 are shown in Supplementary Table 3, http://links.lww.com/RHU/A174. The ACR50 responses were higher in patients treated with secukinumab 300 mg who had one of the following baseline characteristics: did not use concomitant MTX or had presence of enthesitis at baseline (Fig. 2A). PASDAS-LDA, including remission (PASDAS-LDA + REM; PASDAS score <3.2) is reported as a recommended disease activity target in clinical trials. Current analysis showed that significantly higher proportions of patients treated with secukinumab 300 mg who had one of the following characteristics: no previous anti-TNF therapy (p < 0.05), no use of concomitant MTX (p < 0.01), presence of enthesitis at baseline (p < 0.001), and earlier time since PsA diagnosis (<2 or 2–7 years; p < 0.05), reached PASDAS-LDA + REM compared with secukinumab 150 mg (Fig. 2B).

FIGURE 2. Covariates that predicted a higher proportion of patients achieving (A) ACR50 and (B) PASDAS-LDA + REM with secukinumab 300 versus 150 mg. *p < 0.0001, †p < 0.001, ‡p < 0.01, §p < 0.05 versus secukinumab 150 mg. Data reported as nonresponder imputation. Data presented from estimates of logistic regression model with study, treatment, and randomization stratum (TNF status: naive or IR) as factors, baseline score and weight as a covariate. PASDAS-LDA including REM defined as PASDAS score <3.2. LS indicates least squares; N, number of evaluable patients; SF-36 MCS, Short Form-36 Mental Component Summary.
IPEM Results (Overall Population and Subgroups)

Improvements were observed with secukinumab 300-mg, 150-mg load, and 150-mg no-load regimens versus placebo for all endpoints at week 16 in the overall population (Fig. 3). Secukinumab 300 mg was associated with greater improvements as compared with both 150-mg dose regimens for all higher hurdle endpoints. Secukinumab 150-mg load had higher responses (%) in ACR50, PASI 90, and MDA responses as compared with no-load regimen at week 16.

At week 16, greater treatment effects versus placebo were observed for ACR50/70 and PASI 90 responses with all secukinumab doses in anti-TNF–naive and anti–TNF-IR patients (Fig. 4A). For all three endpoints, greater response rates were observed with secukinumab 300 mg as compared with 150-mg load and no-load regimens in anti–TNF-IR patients. Secukinumab 150-mg load showed higher responses than the 150-mg no-load regimens in anti–TNF-naive and anti–TNF-IR patients.

In patients with or without concomitant MTX use, all secukinumab regimens demonstrated greater treatment effect in ACR50/70 and PASI 90 responses versus placebo at week 16. Secukinumab 300 mg was associated with numerically higher PASI 90 response compared with 150-mg load and no-load dose regimens in patients with and without concomitant MTX. The ACR50 response was numerically similar in 300-mg and 150-mg load regimens in patients with concomitant MTX use. Secukinumab 150-mg load showed higher responses than the no-load regimen in the concomitant MTX group (Fig. 4B).

The ACR50, ACR70, and PASI 90 response rates were superior to placebo at week 16 in all dose groups analyzed by baseline DAS28-CRP, baseline CRP level, and baseline BSA with psoriasis (Figs. 5A, B and Fig. 6). Higher responses were observed for secukinumab 300 mg compared with the 150-mg dose in all subgroups for most endpoints (Figs. 5A, B and Fig. 6). Secukinumab 150-mg load showed higher responses than no-load regimen for most endpoints across subgroups (Fig. 5A, B and Fig. 6).

Pooled Safety of Secukinumab

The safety profile of secukinumab over long-term treatment (up to 5 years) in patients with PsA, psoriasis, and ankylosing spondylitis has been previously reported. The safety profile of secukinumab was consistent in the pooled population with what has been reported for individual studies of secukinumab in PsA, and no dose-response relationship was observed.

DISCUSSION

We have used machine learning approach to analyze predictors of response. Because machine learning is a novel and complicated approach, so to further validate these results, the predictors thus identified were further subjected to evaluation of the treatment effect of secukinumab 300 versus 150 mg at week 16 for clinically important endpoints, including remission in patients with active PsA using data from FUTURE 2, FUTURE 3, FUTURE 4, and FUTURE 5 studies using IPEM.

Psoriatic arthritis is a heterogeneous chronic inflammatory disease that has clinical manifestations that include peripheral arthritis, dactylitis, enthesitis, or axial involvement. It has different disease courses (e.g., mild, intermittent, or with high structural damage and disability). Considering the heterogeneity of the disease, predictors of response and remission should be identified in order to individualize the treatment and prevent further worsening of the disease.
The machine learning technique investigated whether there were specific baseline clinical characteristics that can predict which patients could gain additional benefit from the secukinumab 300-mg dose using pooled data. The performance of Bayesian elastic net model employed for predictor analysis was assessed by AUC scores. The closer the AUC score is to 1, the better the performance of the predicting model. The AUC scores ranged from 0.75 to 0.81 for various outcomes indicating the discriminatory power of the model used. The common key covariate that predicted higher response of secukinumab 300 mg over 150 mg for higher hurdle endpoints such as ACR50, PASI 90, and PASDAS (change from baseline) was presence of enthesitis at baseline. Higher responses in most of the efficacy endpoints tested were predicted to be achieved with the secukinumab 300 mg as compared with the 150-mg dose in patients with no concomitant use of MTX and patients with a diagnosis of PsA between 2 and 7 years. Patients with a diagnosis of PsA between 2 and 7 years (early PsA) and patients who have enthesitis were identified as being likely to achieve higher efficacy response rates, as assessed by PASDAS-LDA including remission when treated with secukinumab 300 mg compared with 150 mg. Similarly, patients who had enthesitis and did not use concomitant MTX at baseline were predicted to have higher ACR50 response with secukinumab 300 mg compared with the 150-mg dose.

Machine learning identified possible baseline variables where starting patients on 300-mg dose could be more beneficial than on 150 mg. These baseline variables identified via machine learning were further analyzed using subgroup analysis.

In the IPEM, all secukinumab dose regimens (300 mg, 150 mg load, and 150 mg no-load) showed superiority over placebo in improving clinical signs and symptoms and physical function in patients with PsA in the overall population. These findings are in corroboration with those reported previously. Results showed that the secukinumab 300-mg dose provided additional benefits over the 150-mg dose for higher hurdle endpoints such as ACR50/70, PASI 90, PASDAS-LDA + REM, and MDA. Similar findings were reported earlier, further substantiating the results of this analysis.

All secukinumab regimens versus placebo showed improvement in ACR50/70 and PASI 90 responses across subgroups regardless of prior anti-TNF status, use of concomitant MTX, baseline DAS-28 CRP, baseline CRP, and baseline BSA with...
Secukinumab 300 mg was associated with higher responses than the 150-mg regimens across most subgroups, particularly in TNF-IR subset and in patients with psoriasis, which is consistent with previous reports.2,3,6,7,16 Patients who did not use concomitant MTX showed greater treatment effect in ACR50 and PASI 90 responses with secukinumab 300 mg than secukinumab 150-mg dose regimens. Secukinumab 300 mg showed higher ACR50/70 and PASI 90 responses in patients with baseline DAS28 CRP levels of >5.1, baseline CRP levels of \( \leq 10 \) mg/L, and patients with \( \geq 10\% \) of baseline BSA with psoriasis in comparison to secukinumab 150-mg dose regimens.

Secukinumab 150-mg load showed higher responses than the 150-mg no-load regimen for most endpoints across the various subgroups supporting the use of the loading regimen for the achievement of more rapid responses by week 16 in line with the results previously reported in the FUTURE 5 study.7

The results of these analyses should be interpreted in light of associated limitations. It is important to understand that certain predictors may not have clinical relevance in specific patients. Therefore, meta-analysis models or machine learning techniques should not replace the medical or scientific judgment of trained professionals. The use of meta-analysis data and machine learning algorithms in combination with targeted clinical evaluations may be more effective in obtaining better treatment results and management of the disease.

**CONCLUSIONS**

Machine learning predicted additional benefit of secukinumab 300 mg over 150 mg in anti-TNF-IR patients, patients treated without concomitant MTX, and patients with psoriasis. In addition, early PsA and the presence of enthesitis were identified as predictors of PASDAS-LDA including remission that warrant further research. Individual meta-analysis of 2049 patients in four phase 3 studies showed that secukinumab 300-mg, 150-mg load, and 150-mg no-load regimens provided improvements in higher hurdle endpoints versus placebo in patients with active PsA. These results were observed in the overall population and across subgroups regardless of prior anti-TNF use, use of concomitant MTX, and various levels of baseline disease activity and BSA.

**FIGURE 5.** Treatment effect with secukinumab versus placebo by (A) baseline DAS28-CRP and (B) baseline CRP levels at week 16. The PASI 90 response was analyzed in patients with psoriasis \( \geq 3 \) BSA.
of psoriasis. Secukinumab 300 mg was associated with greater improvements compared with 150-mg dose in the overall population and in most subgroups.

ACKNOWLEDGMENTS

The authors thank the patients who participated in this study, the study investigators, and John Gallagher, Novartis Pharma AG, Basel, Switzerland.

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