Impact of Secukinumab on Patient-Reported Outcomes in Patients With Active Psoriatic Arthritis in a Randomized Phase 3 Trial

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Target journal: *The Lancet Rheumatology*

Abstract word count: 318 (maximum: 300)

Word count: 3547 (maximum: 3500)

Tables and figures: 6 (maximum: 6)

References: 34 (maximum: 30)

ABSTRACT

Background: The phase 3 FUTURE 5 trial (NCT02404350) demonstrated the clinical and radiographic efficacy of secukinumab in patients with psoriatic arthritis (PsA). This analysis evaluated its impact on patient-reported outcomes (PROs).

Methods: Patients received secukinumab 300 mg, 150 mg, 150 mg no loading dose (NL), or placebo weekly from baseline to week 4 and every 4 weeks thereafter. Mean changes from baseline and proportions of patients reporting improvements ≥ minimum clinically important differences (MCIDs) and scores ≥ normative values were determined for patient global assessments (PtGA) of disease activity, psoriasis and arthritis visual analog scale (VAS) scores, pain VAS, Health Assessment Questionnaire Disability Index (HAQ-DI), 36-item Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F), and quality of life questionnaires. Patients were stratified by prior tumor necrosis factor inhibitor (TNFi) use.

Findings: Patients in all secukinumab groups reported significantly greater improvements vs placebo in all PROs except SF-36 mental component summary (MCS), irrespective of TNFi use. Treatment responses were generally higher with secukinumab 300 mg vs 150 mg and 150 mg NL at week 16. By week 16, the proportion of overall, TNF naive, and TNF–inadequate responder patients reporting improvements ≥ MCID in PtGA (18%, 13%, 30%), pain VAS (16%, 16%, 16%), HAQ-DI (26%, 24%, 32%), and FACIT-F (20%, 15%, 31%), respectively, significantly increased, ($p<0{\cdot}0005$) relative to baseline. Patients receiving secukinumab 300 mg reported significantly shorter ($p<0{\cdot}0005$) median days to response in PtGA (9·0), pain (9·0), HAQ-DI (22·0), and FACIT-F (34·5) vs placebo. More secukinumab-treated patients reported scores ≥ normative values in PROs at week 16 vs placebo, and these improvements continued through week 104.

Interpretation: Secukinumab resulted in early, statistically significant, clinically meaningful, sustained improvements in PROs across all doses compared with placebo in patients with active PsA, irrespective of prior TNFi use. These results demonstrate secukinumab as a treatment to provide comprehensive improvement for patients with PsA, regardless of previous therapy.

Funding: Novartis Pharmaceuticals Corporation.

RESEARCH IN CONTEXT

Evidence before this study

Secukinumab is a fully human anti–interleukin 17A monoclonal antibody approved for the treatment of psoriatic arthritis (PsA). Secukinumab has shown efficacy improving clinical disease activity in all GRAPPA-OMERACT PsA core domains in randomized controlled trials (RCTs) and longitudinal observational studies. Patient-reported outcomes (PROs) are important measures for evaluating treatment effectiveness from the patient's perspective. We searched PubMed on 1 March 2021, using the terms "secukinumab," "psoriatic arthritis," "patient reported outcomes," and "tumor necrosis factor" with no language or date restrictions. In the FUTURE 2-4 trials, patients receiving secukinumab reported greater improvements in PROs at 16 or 24 weeks compared with those receiving placebo; the long-term extension of FUTURE 2 showed that improvements at week 24 were maintained at 2 years. However, the clinical significance of improvements across a wide variety of PROs resulting from secukinumab treatment in PsA has not been extensively evaluated in the context of minimal clinically important differences or relative to normative values. The effect of previous TNF inhibitor exposure on improvements in PROs in patients with PsA treated with secukinumab has not been rigorously evaluated or described.

Added value of this study

FUTURE 5 is the largest phase 3 RCT of secukinumab in patients with PsA to date. This pre-defined analysis of FUTURE 5 provides a comprehensive assessment of the impact of treatment with secukinumab 300 mg, 150 mg, and 150 mg without a loading dose on a

large number of PRO measures, in addition to a post hoc analysis stratifying patients by prior tumor necrosis factor inhibitor (TNFi) use. Statistically significant and clinically meaningful improvements were reported as early as week 1 in the secukinumab 300-mg group. Across all secukinumab dose groups, secukinumab treatment resulted in improvements in PROs ≥ minimum clinically important differences and PRO scores ≥ age- and sex-matched normative values at week 16; improvements were maintained to weeks 52 and 104, irrespective of prior TNFi experience.

Implications of all the available evidence

PROs provide unique information on the impact of PsA and its treatment from a patient frame of reference and are increasingly recognized as valuable tools when assessing treatment efficacy. Previous studies have shown that secukinumab treatment improves PROs in patients with PsA. This analysis of FUTURE 5 indicates that secukinumab treatment results in early, statistically significant, and clinically meaningful improvements across a variety of PRO measures. Taken together, results of PRO assessments in secukinumab trials in PsA indicate that secukinumab is effective for improving PsA symptoms and disease impact from a patient perspective as well as improving clinical and radiographic outcomes.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease with heterogeneous presentations that affect skin and musculoskeletal systems.[1] Clinical manifestations of PsA include peripheral arthritis, enthesitis, dactylitis, axial inflammation, and skin and nail disease[1]; these manifestations may present alone or in combination and result in significant impairments in health-related quality of life (HRQOL).[2] Patients with PsA often experience a substantial disease burden, including more bodily pain and fatigue, worse physical function, and greater work and activity impairment than the general population or patients with psoriasis alone.[3,4] To ensure patient perspectives are incorporated into the evaluation of disease burden and treatment response, the Outcome Measures in Rheumatology (OMERACT) PsA Core Domain set of outcome measures for randomized controlled trials (RCTs) and longitudinal observational studies includes patient assessments of pain, global disease activity, psoriasis and arthritis, physical function, fatigue, and HRQOL in addition to clinical disease activity measures.[5] Thus, effective treatment for PsA should improve both clinical disease activity and HRQOL.

For patients with persistently active PsA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or biologics may be necessary for disease control. In clinical practice, tumor necrosis factor inhibitors (TNFis) are often the first-choice biologic. However, data from RCTs and real-world studies show that 20%-40% of patients discontinue TNFi due to primary and/or secondary loss of effectiveness, adverse effects, or other reasons.[6] TNF–inadequate responder (IR) patients may switch to a different TNFi or to an interleukin (IL)-17, IL-12/23, or IL-23 inhibitor.[7] The head-to-head SPIRIT-H2H and EXCEED trials directly

comparing IL-17 inhibitors to TNFi suggest that IL-17 inhibitors may be used as first-line treatment in biologic-naive patients with PsA.[8,9]

Secukinumab is an IL-17A antagonist approved for the treatment of active PsA. Multiple RCTs have demonstrated the efficacy of secukinumab improving disease activity across all clinical manifestations of PsA, including PRO measures of pain, fatigue, physical function, and HRQOL.[10-13] However, improvements in PROs in PsA patients treated with secukinumab as a first- or later-line biologic has not been rigorously evaluated.

The phase 3 FUTURE 5 RCT evaluated the efficacy of secukinumab 300 mg or 150 mg with or without a loading dose for the treatment of patients with active PsA. Secukinumab treatment led to significantly greater improvements in clinical symptoms and physical function at 16 weeks and reduction in radiographic progression at 24 weeks compared with placebo[14]; these effects were sustained through week 104.[15,16] The objective of this pre-defined analysis was to evaluate the impact of secukinumab on a comprehensive set of PROs in patients with active PsA in FUTURE 5, in addition to a post-hoc analysis stratifying patients by TNFi experience.

METHODS

Study design and patient population

FUTURE 5 (NCT02404350) was a phase 3, multicenter, parallel-group RCT that evaluated the efficacy of secukinumab 300 mg, 150 mg, and 150 mg with no loading dose (NL) for improvements in clinical signs and symptoms of PsA and radiographic progression in

patients with active PsA compared to placebo. Details of the study design, treatment randomization, patient inclusion and exclusion criteria, and primary analyses have been previously described.[14-16] A post hoc analysis included patients stratified by prior TNFi use. Based on the enrollment target, 70% of randomized subjects were TNF naive and 30% were TNF-IR to ensure a representative subject population for the assessment of efficacy and safety.

Data were collected according to the Good Clinical Practice guidelines by the study investigators and all enrolled patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by institutional review boards or independent ethics committees at each participating center.

Patient-reported outcomes

PROs assessed in FUTURE 5 included patient global assessment of disease activity (PtGA), patient global assessment of psoriasis and arthritis ($PtGA_{PsO/arthritis}$), and pain on a visual analog scale (VAS; 0-100); Health Assessment Questionnaire-Disability Index (HAQ-DI; 0-3); Psoriatic Arthritis Quality of Life questionnaire (PsAQOL; 0-20); 36-item Short Form Health Survey (SF-36) physical (PCS; 0-100) and mental (MCS, 0-100) component summary and 8 individual domain scores (0-100); Dermatology Life Quality Index (DLQI; 0-30; patients with ≥3% body surface area affected by psoriasis only); and Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) (0-52). PROs were assessed at baseline and selected patient visits through week 104. Pain, PtGA, and HAQ-DI questionnaires were evaluated weekly from baseline to week 4, every 4 weeks (q4w) to week 52, every 8 weeks (q8w) to week 92, and at week 104. $PtGA_{PsO/arthritis}$ was assessed every 2 weeks from baseline to week 4, q4w to week 52, q8w to week 92, and at week 104.

SF-36 was assessed weekly from baseline to week 4, q4w to week 24, and at weeks 52, 76, and 104. DLQI, FACIT-F, and PsAQOL were evaluated q4w from baseline to week 24 and at weeks 52 and 104.

Statistical analysis

Analyses were performed in the FUTURE 5 overall, TNF naive, and TNF-IR populations and were exploratory in nature, without correcting for multiple comparisons. PROs were compared separately between patients who received secukinumab 300 mg, 150 mg, or 150 mg NL and those who received placebo through week 16 (primary endpoint). Treatment effects for improvement in PROs through week 16 were compared using least-squares mean changes from baseline calculated with observed data using mixed-model repeated measures with treatment, prior TNFi use, and analysis visit as factors; weight and baseline score as continuous covariates; and treatment by analysis visit and baseline score by analysis visit as interaction terms.

The proportion of patients reporting improvements from baseline ≥ minimum clinically important differences (MCIDs) and number needed to treat were compared in a pairwise manner with placebo using Fisher exact test through week 16 for all PROs. The proportion of patients reporting improvements ≥ MCID at weeks 52 and 104 was determined for PtGA; pain; HAQ-DI; FACIT-F; and SF-36 PCS, MCS, and domain scores. The proportions of patients reporting improvements ≥ MCID and scores ≥ established normative values were determined using non-responder imputation through week 52 and observed data thereafter through week 104. MCIDs were defined as follows: PtGA, $PtGA_{PsO/arthritis}$, and pain VAS, improvement ≥10[17-19]; HAQ-DI, reduction ≥0·35[18,20]; SF-36 PCS and MCS, improvement ≥2·5[17,18]; SF-36 0-100 scored domains, improvement ≥5·0[18]; DLQI scores of 0 or 1[21]; and FACIT-F

≥4·0.[18,22] The proportion of patients reporting scores ≥ normative values in HAQ-DI; FACIT-F; and SF-36 PCS and MCS scores and United States age- and sex-matched normative values for SF-36 domains[23-25] were determined at baseline and follow-up. Normative values for PROs were defined as follows: HAQ-DI, ≤0·25; FACIT-F, ≥40·1; and SF-36 PCS and MCS, ≥50. Normative values matched to the age and sex distribution of the FUTURE 5 protocol participants for SF-36 domains were defined as follows: physical function, ≥81·8; role-physical, ≥82·5; bodily pain, ≥72·7; general health, ≥70·2; vitality, ≥59·0; social function, ≥85·1; role-emotional, ≥88·2; and mental health, ≥76·0.

Median time to response (change from baseline in PRO scores ≥ MCID) was determined for PtGA, pain, HAQ-DI, and FACIT-F using Kaplan-Meier analysis and compared between treatment groups vs placebo using a stratified log-rank test. Due to optional rescue therapy with secukinumab at week 16 in non-responders in the placebo group, time to response analyses was truncated at week 16. Due to optional switching from placebo to secukinumab in placebo non-responders at week 16 and protocol-mandated switching of all patients in the placebo group to secukinumab at week 24, patients originally randomized to receive placebo were excluded from long-term analyses.

This study was not powered nor designed to assess differences between secukinumab doses or compare responses between TNF-naive vs TNF-IR patients. All subgroup analyses were exploratory and conducted without adjustment for multiple comparisons.

Role of the funding source

The funder participated in the study design, data collection, data analysis, interpretation of data, and review and approval of the manuscript. The corresponding author had full access to all data included in the study and had final responsibility for the decision to submit for publication.

RESULTS

A total of 996 patients were randomized to receive secukinumab 300 mg (n=222), secukinumab 150 mg (n=220), secukinumab 150 mg NL (n=222), or placebo (n=332). Of the intention-to-treat population, 697 (70%) were TNF naive and 299 (30%) TNF-IR (Table S1). The study population and patient characteristics have previously been described in detail.[14] Overall, the mean age was 48·8 years, approximately half of patients were female, and the mean time since PsA diagnosis was 6·6 years. Mean time since diagnosis was higher in TNF-IR patients than TNF-naive patients. At baseline, approximately 50% of patients were receiving methotrexate (≤25 mg/week per study protocol; Table 1; Table S1). Overall, baseline PRO scores were comparable across treatment arms and showed that patients' HRQOL was substantially impacted by their disease (Table 1). When stratified by prior TNFi use, PRO scores were worse in the TNF-IR population than in the TNF-naive population.

Patients in all secukinumab treatment groups reported clinically and statistically significantly greater improvements from baseline in all PROs except SF-36 MCS scores (300-mg group only reached significance; p=0·0417) at week 16 compared with placebo (Table 2). Overall, patients in the secukinumab 300-mg arm reported least-square mean (SE) changes from baseline of −17·9 (1·6), −27·3

(1·6), and −3·4 (0·3) in PtGA, $PtGA_{PsO/arthritis}$, and PsAQOL at week 16, respectively. Significant differences in least-squares mean changes from baseline compared with placebo in pain and HAQ-DI scores were reported as early as week 1 in the secukinumab 300-mg treatment arm and week 2 in the secukinumab 150-mg and 150-mg NL arms. Significant differences compared with the placebo group in PtGA were also observed at week 1 in the secukinumab 300-mg arm and at week 4 in the secukinumab 150-mg and 150-mg NL arms. Similar improvements were reported in TNF-naive and TNF-IR patients (Tables S2 and S3). Reported least-square mean (SE) improvements were generally higher in TNF-naive than TNF-IR patients ($PtGA_{PsO/arthritis}$, 300-mg: −29·1 [1·8] vs −27·4 [3·1]; Pain 300-mg: −22·6 [1·8] vs −21·0 [3·2]; HAQ-DI, 300-mg: −0·57 [0·04] vs −0·56 [0·07]), although TNF-IR patients reported lower placebo responses. Treatment responses were higher in the secukinumab 300-mg vs the 150-mg and 150-mg NL arms at week 16 across most PROs. Patients in all secukinumab dose groups reported higher mean scores across all SF-36 domains, which more closely approached age- and sex-matched normative values, at week 16 compared with baseline scores, with the highest scores reported in the 300-mg dose group (Figure 1).

Significantly higher proportions of overall, TNF-naive, and TNF-IR patients reported improvements ≥ MCID in HAQ-DI as early as week 1 in the secukinumab 300-mg treatment group and by week 8 in all treatment groups compared with placebo (Figure 2). The proportion of patients reporting improvements ≥ MCID in PtGA, pain VAS, and FACIT-F was significantly higher in all secukinumab groups by weeks 4 and 8, respectively, compared with the placebo group (Figure 2). The proportion of patients in the 300-mg secukinumab arm reporting improvements ≥ MCID generally increased through week 16 in PtGA (Overall, 60% vs 42% [$p<0·0001$];

TNF naive, 60% vs 47% [p=0·0126]; TNF IR, 60% vs 30% [p=0·0001]), pain VAS (Overall, 59% vs 43% [p=0·0004]; TNF naive, 63% vs 47% [p=0·0026]; TNF IR, 48% vs 32% [p=0·0375]), HAQ-DI (Overall, 62% vs 36% [p<0·0001]; TNF naive, 65% vs 41% [p<0·0001]; TNF IR, 54% vs 22% [p<0·0001]), and FACIT-F (Overall, 57% vs 37% [p<0·0001]; TNF naive, 56% vs 41% [p=0·0049]; TNF IR, 59% vs 27% [p<0·0001]). At week 16, significantly higher proportions of patients in all secukinumab dose groups reported improvements ≥ MCID across most PROs compared with placebo (Table S4; Table S5). Significantly higher proportions of secukinumab-treated patients also reported improvements ≥ MCID in most SF-36 domains at week 16 compared with placebo (Table S4; Table S5).

Time to PtGA, pain, HAQ-DI, and FACIT-F response was significantly shorter in all secukinumab treatment groups compared with placebo (Figure 3). In the secukinumab 300-mg group, the median (95% CI) time to response was 9·0 (8·0 to 15·0) days for both PtGA and pain VAS improvements ≥10 compared with 15·0 (15·0 to 22·0) days (p=0·0003) and 15·0 (10·0 to 15·0) days (p=0·0336), respectively, in the placebo group. Median (95% CI) time to HAQ-DI reduction ≥0·35 was 22·0 (15·0 to 22·0) days with secukinumab 300-mg vs 57·0 (29·0 to 91·0) days with placebo (p<0·0001). Median (95% CI) time to FACIT-F improvement ≥4·0 was 34·5 (30·0 to 57·0) days in the secukinumab 300-mg group vs 58·0 (57·0 to 85·0) days in the placebo group (p=0·0063). Similar trends in time to response were observed in the 150-mg and 150-mg NL groups.

Overall, significantly higher proportions of patients in all secukinumab dose groups reported scores ≥ normative values in HAQ-DI,

SF-36 PCS, and FACIT-F at week 16 compared with patients in the placebo group (Figure 4A). Compared to baseline, the proportion of patients who reported scores ≥ normative values at week 16 in the secukinumab 300-mg arm increased from 9% to 40% (p<0·0001) in HAQ-DI, 6% to 32% (p<0·0001) in SF-36 PCS, 38% to 48% (p=0·0965) in SF-36 MCS, and 19% to 47% (p<0·0001) in FACIT-F. This trend was also observed with regard to five SF-36 domains (physical function, role-physical, bodily pain, general health, and vitality; Figure S1). Patients receiving secukinumab 300 mg more frequently reported scores ≥ established normative values in HAQ-DI (45%, 29%), SF-36 PCS (34%, 25%), and FACIT-F (50%, 40%) scores at week 16 compared with patients receiving placebo (HAQ-DI, 12%, 3%; SF-36 PCS, 7%, 3%; FACIT-F, 22%, 13%) in both the TNF-naive and TNF-IR populations, respectively (Figure 4B, 4C). TNF-naive patients receiving secukinumab 150 mg or 150 mg NL more frequently reported scores ≥ normative values in HAQ-DI and SF-36 PCS scores at week 16 compared with patients receiving placebo.

Improvements in PROs at 16 weeks were sustained at weeks 52 and 104. The proportions of patients reporting improvements ≥ MCID in PtGA, pain, HAQ-DI, and FACIT-F increased from week 16 through week 104 (Figure S2) in all secukinumab treatment groups. Similarly, the proportion of patients reporting scores ≥ normative values in HAQ-DI, FACIT-F, and SF-36 PCS and MCS scores at weeks 52 and 104 were maintained or further increased from those at week16 (Figure S3).

DISCUSSION

In this analysis of FUTURE 5, patients treated with secukinumab reported significantly greater improvements in most PROs at week 16 than placebo. Significantly higher proportions of patients receiving secukinumab reported improvements ≥ MCID as early as week 1 in PtGA and HAQ-DI and at week 16 across all PROs except SF-36 MCS scores compared with patients receiving placebo. Additionally, times to clinically meaningful responses in PtGA, pain, HAQ-DI, and FACIT-F were significantly shorter in all secukinumab treatment groups compared with placebo. Significantly higher proportions of secukinumab-treated patients also reported scores ≥ normative values in HAQ-DI, SF-36 PCS, FACIT-F, and five SF-36 domains at week 16 vs patients receiving placebo. In general, PRO responses were greater with secukinumab 300 mg vs 150 mg and 150 mg NL. These results are consistent with the improvements in clinical and radiographic outcomes observed in the FUTURE 5 primary analysis as well as improvements in HRQOL measures reported in the FUTURE 1-4 RCTs.[12,14,26]

This study comprehensively evaluated the long-term efficacy of secukinumab improving a broad range of PROs. Our study includes an extensive selection of PROs recommended by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)-OMERACT for use in RCTs and longitudinal observational studies.[5] Previous analyses of other FUTURE trials involving secukinumab have shown improvements in PROs based on mean change from baseline; however, these do not provide information on whether the change is clinically meaningful.[13,15,27,28] In this analysis, the proportions of secukinumab-treated patients reporting improvements ≥ MCID in PtGA, pain, HAQ-DI, and FACIT-F continued from week 16 through week 104, indicating that patients experienced sustained clinically meaningful improvements across PROs with secukinumab treatment. Additionally, the proportion of patients reporting scores ≥ normative values in HAQ-DI, FACIT-F, and SF-36 PCS, MCS, and individual domains at week 104

continued or further improved from week 16. Normative values provide an objective comparison between the health state of patients with PsA vs the general population. Thus, our results indicate that secukinumab treatment resulted in improvement in PROs that more closely approach those in populations without arthritis. Taken together, the results of this analysis show that patients treated with secukinumab experienced early and clinically meaningful improvements in PROs that were sustained over 104 weeks.

Within the FUTURE 5 trial, TNF-IR patients had longer disease duration and worse baseline PRO scores than TNF-naive patients, indicative of higher disease activity and more refractory disease. Additionally, TNF-IR patients reported numerically lower placebo responses than TNF-naive patients, which is characteristic of treatment-experienced patients. Although response rates were higher in TNF-naive patients, the magnitude of response was generally similar between TNF-naive and TNF-IR patients, supporting the efficacy of secukinumab as first-line biologic therapy and as later-line therapy in patients who may have more refractory disease. Data from this analysis described similar patient characteristics seen in other recent RCTs (Table S6). Disease duration seen in the FUTURE 5 TNF-naive population (5·2-5·8 years) and the TNF-IR population (5·9-10·1 years) were similar to those seen in phase 3 studies of tofacitinib,[29] upadacitinib,[30] and ixekizumab.[31] Similarly, the proportion of TNF-naive patients (49%-56%) and TNF-IR patients (34%-58%) concurrently using methotrexate were consistent with other RCTs of upadacitinib[30] and ixekizumab.[31] Across all trials, patients reported similar magnitudes of improvement in PROs including HAQ-DI, SF-36 PCS, and SF-MCS; however, previous RCTs only enrolled patients who were IRs to biologics or csDMARDs or who were biologic naive only (Table S6). The mixed population of TNF-naive and TNF-IR patients in FUTURE 5 enabled these exploratory analyses to examine outcomes stratified by

prior TNFi use within the same RCT, which may provide better internal control from a trial design and patient composition perspective.

Differences in least-squares mean changes from baseline in SF-36 MCS and role-emotional and mental health domain scores were not statistically significant between patients treated with secukinumab vs placebo in either TNF-naive or TNF-IR patients. Baseline SF-36 MCS scores were consistently high across all subgroups of TNF-naive and TNF-IR patients, contributing to the lack of significant differences from baseline observed at week 16. However, numerical improvements in SF-36 MCS scores from baseline and increased proportions of patients reporting improvements ≥ MCID and scores ≥ normative values at week 16 suggest that secukinumab may ameliorate the psychosocial aspects of PsA. In addition to general PROs that assess pain, fatigue, and overall quality of life, disease-specific measures that include assessments of psychological impacts of PsA, such as the PsAQOL[32] and Psoriatic Arthritis Impact of Disease[33] questionnaires, may provide more comprehensive information on early treatment efficacy improving the mental and emotional burden of PsA.

This analysis provides a comprehensive assessment of the efficacy of secukinumab improving PROs in patients with PsA. FUTURE 5 is the largest phase 3 trial of secukinumab in PsA to date. In this RCT, secukinumab treatment resulted in significant improvements across a broad range of generic and disease-specific PRO measures validated by the GRAPPA-OMERACT initiative.[34] More than 50% of patients reported improvements ≥ MCID in most PROs at week 16 across all secukinumab dose groups. Additionally, up to 52% of patients who received secukinumab reported PRO scores ≥ established normative values at week 16, suggesting that achievement of PRO scores that more closely approach scores in populations without chronic illness is an attainable

goal in PsA treatment, even in TNF-naive and TNF-IR patients. Importantly, improvements in PROs were maintained or further increased at weeks 52 and 104, providing evidence of long-term efficacy of secukinumab. The results of this trial provide scientific evidence to demonstrate that secukinumab provides significant and clinically meaningful improvements in PROs and further support the use of IL-17A antagonists for comprehensive treatment of PsA.

This study was not designed to assess differences between secukinumab doses or to make statistical comparisons using the chosen MCID cutoffs; therefore, the results of this analysis should be interpretated with caution. Trials evaluating PROs are subject to the potential for patient anticipation of improvements due to initiation of new therapy, which may influence patient-reported results. PROs were assessed at scheduled follow-up visits, which may have led to an increased time to response in patients who may have reported scores consistent with responder thresholds between visits. All subgroup analyses were exploratory and conducted without adjustment for multiple comparisons. These analyses were not designed to assess differences between secukinumab doses or compare responses between TNF-naive vs TNF-IR patients.

Secukinumab resulted in early, statistically significant, and clinically meaningful improvements in PROs across all doses compared with placebo in patients with active PsA. TNF-naive and TNF-IR patients also reported significant and clinically meaningful improvements with secukinumab as a later-line therapy. Patients treated with secukinumab more frequently reported improvements ≥ MCID and scores ≥ normative values compared with those who received placebo. TNF-naive patients more frequently reported

improvements ≥ MCID and scores better than or equal to normative values vs TNF-IR patients, although TNF-IR patients had lower baseline PRO scores and reported lower placebo responses. Statistically significant and clinically meaningful improvements were reported across almost all PROs, including most SF-36 domains, at week 16, which were maintained or further increased over 52 and 104 weeks. The results of this RCT indicate that secukinumab can provide early and sustained improvements in PROs in patients with PsA and complement the clinical and radiographic benefits observed in FUTURE 5, demonstrating comprehensive improvement in the treatment of PsA regardless of line of therapy.

Data sharing

The data sets generated or analyzed during this study are not publicly available. Novartis is committed to sharing with qualified external researchers the 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 is anonymized to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. The data and study protocol may be made available on request by contacting the corresponding author of the manuscript.

Acknowledgments

This analysis was funded by Novartis Pharmaceuticals Corporation. Medical writing support was provided by Elizabeth Ohneck, PhD, and Samantha O'Dwyer, PhD, of Health Interactions, Inc, and was funded by Novartis Pharmaceuticals Corporation. This manuscript was developed in accordance with Good Publication Practice (GPP3) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, were involved in 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. VS, PH, BP, and IG conceived and designed the study. VS and BS acquired and analyzed the raw data. VS, GSK, MJB, DDG, LCC, IG, and PJM verified and interpreted the data.

Declaration of interests

V. Strand has received consulting fees from Novartis, AbbVie, Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Crescendo/Myriad, Galapagos, Genentech/Roche, Glenmark, GSK, Janssen, Lilly, Merck, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, Servier, Setpoint, and UCB. G. S. Kaeley has received consultancy fees from Novartis Pharmaceuticals Corporation.

M. J. Bergman has received consultancy fees and speakers bureau fees from AbbVie, Amgen, Bristol Myers Squibb, Genentech/Roche, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Sandoz, and Sanofi and is a shareholder of Johnson & Johnson. D. D. Gladman has received research grant support from AbbVie, Amgen, Celgene, Lilly, Novartis, Pfizer, and UCB and consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB. L. C. Coates has received grant support from AbbVie, Amgen, Celgene, Eli Lilly, Novartis, Pfizer, and UCB; consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB; and speakers bureau fees from AbbVie, Biogen, Celgene, GSK, Janssen, Lilly, Medac, Novartis, and UCB. B. Sherif is a full-time employee of RTI Health Solutions. P. Hur was an employee of Novartis at the time of this analysis and is a current employee of Pfizer, Inc. B. Parikh, and I. Gilloteau are employees of Novartis. P. J. Mease has received research grants from AbbVie, Amgen, Bristol Myers Squibb, Janssen, Lilly, Novartis, Pfizer, Sun, and UCB; consulting fees from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Sun, and UCB; and speakers bureau fees from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Genentech, Janssen, Lilly, Novartis, Pfizer, and UCB.

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Table 1. Baseline demographics and PRO scores in patients in the FUTURE 5 study population

Characteristic*	**Secukinumab 300 mg (n=222)**	**Secukinumab 150 mg (n=220)**	**Secukinumab 150 mg NL (n=222)**	**Placebo (n=332)**
Age, years	48·9 (12·8)	48·4 (12·9)	48·8 (11·8)	49·0 (12·1)
Female, n (%)	114 (51)	109 (50)	102 (46)	171 (52)
Race, n (%)				
White	184 (82·9)	178 (80·9)	180 (81·1)	274 (82·5)
Asian	24 (10·8)	29 (13·2)	27 (12·2)	33 (9·9)
American Indian or Alaska native	1 (0·5)	1 (0·5)	6 (2·7)	2 (0·6)
Black or African American	1 (0·5)	–	–	5 (1·5)
Other	12 (5·4)	12 (5·5)	7 (3·2)	16 (4·8)
Time since diagnosis, years	6·7 (8·3)	6·8 (7·1)	6·2 (6·2)	6·6 (7·6)
Prior TNFi status, n (%)				
TNFi naive	154 (69)	153 (70)	157 (71)	233 (70)

TNFi IR	68 (31)	67 (30)	65 (29)	99 (30)
Current MTX use, n (%)	113 (51)	109 (50)	123 (55)	163 (49)
PtGA disease activity, VAS 0-100	55·0 (22·8)	53·9 (22·6)	54·6 (23·5)	52·5 (22·2)
$PtGA_{PsO/arthritis}$, VAS 0-100	61·8 (21·4)	65·2 (20·9)	62·5 (22·2)	60·6 (21·7)
Pain, VAS 0-100	52·8 (24·8)	56·5 (22·8)	54·5 (22·9)	53·6 (24·5)
HAQ-DI, 0-3	1·2 (0·6)	1·3 (0·6)	1·3 (0·7)	1·3 (0·6)
PsAQOL, 0-20	9·5 (5·6)	11·1 (5·8)	10·4 (6·1)	10·0 (6·0)
SF-36 PCS, 0-100	37·1 (8·0)	36·6 (8·2)	36·3 (8·9)	36·2 (8·3)
SF-36 MCS, 0-100	45·1 (11·8)	41·6 (10·5)	43·3 (11·2)	44·0 (11·4)
SF-36 domains, 0-100				
Physical functioning	45·8 (24·4)	43·9 (26·5)	43·4 (26·4)	43·1 (26·1)
Role-physical	45·7 (22·7)	41·6 (24·3)	42·4 (25·7)	43·0 (24·6)
Bodily pain	39·9 (19·5)	37·5 (18·2)	37·7 (20·0)	38·8 (18·4)
General health	45·6 (18·9)	40·5 (17·4)	40·9 (19·2)	41·7 (18·1)
Vitality	42·5 (20·0)	38·6 (19·6)	41·2 (21·4)	40·5 (20·1)

Social functioning	63·5 (25·3)	55·6 (25·3)	59·8 (26·6)	61·6 (26·7)
Role-emotional	66·3 (28·2)	58·7 (26·5)	61·4 (27·0)	62·9 (27·5)
Mental health	61·3 (20·7)	56·5 (19·8)	58·4 (21·3)	59·7 (20·6)
BSA ≥3%, n (%)	110 (50)	125 (57)	117 (53)	162 (49)
DLQI total, 0-30[†]	10·3 (7·6)	11·7 (7·7)	11·2 (7·4)	11·0 (7·8)
FACIT-F, 0-52	29·9 (11·3)	27·0 (11·6)	28·8 (11·8)	29·4 (10·5)

BSA, body surface area; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate response; MCS, mental component summary; MTX, methotrexate; NL, no loading dose; PCS, physical component summary; PsAQOL, Psoriatic Arthritis Quality of Life questionnaire; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; TNFi, tumor necrosis factor inhibitor; VAS, visual analog scale.

* Data are presented as mean (SD) unless otherwise indicated.

[†] DLQI assessed in patients with ≥3% BSA involvement at baseline.

Table 2. LSM (SE) changes from baseline and LSM (95% CI) difference from placebo in PRO measures at 16 weeks in FUTURE 5*

PRO Measure	Secukinumab 300 mg (n=211)			Secukinumab 150 mg (n=210)			Secukinumab 150 mg, NL (n=211)			Placebo (n=300)
	LSM (SE)	Treatment contrast in LSM (95% CI)		LSM (SE)	Treatment contrast in LSM (95% CI)		LSM (SE)	Treatment contrast in LSM (95% CI)		LSM (SE)
PtGA, VAS 0-100	−17·9 (1·6)	−12·2 (−16·3, −8·1)	<0·0001	−13·9 (1·6)	−8·22 (−12·4, −4·1)	0·0001	−14·0 (1·6)	−8·3 (−12·5, −4·2)	<0·0001	−5·7 (1·4)
$PtGA_{PsO/arthritis}$, VAS 0-100	−27·3 (1·6)	−16·5 (−20·5, −12·6)	<0·0001	−22·0 (1·6)	−11·2 (−15·2, −7·2)	<0·0001	−21·1 (1·6)	−10·4 (−14·4, −6·4)	<0·0001	−10·7 (1·3)
Pain, VAS 0-100	−20·9 (1·6)	−14·3 (−18·3, −10·2)	<0·0001	−18·1 (1·6)	−11·5 (−15·6, −7·5)	<0·0001	−17·8 (1·6)	−11·3 (−15·3, −7·2)	<0·0001	−6·6 (1·3)
HAQ-DI, 0-3	−0·55 (0·03)	−0·33 (−0·42, −0·24)	<0·0001	−0·44 (0·03)	−0·23 (−0·32, −0·14)	<0·0001	−0·45 (0·03)	−0·24 (−0·33, −0·15)	<0·0001	−0·21 (0·03)
PsAQOL, 0-20	−3·4 (0·3)	−2·4 (−3·2, −1·5)	<0·0001	−3·0 (0·3)	−2·0 (−2·9, −1·2)	<0·0001	−2·7 (0·3)	−1·7 (−2·6, −0·85)	<0·0001	−1·0 (0·3)
SF-36 PCS, 0-100	7·6 (0·5)	5·7 (4·5, 7·0)	<0·0001	6·3 (0·5)	4·5 (3·2, 5·7)	<0·0001	5·9 (0·5)	4·0 (2·7, 5·3)	<0·0001	1·8 (0·4)
SF-36 MCS, 0-100	3·7 (0·6)	1·6 (0·06, 3·1)	0·0417	3·5 (0·6)	1·4 (−0·16, 2·9)	0·0788	3·6 (0·6)	1·5 (−0·05, 3·0)	0·0582	2·1 (0·5)
SF-36 domains, 0-100										
Physical functioning	20·2 (1·5)	14·1 (10·4, 17·9)	<0·0001	15·6 (1·5)	9·5 (5·8, 13·2)	<0·0001	16·6 (1·5)	10·5 (6·8, 14·2)	<0·0001	6·1 (1·2)
Role-physical	18·9 (1·5)	12·1 (8·3, 15·9)	<0·0001	15·2 (1·5)	8·4 (4·6, 12·2)	<0·0001	14·6 (1·5)	7·7 (3·9, 11·5)	<0·0001	6·8 (1·3)
Bodily pain	19·8 (1·4)	13·3 (9·8, 16·7)	<0·0001	17·6 (1·4)	11·1 (7·6, 14·6)	<0·0001	16·6 (1·4)	10·1 (6·6, 13·6)	<0·0001	6·5 (1·1)
General health	10·7 (1·1)	10·1 (7·4, 12·8)	<0·0001	9·7 (1·1)	9·2 (6·5, 11·9)	<0·0001	7·6 (1·1)	7·1 (4·4, 9·8)	<0·0001	0·5 (0·9)
Vitality	14·0 (1·3)	9·1 (5·8, 12·4)	<0·0001	13·4 (1·3)	8·5 (5·2, 11·8)	<0·0001	11·7 (1·3)	6·8 (3·5, 10·1)	<0·0001	4·9 (1·1)

Social functioning	14·3 (1·5)	9·4 (5·7, 13·1)	<0·0001	12·5 (1·5)	7·6 (3·9, 11·3)	<0·0001	11·6 (1·5)	6·7 (3·0, 10·4)	0·0004	4·9 (1·2)
Role-emotional	11·2 (1·4)	4·7 (1·1, 8·3)	0·0111	8·7 (1·4)	2·2 (−1·4, 5·8)	0·2339	10·6 (1·4)	4·1 (0·49, 7·7)	0·0261	6·5 (1·2)
Mental health	8·3 (1·2)	4·6 (1·6, 7·5)	0·0022	7·2 (1·2)	3·5 (0·57, 6·4)	0·0191	7·5 (1·2)	3·8 (0·86, 6·7)	0·0112	3·7 (1·0)
DLQI Total, 0-30[†]	−8·5 (0·5)	−6·1 (−7·5, −4·8)	<0·0001	−7·5 (0·5)	−5·1 (−6·4, −3·8)	<0·0001	−7·0 (0·5)	−4·6 (−6·0, −3·3)	<0·0001	−2·4 (0·4)
FACIT-F, 0-52	6·8 (0·6)	4·8 (3·2, 6·4)	<0·0001	6·2 (0·6)	4·2 (2·6, 5·8)	<0·0001	5·6 (0·6)	3·5 (1·9, 5·1)	<0·0001	2·0 (0·5)

BSA, body surface area; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment Of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least-squares mean; MCS, mental component summary; NL, no loading dose; PCS, physical component summary; PRO, patient-reported outcome; PsAQOL, Psoriatic Arthritis Quality of Life questionnaire; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

* LSM changes assessed in patients with measurements at both baseline and postbaseline visits.

[†] DLQI assessed in patients with ≥3% BSA involvement at baseline.

Figure 1.

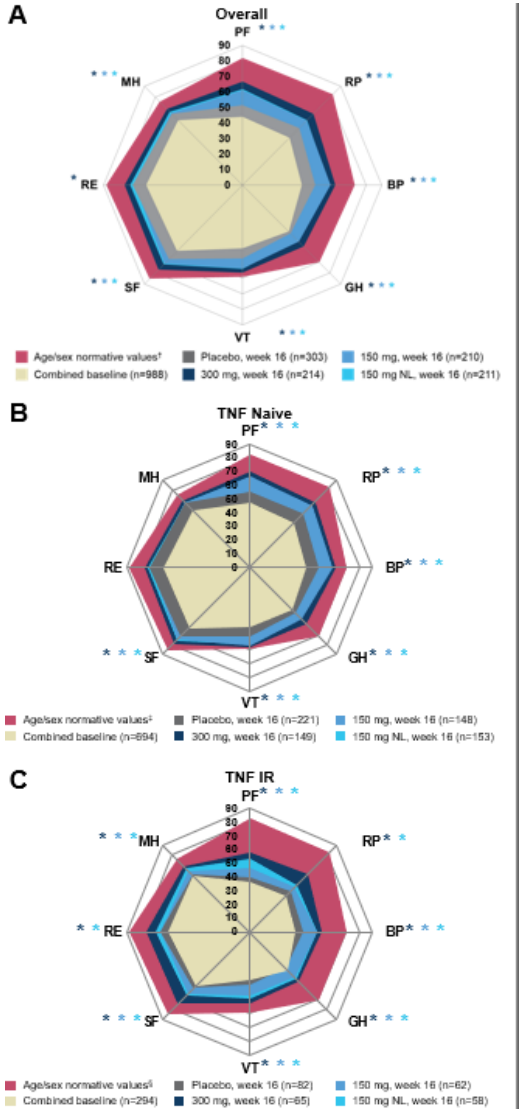

A
Overall
PF
RP
BP
GH
VT
SF
RE
MH
Age/sex normative values†
Combined baseline (n=988)
Placebo, week 16 (n=303)
300 mg, week 16 (n=214)
150 mg, week 16 (n=210)
150 mg NL, week 16 (n=211)
B
TNF Naive
Age/sex normative values‡
Combined baseline (n=694)
Placebo, week 16 (n=221)
300 mg, week 16 (n=149)
150 mg, week 16 (n=148)
150 mg NL, week 16 (n=153)
C
TNF IR
Age/sex normative values§
Combined baseline (n=294)
Placebo, week 16 (n=82)
300 mg, week 16 (n=65)
150 mg, week 16 (n=62)
150 mg NL, week 16 (n=58)

Figure 2.

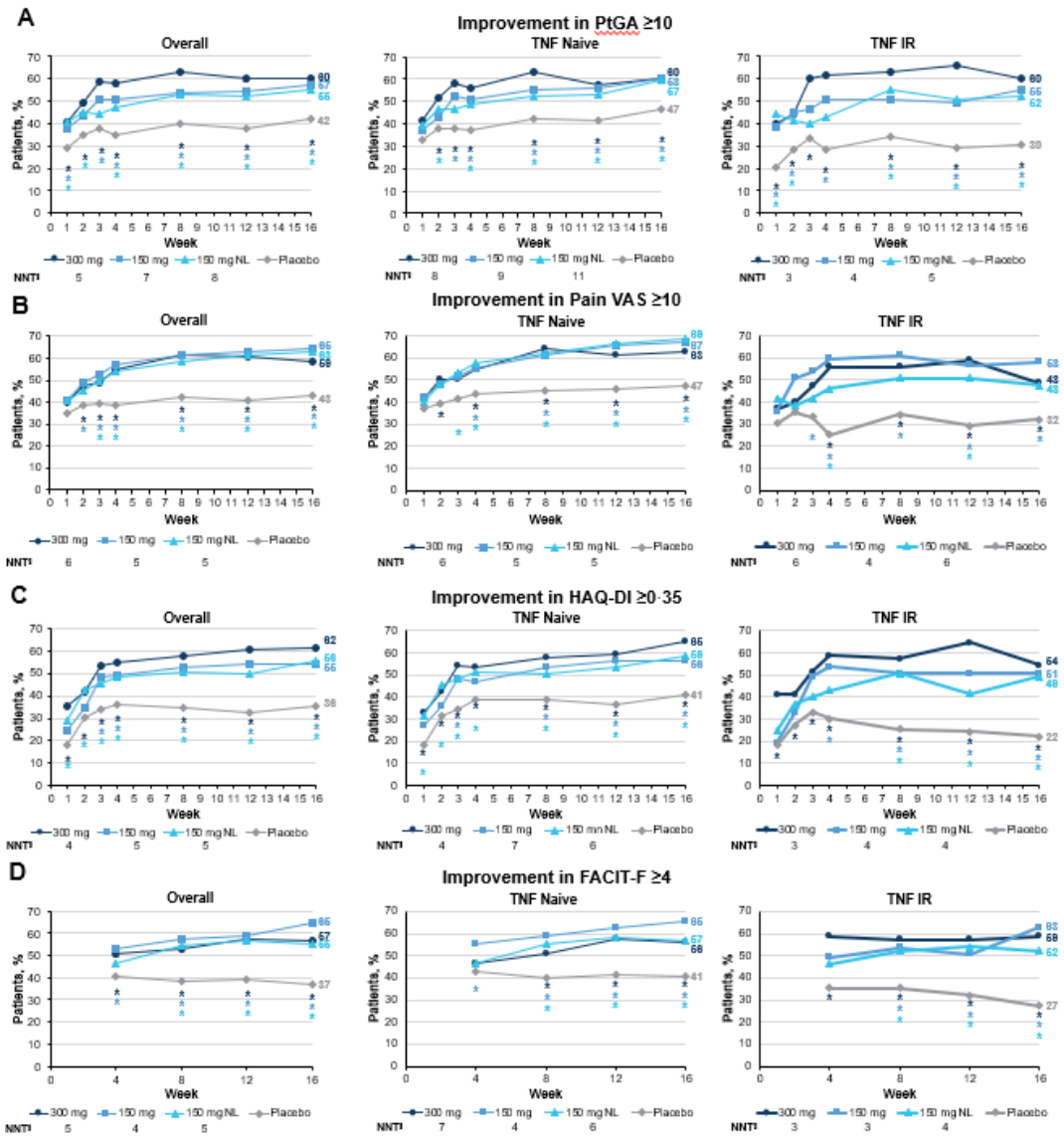

A
Improvement in PtGA ≥10
Overall
TNF Naive
TNF IR
B
Improvement in Pain VAS ≥10
Overall
TNF Naive
TNF IR
C
Improvement in HAQ-DI ≥0·35
Overall
TNF Naive
TNF IR
D
Improvement in FACIT-F ≥4
Overall
TNF Naive
TNF IR
Patients, %
Week
300 mg
150 mg
150 mg NL
Placebo
NNT‡

Figure 3.

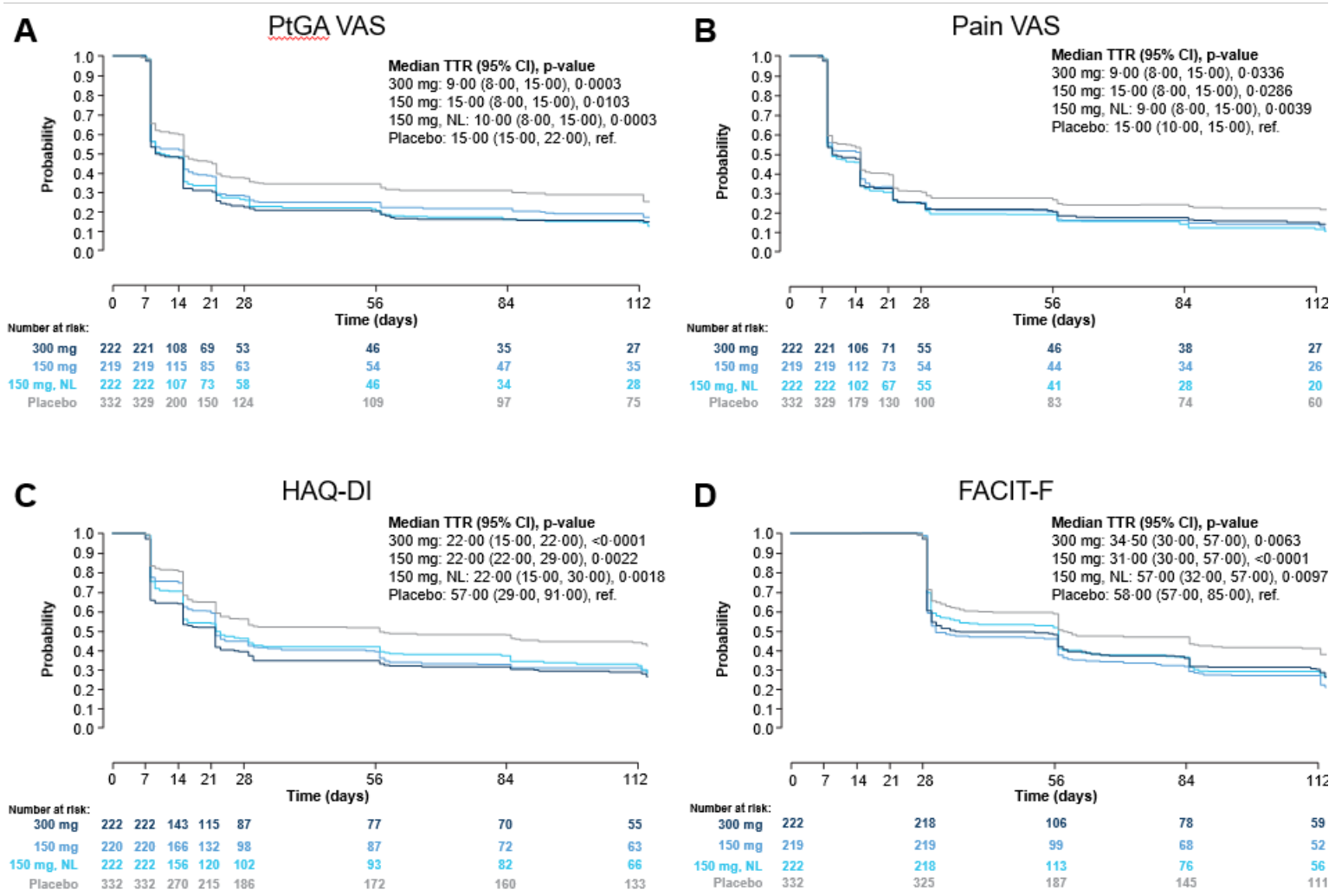
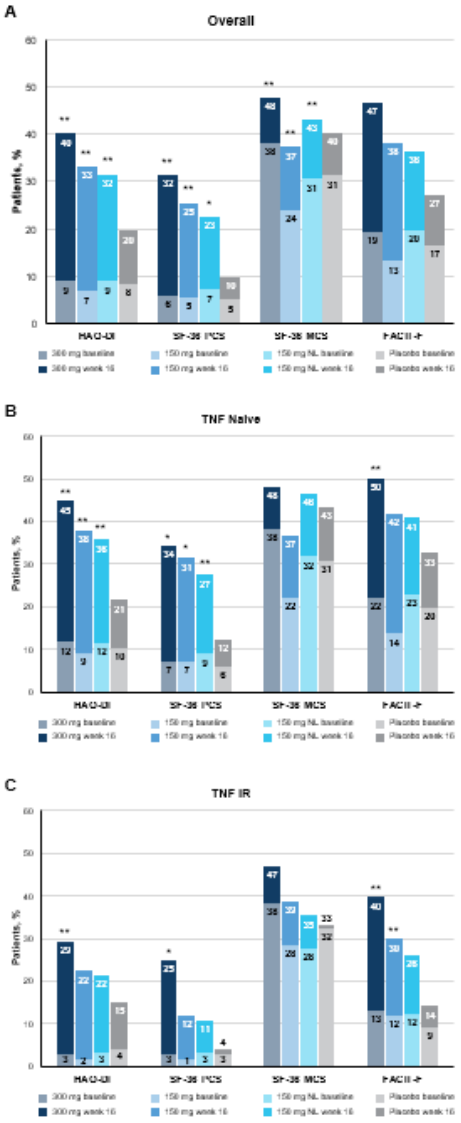

A
PtGA VAS
Median TTR (95% CI), p-value
300 mg: 9·00 (8·00, 15·00), 0·0003
150 mg: 15·00 (8·00, 15·00), 0·0103
150 mg, NL: 10·00 (8·00, 15·00), 0·0003
Placebo: 15·00 (15·00, 22·00), ref.
Probability
Time (days)
Number at risk:
300 mg 222 221 108 69 53 46 35 27
150 mg 219 219 115 85 63 54 47 35
150 mg, NL 222 222 107 73 58 46 34 28
Placebo 332 329 200 150 124 109 97 75
B
Pain VAS
Median TTR (95% CI), p-value
300 mg: 9·00 (8·00, 15·00), 0·0336
150 mg: 15·00 (8·00, 15·00), 0·0286
150 mg, NL: 9·00 (8·00, 15·00), 0·0039
Placebo: 15·00 (10·00, 15·00), ref.
Probability
Time (days)
Number at risk:
300 mg 222 221 106 71 55 46 38 27
150 mg 219 219 112 73 54 44 34 26
150 mg, NL 222 222 102 67 55 41 28 20
Placebo 332 329 179 130 100 83 74 60
C
HAQ-DI
Median TTR (95% CI), p-value
300 mg: 22·00 (15·00, 22·00), <0·0001
150 mg: 22·00 (22·00, 29·00), 0·0022
150 mg, NL: 22·00 (15·00, 30·00), 0·0018
Placebo: 57·00 (29·00, 91·00), ref.
Probability
Time (days)
Number at risk:
300 mg 222 222 143 115 87 77 70 55
150 mg 220 220 166 132 98 87 72 63
150 mg, NL 222 222 156 120 102 93 82 66
Placebo 332 332 270 215 186 172 160 133
D
FACIT-F
Median TTR (95% CI), p-value
300 mg: 34·50 (30·00, 57·00), 0·0063
150 mg: 31·00 (30·00, 57·00), <0·0001
150 mg, NL: 57·00 (32·00, 57·00), 0·0097
Placebo: 58·00 (57·00, 85·00), ref.
Probability
Time (days)
Number at risk:
300 mg 222 218 106 78 59
150 mg 219 219 99 68 52
150 mg, NL 222 218 113 76 56
Placebo 332 325 187 145 111

Figure 4.



Supplementary Materials

Table S1. Baseline demographics and PRO scores in patients in the FUTURE 5 study population stratified by prior TNFi use

	TNF Naive				TNF IR			
Characteristic*	**300 mg (n=154)**	**150 mg (n=153)**	**150 mg NL (n=157)**	**Placebo (n=233)**	**300 mg (n=68)**	**150 mg (n=67)**	**150 mg NL (n=65)**	**Placebo (n=99)**
Age, years	47·1 (11·5)	47·4 (13·2)	48·3 (12·1)	48·2 (11·7)	52·7 (11·8)	50·7 (11·9)	50·3 (14·3)	50·9 (12·9)
Female, n (%)	73 (47)	76 (50)	73 (47)	117 (50)	29 (45)	33 (49)	41 (60)	54 (55)
Race, n (%)								
White	134 (87·0)	123 (80·4)	130 (82·8)	192 (82·4)	50 (73·5)	55 (82·1)	50 (76·9)	82 (82·8)
Asian	16 (10·4)	22 (14·4)	16 (10·2)	28 (12·0)	8 (11·8)	7 (10·4)	11 (16·9)	5 (5·1)
American Indian or Alaska native	–	–	4 (2·5)	1 (0·4)	1 (1·5)	1 (1·5)	2 (3·1)	1 (1·0)
Black or African American	–	–	–	2 (0·9)	1 (1·5)	–	–	3 (3·0)
Unknown	–	–	2 (1·3)_	2 (0·9)	–	–	–	–
Other	4 (2·6)	8 (5·2)	5 (3·2)	8 (3·4)	8 (11·8)	4 (6·0)	2 (3·1)	8 (8·1)
Time since diagnosis, years	5·8 (6·2)	5·7 (6·6)	5·2 (6·9)	5·5 (7·6)	7·1 (5·9)	9·2 (7·7)	10·1 (10·1)	9·2 (6·8)
Current MTX use, n (%)	85 (54)	86 (56)	80 (52)	115 (49·4)	38 (58)	23 (34·3)	33 (49)	41 (41·4)
PtGA disease activity, VAS 0-100	52·6 (22·6)	52·6 (22·7)	52·3 (23·9)	52·0 (22·2)	60·5 (22·3)	56·9 (22·3)	60·1 (21·8)	53·8 (22·2)
$PtGA_{PsO/arthritis}$, VAS 0-100	59·2 (21·4)	63·8 (20·2)	60·5 (22·7)	59·1 (20·6)	67·9 (20·4)	68·5 (22·1)	67·3 (20·4)	64·3 (23·8)
Pain, VAS 0-100	50·6 (24·6)	54·4 (23·6)	53·4 (22·9)	52·2 (24·6)	57·9 (24·4)	61·1 (20·2)	57·3 (22·8)	57·0 (24·2)
HAQ-DI, 0-3	1·1 (0·6)	1·2 (0·6)	1·2 (0·7)	1·2 (0·6)	1·5 (0·6)	1·5 (0·6)	1·4 (0·6)	1·4 (0·6)
PsAQOL, 0-20	9·4 (5·7)	10·6 (5·8)	10·2 (6·3)	9·7 (6·0)	9·8 (5·9)	12·0 (5·6)	10·8 (5·8)	10·9 (5·9)
SF-36 PCS, 0-100	38·4 (7·9)	37·9 (7·9)	37·2 (5·5)	37·3 (8·3)	34·1 (7·5)	33·6 (8·1)	33·9 (8·6)	33·8 (7·7)
SF-36 MCS, 0-100	44·8 (12·0)	41·5 (10·3)	43·9 (11·4)	44·6 (10·9)	45·6 (11·6)	42·0 (11·0)	42·1 (10·9)	42·6 (12·4)
SF-36 domains, 0-100								
Physical functioning	49·7 (24·1)	47·9 (26·0)	45·6 (26·7)	45·5 (26·2)	37·2 (22·8)	34·8 (25·5)	37·9 (25·0)	37·4 (25·1)
Role-physical	48·4 (22·2)	43·6 (24·1)	45·6 (25·4)	45·9 (24·0)	39·6 (23·0)	36·8 (24·2)	34·7 (25·0)	36·1 (24·7)
Bodily pain	42·6 (20·1)	39·5 (17·6)	39·9 (19·9)	41·1 (18·8)	33·6 (16·6)	32·9 (18·7)	32·5 (19·5)	33·3 (16·4)
General health	45·9 (19·0)	41·4 (16·0)	41·9 (19·9)	43·6 (17·9)	45·1 (19·1)	38·5 (20·1)	38·4 (17·6)	37·2 (17·9)
Vitality	44·0 (20·2)	41·0 (18·8)	43·6 (21·9)	43·6 (19·9)	39·0 (19·2)	33·0 (20·6)	35·5 (19·2)	33·1 (18·8)
Social functioning	64·5 (24·5)	57·6 (24·3)	62·7 (26·6)	63·2 (25·6)	61·0 (27·1)	50·9 (27·1)	52·7 (25·6)	57·7 (29·0)
Role-emotional	66·4 (28·2)	58·6 (25·9)	62·9 (26·7)	64·8 (25·6)	66·0 (28·5)	59·1 (27·9)	57·7 (27·7)	58·3 (31·3)
Mental health	61·3 (21·0)	56·1 (19·2)	58·9 (21·0)	60·4 (19·7)	61·3 (20·2)	57·3 (21·0)	57·5 (22·2)	58·1 (22·6)
BSA ≥3%, n (%)	75 (49)	94 (61)	92 (59)	115 (49)	35 (51)	31 (46)	25 (38)	47 (47)
DLQI total, 0-30[†]	9·2 (6·8)	11·5 (7·5)	10·9 (7·2)	9·8 (7·1)	12·8 (8·7)	12·3 (8·5)	12·5 (8·0)	14·2 (8·6)
FACIT-F, 0-52	30·8 (11·2)	28·4 (10·8)	30·0 (11·7)	30·8 (10·4)	27·9 (11·2)	23·8 (12·9)	25·8 (11·6)	25·9 (10·3)

BSA, body surface area; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate response; MCS, mental component summary; MTX, methotrexate; NL, no loading dose; PCS, physical component summary; PsAQOL, Psoriatic Arthritis Quality of Life questionnaire; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; TNF, tumor necrosis factor; VAS, visual analog scale.

* Data are presented as mean (SD) unless otherwise indicated.

[†] DLQI assessed in patients with ≥3% BSA involvement at baseline.

Table S2. LSM (SE) changes from baseline and LSM (95% CI) changes from placebo in PRO measures at 16 weeks in TNF-naive patients in FUTURE 5*

PRO Measure	300 mg (n=154)			150 mg (n=153)			150 mg NL (n=157)			Placebo (n=233)
	LSM (SE)	Treatment contrast in LSM (95% CI)	p value vs placebo	LSM (SE)	Treatment contrast in LSM (95% CI)	p value vs placebo	LSM (SE)	Treatment contrast in LSM (95% CI)	p value vs placebo	LSM (SE)
PtGA disease activity, VAS 0-100	−18·7 (1·9)	−10·1 (−15·0, −5·3)	<0·0001	−14·9 (1·9)	−6·4 (−11·2, −1·5)	0·0101	−15·8 (1·9)	−7·3 (−12·1, −2·5)	0·0030	−8·5 (1·6)
PtGAPsO/arthritis, VAS 0-100	−29·1 (1·8)	−15·3 (−19·9, −10·8)	<0·0001	−24·1 (1·8)	−10·3 (−14·9, −5·7)	<0·0001	−23·7 (1·8)	−9·9 (−14·5, −5·4)	<0·0001	−13·7 (1·5)
Pain, VAS 0-100	−22·6 (1·8)	−12·9 (−17·4, −8·3)	<0·0001	−20·9 (1·8)	−11·2 (−15·8, −6·7)	<0·0001	−21·6 (1·8)	−11·9 (−16·4, −7·4)	<0·0001	−9·7 (1·5)
HAQ-DI, 0-3	−0·57 (0·04)	−0·28 (−0·38, −0·18)	<0·0001	−0·47 (0·04)	−0·19 (−0·29, −0·09)	0·0002	−0·49 (0·04)	−0·21 (−0·31, −0·11)	<0·0001	−0·28 (0·03))
PsAQOL, 0-20	−3·6 (0·4)	−1·9 (−2·9, −0·93)	0·0001	−3·6 (0·4)	−1·9 (−2·8, −0·88)	0·0002	−3·3 (0·4)	−1·6 (−2·6, −0·61)	0·0014	−1·7 (0·3))
SF-36 PCS, 0-100	8·2 (0·6)	5·6 (4·1, 7·1)	<0·0001	7·4 (0·6)	4·8 (3·3, 6·2)	<0·0001	6·7 (0·6)	4·1 (2·6, 5·5)	<0·0001	2·6 (0·5)
SF-36 MCS, 0-100	3·7 (0·7)	0·78 (−0·94, 2·5)	0·3724	4·0 (0·7)	1·0 (−0·72, 2·7)	0·2524	3·4 (0·7)	0·48 (−1·23, 2·2)	0·5829	3·0 (0·5)
SF-36 domains, 0-100										
Physical functioning	21·4 (1·7)	12·5 (8·2, 16·9)	<0·0001	18·5 (1·7)	9·6 (5·3, 14·0)	<0·0001	18·6 (1·7)	9·7 (5·4, 14·0)	<0·0001	8·9 (1·4))
Role-physical	19·6 (1·7)	10·5 (6·0, 14·9)	<0·0001	19·0 (1·7)	9·9 (5·5, 14·3)	<0·0001	16·8 (1·7)	7·6 (3·3, 12·0)	0·0006	9·1 (1·4))
Bodily pain	21·3 (1·6)	13·0 (9·0, 16·9)	<0·0001	19·9 (1·6)	11·6 (7·6, 15·5)	<0·0001	18·6 (1·5)	10·3 (6·4, 14·2)	<0·0001	8·3 (1·3))
General health	13·0 (1·2)	10·5 (7·5, 13·6)	<0·0001	11·3 (1·2)	8·9 (5·8, 11·9)	<0·0001	8·5 (1·2)	6·0 (3·0, 9·0)	0·0001	2·5 (1·0))
Vitality	14·6 (1·5)	8·3 (4·5, 12·0)	<0·0001	14·9 (1·5)	8·6 (4·8, 12·4)	<0·0001	12·1 (1·5)	5·8 (2·0, 9·5)	0·0026	6·3 (1·2))
Social functioning	14·5 (1·6)	7·0 (2·8, 11·1)	0·0011	14·4 (1·6)	6·8 (2·6, 11·0)	0·0014	12·2 (1·6)	4·6 (0·46, 8·7)	0·0296	7·6 (1·3))
Role-emotional	11·4 (1·6)	3·5 (−0·64, 7·6)	0·0972	10·6 (1·6)	2·7 (−1·4, 6·9)	0·1976	10·7 (1·6)	2·8 (−1·3, 6·9)	0·1780	7·9 (1·3))
Mental health	8·9 (1·3)	2·8 (−0·59, 6·2)	0·1054	8·6 (1·3)	2·4 (−0·97, 5·9)	0·1601	8·0 (1·3)	1·9 (−1·5, 5·3)	0·2731	6·1 (1·1))
DLQI total, 0-30†	−8·4 (0·6)	−5·4 (−6·9, −3·9)	<0·0001	−7·6 (0·5)	−4·6 (−6·0, −3·3)	<0·0001	−6·8 (0·5)	−3·8 (−5·2, −2·4)	<0·0001	−3·0 (0·5)
FACIT-F, 0-52	7·2 (0·7)	3·7 (1·9, 5·5)	<0·0001	7·1 (0·7)	3·6 (1·8, 5·4)	<0·001	6·1 (0·7)	2·6 (0·80, 4·3)	0·0045	3·5 (0·6))

BSA, body surface area; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate response; LSM, least-squares mean; MCS, mental component summary; NL, no loading dose; PCS, physical component summary; PsAQOL, Psoriatic Arthritis Quality of Life questionnaire; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; TNF, tumor necrosis factor; VAS, visual analog scale.

* LSM changes assessed in patients with measurements at both baseline and postbaseline visits.

† DLQI assessed in patients with ≥3% BSA involvement at baseline.

Table S3. LSM (SE) changes from baseline and LSM (95% CI) changes from placebo in PRO measures at 16 weeks in TNF-IR patients in FUTURE 5*

PRO Measure	300 mg (n=68)			150 mg (n=67)			150 mg NL (n=65)			Placebo (n=99)
	LSM (SE)	Treatment contrast in LSM (95% CI)	p value vs placebo	LSM (SE)	Treatment contrast in LSM (95% CI)	p value vs placebo	LSM (SE)	Treatment contrast in LSM (95% CI)	p value vs placebo	LSM (SE)
PtGA disease activity, VAS 0-100	−19·0 (3·1)	−17·7 (−25·8, −9·7)	<0·0001	−14·5 (3·1)	−13·2 (−21·3, −5·2)	0·0014	−12·7 (3·2)	−11·4 (−19·6, −3·2)	0·0068	−1·3 (2·7)
PtGAPsO/arthritis, VAS 0-100	−27·3 (3·1)	−20·2 (−28·2, −12·1)	<0·0001	−21·3 (3·1)	−14·1 (−22·2, −6·0)	0·0007	−18·6 (3·2)	−11·5 (−19·7, −3·2)	0·0064	−7·2 (2·7)
Pain, VAS 0-100	−21·0 (3·2)	−18·0 (−26·4, −9·6)	<0·0001	−15·7 (3·3)	−12·7 (−21·2, −4·2)	0·0035	−13·0 (3·3)	−10·0 (−18·6, −1·4)	0·0228	−3·0 (2·8)
HAQ-DI, 0-3	−0·56 (0·07)	−0·49 (−0·68, −0·30)	<0·0001	−0·42 (0·07)	−0·35 (−0·54, −0·16)	0·0003	−0·39 (0·07)	−0·32 (−0·51, −0·13)	0·0011	−0·08 (0·06)
PsAQOL, 0-20	−3·5 (0·7)	−3·63 (−5·4, −1·9)	<0·0001	−2·4 (0·7)	−2·6 (−4·3, −0·81)	0·0043	−2·0 (0·7)	−2.1 (−3·9, −0·32)	0·0207	0·13 (0·6)
SF-36 PCS, 0-100	7·4 (1·0)	6·4 (3·8, 8·9)	<0·0001	5·1 (1·0)	4·1 (1·5, 6·6)	0·0019	5·0 (1·0)	3·9 (1·3, 6·5)	0·0029	1·0 (0·8)
SF-36 MCS, 0-100	3·8 (1·2)	3·4 (0·31, 6·5)	0·0312	2·7 (1·2)	2·3 (−0·83, 5·4)	0·1506	4·4 (1·2)	4·0 (0·86, 7·1)	0·0128	0·4 (1·0)
SF-36 domains, 0-100										
Physical functioning	20·4 (2·8)	18·5 (11·2, 25·9)	<0·0001	11·8 (2·9)	9·9 (2·5, 17·3)	0·0089	14·8 (2·9)	12·9 (5·4, 20·3)	0·0008	1·9 (2·4)
Role-physical	20·9 (2·8)	16·4 (9·1, 23·8)	<0·0001	9·7 (2·9)	5·3 (−2·1, 12·7)	0·1623	12·5 (2·9)	8·1 (0·63, 15·6)	0·0337	4·4 (2·4)
Bodily pain	19·5 (2·7)	14·5 (7·4, 21·6)	<0·0001	15·6 (2·8)	10·6 (3·4, 17·8)	0·0039	14·7 (2·8)	9·7 (2·4, 16·9)	0·0090	5·0 (2·4)
General health	7·6 (2·1)	9·4 (3·8, 15·0)	0·0011	8·2 (2·2)	10·0 (4·4, 15·6)	0·0005	8·1 (2·2)	9·9 (4·3, 15·5)	0·0006	−1·8 (1·8)
Vitality	14·5 (2·6)	10·8 (4·1, 17·5)	0·0016	11·7 (2·6)	8·0 (1·3, 14·8)	0·0189	12·6 (2·6)	8·9 (2·1, 15·7)	0·0102	3·7 (2·2)
Social functioning	16·0 (2·9)	15·9 (8·3, 23·6)	<0·0001	10·3 (3·0)	10·2 (2·5, 17·9)	0·0095	12·4 (3·0)	12·3 (4·5, 20·1)	0·0020	0·05 (2·5)
Role-emotional	11·8 (2·8)	7·7 (0·31, 15·1)	0·0412	5·5 (2·9)	1·4 (−6·0, 8·8)	0·7091	11·7 (2·9)	7·6 (0·08, 15·1)	0·0476	4·1 (2·5)
Mental health	8·1 (2·2)	8·7 (3·0, 14·3)	0·0027	5·4 (2·2)	5·9 (0·25, 11·6)	0·0408	8·0 (2·2)	8·6 (2·8, 14·4)	0·0037	−0·6 (1·9)
DLQI total, 0-30†	−9·7 (1·1)	−8·1 (−11·1, −5·0)	<0·0001	−7·9 (1·3)	−6·2 (−9·5, −3·0)	0·0002	−8·7 (1·4)	−7·1 (−10·5, −3·6)	<0·0001	−1·7 (1·1)
FACIT-F, 0-52	7·3 (1·3)	7·4 (4·0, 10·7)	<0·0001	5·7 (1·3)	5·8 (2·4, 9·1)	0·0009	5·8 (1·3)	5·9 (2·5, 9·3)	0·0008	−0·1 (1·1)

BSA, body surface area; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate response; LSM, least-squares mean; MCS, mental component summary; NL, no loading dose; PCS, physical component summary; PsAQOL, Psoriatic Arthritis Quality of Life questionnaire; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; TNF, tumor necrosis factor; VAS, visual analog scale.

* LSM changes assessed in patients with measurements at both baseline and postbaseline visits.

† DLQI assessed in patients with ≥3% BSA involvement at baseline.

Table S4. Number and proportion (%) of patients reporting changes from baseline in PRO measures ≥ MCID* at 16 weeks in FUTURE 5

PRO measure	Secukinumab 300 mg (n=222)			Secukinumab 150 mg (n=220)			Secukinumab 150 mg NL (n=222)			Placebo (n=332)
	n (%)	p value vs placebo	NNT vs placebo	n (%)	p value vs placebo	NNT vs placebo	n (%)	p value vs placebo	NNT vs placebo	n (%)
$PtGA_{PsO/arthritis}$, VAS 0-100	156 (70)	<0·0001	4	154 (70)	<0·0001	4	146 (66)	<0·0001	5	158 (48)
SF-36 PCS, 0-100	153 (69)	<0·0001	4	141 (64)	<0·0001	5	150 (68)	<0·0001	4	142 (43)
SF-36 MCS, 0-100	105 (47)	0·2951	21	110 (50)	0·0971	13	109 (49)	0·1387	15	141 (42)
SF-36 domains, 0-100										
Physical functioning	165 (74)	<0·0001	5	149 (68)	0·0011	7	153 (69)	0·0004	7	178 (54)
Role-physical	151 (68)	<0·0001	5	148 (67)	<0·0001	6	147 (66)	0·0001	6	164 (49)
Bodily pain	148 (67)	<0·0001	5	151 (69)	<0·0001	4	153 (69)	<0·0001	4	153 (46)
General health	135 (61)	<0·0001	5	140 (64)	<0·0001	4	130 (59)	<0·0001	5	129 (39)
Vitality	144 (65)	<0·0001	5	151 (69)	<0·0001	4	139 (63)	0·0001	6	152 (46)
Social functioning	128 (58)	0·0004	6	127 (58)	0·0004	6	127 (57)	0·0005	7	139 (42)
Role-emotional	106 (48)	0·1628	16	111 (50)	0·0446	11	111 (50)	0·0554	12	138 (42)
Mental health	130 (59)	0·0152	9	138 (63)	0·0007	7	121 (55)	0·1407	15	159 (48)
DLQI total, 0-30[†]	70/110 (64)	<0·0001	2	59/125 (47)	<0·0001	3	46/117 (39)	<0·0001	4	27/162 (17)

BSA, body surface area; DLQI, Dermatology Life Quality Index; LSM, least-squares mean; MCID, minimal clinically important difference; MCS, mental component summary; NL, no loading dose; NNT, number needed to treat; PCS, physical component summary; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale.

* MCIDs were defined as follows: PtGA disease activity, improvement ≥10; $PtGA_{PsO/arthritis}$, improvement ≥10; pain, improvement ≥10; SF-36 PCS and MCS, improvement ≥2·5; SF-36 domains, improvement ≥5·0; and DLQI score of 0 or 1.

[†] DLQI assessed in patients with ≥3% BSA involvement at baseline.

Table S5. Number and proportion (%) of patients reporting changes from baseline in PRO measures ≥ MCID* at 16 weeks in TNF-naive and TNF-IR patients in FUTURE 5

	TNF Naive							TNF IR						
PRO measure	**300 mg (n=154)**		**150 mg (n=153)**		**150 mg NL (n=157)**		**Placebo (n=233)**	**300 mg (n=68)**		**150 mg (n=67)**		**150 mg NL (n=65)**		**Placebo (n=99)**
	n (%)	**p value vs placebo**	**n (%)**	**p value vs placebo**	**n (%)**	**p value vs placebo**	**n (%)**	**n (%)**	**p value vs placebo**	**n (%)**	**p value vs placebo**	**n (%)**	**p value vs placebo**	**n (%)**
PtGA, VAS 0-100	93 (60)	0·0126	89 (58)	0·0378	89 (57)	0·0791	110 (47)	41 (60)	0·0001	37 (55)	0·0021	34 (52)	0·0056	30 (30)
$PtGA_{PsO/arthritis}$, VAS 0-100	108 (70)	0·0002	113 (74)	<0·0001	109 (69)	0·0004	119 (51)	48 (71)	<0·0001	41 (61)	0·0072	37 (57)	0·0372	39 (39)
Pain, VAS 0-100	97 (63)	0·0026	103 (67)	0·0001	108 (69)	<0·0001	110 (47)	33 (49)	0·0375	39 (58)	0·0013	31 (48)	0·0512	32 (32)
HAQ-DI, 0-3	100 (65)	<0·0001	86 (56)	0·0048	92 (59)	0·0009	96 (41)	37 (54)	<0·0001	34 (51)	0·0002	32 (49)	0·0006	22 (22)
SF-36 PCS, 0-100	108 (70)	<0·0001	107 (70)	<0·0001	116 (74)	<0·0001	112 (48)	45 (66)	<0·0001	34 (51)	0·0095	34 (52)	0·0056	30 (30)
SF-36 MCS, 0-100	76 (49)	0·6036	82 (54)	0·1769	76 (48)	0·7564	108 (46)	29 (43)	0·2551	28 (42)	0·3252	33 (51)	0·0342	33 (33)
SF-36 domains, 0-100														
Physical functioning	115 (75)	0·0031	109 (71)	0·0227	115 (73)	0·0067	139 (60)	50 (74)	<0·0001	40 (60)	0·0116	38 (58)	0·0248	39 (39)
Role-physical	105 (68)	0·0145	112 (73)	0·0004	107 (68)	0·0115	129 (55)	46 (68)	<0·0001	36 (54)	0·0250	40 (62)	0·0013	35 (35)
Bodily pain	106 (69)	0·0002	111 (73)	<0·0001	118 (75)	<0·0001	115 (49)	42 (62)	0·0044	40 (60)	0·0075	35 (54)	0·0559	38 (38)
General health	105 (68)	<0·0001	100 (65)	<0·0001	93 (59)	0·0038	102 (44)	30 (44)	0·0308	40 (60)	<0·0001	37 (57)	0·0002	27 (27)
Vitality	103 (67)	0·0005	109 (71)	<0·0001	104 (66)	0·0009	114 (49)	41 (60)	0·0072	42 (63)	0·0026	35 (54)	0·0559	38 (38)
Social functioning	93 (60)	0·0050	90 (59)	0·0125	90 (57)	0·0234	106 (45)	35 (51)	0·0248	37 (55)	0·0065	37 (57)	0·0036	33 (33)
Role-emotional	73 (47)	0·6038	82 (54)	0·0959	77 (49)	0·4089	104 (45)	33 (49)	0·0780	29 (43)	0·2581	34 (52)	0·0245	34 (34)
Mental health	93 (60)	0·1173	104 (68)	0·0022	89 (57)	0·4075	121 (52)	37 (54)	0·0571	34 (51)	0·1507	32 (49)	0·1978	38 (38)
DLQI total, 0-30†	49/75 (65)	<0·0001	46/94 (49)	<0·0001	39/92 (42)	0·0007	23/115 (20)	21/35 (60)	<0·0001	13/31 (42)	0·0007	7/25 (28)	0·0407	4/47 (9)
FACIT-F, 0-52	86 (56)	0·0049	100 (65)	<0·0001	89 (57)	0·0027	95 (41)	40 (59)	<0·0001	42 (63)	<0·0001	34 (52)	0·0016	27 (27)

BSA, body surface area; DLQI, Dermatology Life Quality Index; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate response; MCID, minimum clinically important difference; MCS, mental component summary; NL, no loading dose; PCS, physical component summary; PRO, patient-reported outcome; PsO, psoriasis; PtGA, patient global assessment; SF-36, 36-item Short Form Health Survey; TNF, tumor necrosis factor.

* MCIDs were defined as follows: PtGA disease activity, improvement ≥10; $PtGA_{PsO/arthritis}$, improvement ≥10; pain, improvement ≥10; HAQ-DI, reduction ≥0·35; SF-36 PCS and MCS, improvement ≥2·5; SF-36 domains, improvement ≥5·0; DLQI, response of 0/1; FACIT-F ≥4·0.

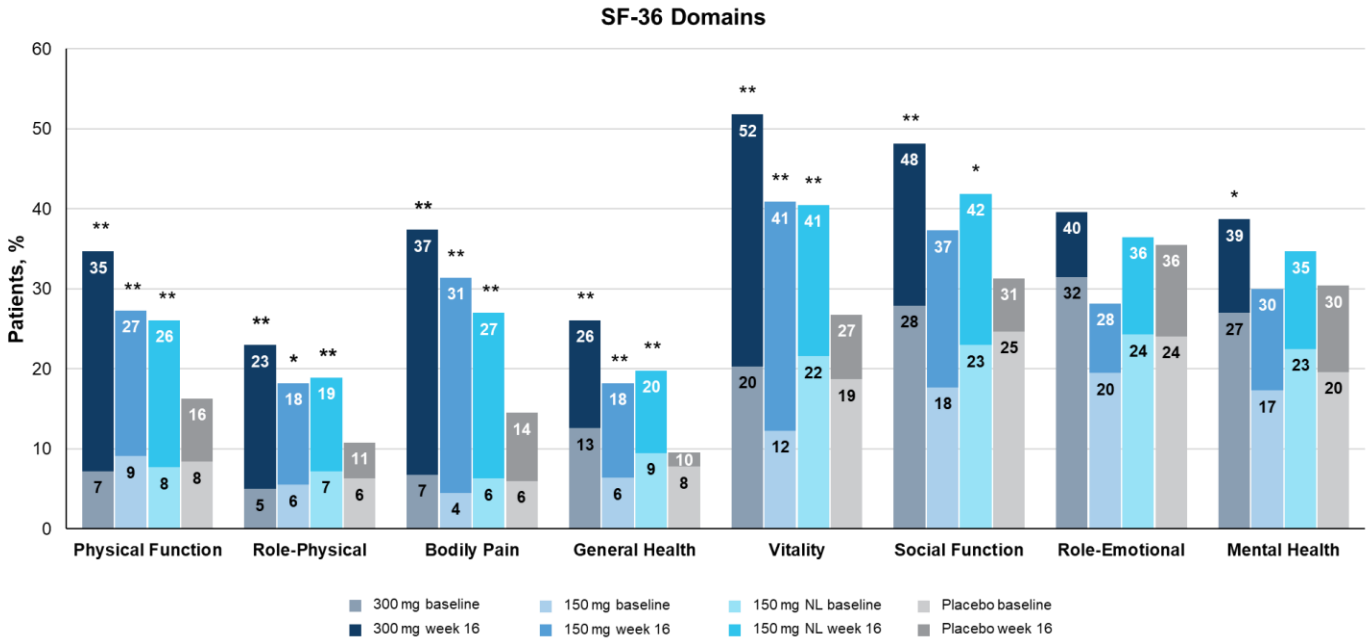
† DLQI assessed in patients with ≥3% BSA involvement at baseline.

Table S6. Number of TNF-naive and TNF-IR patients, disease duration, and proportion of patients receiving MTX in recent RCTs

RCT	TNF Naive	TNF IR	Disease Duration (years)	Concomitant MTX (%)
FUTURE 5				
TNF-naive	697		5·2-5·8	49-56
TNF-IR		299	5·9-10·1	34-58
OPAL BROADEN[1]	422		5·3-7·3	100
OPAL BEYOND[2]		395	9·1-9·6	100
SELECT-PsA 1[3]	1705		6·1	64
SELECT-PsA 2[4]		642	9·6-11·0	35
SPIRIT-P1[5]	417		6·2-6·9	52-56
SPIRIT-P2[6]		363	9·2-11·0	34-50

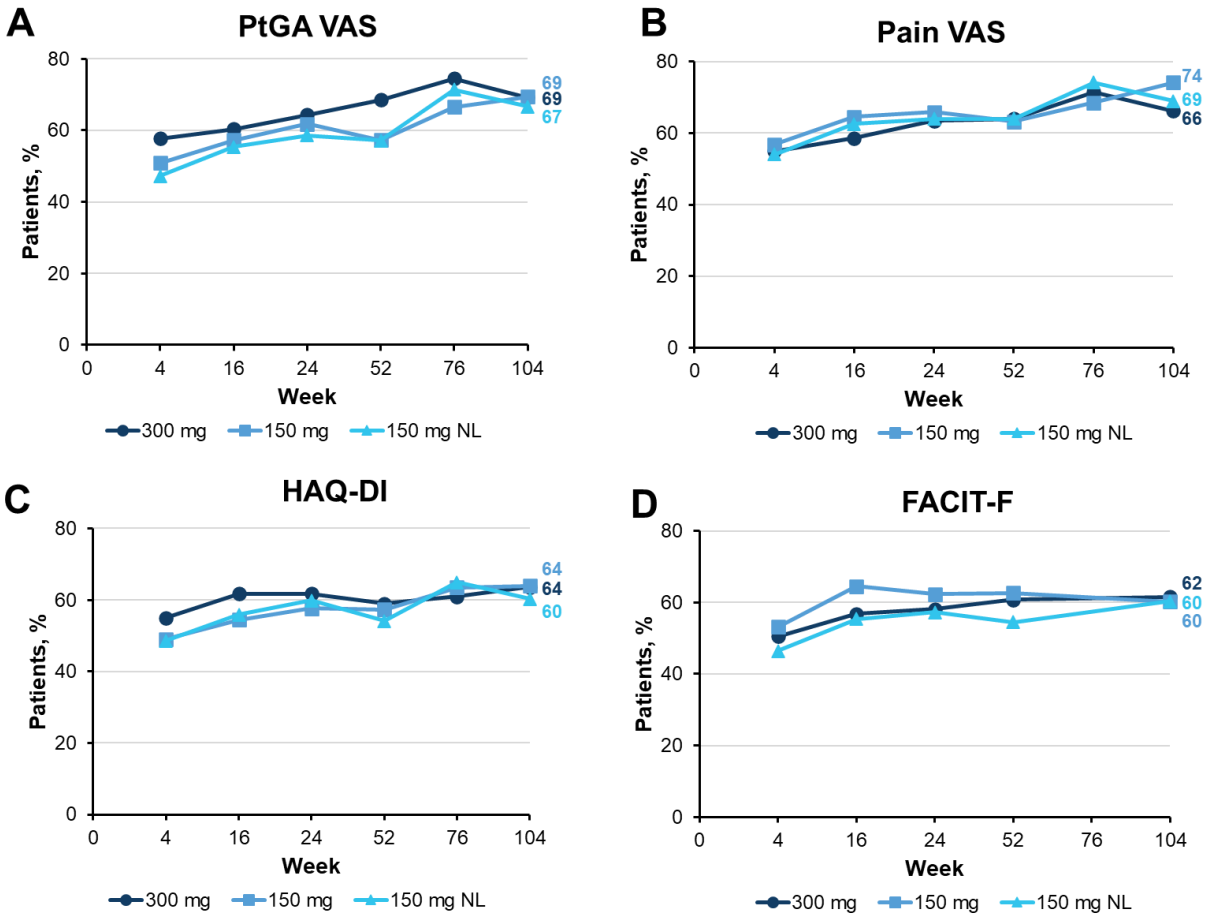
IR, inadequate response; MTX, methotrexate; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Figure S1. Proportion of overall patients reporting scores ≥ normative values in SF-36 domain† scores at baseline and week 16 in FUTURE 5



SF-36, 36-item Short Form Health Survey.
* p<0·05 and ** p<0·01 compared with placebo.
† Age- and sex-matched normative values for SF-36 domains were defined as follows: physical function, ≥81·8; role-physical, ≥82·5; bodily pain, ≥72·7; general health, ≥70·2; vitality, ≥59·0; social function, ≥85·1; role-emotional, ≥88·2; and mental health, ≥76·0.

Figure S2. Proportion of overall patients reporting improvement from baseline ≥ MCID* in **(A)** PtGA, **(B)** pain, **(C)** HAQ-DI, and **(D)** FACIT-F over 104 weeks† in FUTURE 5

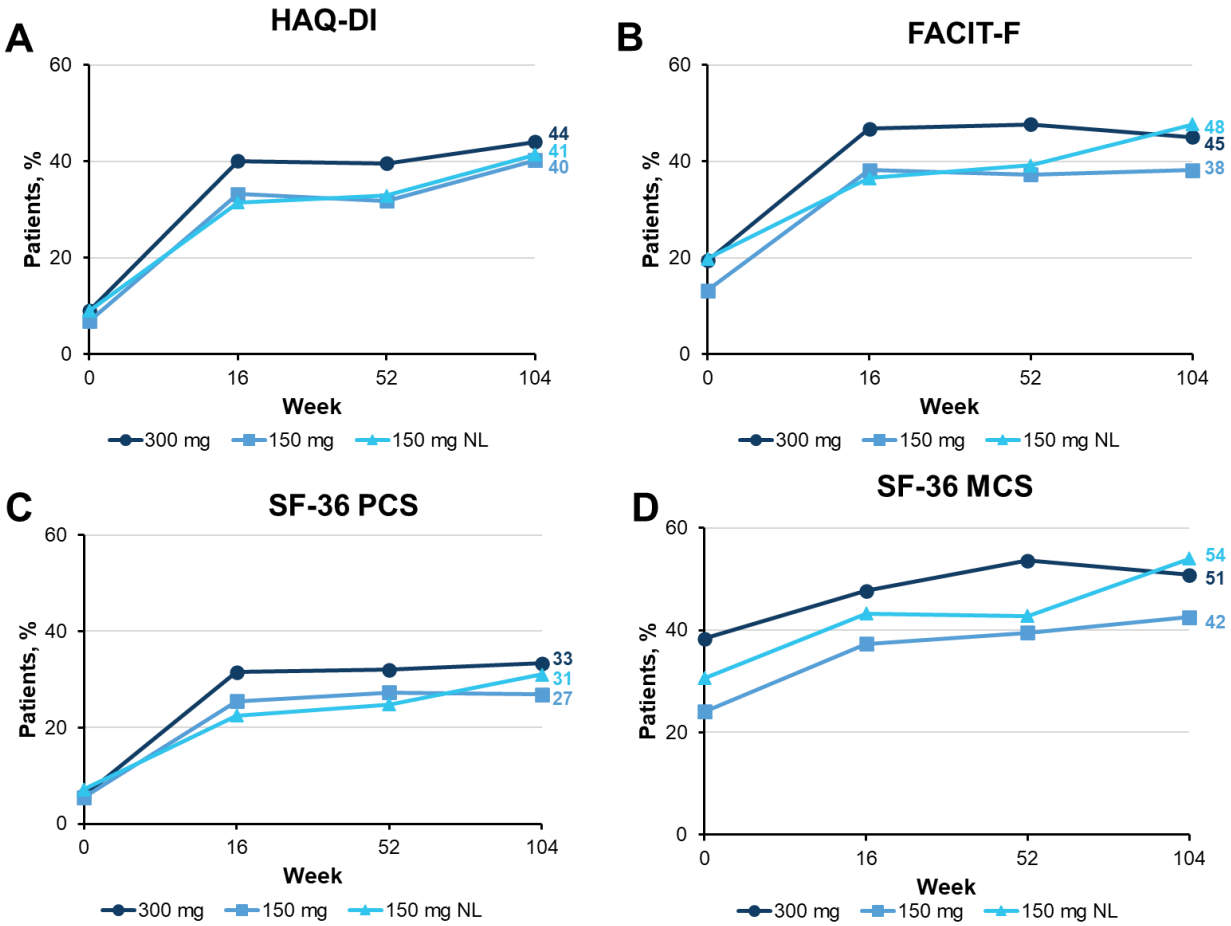


FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; MCID, minimum clinically important difference; NL, no loading dose; PRO, patient-reported outcome measure; PtGA, patient global assessment of disease activity; VAS, visual analog scale.

* MCIDs for PROs were defined as follows: PtGA VAS, ≥10; pain VAS, ≥10; HAQ-DI, reduction ≥0·35; FACIT-F, ≥4·0; and SF-36 PCS and MCS, ≥2·5.

† Non-responder imputation (i.e., individuals with missing responses are considered as non-responders) was used for the analysis up to week 52, and observed/available data was used after week 52.

Figure S3. Proportion of overall patients reporting scores better than or equal to age- and sex-matched normative values* in **(A)** HAQ-DI, **(B)** FACIT-F, **(C)** SF-36 PCS, and **(D)** SF-36 MCS over 104 weeks† in FUTURE 5



FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCS, mental component summary; NL, no loading dose; PCS, physical component summary; PRO, patient-reported outcome; SF-36, 36-item Short Form Health Survey.
* Normative values for PROs were defined as follows: HAQ-DI, ≤0·25; FACIT-F, ≥40·1; SF-36 PCS, ≥50; and SF-36 MCS, ≥50.
† Non-responder imputation (i.e., individuals with missing responses are considered as non-responders) was used for the analysis up to week 52, and observed/available data was used after week 52.

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