Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background **Interleukin 17A is a proinflammatory cytokine that is implicated in the pathogenesis of psoriatic arthritis. We assessed the efficacy and safety of subcutaneous secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis.**

Methods **In this phase 3, double-blind, placebo-controlled study undertaken at 76 centres in Asia, Australia, Canada, Europe, and the USA, adults (aged ≥18 years old) with active psoriatic arthritis were randomly allocated in a 1:1:1:1 ratio with computer-generated blocks to receive subcutaneous placebo or secukinumab 300 mg, 150 mg, or 75 mg once a week from baseline and then every 4 weeks from week 4. Patients and investigators were masked to treatment assignment. The primary endpoint was the proportion of patients achieving at least 20% improvement in the American College of Rheumatology response criteria (ACR20) at week 24. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01752634.**

Findings **Between April 14, and Nov 25, 2013, 397 patients were randomly assigned to receive secukinumab 300 mg (n=100), 150 mg (n=100), 75 mg (n=99), or placebo (n=98). A significantly higher proportion of patients achieved an ACR20 at week 24 with secukinumab 300 mg (54 [54%] patients; odds ratio versus placebo 6·81, 95% CI 3·42–13·56; p<0·0001), 150 mg (51 [51%] patients; 6·52, 3·25–13·08; p<0·0001), and 75 mg (29 [29%] patients; 2·32, 1·14–4·73; p=0·0399) versus placebo (15 [15%] patients). Up to week 16, the most common adverse events were upper respiratory tract infections (four [4%], eight [8%], ten [10%], and seven [7%] with secukinumab 300 mg, 150 mg, 75 mg, and placebo, respectively) and nasopharyngitis (six [6%], four [4%], six [6%], and eight [8%], respectively). Serious adverse events were reported by five (5%), one (1%), and four (4%) patients in the secukinumab 300 mg, 150 mg, and 75 mg groups, respectively, compared with two (2%) in the placebo group. No deaths were reported.**

Interpretation **Subcutaneous secukinumab 300 mg and 150 mg improved the signs and symptoms of psoriatic arthritis, suggesting that secukinumab is a potential future treatment option for patients with this disorder.**

Funding **Novartis.**

Published **Online** June 29, 2015 http://dx.doi.org/10.1016/S0140-6736(15)61134-5

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(15)61170-9

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Introduction

Psoriatic arthritis, a chronic inflammatory disease that can affect peripheral and axial joints, entheses, and the skin, is associated with impaired physical function and poor quality of life.[1,2] Pathogenesis-based interventions, particularly therapies targeting tumour necrosis factor (TNF), have improved outcomes in patients with psoriatic arthritis.[3–7] Recently, the interleukin 12/23 inhibitor ustekinumab and the phosphodiesterase-4 inhibitor apremilast have also shown efficacy.[8–10] Despite this progress, not all patients respond to or tolerate therapy, and clinical needs are largely unmet.

Interleukin 17A and its receptor are expressed in synovial tissues and as such the interleukin-17 pathway is proposed to contribute to the pathogenesis of psoriatic arthritis.[11–15] Interleukin 17A can mediate a variety of effector biological functions that can result in joint and enthesial inflammation, damage, and tissue remodelling.[16]

Secukinumab, a human monoclonal antibody that inhibits the effector function of interleukin 17A, has been shown to be better than placebo and etanercept in improving the signs and symptoms of psoriasis.[17] In the phase 3 FUTURE 1 study of 606 patients with psoriatic arthritis, intravenous loading with secukinumab followed by subcutaneous maintenance dosing significantly improved key clinical domains of disease versus placebo, including signs and symptoms, radiographic disease progression, physical functioning, and quality of life.[18]

We report the main results from FUTURE 2, an ongoing phase 3 trial of the efficacy and safety of subcutaneous loading and maintenance dosing of secukinumab versus placebo in patients with psoriatic arthritis.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled phase 3 trial was done at 76 centres in Asia, Australia,

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Research in context

Evidence before this study

We searched PubMed using the terms "psoriatic arthritis (PsA)", "biologic", and "interleukin-17 (IL-17)" for English language articles published up to April 29, 2015, with no limitation or restriction for year of publication or article type. Increasing clinical and laboratory evidence has linked interleukin 17 to the pathogenesis of immune-mediated inflammatory diseases, such as psoriasis and psoriatic arthritis. The results of several studies, including large phase 3 studies with secukinumab, have shown that inhibition of interleukin 17 improves signs and symptoms in patients with moderate to severe psoriasis, and secukinumab is approved for this indication. Recent clinical data suggested that interleukin-17 inhibition has therapeutic benefit in psoriatic arthritis. Improvements in clinical response, markers of inflammation, and quality-of-life measures were reported in a phase 2, proof-of-concept study of intravenous secukinumab in patients with psoriatic arthritis, but the study did not meet its primary endpoint of a greater proportion of patients achieving at least 20% improvement in the American College of Rheumatology (ACR20) response criteria with secukinumab than with placebo at week 6. More recently, the results of a phase 2 study have shown that inhibition of the interleukin-17 receptor improves the signs and symptoms of psoriatic arthritis.

Added value of this study

FUTURE 2 is the first large phase 3 study in which inhibition of interleukin 17 with a subcutaneous dosing regimen provides significant improvements in important clinical domains of psoriatic arthritis, including joint and skin symptoms, physical function, and quality of life. Moreover, 52-week data from this study suggest that efficacy with secukinumab is sustained over long periods. The safety profile of secukinumab in this study was similar to that reported in patients with moderate to severe psoriasis.

Implications of all the available evidence

Our findings build and expand on previous reports suggesting that interleukin 17 has an important role in the pathogenesis of psoriatic arthritis and suggest that secukinumab might be a suitable alternative biological treatment for this disease.

See Online for appendix

Canada, Europe, and the USA. Changes to the protocol after the start of the study are summarised in the appendix. The study protocol is available from the funder.

Patients were aged 18 years and older, met the ClASsification criteria for Psoriatic ARthritis (CASPAR), and had active disease, defined as at least three tender joints and at least three swollen joints, despite previous treatment with non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, or anti-TNF agents. Concomitant oral corticosteroids (≤10 mg/day prednisone or equivalent) and methotrexate (≤25 mg/week) were allowed provided the dose was stable for at least 2 weeks and at least 4 weeks before randomisation, respectively. Patients who had previously used up to three anti-TNF agents could enrol if they had had an inadequate response or stopped treatment because of safety or tolerability reasons (anti-TNF-IR). Patients who were taking anti-TNF therapy at screening and were judged to be eligible discontinued their treatment for a washout of 4–10 weeks (depending on the drug's half-life) before randomisation. Key exclusion criteria included: previous use of any biological agent other than anti-TNF agents; active inflammatory diseases other than psoriatic arthritis; active infection in the 2 weeks before randomisation, or a history of ongoing, chronic, or recurrent infections; history of malignant disease within the past 5 years (excluding basal cell carcinoma or actinic keratosis, in-situ cervical cancer, or non-invasive malignant colon polyps); and pregnancy. Additional information about the inclusion and exclusion criteria is provided in the appendix.

The study was done in accordance with the principles of the Declaration of Helsinki. All centres received approval from independent ethics committees or institutional review boards. Patients provided written informed consent before the study-related procedures were undertaken.

Randomisation and masking

After 4–10 weeks of screening, patients were randomly assigned in a 1:1:1:1 ratio to receive subcutaneous secukinumab 300 mg, 150 mg, 75 mg, or placebo once a week from baseline to week 4 and then every 4 weeks thereafter. At week 16, patients were classified as responders (≥20% improvement from baseline in tender and swollen joint counts) or non-responders. Placebo-treated patients were randomly assigned again in a 1:1 ratio to receive subcutaneous secukinumab 300 mg or 150 mg every 4 weeks from week 16 (non-responders) or week 24 (responders).

Randomisation was done with an interactive voice or web response system that assigned patients to randomisation numbers identifying assigned treatments and unique medication numbers for the packages of study treatment to be given. Randomisation was stratified according to previous anti-TNF therapy use, with patients being anti-TNF-naive (planned enrolment about 60%) or anti-TNF-IR. Patients and investigators were masked to treatment assignment. Doses were provided in identical prefilled syringes supplied by Novartis. Data analysts remained masked until the week 24 analysis.

Procedures

Additional information about the assessments undertaken during the trial is provided in the appendix. Key efficacy, safety, tolerability, and biochemical assessments were

done at screening, baseline, weeks 24 (primary endpoint) and 52 (prespecified interim follow-up), and timepoints in between. Secukinumab immunogenicity was assessed with a MesoScale Discovery bridging assay[19] using blood samples obtained at baseline, week 24, and week 52.

Outcomes

The primary endpoint was the proportion of patients achieving an ACR20 response at week 24, defined as at least 20% improvement from baseline in the number of tender and swollen joints and at least three of the following five domains with the American College of Rheumatology response criteria: patient's global assessment; physician's global assessment; pain; disability; and an acute-phase reactant.[20]

Secondary endpoints at week 24 were the proportion of patients achieving at least a 75% and at least a 90% improvement in Psoriasis Area-and-Severity Index score (PASI75 and PASI90, respectively);[21] change from baseline in 28-joint Disease Activity Score using C-Reactive Protein (DAS28-CRP);[22] change from baseline in Medical Outcomes Study 36-item Short Form Health Survey version 2 Physical Component Summary (SF36-PCS) score;[23] change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) score;[24] proportion of patients achieving at least 50% improvement in the American College of Rheumatology response criteria (ACR50); resolution of dactylitis and enthesitis; and overall safety and tolerability. PASI75 and PASI90 responses were assessed in patients with at least 3% of their body surface area affected by psoriasis at baseline. Resolution of dactylitis and enthesitis was assessed in patients with these characteristics at baseline, using pooled data (all secukinumab groups combined) for analysis.

Prespecified exploratory endpoints were the proportion of patients achieving at least 70% improvement in the American College of Rheumatology response criteria (ACR70); presence of dactylitis and enthesitis in each

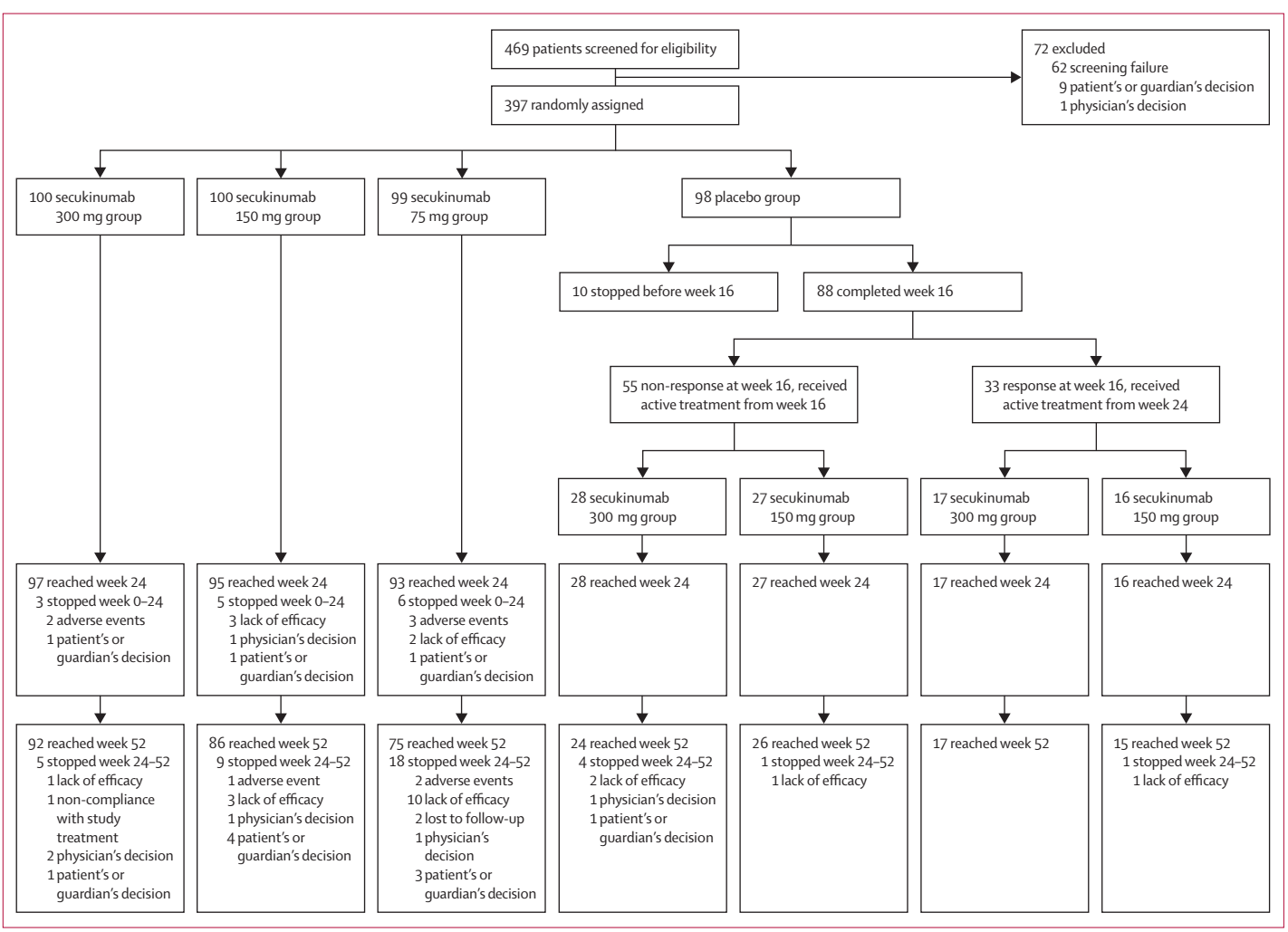

Figure 1: **Trial profile**
All patients who were randomly allocated to treatment were included in the analysis of the prespecified primary and secondary endpoints at week 24.

treatment group (unpooled data); primary and secondary efficacy assessments at week 52; and subgroup analyses according to previous anti-TNF use. Analysis of secukinumab efficacy with and without concomitant methotrexate therapy was done post hoc.

In the safety analyses, we assessed adverse events, serious adverse events, and routine laboratory values. Biochemical investigations were classified according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03).[25]

	Secukinumab 300 mg (n=100)	Secukinumab 150 mg (n=100)	Secukinumab 75 mg (n=99)	Placebo (n=98)
Age (years)	46·9 (12·6)	46·5 (11·7)	48·6 (11·4)	49·9 (12·5)
Women	49 (49%)	45 (45%)	52 (53%)	59 (60%)
Ethnic origin				
White	96 (96%)	90 (90%)	90 (91%)	94 (96%)
Black	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Asian	2 (2%)	6 (6%)	5 (5%)	1 (1%)
Unknown	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Other	1 (1%)	4 (4%)	3 (3%)	3 (3%)
Weight (kg)	85·4 (18·4)	91·2 (19·8)	85·6 (20·6)	86·2 (19·8)
Number of previous anti-TNF treatments for psoriatic arthritis				
0	67 (67%)	63 (63%)	65 (66%)	63 (64%)
1	16 (16%)	26 (26%)	21 (21%)	16 (16%)
2 or 3	17 (17%)	11 (11%)	13 (13%)	19 (19%)
Methotrexate use at randomisation	44 (44%)	44 (44%)	47 (47%)	50 (51%)
Systemic glucocorticoid use at randomisation	18 (18%)	23 (23%)	19 (19%)	21 (21%)
Patients with specific disease characteristics				
Psoriasis body surface area ≥3%	41 (41%)	58 (58%)	50 (51%)	43 (44%)
PASI ≤10*	21 (51%)	25 (43%)	28 (56%)	23 (53%)
PASI score >10*	20 (49%)	33 (57%)	22 (44%)	20 (47%)
Dactylitis	46 (46%)	32 (32%)	33 (33%)	27 (28%)
Dactylitis count	3·6 (3·5)	4·5 (5·1)	3·0 (3·6)	2·7 (2·2)
Enthesitis	56 (56%)	64 (64%)	68 (69%)	65 (66%)
Enthesitis count	2·8 (1·7)	3·2 (1·6)	3·2 (1·7)	3·1 (1·7)
Baseline disease and quality-of-life scores				
Tender joint count (78 joints)	20·2 (13·3)	24·1 (19·4)	22·2 (16·3)	23·4 (19·0)
Swollen joint count (76 joints)	11·2 (7·8)	11·9 (10·1)	10·8 (9·2)	12·1 (10·7)
DAS28-CRP	4·8 (1·0)	4·9 (1·1)	4·7 (1·0)	4·7 (1·0)
PASI*	11·9 (8·4)	16·2 (14·3)	12·1 (10·2)	11·6 (8·3)
Physician's global assessment (VAS)	55·0 (14·7)	56·7 (16·6)	59·0 (17·9)	55·0 (16·0)
HAQ-DI	1·3 (0·6)	1·2 (0·6)	1·2 (0·6)	1·2 (0·7)
Pain (VAS)	57·7 (19·0)	58·9 (19·8)	56·7 (21·1)	55·4 (22·1)
Patient's global assessment (VAS)	60·7 (18·9)	62·0 (19·5)	59·0 (19·1)	57·6 (19·8)
SF36-PCS	36·9 (8·0)	36·2 (8·1)	36·2 (8·1)	37·4 (8·8)

Data are number (%) or mean (SD). TNF=tumour necrosis factor. PASI=Psoriasis Area and Severity Index. DAS28-CRP=28-joint Disease Activity Score using C-Reactive Protein. VAS=Visual Analogue Scale. HAQ-DI=Health Assessment Questionnaire Disability Index. SF36-PCS=36-item Short Form Health Survey. *Assessed in patients with psoriasis on at least 3% of their body surface area.

Table 1: **Baseline characteristics of patients in the secukinumab and placebo groups**

Statistical analysis

A sample size of 100 patients per group was estimated to provide about 92% power to detect a treatment difference of 26% for the primary endpoint of ACR20 response at week 24 with Fisher's exact test, and about 80% power for secondary endpoints. The expected treatment difference of 26% for the primary endpoint was based on an expected overall placebo response of 21% (weighted mean of placebo data in anti-TNF-naive [25%] and anti-TNF-IR [15%] patients from PSUMMIT I and II[8,9]) and an expected overall secukinumab response of 47% (weighted average of expected response in anti-TNF-naive [55%] and anti-TNF-IR [35%] patients). Weighted averages were based on the planned enrolment of about 40% anti-TNF-IR patients.

Data were gathered according to Good Clinical Practice guidelines by the study investigators. The primary and secondary and relevant prespecified exploratory endpoints were analysed according to the prespecified analysis plan with SAS software (version 9.3). Safety data are presented for week 16, when all patients remained in the originally randomised groups, and across the entire study period; efficacy was assessed at week 24 (primary analysis) and up to week 52. A sequential hierarchical testing method was used to maintain the familywise type 1 error rate at 5% across the primary and ranked secondary endpoints. If the primary efficacy analysis was significant, secondary analyses were completed in the following sequence: ACR20, PASI75, PASI90, DAS28-CRP, SF36-PCS, HAQ-DI, ACR50, dactylitis (pooled data across doses), and enthesitis (pooled data across doses; see appendix for further details).

For week 24 analyses of binary variables, patients who switched from placebo to secukinumab at week 16 because of non-response were imputed as non-responders at week 24 (early escape penalty). Week 16 non-responders in the secukinumab groups were also imputed as non-responders at week 24. Patients with missing data or who had discontinued treatment early were imputed as non-responders. Odds ratios (ORs), 95% CIs, and p values were computed for comparisons of secukinumab doses versus placebo from a logistic regression model with treatment and previous anti-TNF use as factors and baseline weight as a covariate. Baseline PASI score was a covariate in PASI75 and PASI90 analyses.

For analyses of continuous variables at week 24, we used a mixed-effects model with treatment regimen, analysis visit, and previous anti-TNF use as factors, and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline score by analysis visit were interaction terms, and an unstructured covariance structure was assumed.

Inferential analyses (with imputation) and descriptive summaries (observed data) were done on primary and secondary endpoints from week 28 onwards. In the inferential analysis of binary variables over this period,

patients who withdrew from the study were deemed non-responders from the time of withdrawal, without the penalty for early escape that was applied in the primary analysis. Efficacy analyses from week 28 onwards included only patients originally randomised to secukinumab.

Safety endpoints were assessed for all patients who received at least one dose of study drug and are summarised descriptively. A data monitoring committee reviewed unmasked safety data at regular intervals. Potential major adverse cardiac events were adjudicated by an independent expert committee.

This study is registered with ClinicalTrials.gov, number NCT01752634.

Role of the funding source

A scientific steering committee and the funder designed the study. The statisticians employed by the funder did the data and statistical analyses. All authors had access to the study data and participated in the decision to publish. The corresponding author, with approval from the coauthors, made the final decision to submit for publication.

Results

Between April 14, and Nov 25, 2013, 397 patients were randomly assigned to receive secukinumab 300 mg (n=100), 150 mg (n=100), 75 mg (n=99), or placebo (n=98); 373 (94%) of these patients completed week 24 treatment (figure 1). No patients were excluded from the efficacy and safety analyses.

Baseline demographics, disease characteristics, and previous or concomitant medication use were similar across the study groups, except for imbalances in baseline PASI score, proportion of female patients, patients with psoriasis affecting at least 3% of their body surface area, and patients with dactylitis or enthesitis (table 1). At baseline, 258 (65%) of 397 patients were anti-TNF-naive and 185 (47%) were receiving concomitant methotrexate (table 1).

The primary endpoint was met with all secukinumab doses. ACR20 response rates at week 24 were significantly higher in the secukinumab 300 mg (54%; p<0·0001), 150 mg (51%; p<0·0001), and 75 mg (29%; p=0·0399) groups versus placebo (15%; figure 2; table 2).

We assessed the secondary endpoints in a hierarchical order. PASI75 and PASI90 response rates, and mean changes from baseline in DAS28-CRP and SF36-PCS were all significantly higher with secukinumab 300 mg and 150 mg versus placebo at week 24 (table 2). Secukinumab 300 mg significantly improved HAQ-DI (table 2) and ACR50 (figure 2; table 2). Secukinumab 75 mg did not significantly improve PASI75 response versus placebo; thus, subsequent endpoints in the hierarchy were not achieved with this dose (table 2). Improvements in dactylitis and enthesitis with secukinumab (pooled) versus placebo were not significant in the hierarchical analysis because the testing strategy required all other endpoints for all doses to be significant before further testing, and this requirement was not met. The proportions of patients whose dactylitis and enthesitis resolved at week 24 in each individual treatment group are presented in the appendix.

In prespecified exploratory analyses, ACR70 response was achieved by 20 (20%) of 100 patients in the secukinumab 300 mg group, 21 (21%) of 100 in the 150 mg group, and six (6%) of 99 in the 75 mg group, compared with one (1%) of 98 patients in the placebo group. ACR and PASI response rates were higher with secukinumab than with placebo in both anti-TNF-naive and anti-TNF-IR patients with the magnitude of response generally being higher in the anti-TNF-naive population (prespecified exploratory analysis; table 3). The interaction between treatment and anti-TNF-status was

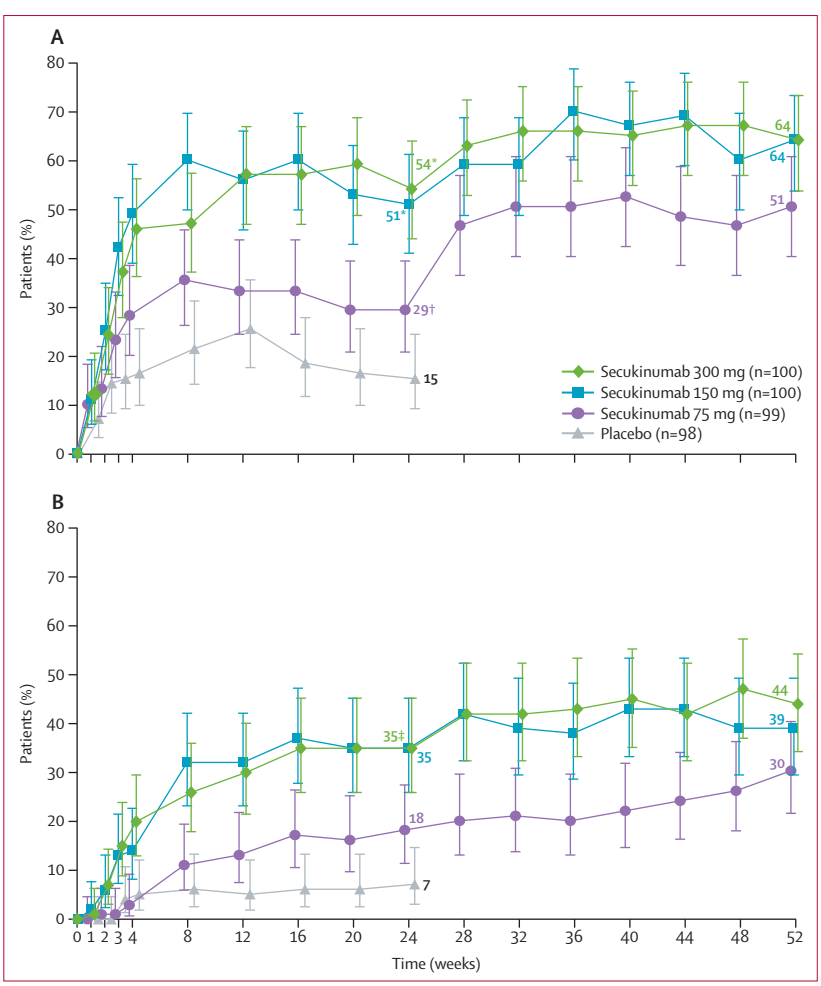

Figure 2: **ACR20 (A) and ACR50 (B) response rates from baseline to week 52**
Missing data were imputed as non-response until week 52. p values at week 24 were analysed as part of the statistical hierarchy and were adjusted for multiplicity of testing. Response rates over time are presented for patients according to their treatment group at randomisation. ACR20=at least 20% improvement in the American College of Rheumatology response criteria. ACR50=at least 50% improvement in the American College of Rheumatology response criteria. *p<0·0001 versus placebo. †p<0·05 versus placebo. ‡p<0·01 versus placebo.

	Secukinumab 300 mg (n=100)			Secukinumab 150 mg (n=100)			Secukinumab 75 mg (n=99)			Secukinumab (pooled data)			Placebo (n=98)
	Value*	Effect size versus placebo (95% CI)	p value versus placebo	Value*	Effect size versus placebo (95% CI)	p value versus placebo	Value*	Effect size versus placebo (95% CI)	p value versus placebo	Value*	Effect size versus placebo (95% CI)	p value versus placebo	Value*
ACR20	54/100 (54%)	OR 6·81 (3·42 to 13·56)	<0·0001	51/100 (51%)	OR 6·52 (3·25 to 13·08)	<0·0001	29/99 (29%)	OR 2·32 (1·14 to 4·73)	0·0399	..	..	..	15/98 (15%)
PASI75†	26/41 (63%)	OR 9·48 (3·33 to 27·00)	<0·0001	28/58 (48%)	OR 5·70 (2·12 to 15·34)	0·0017	14/50 (28%)	OR 2·07 (0·74 to 5·81)	0·1650	..	..	..	7/43 (16%)
PASI90†	20/41 (49%)	OR 10·74 (3·13 to 36·84)	0·0005	19/58 (33%)	OR 6·36 (1·89 to 21·47)	0·0057	6/50 (12%)	OR 1·38 (0·36 to 5·36)	0·6421	..	..	..	4/43 (9%)
DAS28-CRP	–1·61 (0·11)	Difference –0·65 (–1·02 to –0·29)	0·0013	–1·58 (0·11)	Difference –0·62 (–0·98 to –0·26)	0·0057	–1·12 (0·11)	Difference –0·16 (–0·53 to 0·20)	0·6421	..	..	..	–0·96 (0·15)
SF36-PCS	7·25 (0·74)	Difference 5·30 (2·91 to 7·69)	0·0013	6·39 (0·73)	Difference 4·44 (2·05 to 6·83)	0·0057	4·38 (0·75)	Difference 2·42 (0·02 to 4·83)	0·6421	..	..	..	1·95 (0·97)
HAQ-DI	–0·56 (0·05)	Difference –0·25 (–0·40 to –0·10)	0·0040	–0·48 (0·05)	Difference –0·17 (–0·32 to –0·02)	0·0555	–0·32 (0·05)	Difference –0·01 (–0·16 to 0·15)	0·9195	..	..	..	–0·31 (0·06)
ACR50	35/100 (35%)	OR 7·15 (2·97 to 17·22)	0·0040	35/100 (35%)	OR 7·54 (3·11 to 18·25)	0·0555	18/99 (18%)	OR 2·91 (1·15 to 7·36)	0·9195	..	..	..	7/98 (7%)
Resolution of dactylitis‡	..	..	..	..	..	..	..	..	..	52/111 (47%)	OR 4·35 (1·39 to 14·29)	0·9195	4/27 (15%)
Resolution of enthesitis‡	..	..	..	..	..	..	..	..	..	76/188 (40%)	OR 2·56 (1·30 to 5·00)	0·9195	14/65 (22%)

Least-squares mean and 95% CI are from a mixed-model repeated measures with treatment regimen, analysis visit, and randomisation stratum (anti-TNF-naive or anti-TNF-IR) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, and an unstructured covariance structure. OR and 95% CI are from a logistic regression model with treatment and randomisation stratum (anti-TNF-naive or anti-TNF-IR) as factors and baseline weight as a covariate; OR greater than 1 favours secukinumab. All p values are versus placebo and are adjusted for multiplicity. ACR20=at least 20% improvement in the American College of Rheumatology. OR=odds ratio. PASI=Psoriasis Area and Severity Index. DAS28-CRP=28-joint Disease Activity Score using C-Reactive Protein. SF36-PCS=36-item Short Form Health Survey. HAQ-DI=Health Assessment Questionnaire Disability Index. ACR50=at least 50% improvement in the American College of Rheumatology. Anti-TNF-IR=inadequate response to a tumour necrosis factor drug or treatment stopped because of safety or tolerability reasons. *Data are n/N (%) or least-squares mean (SE). †Assessed in patients with psoriasis on at least 3% of their body surface area. ‡Resolution of dactylitis and enthesitis was assessed only in patients with these symptoms at baseline; pooled data are reported for secukinumab 300 mg, 150 mg, and 75 mg.

Table 2: **Comparison of secukinumab versus placebo at week 24 for prespecified primary and secondary endpoints**

not significant (p=0·24); however, clinically meaningful differences were noted between the effect sizes for the 300 mg and 150 mg doses in anti-TNF-IR patients (table 3). In post-hoc analyses, improvements were noted in ACR response rates with secukinumab versus placebo at week 24, with and without concomitant methotrexate use (appendix).

At week 52, 335 (84%) of 397 patients remained in this study. Clinical responses with secukinumab 300 mg and 150 mg across the psoriatic arthritis domains assessed at week 24 were maintained until 52 weeks of treatment in patients initially allocated to these treatments (appendix). Using a conservative estimate of efficacy with missing values imputed as non-response, ACR20, ACR50, and ACR70 responses at week 52 were noted in 64 (64%), 44 (44%), and 24 (24%) of 100 patients, respectively, initially allocated to the secukinumab 300 mg group; 64 (64%), 39 (39%), and 20 (20%) of 100 patients, respectively, in the 150 mg group; and 50 (51%), 30 (30%), and 16 (16%) of 99 patients in the 75 mg group, respectively (figure 2; appendix). Corresponding response rates for ACR20, ACR50, and ACR70 with actual data were 64 (73%), 44 (50%), and 24 (27%) of 88 patients, respectively, in the secukinumab 300 mg group; 64 (73%), 39 (44%), and 20 (23%) of 88 patients, respectively, in the secukinumab 150 mg group, and 50 (67%), 30 (40%), and 16 (21%) of 75 patients, respectively, in the secukinumab 75 mg group.

No deaths were reported during the study. There were no reports of suicide or suicidal ideation in secukinumab-treated patients. The incidence of adverse events during the placebo-controlled period was similar across the study groups, except for a slightly higher incidence of serious adverse events in the secukinumab 300 mg and 75 mg groups than in the 150 mg and placebo groups (table 4). Over the entire treatment (mean exposure: secukinumab 411·7 days [SD 106·9] and placebo 130·6 days [29·0]), the exposure-adjusted rates of serious adverse events were 6·4, 5·1, and 11·2 per 100 patient-years for patients who received at least one dose of secukinumab 300 mg, 150 mg, and 75 mg, respectively, compared with 8·6 per 100 patient-years in placebo-treated patients (table 4). Reported serious adverse events are listed in the appendix. Exposure-adjusted incidence of infections and infestations were 78·7, 86·7, and 63·7 per 100 patient-years in patients who received secukinumab 300 mg, 150 mg, and 75 mg, respectively, compared with

	Secukinumab 300 mg			Secukinumab 150 mg			Secukinumab 75 mg			Placebo
	Value*	Odds ratio versus placebo (95% CI)	p value versus placebo	Value*	Odds ratio versus placebo (95% CI)	p value versus placebo	Value*	Odds ratio versus placebo (95% CI)	p value versus placebo	
Anti-TNF-naive patients										
ACR20 response	39/67 (58%)	7·77 (3·36–17·98)	<0·0001	40/63 (63%)	9·99 (4·22–23·66)	<0·0001	24/65 (37%)	3·17 (1·36–7·40)	0·0075	10/63 (16%)
ACR50 response	26/67 (39%)	9·72 (3·14–30·09)	<0·0001	28/63 (44%)	12·54 (4·03–39·05)	<0·0001	16/65 (25%)	4·90 (1·53–15·64)	0·0074	4/63 (6%)
ACR70 response	15/67 (22%)	NE	0·0003	17/63 (27%)	NE	<0·0001	4/65 (6%)	NE	0·3654	1/63 (2%)
PASI75 response†	19/30 (63%)	7·96 (2·42–26·16)	0·0006	20/36 (56%)	6·33 (1·99–20·15)	0·0018	10/33 (30%)	1·94 (0·59–6·34)	0·2729	6/31 (19%)
PASI90 response†	16/30 (53%)	13·11 (3·09–55·59)	0·0005	14/36 (39%)	8·09 (1·92–34·09)	0·0044	4/33 (12%)	1·40 (0·28–7·02)	0·6825	3/31 (10%)
Anti-TNF-IR patients										
ACR20 response	15/33 (45%)	4·97 (1·53–16·15)	0·0077	11/37 (30%)	2·55 (0·78–8·32)	0·1216	5/34 (15%)	1·03 (0·27–3·95)	0·9639	5/35 (14%)
ACR50 response	9/33 (27%)	4·37 (1·05–18·26)	0·0431	7/37 (19%)	2·39 (0·56–10·15)	0·2374	2/34 (6%)	0·69 (0·11–4·42)	0·6941	3/35 (9%)
ACR70 response	5/33 (15%)	NE	0·0228	4/37 (11%)	NE	0·1151	2/34 (6%)	NE	0·2391	0/35 (0%)
PASI75 response†	7/11 (64%)	19·29 (1·77–210·18)	0·0152	8/22 (36%)	6·17 (0·66–57·30)	0·1094	4/17 (24%)	3·46 (0·33–36·06)	0·2986	1/12 (8%)
PASI90 response†	4/11 (36%)	6·43 (0·58–70·74)	0·1282	5/22 (23%)	3·50 (0·35–34·91)	0·2859	2/17 (12%)	1·37 (0·11–17·30)	0·8098	1/12 (8%)

Data are n/N (%), unless otherwise indicated. p values not adjusted for multiplicity of testing. ACR20=at least 20% improvement in the American College of Rheumatology. ACR50=at least 50% improvement in the American College of Rheumatology. ACR70=at least 70% improvement in the American College of Rheumatology. NE=not estimable. PASI=Psoriasis Area and Severity Index. Anti-TNF-IR=inadequate response to a tumour necrosis factor agent or stopped treatment because of safety or tolerability reasons. *Missing data were imputed as non-response. †Assessed in patients with psoriasis on at least 3% of their body surface area at baseline.

Table 3: **Efficacy of secukinumab at week 24 in anti-TNF-naive and anti-TNF-IR patients in a prespecified exploratory analysis**

108·0 per 100 patient-years in placebo-treated patients (table 4). Upper respiratory tract infections and nasopharyngitis were the most common infections, occurring at similar rates in the secukinumab treatment groups. No cases of active tuberculosis were reported.

Candida infections were reported in 11 patients, all on secukinumab: six cases of oral candidiasis (two patients in the 300 mg group, three patients in the 150 mg group, and one patient in the 75 mg group); four cases of vulvovaginal candidiasis (one patient in the 300 mg group and three patients in the 150 mg group), one case of oesophageal candidiasis (300 mg group), and one candida infection (300 mg group); one patient had concurrent vulvovaginal and oral candidiasis (150 mg group). These events were judged by the investigators to be mild or moderate, resolved spontaneously or with oral therapy, and did not lead to study withdrawal.

Three cases of squamous cell carcinoma were reported with secukinumab (two in the 75 mg group and one in the 150 mg group). Both cases in the 75 mg group resulted in discontinuation of study treatment. A myocardial infarction was recorded in a patient with a history of sinus tachycardia and ongoing hypertension and hyperlipidaemia who received secukinumab 75 mg; the patient continued in the study. Crohn's disease was not reported as an adverse event in any patient. One patient receiving secukinumab 300 mg had haemorrhagic diarrhoea, which resolved by itself; the patient continued in the study. Two cases of ulcerative colitis were reported (one in the 300 mg group, which resolved, and one in the 150 mg group, which did not resolve); both patients continued in the study. Transient CTCAE grade 3 neutropenia occurred in one patient (300 mg group). No patients withdrew from the study because of neutropenia. Treatment-emergent anti-secukinumab antibodies (positive during study but negative at baseline) were detected in one patient originally allocated to placebo who switched to secukinumab 150 mg at week 24. Immunogenicity-related adverse events or loss of efficacy were not reported in this patient.

Discussion

In this phase 3 trial, subcutaneous administration of the anti-interleukin-17A monoclonal antibody secukinumab significantly improved the signs and symptoms of psoriatic arthritis versus placebo. ACR20 response rates at week 24 were better with all secukinumab doses than with placebo. Additional efficacy outcomes at week 24 also showed significant benefits with secukinumab 300 mg and 150 mg versus placebo, but responses with secukinumab 75 mg were lower and not significantly

	Placebo-controlled period (until week 16)				Entire treatment period*			
	Secukinumab 300 mg (n=100)	Secukinumab 150 mg (n=100)	Secukinumab 75 mg (n=99)	Placebo (n=98)	Secukinumab 300 mg (n=145)†	Secukinumab 150 mg (n=143)†	Secukinumab 75 mg (n=99)	Placebo (n=98)
Any adverse event	56 (56%)	57 (57%)	48 (48%)	57 (58%)	113 (189·1)	117 (209·0)	77 (175·3)	61 (323·5)
Serious adverse event	5 (5%)	1 (1%)	4 (4%)	2 (2%)	10 (6·4)	8 (5·1)	12 (11·2)	3 (8·6)
Death	0	0	0	0	0	0	0	0
Discontinuation of treatment because of any adverse event‡	2 (2%)	0	2 (2%)	3 (3%)	2 (2%)	1 (1%)	5 (5%)	4 (4%)
Infection or infestation	29 (29%)	30 (30%)	23 (23%)	30 (31%)	78 (78·7)	82 (86·7)	48 (63·7)	30 (108·0)
Common adverse event§								
Upper respiratory tract infection	4 (4%)	8 (8%)	10 (10%)	7 (7%)	26 (17·9)	25 (17·6)	21 (21·8)	7 (20·7)
Nasopharyngitis	6 (6%)	4 (4%)	6 (6%)	8 (8%)	20 (13·5)	18 (12·3)	11 (10·5)	8 (24·2)
Diarrhoea	2 (2%)	2 (2%)	3 (3%)	3 (3%)	10 (6·3)	8 (5·1)	8 (7·4)	3 (8·8)
Headache	7 (7%)	4 (4%)	2 (2%)	4 (4%)	9 (5·9)	10 (6·5)	5 (4·6)	5 (14·9)
Nausea	3 (3%)	4 (4%)	4 (4%)	4 (4%)	7 (4·5)	8 (5·2)	6 (5·6)	4 (11·9)
Sinusitis	1 (1%)	2 (2%)	0	1 (1%)	10 (6·5)	6 (3·8)	5 (4·6)	1 (2·9)
Psoriatic arthropathy	0	3 (3%)	1 (1%)	2 (2%)	5 (3·1)	10 (6·5)	6 (5·5)	2 (5·8)
Urinary tract infection	2 (2%)	4 (4%)	1 (1%)	4 (4%)	6 (3·8)	6 (3·9)	4 (3·6)	4 (11·8)
Haematuria	2 (2%)	3 (3%)	1 (1%)	1 (1%)	2 (1·3)	4 (2·5)	3 (2·7)	1 (2·9)
Vomiting	2 (2%)	2 (2%)	2 (2%)	1 (1%)	3 (1·9)	4 (2·5)	4 (3·6)	2 (5·8)

Data are number (%) or number (incidence per 100 patient-years). *Defined as the period from baseline up to week 52 visit of the last patient enrolled in the study. †Includes patients who were randomly allocated to receive the stated dose of secukinumab at baseline and patients randomly allocated to placebo at baseline who were rerandomised to receive this dose of secukinumab from week 16 or week 24 depending on the clinical response. ‡Exposure-adjusted incidence rates were not calculated for discontinuations because of adverse events. §The most common adverse events are reported as the preferred terms from the Medical Dictionary for Regulatory Activities, and occurred in at least 2% of patients in the pooled secukinumab group until week 16 or at an incidence of at least five per 100 patient-years in the pooled secukinumab group during the entire treatment period.

Table 4: **Safety and tolerability profile of secukinumab until week 16 (placebo-controlled period) and for the entire treatment period***

different from placebo in the hierarchical analysis. These results confirm and greatly extend the findings of earlier studies with secukinumab in psoriatic arthritis.[18] Consistent with the psoriasis phase 3 programme,[17] improvements in psoriasis symptoms in FUTURE 2 were greater with secukinumab 300 mg than with 150 mg.

Although anti-TNF agents improve outcomes in psoriatic arthritis,[3–7] many patients still have inadequate disease control or are intolerant to these agents, or both. Loss of response over time is also clinically problematic. Although responses were generally higher in the anti-TNF-naive population, the clinical benefits of secukinumab were noted in both anti-TNF-naive and anti-TNF-IR patients. Secukinumab might therefore be an additional treatment option for both populations.

The safety profile of secukinumab was consistent with earlier reports of secukinumab in psoriatic arthritis[18] and psoriasis.[17] The types and incidence of adverse events with secukinumab were similar to placebo at week 16, with no apparent relation to dose. The rate of discontinuations because of adverse events with secukinumab was low. No deaths occurred during the study. Candida infections were more frequent with secukinumab than with placebo. Interleukin 17 is important for mucocutaneous defence against candida[26] and continued vigilance for such infections will be needed during assessment of inhibitors of this pathway. Immunogenicity with secukinumab was low and was not associated with a loss of efficacy or with immunogenicity-related adverse events.

This study has several limitations. The predefined hierarchical testing procedure adequately protected the type 1 error rate and showed the effectiveness of both the 300 mg and 150 mg doses of secukinumab for the primary endpoint and several ranked secondary endpoints. The limitation of this procedure is that it is sensitive to the ordering of the endpoints and, as such, clinically relevant results did not reach significance if a preceding ranked endpoint was not significant. Furthermore, it might not be practical or desirable to extend the statistical hierarchy to include every relevant endpoint in a disease with several clinical manifestations such as psoriatic arthritis. This study did not include assessment of radiographic disease progression, but inhibition of radiographic progression has been shown previously with secukinumab.[18] This trial was not designed to identify a difference between doses or to assess differences in response according to previous anti-TNF use or concomitant methotrexate use. Also, axial disease was not assessed in FUTURE 2.

Secukinumab 300 mg or 150 mg provided significant and sustained improvements in key clinical domains of

psoriatic arthritis, with a safety profile consistent with that noted in other studies with secukinumab. These data provide further evidence that interleukin 17A is an important cytokine in the pathogenesis of psoriatic arthritis, and suggest that secukinumab, by providing an alternative mechanism of action to current treatments, might be a useful future treatment option.

Contributors

All authors were involved in the design of the study. Data gathering was undertaken by the study investigators, including IBM and BK. The funder did the data analysis, with all authors contributing to the interpretation of the data and preparation of the manuscript.

FUTURE 2 study investigators

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Declaration of interests

IBM reports personal fees from Novartis, during the conduct of the study, grants and personal fees from Janssen, Pfizer, AstraZeneca, and UCB, and personal fees from AbbVie and Merck Sharp and Dohme, outside the submitted work. PJM reports grants and personal fees from AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, and UCB, and personal fees from Covagen, outside the submitted work. BK reports personal fees from Novartis, during the conduct of the study, personal fees from Abbvie, Bristol-Myers Squibb, Celgene, Pfizer, Merck Sharp and Dohme, Roche, and Janssen, and grants and personal fees from UCB, outside the submitted work. AK reports grants and personal fees from Novartis, outside the submitted work. CTR reports grants and personal fees from Amgen, UCB, Abbvie, Novartis, and Janssen, outside the submitted work. DvdH is director of Rheumatology Consultancy, which is a registered company under Dutch law. She reports reports personal fees from AbbVie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen Biologics, Merck, Novartis, Novo Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB, and Vertex, and grants from AbbVie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Janssen, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen Biologics, Merck, Novartis, Novo Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB, and Vertex, outside the submitted work. RL is director of Rheumatology Consultancy, which is a registered company under Dutch law; he reports consultation or participation on advisory boards for AbbVie, Ablynx, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, GlaxoSmithKline, Novartis, Novo Nordisk, Merck, Pfizer, Roche, Schering-Plough, TiGenics, UCB, and Wyeth, research grants from Abbott, Amgen, Janssen, Novartis, Pfizer, Roche, Schering-Plough, UCB, and Wyeth, and speaker's fees from Abbott, AbbVie, Amgen, Bristol-Myers Squibb, Janssen, Merck, Pfizer, Roche, Schering-Plough, UCB, and Wyeth, outside the submitted work. PGC reports personal fees from Abbvie, Bristol-Myers Squibb, Merck, Novartis, Roche, Janssen, UCB, and Pfizer, outside the submitted work. ABG reports personal fees from Amgen, Astellas, Akros, Janssen, Celgene, Bristol-Myers Squibb, Beiersdorf, AbbVie, Teva, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor, Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Life, GlaxoSmithKline, Xenoport, Catabasis, Sanofi-Aventis, DUSA Pharmaceuticals, and Meiji Seika Pharma, and grants from Janssen, Amgen, Abbvie, Novartis, Celgene, Pfizer, Lilly, Levia, Merck, and Xenoport, outside the submitted work. GL is an employee of Novartis and owns stock. HR and LP are employees of Novartis. MP is employed at Novartis Healthcare (Hyderabad, India). The other authors declare no competing interests.

Acknowledgments

Novartis provided funding for FUTURE 2. We thank the patients who participated in the study, the study investigators, and John Gallagher, a medical consultant for Novartis Pharma. The initial manuscript draft was written by Chris Strutynskyj-Stannard, with assistance from Joanne Swainston and Jessica Breen, medical writers from Seren Communications, an Ashfield Company, part of UDG Healthcare, the funding for which was provided by Novartis Pharma.

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