Secukinumab provides rapid and persistent relief in pain and fatigue symptoms in patients with ankylosing spondylitis irrespective of baseline C-reactive protein levels or prior tumour necrosis factor inhibitor therapy: 2-year data from the MEASURE 2 study

A. Deodhar[1], P.G. Conaghan[2], T.K. Kvien[3], V. Strand[4], B. Sherif[5], B. Porter[6], S.M. Jugl[7], K.K. Gandhi[6], on behalf of the MEASURE 2 study group.

[1]Oregon Health and Science University, Portland, OR, USA; [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds Biomedical Research Centre, Leeds, UK; [3]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; [4]Stanford University School of Medicine, Palo Alto, CA, USA; [5]RTI Health Solutions, Research Triangle Park, NC, USA; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [7]Novartis Pharma AG, Basel, Switzerland.

Abstract

Objective

To evaluate improvement in pain and fatigue in ankylosing spondylitis (AS) patients treated with secukinumab over 2 years (MEASURE 2 study).

Methods

Patients with active AS were randomised to receive secukinumab 150 mg, 75 mg, or placebo weekly until Week 4, and every 4 weeks thereafter. This post hoc analysis included assessment of spinal and nocturnal back pain, FACIT-Fatigue, and association between pain and either FACIT-Fatigue or ASQoL item 5 (sleep quality) for the approved secukinumab 150 mg dose in the overall population, and stratified by baseline high-sensitivity C-reactive protein (hsCRP) levels (normal [<5 mg/L] or elevated [≥5 mg/L]) or prior TNF inhibitor therapy status (TNFi-naïve or inadequate response [TNFi-IR]).

Results

Secukinumab-treated patients reported rapid improvement in pain and fatigue scores in overall population by Weeks 1 and 4, respectively; this trend of improvement was also observed irrespective of baseline hsCRP levels or prior TNFi therapy. Mean change at Week 16 in spinal/nocturnal pain (secukinumab vs. placebo) for the subgroups were -34.6/-30.2 vs. -16.6/-10.0, p<0.05/0.01 (normal hsCRP); -26.7/-31.6 vs. -7.8/-9.3, p<0.001/0.0001 (elevated hsCRP); -33.2/-35.4 vs. -13.2/-14.9, both p<0.0001 (TNFi-naïve); and -22.5/-22.8 vs. -9.4/-4.0, p=0.06/p<0.01 (TNFi-IR). FACIT-Fatigue was 7.1 vs. 3.3, p=0.15 (normal hsCRP); 8.7 vs. 3.6, p<0.05 (elevated hsCRP); 10.0 vs. 5.2, p<0.05 (TNFi-naïve); and 5.7 vs. 0.5, p=0.06 (TNFi-IR). These improvements were sustained or further improved through Week 104.

Conclusion

Secukinumab provides rapid and sustained relief of pain and fatigue over 2 years in patients with AS regardless of baseline hsCRP levels and prior TNFi therapy.

Key words

ankylosing spondylitis, secukinumab, IL-17A inhibitor, biologics

Atul Deodhar, MD
Philip G. Conaghan, MBBS, PhD, FRACP, FRCP
Tore K. Kvien, MD, PhD
Vibeke Strand, MD, MACR, FACP
Bintu Sherif, MS
Brian Porter, MD, PhD, MPH, MBA
Steffen M. Jugl, MD
Kunal K. Gandhi, MD, MPH

Please address correspondence to:
Dr Atul Deodhar,
Oregon Health and Science University,
3181 SW Sam Jackson Park Road,
Portland, OR 97239, USA.
E-mail: deodhara@ohsu.edu

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B. Sherif is an employee of RTI Health Solutions.
B. Porter, S.M. Jugl, and K.K. Gandhi are employees of Novartis and own Novartis stock

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory condition associated with pain, stiffness of the spine, and sometimes the peripheral joints, fatigue and poor sleep quality. Around 30–35% of patients report pain and 50–65% of patients report fatigue as their major and most troubling symptoms that result in impaired physical function and reduced work productivity and quality of life (QoL) (1-7). While there are some conflicting reports on the correlation between pain and fatigue (8), there have been studies wherein pain was found to be the most strongly associated factor with fatigue (2, 3, 9).

Patients with AS often report multiple nocturnal awakenings and early morning awakening, which leads to sleep disturbance and fatigue (3, 4, 7, 10). Sleep disturbance has been positively correlated with pain and fatigue intensity in patients with AS (11). Similarly, a decrease in pain has been shown to be correlated with improved sleep quality and fatigue status (12, 13). An elevated level of C-reactive protein (CRP) is one of the relevant inflammatory markers in AS (14) and has been reported to be associated with both pain and fatigue (15, 16). Although the relationship between pain, fatigue, and CRP is not well defined, these are independently assessed variables that are components of important composite measures of AS treatment efficacy (*e.g.* Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], AS Disease Activity Score), and are thus associated with improvement in treatment response of patients with active AS (17-21).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the standard of drug management for patients with AS (22). At present, tumour necrosis factor alpha inhibitors (TNFi) and interleukin-17A (IL-17A) inhibitors are the only classes of biologics that have shown effectiveness in controlling disease activity and symptoms of AS and are approved for its treatment (23). While TNFi are commonly used as the first-line biologics, a substantial proportion of patients exhibit inadequate response or become intolerant to TNFi therapy (22, 24). Moreover, response to TNFi in patients with AS is associated with elevated levels of CRP as patients with normal CRP levels may not respond adequately to TNFi (18-21, 25-28).

Secukinumab, a fully human monoclonal IgG1κ antibody that selectively neutralises IL-17A, significantly improved the signs and symptoms of active AS in the phase 3 MEASURE 1 (NCT01358175) and MEASURE 2 (NCT01649375) studies, with responses sustained through Weeks 156 and 104, respectively (29-31). The main objective of this *post hoc* analysis of the MEASURE 2 study was to evaluate improvements in pain and fatigue with secukinumab treatment compared to placebo through Week 16 stratified by baseline high-sensitivity CRP (hsCRP) levels or prior TNFi therapy, and assess the sustainability of the improvements through 104 weeks. Additionally, the association between pain and either fatigue or sleep quality was also assessed.

Methods

Study design and patients

The MEASURE 2 study design, patients, methodology and statistical analysis have been described previously (31). In brief, this is a 5-year phase 3 study to evaluate the efficacy, safety, and tolerability of subcutaneous (s.c.) loading and maintenance dosing of secukinumab in patients with active AS. Patients were randomly assigned to receive s.c. secukinumab 150 mg, 75 mg, or placebo at baseline, Weeks 1, 2, and 3, followed by every 4 weeks starting at Week 4. At Week 16, placebo-treated patients were re-randomised to s.c. secukinumab 150 mg or 75 mg every 4 weeks, regardless of clinical response. Herein, only data for the approved dose of secukinumab 150 mg are reported.

Patients aged ≥18 years with AS fulfilling the Modified New York Criteria (32), with a BASDAI score of ≥4 (scores range from 0–10) (33), and a spinal pain score of ≥4 cm on a 10 cm visual analogue scale (VAS) despite treatment with NSAIDs were eligible for study participation. Patients who had taken not more than one previous TNFi with an inadequate response or intolerance were also allowed to enter the study. This represents a broader

population than studied in pivotal TNFi trials in AS, with a greater proportion of biologic treatment-refractory patients than in earlier phase 3 biologic development programmes in AS. Key exclusion criteria were total spinal ankylosis, evidence of infection (human immunodeficiency virus or hepatitis B or C), malignancy on chest x-ray, active systemic infection 2 weeks before randomisation, and previous treatment with cell-depleting therapies or biologic agents other than TNFi.

MEASURE 2 was conducted in accordance with the Declaration of Helsinki (as revised in Brazil 2013), available at http://www.wma.net/en/30publications/10policies/b3/index.html, and was approved by the institutional review boards or independent ethics committees for each study site. Written informed consent was obtained from all screened patients.

Table I. Baseline demographic and clinical characteristics.

	Secukinumab 150 mg (n=72)	Placebo (n=74)
Age (years), mean (SD)	41.9 (12.5)	43.6 (13.2)
Male, %	63.9	75.7
Caucasian[a], %	95.8	94.6
Weight (kg), mean (SD)	82.3 (18.0)	80.3 (15.2)
BMI (kg/m^2), mean (SD)	27.4 (5.8)	27.1 (5.7)
Positive for HLA-B27, %	79.2	78.4
TNFi-IR, %	38.9	39.2
hsCRP (mg/L), median (min–max), Q1–Q3	7.5 (0.4–237) 3.3–22.8	8.3 (0.5–84.6) 3.2–20.7
Total BASDAI score, mean (SD)	6.6 (1.5)	6.8 (1.3)
BASDAI Question no. 1: Overall level of fatigue, mean (SD)	7.1 (1.4)	7.2 (1.6)
Spinal pain (0–100 mm), mean (SD)	66.2 (16.7)	69.2 (18.8)
Nocturnal pain (0–100 mm), mean (SD)	65.9 (17.2)	64.0 (21.8)
FACIT-Fatigue score, mean (SD)	22.6 (8.8)	24.3 (9.0)

There were no clinically meaningful differences in the baseline characteristics between groups.
[a]Race was self-assessed
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: body mass index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; HLA: human leukocyte antigen; hsCRP: high-sensitivity C-reactive protein; IR: inadequate responders; n: number of patients randomised; Q: quartiles; SD: standard deviation; TNFi: tumour necrosis factor inhibitor.

Outcome measures

The main objectives of this *post hoc* analysis were to assess pain (total spinal and nocturnal back pain) and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue]) scores from baseline through Week 104 in the overall population, and in subgroups of patients stratified by baseline hsCRP levels and prior use of TNFi therapy. In addition, correlations between pain and fatigue, pain and ASQoL item 5 response (sleep quality), and proportion of patients reporting clinically meaningful improvements (≥20% mean change from baseline) in spinal pain were assessed in the overall population and in the subgroup by prior TNFi therapy.

• *Patient's assessment of back pain intensity*

Patient's assessment of back pain intensity was assessed using a 10 cm VAS ranging from no pain to unbearable pain (34). Total spinal pain was based on the question "*what was the amount of back pain at any time that the patient had experienced during the previous week?*" in the BASDAI and nocturnal back pain was based on the question, "*what was the amount of back pain at night that the patient had experienced during the previous week?"* The total spinal pain and nocturnal back pain VAS scores were assessed at baseline; Weeks 1 through 4; every 4 weeks through Week 32; Weeks 40, 52, and 60; every 8 weeks through Week 92; and final assessment at Week 104. A clinically meaningful improvement in pain was defined as ≥20% mean change from baseline score.

• *Functional Assessment of Chronic Illness Therapy-Fatigue*

FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function (35). The total possible range of the fatigue scale was 0 to 52, with higher scores representing lower fatigue levels. The FACIT-Fatigue response was defined as improvement ≥4 points from baseline. FACIT-Fatigue was assessed at baseline and Weeks 4, 8, 12, 16, 24, 52, and 104. Improvement in fatigue using BASDAI Question no. 1: Overall level of fatigue was also assessed through Week 104.

• *Ankylosing Spondylitis Quality of Life item 5 response (sleep quality)*

Sleep quality was assessed using a specific question pertaining to sleep captured as item 5 of the ASQoL (impossible to sleep). ASQoL contains 18 items with a dichotomous "Yes/No" response option (36). Patients were asked to consider the impact "at the moment" and responded "Yes/No" to the item. A single point (one) is assigned for each "Yes" response and zero point for each "No" response, resulting in overall scores that range from zero (least severity) to 18 (highest severity) wherein a lower score indicates a better QoL. ASQoL was assessed at baseline and Weeks 4, 8, 12, 16, 24, and 52; ASQoL was not assessed after Week 52 as per the MEASURE 2 study assessment plan.

Statistical analysis

Results are reported for the overall population, patients stratified by baseline hsCRP levels (normal [<5 mg/L] or elevated [≥5 mg/L]), and prior TNFi therapy (TNFi-naïve or with previous inadequate response or inability to tolerate not more than one TNFi [TNFi-IR]) for those patients who were originally randomised to secukinumab 150 mg s.c. (approved dose). Pain and fatigue scores (mean change) were evaluated from baseline through Week 104 for patients with baseline and at least one post-baseline scores. The proportion of patients who reported clinically meaningful improvements in pain scores were summarised up to Week 104. Between-treatment differences in changes from baseline in pain and fatigue were evaluated using mixed-effects model repeated measure (MMRM) analysis through

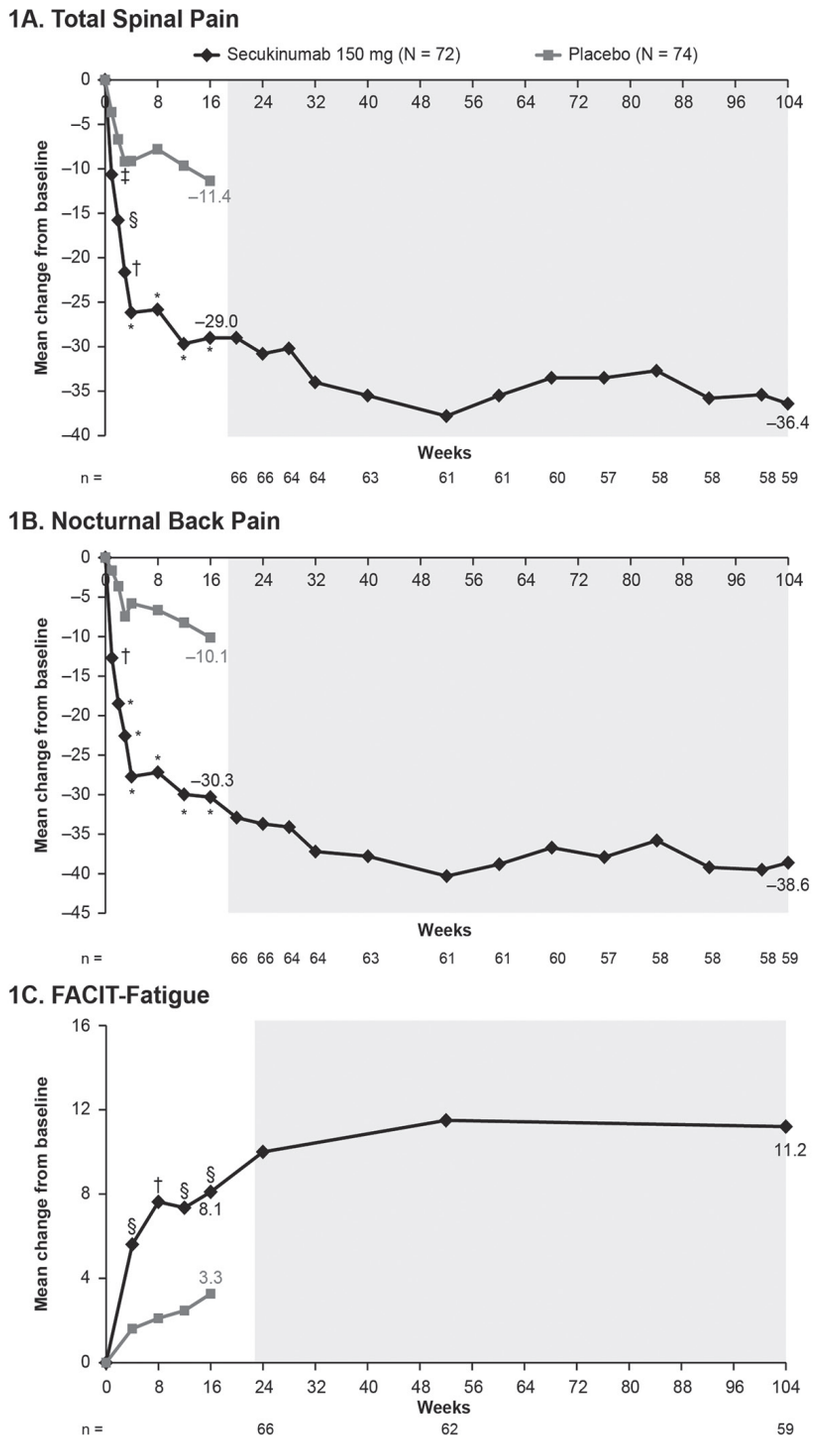

Fig. 1. Improvement in Total Spinal Pain (**A**), Nocturnal Back Pain (**B**) VAS, and FACIT-Fatigue (**C**) scores through Week 104.
*p<0.0001; †p<0.001; §p<0.01; ‡p<0.05 *vs*. placebo; LS mean change using MMRM from Week 1-16 and observed data presented from Week 20-104 (shaded area). FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; LS, least squares; MMRM, mixed-effects model repeated measures; N: number of randomised patients; n: number of evaluable patients; VAS: visual analogue scale.

Week 16 with treatment regimen, analysis visit, and randomisation stratum (TNFi status: -naïve or -IR) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms. Owing to re-randomisation of patients in the placebo group at Week 16 to active treatment, statistical comparisons of secukinumab *versus* the placebo groups are presented up to Week 16. Analyses are exploratory and were conducted using observed data. No adjustments were made for multiple comparisons. Unadjusted summary data are presented for secukinumab 150 mg from Weeks 20 to 104.

Correlation analysis

The correlation coefficients between pain (spinal and nocturnal) and fatigue (FACIT-Fatigue score and response), between pain and fatigue measured by BASDAI Question no. 1 through Week 104, and between pain and sleep quality (ASQoL item 5) through Week 52 were evaluated. Pearson and polyserial correlations were used to calculate the correlation coefficients.

Results

Details regarding patient disposition and retention rates through Week 104 have been reported elsewhere (30, 31). Of the 219 patients randomised at baseline, 174 (79.5%) completed 104 weeks of treatment. Of the 72 patients originally randomised to receive secukinumab 150 mg, 60 (83.3%) patients completed 104 weeks of treatment. The majority of patients randomised to the secukinumab 150 mg and placebo groups were male (63.9% and 75.7%) with a mean age of 41.9 and 43.6 years (standard deviation [SD] = 12.5 and 13.2), respectively. In this *post hoc* analysis, 36.3% of patients had normal (<5 mg/L) hsCRP levels. Baseline disease characteristics were generally comparable between the secukinumab 150 mg and placebo groups (Table I).

Outcome measures

As reported previously, the secukinumab 150 mg dose significantly improved the primary and all key secondary endpoints at Week 16 *versus* placebo, and these clinical improvements were sustained or further improved through Week 104 in patients originally randomised to secukinumab (30, 31).

• *Reductions in total spinal and nocturnal back pain scores*

Patients treated with secukinumab 150 mg (n=72) reported rapid reductions across pain scores by Week 1, which

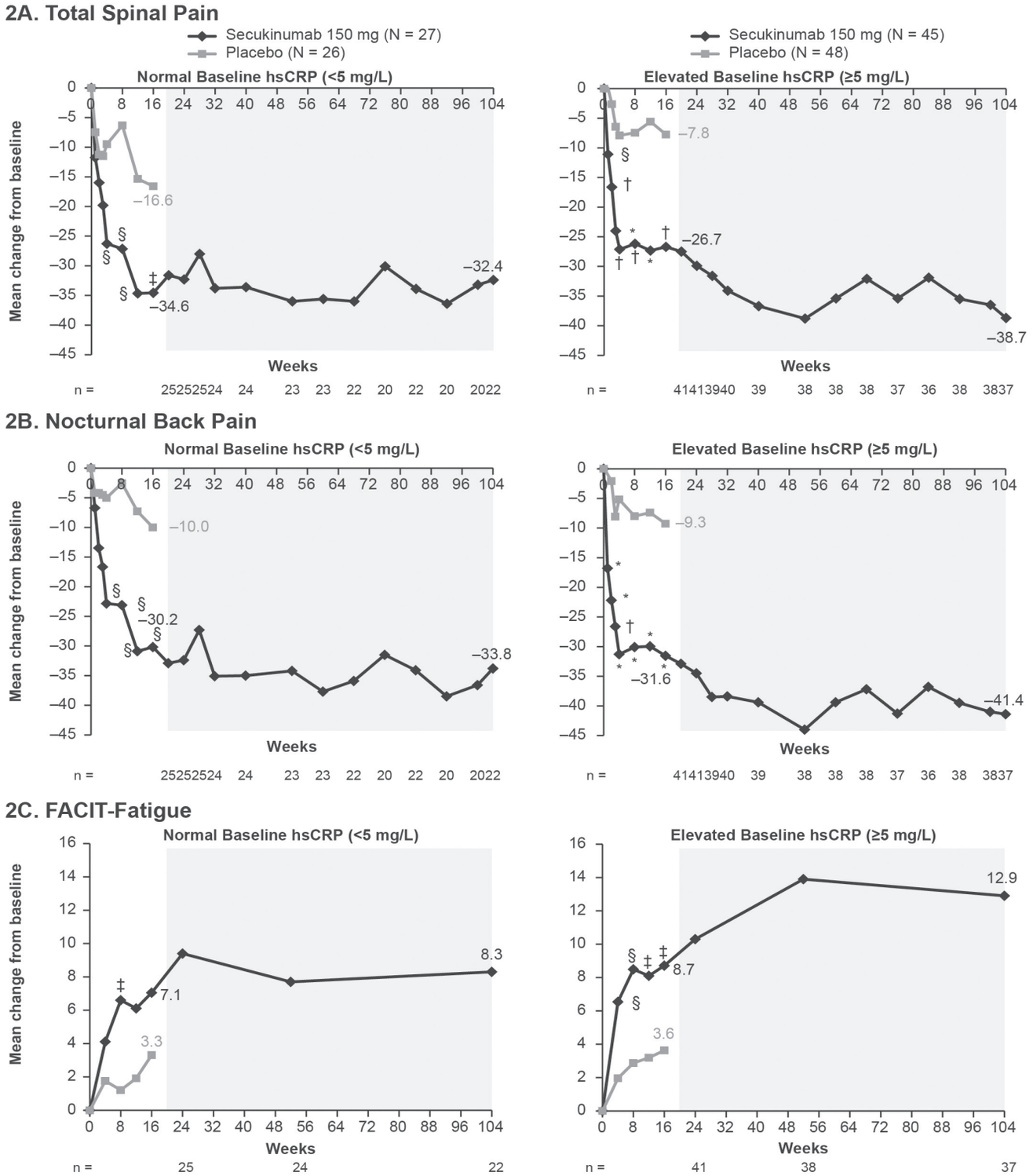

Fig. 2. Improvement in Total Spinal Pain (**A**), Nocturnal Back Pain (**B**) VAS, and FACIT-Fatigue (**C**) scores by baseline hsCRP through Week 104.
**p*<0.0001; †*p*<0.001; §*p*<0.01; ‡*p*<0.05 *vs*. placebo; LS mean change using MMRM from Week 1–16 and observed data presented from Week 20–104 (shaded area).
hsCRP: high-sensitivity C-reactive protein; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; LS: least squares; MMRM: mixed-effects model repeated measures; N: number of randomised patients; n: number of evaluable patients; VAS: visual analogue scale.

were sustained or further improved through Week 104 (Fig. 1A-B). Secukinumab reduced pain scores irrespective of baseline hsCRP levels (Fig. 2A-B). Improvements were seen with secukinumab as early as Week 4 in the normal hsCRP group and by Week 1 in the elevated hsCRP group. The mean change from baseline at Week 16 (secukinumab *vs*. placebo) in spinal pain was -34.6 *versus* -16.6 ($p<0.05$) for normal hsCRP and -26.7 *versus* -7.8 ($p<0.001$)

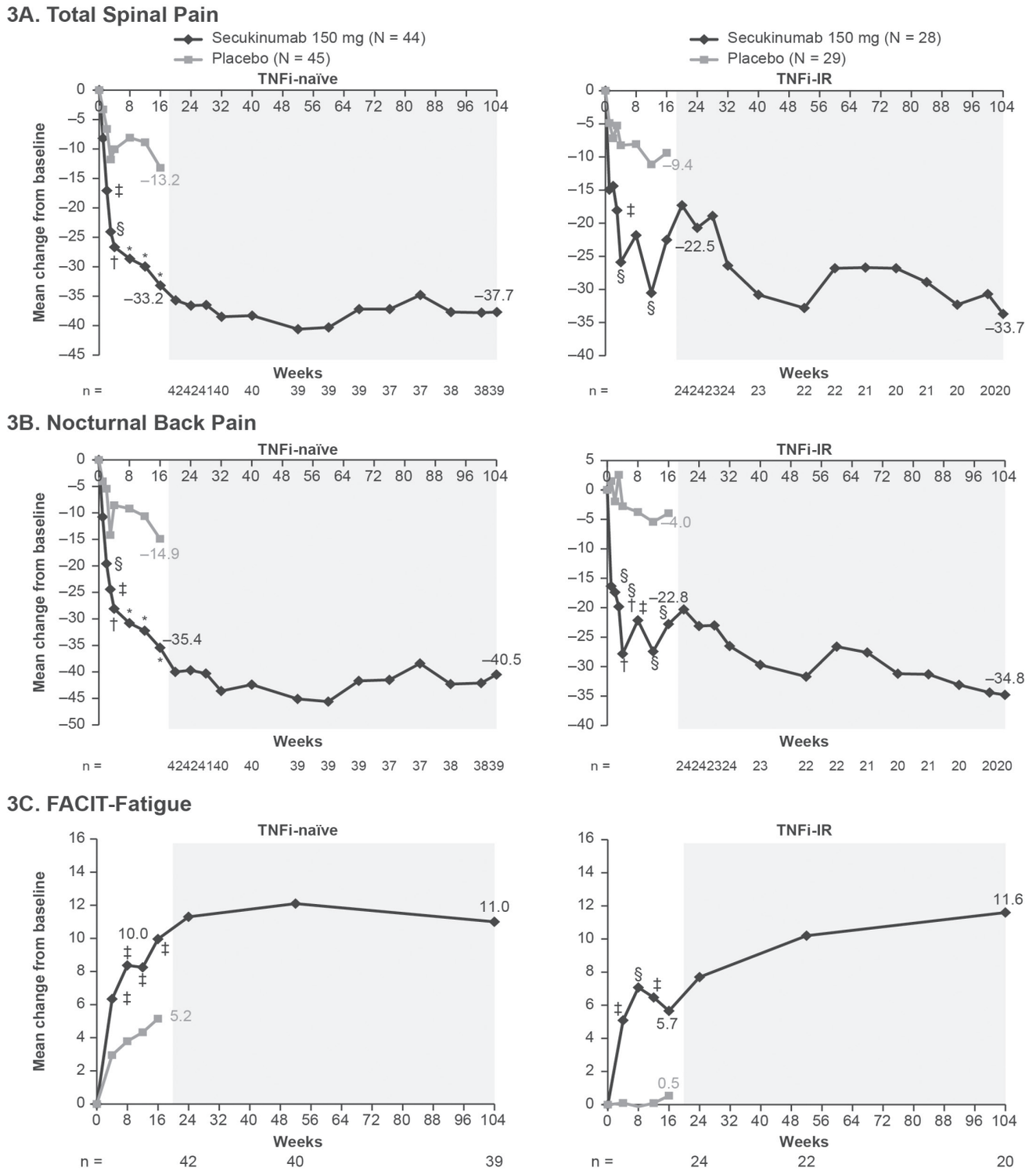

Fig. 3. Improvement in Total Spinal Pain (**A**), Nocturnal Back Pain (**B**) VAS, and FACIT-Fatigue (**C**) score through Week 104 by prior TNFi therapy. *p<0.0001; †p<0.001; §p<0.01; ‡p<0.05 *vs*. placebo; LS mean change using MMRM from Week 1–16 and observed data presented from Week 20–104 (shaded area).

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; IR: inadequate response; LS: least squares; MMRM, mixed-effects model repeated measures; N: number of randomised patients; n: number of evaluable patients; TNFi: tumour necrosis factor inhibitor; VAS: visual analogue scale.

for elevated hsCRP; and in nocturnal pain was -30.2 *versus* -10.0 (p<0.01) for normal hsCRP and -31.6 *versus* -9.3 (p<0.0001) for elevated hsCRP. These improvements in spinal/nocturnal pain were sustained or further improved at Week 104 in the normal hsCRP (-32.4/-33.8) and elevated hsCRP (-38.7/-41.4) groups. Reduction in pain scores showed similar trends among TNFi-naïve and TNFi-IR patients treated with secukinumab, with a greater magnitude

Table II. Correlation coefficients (between pain and either fatigue or sleep quality) and spinal pain VAS response.

Correlation coefficient[a]		Overall population		TNFi-naïve		TNFi-IR	
	Week	Spinal pain	Nocturnal pain	Spinal pain	Nocturnal pain	Spinal pain	Nocturnal pain
FACIT-Fatigue score	16	-0.49‡	-0.48‡	-0.51‡	-0.55‡	-0.42‡	-0.31‡
	104	-0.58‡	-0.50‡	-0.59‡	-0.50‡	-0.55‡	-0.51‡
FACIT-Fatigue response	16	-0.48‡	-0.51‡	-0.45‡	-0.59‡	-0.49‡	-0.34‡
	104	-0.68‡	-0.58‡	-0.68‡	-0.56‡	-0.68‡	-0.61‡
BASDAI Question no. 1: Overall level of fatigue	16	0.72‡	0.65‡	0.73‡	0.70‡	0.70‡	0.54‡
	104	0.66‡	0.62‡	0.73‡	0.69‡	0.52‡	0.53‡
ASQoL Item 5 response	16	-0.46‡	-0.43‡	-0.47‡	-0.41‡	-0.46	-0.57‡
	52	-0.31‡	-0.34‡	-0.39‡	-0.49‡	-0.10	-0.07

Spinal pain VAS response (≥20% mean change from baseline), n (%)

		Overall population		TNFi-naïve		TNFi-IR	
	Week	Secukinumab 150 mg (n=72)	Placebo (n=74)	Secukinumab 150 mg (n=44)	Placebo (n=45)	Secukinumab 150 mg (n=28)	Placebo (n=29)
	16	52 (77.6)§	31 (49.2)	36 (83.7)§	21 (50.0)	16 (66.7)	10 (47.6)
	104	46 (78.0)	-	29 (74.4)	-	17 (85.0)	-

[a]Data presented as observed, Pearson correlation coefficients calculated for FACIT-Fatigue score and polyserial correlation coefficients calculated for FACIT-Fatigue response and ASQoL item 5 response.
FACIT-Fatigue response dichotomised (using observed data) as 1 if FACIT-Fatigue score improvement of ≥4 points, or otherwise 0. ASQoL item 5 response dichotomised (using observed data) as 1 if item response went from 1 at baseline to 0 at the specified visit, or otherwise 0.
‡$p<0.05$ for all values, p-value calculated using the Chi-Square likelihood ratio test
§$p<0.01$ *vs*. placebo, p-value calculated using Fisher's exact test
ASQoL: Ankylosing Spondylitis Quality of Life; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; IR: inadequate responders; n: number of randomised patients; TNFi: tumour necrosis factor inhibitor; VAS: visual analogue scale.

of improvement observed in the TNFi-naïve group (Fig. 3A-B). Improvement was seen by Week 2 in TNFi-naive patients (spinal and nocturnal back pain) and by Weeks 1 (nocturnal back pain) and 3 (spinal pain) in TNFi-IR patients. The mean change from baseline at Week 16 (secukinumab *vs*. placebo) in spinal pain was -33.2 *versus* -13.2 ($p<0.0001$) for TNFi-naïve and -22.5 *versus* -9.4 ($p=0.06$) for TNFi-IR patients; and in nocturnal pain was -35.4 *versus* -14.9 ($p<0.0001$) for TNFi-naïve and -22.8 *versus* -4.0 ($p<0.01$) for TNFi-IR patients. These improvements in spinal/nocturnal pain were sustained or further improved at Week 104 in the TNFi-naïve (-37.7/-40.5) and TNFi-IR (-33.7/-34.8) groups.

• *Clinically meaningful improvements in pain*

A majority (63%) of patients from the secukinumab 150 mg dose group reported clinically meaningful improvements (≥20% mean change from baseline) *versus* placebo (36%, $p<0.01$) in spinal pain as early as Week 3, which increased to 78% at Week 104; improvements were also observed regardless of prior TNFi therapy status (Table II).

• *Improvements in FACIT-Fatigue scores*

The mean improvement in FACIT-Fatigue total score from baseline was higher in the secukinumab 150 mg group compared to the placebo group at Week 4, which continued to improve through Week 104 (Fig. 1C). Fatigue scores also improved in patients stratified by baseline hsCRP levels (Fig. 2C) and prior TNFi therapy status (Fig. 3C). Improvement was seen with secukinumab at the earliest assessed time point of Week 4 in both hsCRP and TNFi subgroups. The mean change from baseline at Week 16 (secukinumab *vs*. placebo) was 7.1 *versus* 3.3 for normal hsCRP ($p=0.15$), 8.7 *versus* 3.6 ($p<0.05$) for elevated hsCRP, 10.0 *versus* 5.2 ($p<0.05$) for TNFi-naïve and 5.7 *versus* 0.5 ($p=0.06$) for TNFi-IR groups. At Week 104, higher magnitudes of improvements in FACIT-Fatigue scores were observed in patients with elevated hsCRP (12.9) than normal hsCRP (8.3); however, improvements were comparable between TNFi-naïve (11.0) and TNFi-IR (11.6) patients. Improvements in fatigue measured by BASDAI Question no. 1 were also observed in patients treated with secukinumab *versus* placebo at Week 16 across all groups (overall population, by baseline hsCRP levels, and by TNF status), which were sustained or further improved through Week 104 (Fig. 4).

• *Correlation analysis*

At Week 16, associations between spinal and nocturnal pain and fatigue (spinal/nocturnal pain correlation coefficients with FACIT-Fatigue score: -0.49/-0.48 [$p<0.05$ for both correlations] and with FACIT-Fatigue response: -0.48/-0.51 [$p<0.05$ for both correlations]; Table II), between pain and overall level of fatigue (BASDAI Question no. 1: 0.72/0.65 [$p<0.05$ for both correlations]), and between pain and ASQoL item 5 (sleep quality) response (-0.46/-0.43 [$p<0.05$ for both correlations]; Table II) were observed in patients treated with secukinumab 150 mg. Correlation coefficients between pain and either

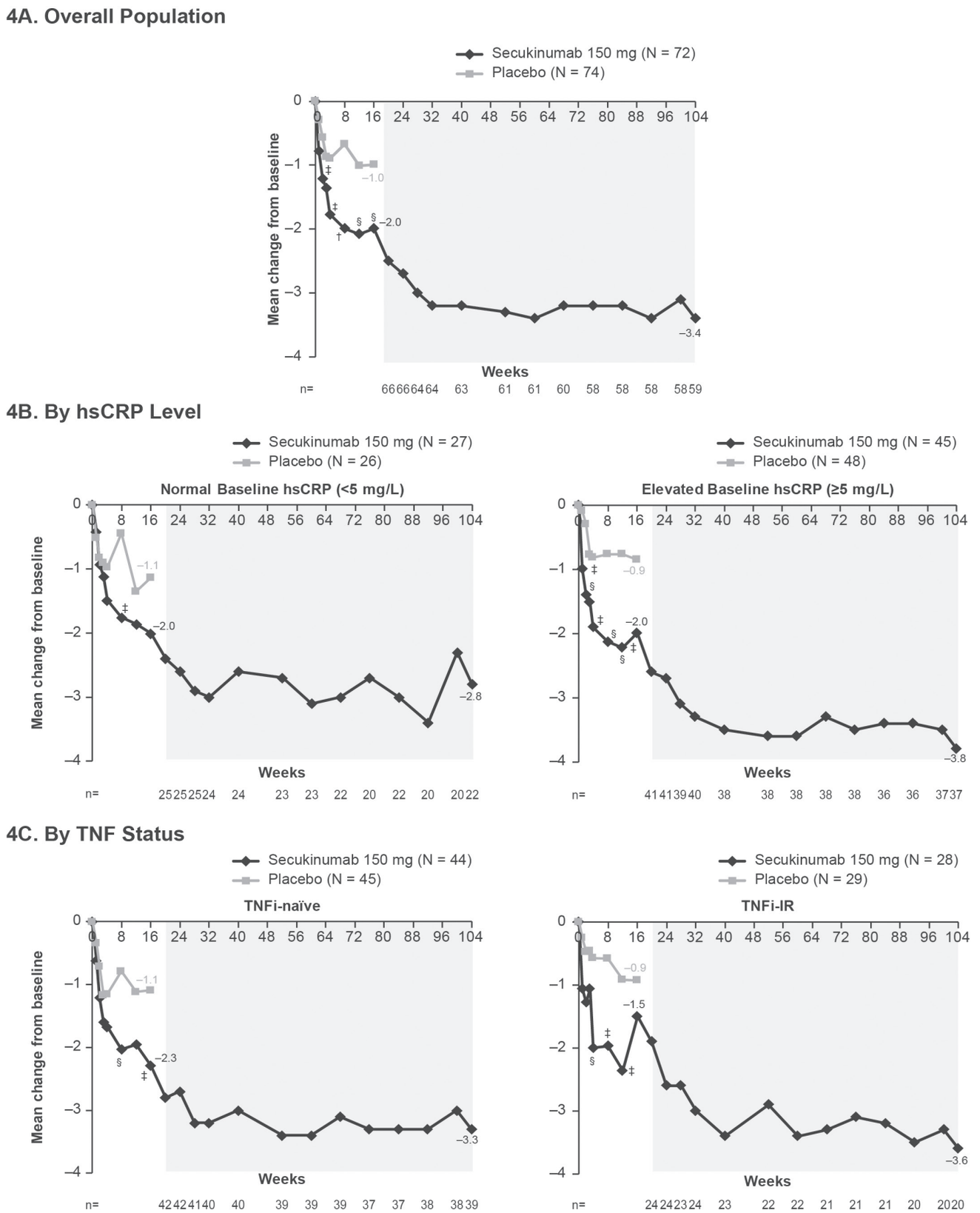

Fig. 4. Improvement in BASDAI Question no. 1 (Overall Level of Fatigue): Overall Population (**A**), by hsCRP Level (**B**), and by TNF Status (**C**) through Week 104.
$^{\dagger}p<0.001$; $^{\S}p<0.01$; $^{\ddagger}p<0.05$ *vs*. placebo; LS mean change using MMRM from Week 1–16 and observed data presented from Week 20–104 (shaded area).
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; hsCRP: high-sensitivity C-reactive protein; IR: inadequate response; LS: least squares; MMRM: mixed-effects model repeated measures; N, number of randomised patients; n: number of evaluable patients; TNFi: tumour necrosis factor inhibitor.

FACIT-Fatigue, overall level of fatigue (BASDAI Question no. 1), or ASQoL item 5 (sleep quality) followed a similar trend among TNFi-naïve and TNFi-IR patients treated with secukinumab, with a greater magnitude of improvement reported in the TNFi-naïve group (Table II).

Discussion

The long-term (Week 104) efficacy and safety data of secukinumab in AS from the MEASURE 2 study has been published previously (30). This is the first report detailing the effects of secukinumab treatment specifically on pain and fatigue over 2 years in patients with AS from the MEASURE 2 study at the approved dose of 150 mg. These findings demonstrated that secukinumab provided rapid and sustained improvement in pain and fatigue, two of the most troubling symptoms in patients with AS, and that improvements were observed regardless of baseline hsCRP levels or prior TNFi therapy.

Elevated baseline CRP levels have been reported to be associated with pain and fatigue symptoms in patients with AS (15-16) and reported as a predictor of treatment response to TNFi (18-21, 25-28). It has been shown that serum IL-17 levels are strongly correlated with inflammation and CRP levels in rheumatoid arthritis (37). However, this correlation is not fully known or understood in AS, with CRP being one of many inflammatory markers involved in the pathogenesis of AS (14-16, 37). In this *post hoc* analysis, secukinumab 150 mg improved pain and fatigue scores in AS patients with normal baseline hsCRP, suggesting IL-17A inhibition may have an effect on patients' symptoms that is independent of detectable levels of baseline inflammation. Secukinumab improved pain and fatigue scores in patients regardless of prior TNFi therapy, with a higher magnitude of improvement in pain scores in TNFi-naïve patients; improvements in fatigue scores were similar in TNFi-naïve and TNFi-IR patients.

According to literature reports, spinal and nocturnal back pain are the greatest factors contributing to the severity of fatigue in patients with AS during the daytime (3, 4, 7, 10). In this study, a correlation between pain (spinal or nocturnal) scores and FACIT-Fatigue, as well as between pain and fatigue assessed by BASDAI Question no. 1, were observed. Thus, improvement in pain may lead to improvement in fatigue, suggesting that an early reduction in pain symptoms could play a role in controlling fatigue in AS patients treated with secukinumab. A correlation was also observed between pain scores and ASQoL item 5 (sleep quality) response in patients treated with secukinumab 150 mg. Although there are conflicting reports regarding the correlation between AS-associated pain and fatigue in patients, studies have shown that pain reduces the quality of sleep, which ultimately could increase the levels of fatigue (2, 3, 9, 13). TNFi have been reported to reduce sleep disturbance by reducing AS-associated pain and thereby decreasing fatigue (12, 13, 15). Similarly, in this study, the improvements in fatigue and sleep with secukinumab may have been as a result of improvements in pain. However, additional multivariate analysis is needed to establish the associations among these symptoms and to further characterise the treatment response to secukinumab.

The MEASURE 2 study was not designed to evaluate the impact of pain and fatigue in patients with AS, which are presented here as *post hoc* analyses. Moreover, according to the predefined patient population in the protocol, the MEASURE 2 study only included patients with AS, as opposed to the broader population of patients with axial spondyloarthritis, which includes non-radiographic axial spondyloarthritis. In addition, there was no placebo comparator group beyond Week 16 for ethical reasons, as per the MEASURE 2 study design. The ASQoL item 5 (sleep quality) data was not derived from a dedicated and validated instrument for sleep assessment, as has been used in other studies (13). Despite these limitations, multivariate analyses could better characterise the relationship between pain, sleep quality, and fatigue as concurrent phenomena. Also, further analysis needs to be done to establish the relationship between hsCRP levels and pain or fatigue symptom in AS.

In conclusion, secukinumab provided rapid and sustained relief in pain and fatigue symptoms over 2 years in patients with active AS, regardless of baseline hsCRP levels or prior TNFi therapy, providing further evidence that IL-17A inhibition with secukinumab is an effective treatment for the signs and symptoms of AS.

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