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ORIGINAL ARTICLE

Secukinumab demonstrates superiority over narrow-band ultraviolet B phototherapy in new-onset moderate to severe plaque psoriasis patients: Week 52 results from the STEPIn study

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Abstract

Background: Biologic treatments have been studied mainly in patients with a long-term history of psoriasis and previous treatment failures.

Objectives: The purpose of this primary analysis of the STEPIn study is to determine whether early intervention with secukinumab in patients with new-onset moderate to severe plaque psoriasis is superior to standard of care treatment with narrow band ultraviolet B (nb-UVB) phototherapy.

Methods: The STEPIn study is a randomized, open-label, multicentre study to investigate early intervention with 52 weeks of secukinumab 300 mg administered subcutaneously versus standard treatment with nb-UVB phototherapy in patients with new-onset (≤12 months) moderate to severe plaque psoriasis (NCT03020199). The primary and additional secondary endpoints were ≥90% improvement in Psoriasis Area and Severity Index (PASI 90) at Week 52 and Investigator's Global Assessment (IGA mod 2011) 0/1 response at Week 52, respectively.

Results: In the secukinumab and nb-UVB study arms, 77/80 and 76/80 randomized patients received at least one dose of study treatment, respectively. The primary endpoint was achieved: 91.1% (70/77) of patients achieved a PASI 90 response at Week 52 in the secukinumab arm versus 42.3% (32/76) in the nb-UVB arm ($p < 0.0001$, odds ratio [OR] estimate [95% confidence intervals, CI] = 16.3 [5.6, 46.9]). The additional secondary endpoint was also achieved: 85.7% of patients achieved an IGA 0/1 response at Week 52 in the secukinumab arm versus 36.8% in the nb-UVB arm ($p < 0.0001$). The safety data were consistent with the safety profiles of secukinumab and nb-UVB with no new or unexpected safety signals.

Conclusions: Secukinumab was superior to nb-UVB in treating patients with new-onset moderate to severe plaque psoriasis. The high and sustained skin clearance observed indicates that biologic treatment for psoriasis may be more effective if used early in the disease course.

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INTRODUCTION

Psoriatic disease is a systemic inflammatory disorder associated with a wide spectrum of clinical manifestations and comorbidities that can lead to severe impairment on patients' health-related quality of life (HR-QoL).[1–8] Psoriatic disease manifestations, including psoriasis and psoriatic arthritis (PsA), can be effectively treated with biologic systemic agents.[6,9–17] So far, biologic treatments for psoriasis have been studied mostly in patients with long-established disease and previous treatment failures, reflecting the current step-up approach treatment paradigm.[9–19] Evidence suggests that the use of systemic agents and biologics in moderate to severe psoriasis is delayed by >3 years in almost 50% of patients.[20,21] This results in long delays in achieving a high level of skin clearance and may increase the risk of comorbidities such as PsA, with long-term HR-QoL implications.[21,22]

In the case of chronic plaque psoriasis, a relapse to pre-treatment disease severity occurs following treatment cessation in the majority of patients, with psoriatic skin lesions often recurring at previously affected locations.[15–17,23–27] In early rheumatoid arthritis or pre-rheumatoid arthritis and other immune-mediated inflammatory diseases, the potential of early biological therapy to induce treatment-free remission has been demonstrated.[28–31] Early intervention with systemic agents and biologics in moderate to severe psoriasis has been proposed as a potential new treatment paradigm to improve long-term outcomes; however, current evidence is sparse and inconsistent.[19,21]

Secukinumab is a fully human monoclonal antibody that selectively neutralizes interleukin (IL)-17A,[32] a cornerstone cytokine in the development of psoriatic disease.[33–38] Randomized controlled trials with secukinumab have shown sustained efficacy and a favourable safety profile in multiple manifestations of psoriatic disease, including the skin (with dedicated Phase III studies of scalp and palmoplantar psoriasis), nails, joints, enthesitis and dactylitis for up to 5 years of exposure.[9,39–47] A meta-analysis of 43 observational studies further supported the clinical effectiveness of secukinumab in patients with moderate to severe psoriasis up to 12 months of treatment.[48]

STEPIn (NCT03020199) is the first study to investigate early intervention with secukinumab versus standard of care with narrow-band ultraviolet B (nb-UVB) phototherapy in patients with new-onset psoriasis.

Study objective

The purpose of this primary analysis of the STEPIn study is to determine whether early intervention with secukinumab in patients with new-onset (<12 months since time of diagnosis) moderate to severe plaque psoriasis is superior to standard of care treatment with nb-UVB phototherapy in achieving sustained skin clearance.

PATIENTS AND METHODS

Study design

The STEPIn study (NCT03020199) design has been reported previously.[49] Briefly, the STEPIn Main Study (Figure 1) is an ongoing, randomized, open-label, multicentre study to investigate early intervention with secukinumab 300 mg via subcutaneous (sc) injection versus treatment with nb-UVB

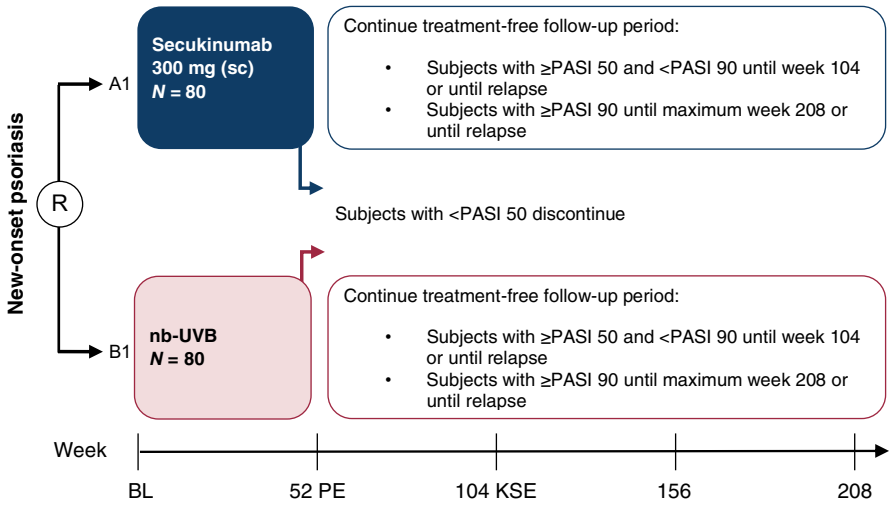

FIGURE 1 Study design. New-onset psoriasis was defined as appearance of the first psoriasis plaques within 12 months before randomisation. The key secondary endpoint is to evaluate the superiority of early treatment with secukinumab (Arm A1) versus nb-UVB (Arm B1) based on the proportion of all randomized patients who achieve at least PASI 90 at Week 104. Relapse was defined as a loss of 50% of the maximum improvement in PASI score. BL, baseline; KSE, key secondary endpoint; N, number of subjects; nb-UVB, narrow-band ultraviolet B; PASI, Psoriasis Area and Severity Index; PE, primary endpoint; R, randomisation; sc, subcutaneous.

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phototherapy over 52 weeks in patients with new-onset (≤12 months) moderate to severe plaque psoriasis. After Week 52, patients who achieve a ≥50% improvement in Psoriasis Area and Severity Index (PASI 50 response) will not receive any study treatment and will be followed up and monitored for disease activity up to Week 208.

Additionally, a Sub-study, in which skin biopsies of new-onset patients are obtained, aims to understand the impact of secukinumab and nb-UVB on skin biomarkers and includes patients with chronic plaque psoriasis (appearance of first symptoms ≥5 years ago). This will enable the comparison of the effects of secukinumab in chronic patients versus those with new-onset plaque psoriasis on a clinical, cellular and molecular level. Further details regarding the Sub-study have been published.[49]

Herein, we present the Week 52 primary analysis results of the Main Study.

Study population

Inclusion and exclusion criteria

The full inclusion and exclusion criteria were reported previously.[49] Patients enrolled in the Main Study had new-onset moderate to severe plaque psoriasis, defined at screening and baseline by all of the following: Psoriasis Area and Severity Index (PASI) ≥10; body surface area (BSA) ≥10%; and Investigator's Global Assessment modified 2011 (IGA mod 2011) ≥3, with appearance of the first psoriasis plaques within the 12 months before randomisation. Patients were naïve to any previous systemic treatment and phototherapy.

Treatment and randomisation

At the baseline visit, patients were randomized to one of the following two treatment arms (Figure 1). In Arm A1, 80 patients with new-onset psoriasis received 300 mg secukinumab by sc injection at baseline, Weeks 1, 2, 3, 4 and then every 4 weeks until Week 48 inclusive. Secukinumab 300 mg was administered in an open-label fashion according to the product label as two sc injections of secukinumab 150 mg (1 ml liquid formulation in a pre-filled syringe). In Arm B1, 80 patients with new-onset psoriasis received one or two cycles of nb-UVB of 12 weeks each with two to three treatment sessions per week totalling 24–36 sessions per cycle. There was a maximum break of 28 weeks between cycles (patients with PASI 90 response at Week 40 did not receive a second treatment cycle). To reflect the standard of care as realistically as possible, the investigational site's protocol was followed, taking into account the patient's skin type. A maximum dose of 3 J/cm^2 on the body and 1 J/cm^2 on the face was recommended.[50] During the first 4 weeks of each cycle, nb-UVB treatment could be applied in combination with topical calcipotriol 50 µg/g and betamethasone 0.5 mg/g once daily.

Outcomes and assessments

The primary endpoint of the study was to demonstrate that early treatment with secukinumab 300 mg is superior to nb-UVB in patients with respect to the proportion of patients achieving a ≥90% improvement in PASI (PASI 90 response) at Week 52.

The additional secondary endpoint was the proportion of patients who achieved an IGA mod 2011 response of 0 or 1 (indicating clear or almost clear skin) at Week 52.

Exploratory endpoints included PASI response up to Week 52 and the following patient-reported outcomes collected at baseline, Weeks 16, 24, 36 and 52: Dermatology Life Quality Index (DLQI), consisting of 10 questions rated from 0 (not at all) to 3 (very much) and a total score ranging from 0 to 30, with a higher total score indicating a greater impairment; Subject's Assessment of Pain, Itching and Scaling (SAPIS), an 11-point numeric rating questionnaire (0 = absence of pain/itching/scaling over the past 24 h and 10 = pain/itching/scaling as bad as it could be over the past 24 h); Subject's Global Assessment (SGA) of psoriatic disease during the previous week was measured on a 100-mm visual analogue scale, where 0 = "not severe" and 100 = "very severe"; and the Work Productivity and Activity Impairment (WPAI) questionnaire for psoriasis, comprising of six questions on a 10-point scale regarding the effects of psoriasis on the patient's ability to work and to perform regular activities based on their experiences over the previous 7 days. For respondents who were not in employment, the questionnaire evaluated the extent to which the respondent's psoriasis affected their ability to perform regular daily activities.

To assess the effects of treatment with secukinumab compared with nb-UVB over time, serum β-defensin 2 concentration was measured as a biomarker for psoriasis skin clearance and relapse at baseline, Weeks 16 and 52, while high sensitivity C-reactive protein (hsCRP) was measured as a marker of systemic inflammation at baseline, Weeks 16, 24, 36 and 52.

The clinical safety, laboratory parameters, vital signs and adverse events (AEs) were reported for secukinumab and nb-UVB up to Week 52.

Statistical methods

For the primary analysis, the following hypothesis testing was performed: H_{01}:$P_{sec} = P_{nbUVB}$ versus H_{A1}:$P_{sec} > P_{nbUVB}$, where P_{sec} and P_{nbUVB} are the proportion of PASI 90 responders in the secukinumab 300 mg sc (Arm A1) and nb-UVB (Arm B1) groups, respectively.

The primary analysis method for PASI 90 response at Week 52 was a logistic regression model with treatment as an explanatory variable and significant covariates among baseline PASI score, age and body mass index (BMI). The best subset of the significant covariates was selected using a forward selection method based on the likelihood ratio test.

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Interaction terms were also considered, if significant, among the best subset of selected covariates and the treatment term.

Statistical significance was evaluated at a 1-sided alpha level of 0.025. The estimated adjusted odds ratio (OR) was displayed along with the associated 2-sided 95% confidence interval (CI) and *p* value. Modified multiple imputation was the primary method for handling missing data for the primary analysis. Patients who discontinued the study before Week 52 because of lack of efficacy or AEs were considered non-responders. Missing values for other reasons were inserted by means of the multiple imputation method. Sensitivity analysis was performed by repeating the logistic regression model with treatment as an explanatory variable and all three covariates, baseline PASI, age and BMI. Interaction terms with treatment also were considered.

The method for IGA 0/1 response at Week 52 used a logistic regression model similar to the primary analysis. Missing IGA 0/1 and PASI values up to Week 52 were imputed with non-response regardless of the reason for the missing data (e.g. premature study discontinuation, missed visit or administrative issue). The last observation carried forward (LOCF) method was used to impute missing values for the exploratory variables of DLQI, SAPIS, SGA and WPAI. Between-treatment differences for SAPIS, SGA and WPAI were analysed using a multiple regression model, while DLQI 0/1 response treatment arms were compared by means of the one-sided Wald test. Standard descriptive statistics were used to summarize β defensin-2 concentrations over time and Pearson's correlation coefficient was used to measure correlation of percentage change in β defensin-2 concentrations and PASI score (observed data).

Efficacy and safety analyses were conducted on the modified Full Analysis Set (mFAS), which contained all randomized patients who received at least one dose of study treatment.

The power calculations for the primary endpoint were based on the asymptotic Wald test to compare secukinumab 300 mg sc versus nb-UVB using the hierarchical method to adjust for multiplicity. Based on previous studies, it was estimated that the proportion of PASI 90 responders at Week 52 would be around 35% after one or two cycles of nb-UVB treatment and around 70% after early treatment with secukinumab 300 mg sc. The dropout rate at Week 52 due to lack of efficacy (considered non-responders) was assumed to be 0% in the secukinumab group and 20% in the nb-UVB group, changing the estimated response rates to 70% and 28%, respectively. Assuming an absolute difference of 42% in the proportion of patients achieving PASI 90 response at Week 52, the sample size of 80 patients in each arm would provide 99% power at the one-sided significance level of 0.025 using the asymptotic Wald test for equality of proportions (using PASS 11).

Ethical consent

This clinical study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21 and Japanese Ministry of Health, Labour, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

The study protocol was approved by the independent ethics committee or institutional review board of each participating centre, and written informed consent was obtained from each study participant before enrolment in the study.

RESULTS

Patient disposition and baseline characteristics

In the secukinumab and nb-UVB study arms, 77/80 and 76/80 randomized patients received at least one dose of study treatment, respectively, and were included in the efficacy and safety analyses (Figure 2).

Five patients (6.5%) in the secukinumab arm discontinued the study by Week 52, compared with 31 patients (40.8%) in the nb-UVB arm. Reasons for discontinuation are displayed in Figure 2.

Patient baseline demographics and clinical characteristics were generally balanced between secukinumab and nb-UVB study arms (Table 1). The mean time since diagnosis of psoriasis was 6.6 months in the secukinumab arm and 6.8 months in the nb-UVB arm.

Mean PASI was 17.7 in the secukinumab group and 17.4 in the nb-UVB group. Mean BSA affected was 25.6% in the secukinumab group and 24.4% in the nb-UVB group. Overall, 21.1% patients in the nb-UVB arm had a baseline IGA mod 2011 of 4 (severe), compared with 7.8% in the secukinumab arm. At baseline, two patients in the secukinumab arm and one patient in the nb-UVB arm had a previous PsA diagnosis.

Efficacy

The primary endpoint was achieved: 91.1% (70/77) of patients achieved a PASI 90 response at Week 52 in the secukinumab arm versus 42.3% (32/76) of patients in the nb-UVB arm ($p < 0.0001$, OR estimate [95% CI] = 16.3 [5.6, 46.9]; Figure 3). Sensitivity analysis confirmed these results ($p < 0.0001$, OR estimate [95% CI] = 25.9 [6.2, 107.7]).

The additional secondary endpoint was also met: 85.7% of patients achieved an IGA 0/1 score at Week 52 in the secukinumab arm versus 36.8% of patients in the nb-UVB arm ($p < 0.0001$; Figure 4).

Psoriasis Area and Severity Index 50/75/90/100 responses over time up to Week 52 are shown in Figure S1. At Week 52, PASI 100 response was significantly greater in the secukinumab arm (68.8%) compared with the nb-UVB arm (22.4%; $p < 0.0001$).

Concomitant topical calcipotriol/betamethasone was used by 67.1% of patients in the nb-UVB arm, in accordance with the protocol.

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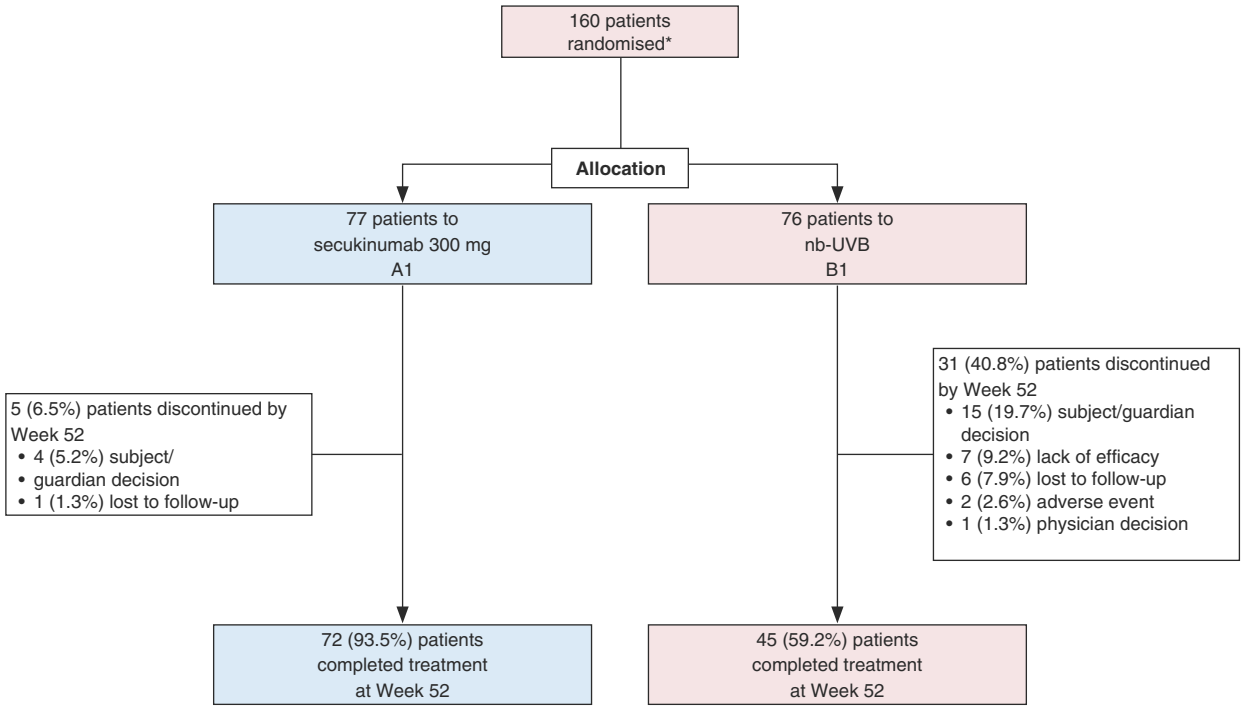

FIGURE 2 Patient disposition. *Seven patients did not receive any study medication and were not included in the modified full analysis set. nb-UVB, narrow-band ultraviolet B.

The proportion of patients achieving a DLQI of 0 or 1 (little to no impact on quality of life) at Week 52 was significantly greater in the secukinumab arm compared with the nb-UVB arm (80.0% versus 25.4%, respectively, $p < 0.0001$; Figure 5).

Patients in the secukinumab arm had a significantly greater reduction in pain, itching and scaling from baseline to Week 52 compared with patients in the nb-UVB arm (all $p < 0.0001$; Figure 6).

Reduction in SGA from baseline to Week 52 was significantly greater in patients in the secukinumab arm compared with patients in the nb-UVB arm (within treatment mean change [standard error]: −55.2 [2.35] versus −30.1 [2.49], respectively, $p < 0.0001$; Figure 7).

Reduction in percent of activity impairment due to psoriasis, percent of impairment while working due to psoriasis and percent of overall work impairment due to psoriasis (WPAI) from baseline to Week 52 was significantly greater in patients in the secukinumab arm compared with patients in the nb-UVB arm (Figure 8). However, there was no difference in proportion of working time missed due to psoriasis between the secukinumab and nb-UVB groups.

There was a greater reduction in β-defensin 2 levels with secukinumab versus nb-UVB at Weeks 16 and 52 (Figure 9b). β-defensin 2 levels correlated moderately with PASI for both secukinumab (Figure 9c) and nb-UVB (Figure 9e) patients. However, while change in PASI with secukinumab significantly correlated with change in β-defensin 2 (Figure 9d; $p < 0.05$), change in PASI with nb-UVB did not significantly correlate with change in in β-defensin 2 (Figure 9f; $p = 0.5473$).

Safety

The safety of secukinumab and nb-UVB during the STEPIn study was consistent with that established for both treatments and no new or unexpected safety signals were identified (Table 2). In total, 61.0% and 31.6% of patients in the secukinumab and nb-UVB arms experienced any AE, respectively. No patients in the secukinumab arm discontinued treatment due to an AE, while 2.6% of patients discontinued treatment due to an AE in the nb-UVB arm. The most common AEs in the study were infections and infestations which were experienced by 35.1% of patients in the secukinumab arm and 15.8% of patients in the nb-UVB arm.

Adverse events deemed by the investigator to be possibly related to study treatment were experienced by 20.8% of patients in the secukinumab arm and 3.9% of patients in the nb-UVB arm. The most common AEs possibly related to study treatment were infections and infestations, occurring in 14.3% of patients in the secukinumab arm and no patients in the nb-UVB arm. The majority of AEs possibly related to secukinumab treatment were associated with the upper respiratory tract (9.1%). There were no AEs related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection reported.

One case each of oral candidiasis and tinea versicolour were reported in the secukinumab group; both were mild in severity and resolved with treatment, without discontinuation of secukinumab. Scalp pruritus was reported by one patient in the nb-UVB group; it was not deemed to be related to study treatment. No cases of inflammatory bowel disease were reported in the study. There were no treatment-emergent

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TABLE 1 Patient baseline characteristics and demographics

Demographic/baseline characteristic	Secukinumab 300 mg, *N* = 77	nb-UVB, *N* = 76
Age[a] (years), mean ± SD	31.6 ± 8.68	32.5 ± 9.01
Gender, male, *n* (%)	49 (63.6)	52 (68.4)
Race, white, *n* (%)	74 (96.1)	68 (89.5)
Body weight (kg), mean ± SD	81.0 ± 19.53	83.7 ± 19.37
BMI (kg/m^2), mean ± SD	26.7 ± 6.21	27.4 ± 6.07
Overweight, BMI ≥25 to <30 (kg/m^2), *n* (%)	21 (27.3)	22 (28.9)
Obese, BMI ≥30 (kg/m^2), *n* (%)	19 (24.7)	21 (27.6)
Skin type, *n* (%)		
I	3 (3.9)	2 (2.6)
II	33 (42.9)	39 (51.3)
III	30 (39.0)	26 (34.2)
IV	7 (9.1)	6 (7.9)
V	4 (5.2)	3 (3.9)
Smoking status, *n* (%)		
Current	28 (36.4)	32 (42.1)
Former	7 (9.1)	8 (10.5)
Never	42 (54.5)	36 (47.4)
Baseline PASI, mean ± SD	17.7 ± 7.41	17.4 ± 7.63
Baseline IGA mod 2011, *n* (%)		
3 = Moderate	71 (92.2)	60 (78.9)
4 = Severe	6 (7.8)	16 (21.1)
Baseline BSA affected (%), mean ± SD	25.6 ± 15.2	24.4 ± 16.0
Time since first diagnosis of plaque psoriasis (months), mean ± SD	6.6 ± 4.0	6.8 ± 4.0
Concomitant PsA at inclusion in the study, *n* (%)	2 (2.6)	1 (1.3)

Abbreviations: BMI, body mass index; BSA, body surface area; IGA, Investigator's Global Assessment; nb-UVB, narrow-band ultraviolet B; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SD, standard deviation.

[a]Patients aged 18–50 years were enrolled.

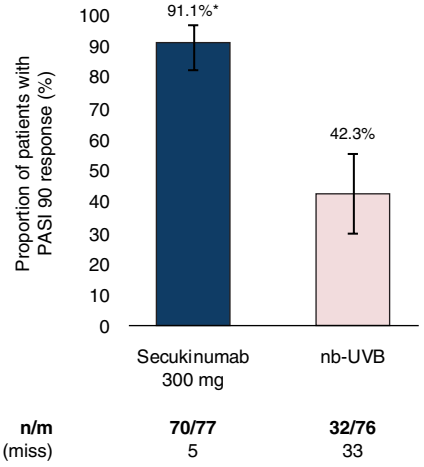

FIGURE 3 Proportion of patients with PASI 90 response at Week 52. *p < 0.0001, odds ratio estimate (95% confidence interval) = 16.3 (5.6, 46.9). Missing values are imputed via modified multiple imputation. *m*, number of subjects evaluable; *n*, rounded average number of subjects with PASI 90 response in 500 imputations; nb-UVB, narrow-band ultraviolet B; *n* (miss), number of subjects with missing values; PASI, Psoriasis Area and Severity Index.

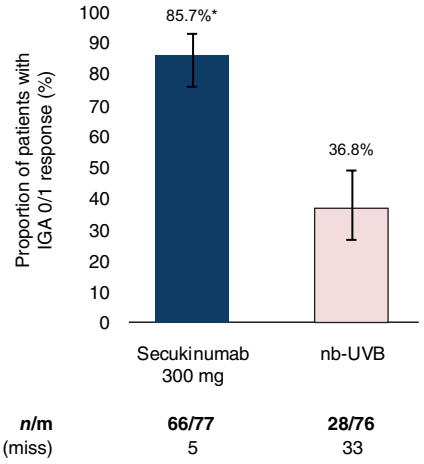

FIGURE 4 Proportion of patients with IGA 0/1 response at Week 52. *p < 0.0001, odds ratio estimate (95% confidence interval) = 11.5 (5.0, 26.7). Missing values are imputed via non-responder imputation. IGA 0/1, Investigator Global Assessment score of 0 or 1; *m*, number of subjects evaluable; *n*, number of subjects with IGA 0/1 response; nb-UVB, narrow-band ultraviolet B; *n* (miss), number of subjects with missing values.

cases of concomitant PsA in either treatment group during the study. Neoplasms were reported in three patients in the secukinumab arm and included two cases of skin papilloma and one case of melanocytic naevus; all were mild in severity.

Serious AEs (SAEs) were experienced by 5.2% and 1.3% of patients in the secukinumab and nb-UVB arms, respectively, but none were related to the study treatment and none resulted in treatment discontinuation (Table S1). No deaths were reported during the course of the study.

Mean hsCRP levels in the secukinumab and nb-UVB arms remained relatively constant between baseline and Week 52.

DISCUSSION

Biologic treatments for plaque psoriasis have been studied mostly in patients with a long-term history of psoriasis and previous use of multiple systemic treatments.[9–17] In two pivotal Phase III trials of secukinumab in patients with moderate to severe plaque psoriasis, the average disease duration at baseline was ~17 years.[9] The STEPIn study is the first to investigate the impact of early treatment with a biologic on sustained skin clearance in patients with new-onset psoriasis (<12 months since diagnosis).[19]

The primary and secondary endpoints of the study were met: superior skin clearance was achieved with secukinumab versus nb-UVB as measured by PASI 90 and IGA 0/1 responses at Week 52.

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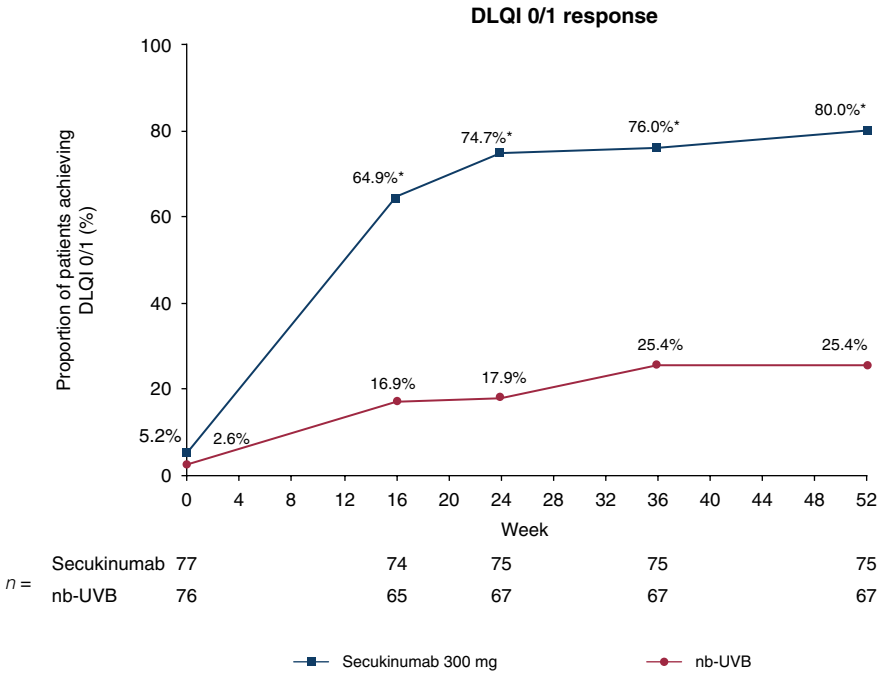

FIGURE 5 Proportion of patients with DLQI 0/1 response up to Week 52. *$p < 0.0001$ between treatment arms. Wald's test by visit till Week 52 (missing values are replaced by a last observation carried forward method). DLQI, Dermatology Life Quality Index; *n*, number of subjects evaluable; nb-UVB, narrow-band ultraviolet B; PASI, Psoriasis Area and Severity Index.

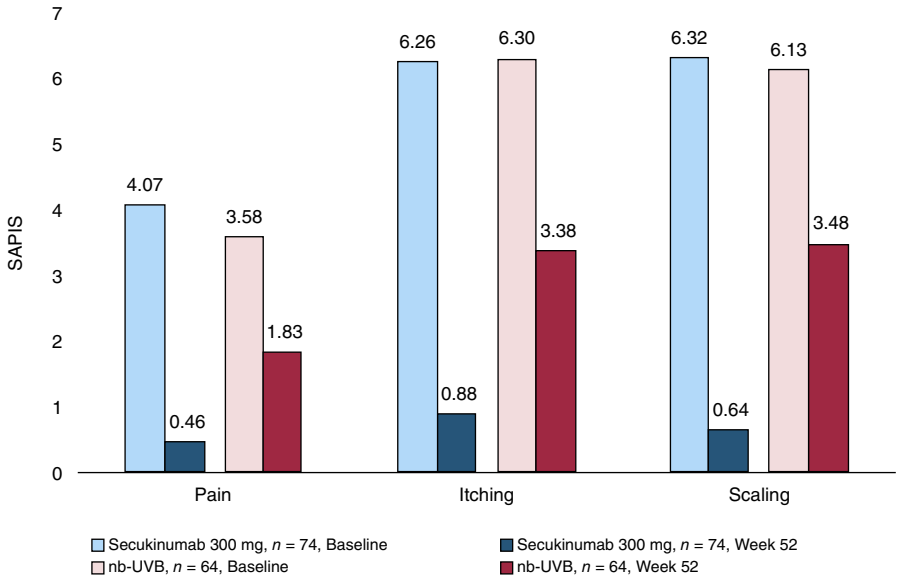

FIGURE 6 Change in subject's assessment of pain, itching and scaling from baseline to Week 52. Reduction in pain, itching and scaling from baseline to Week 52 was significantly greater in the secukinumab arm compared with the nb-UVB arm (all $p < 0.0001$). Last observation carried forward analysis used. The range for subject's assessment of pain, itching and scaling is 0–10 (higher scores represent worse condition). *n*, number of subjects with non-missing assessment; nb-UVB, narrow-band ultraviolet B; PASI, Psoriasis Area and Severity Index; SAPIS, Subject's Assessment of Pain, Itching and Scaling.

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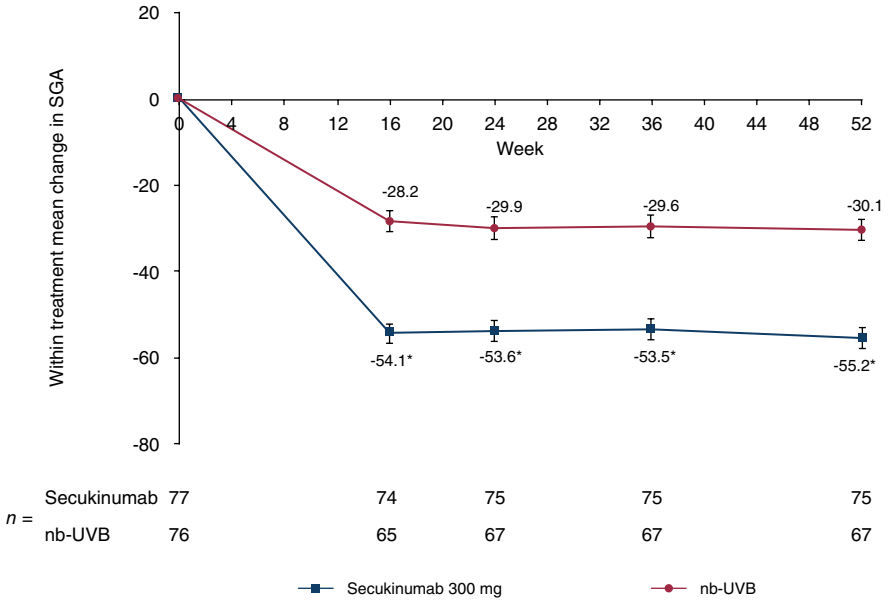

FIGURE 7 Change in subject's global assessment from baseline up to Week 52. *$p < 0.0001$ between treatment arms. Last observation carried forward analysis used. Subject's global assessment of psoriasis was captured using a 100-mm visual analogue scale, where 0 = "Not severe" and 100 = "Very severe". *n*, number of subjects with non-missing assessment; nb-UVB, narrow-band ultraviolet B; SGA subject's global assessment.

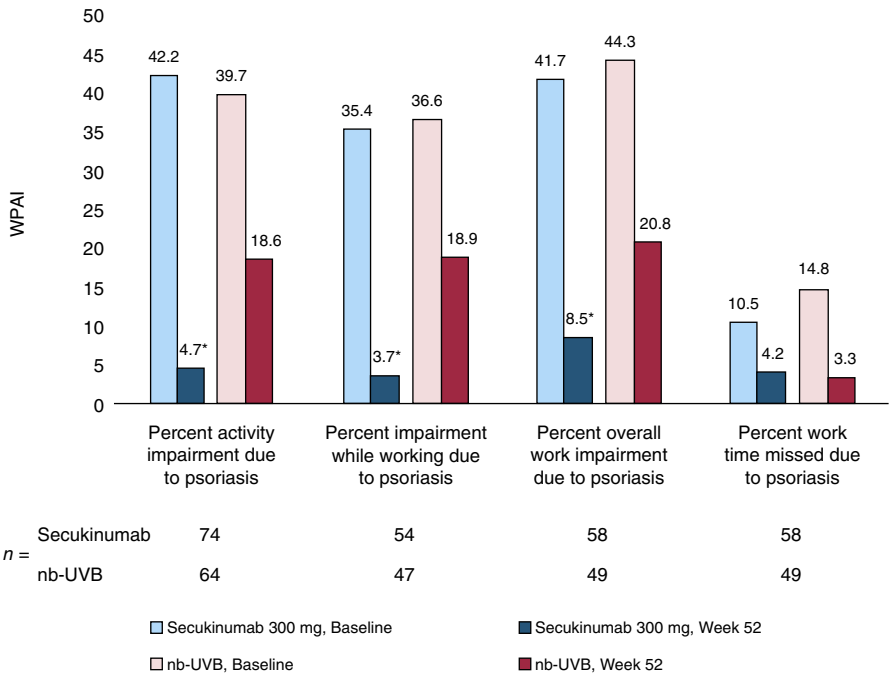

FIGURE 8 Change in work productivity and activity impairment from baseline to Week 52. *Reduction in WPAI parameter from baseline to Week 52 was significantly greater in patients in the secukinumab arm compared with patients in the nb-UVB arm ($p < 0.01$). Last observation carried forward analysis used. *n*, number of subjects with non-missing assessment; nb-UVB, narrow-band ultraviolet B; WPAI, work productivity and activity impairment.

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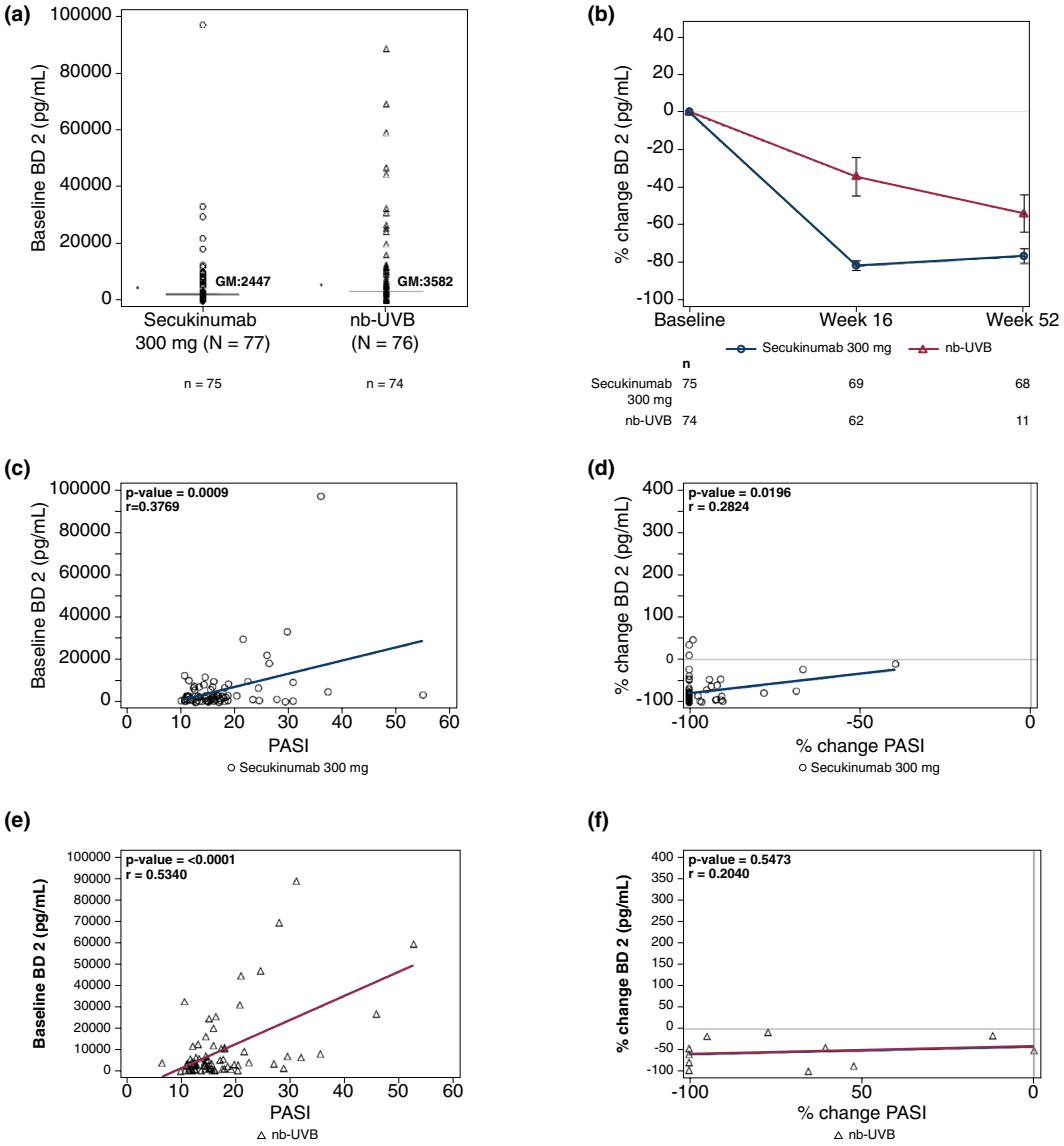

FIGURE 9 β-Defensin 2 levels at baseline, Weeks 16 and 52, and correlation of change in β-defensin 2 levels with change in Psoriasis Area and Severity Index (observed data). (a) Baseline human β-defensin 2 levels. Mean (SD) baseline β-defensin 2 levels were 5706.6 (12,229.6) pg/ml in the secukinumab arm (n = 75) and 9649.7 (16,299.4) pg/ml in the nb-UVB arm (n = 74). (b) Percentage change (standard error) in human β-defensin 2 levels over 52 weeks. (c) Baseline human β-defensin 2 levels and baseline PASI correlation for secukinumab. (d) Percentage change of human β-defensin 2 at Week 52 plotted against the percentage change in PASI at Week 52 for secukinumab. (e) Baseline human β-defensin 2 levels and baseline PASI correlation for nb-UVB. (f) Percentage change of human β-defensin 2 at Week 52 plotted against the percentage change in PASI at Week 52 for nb-UVB. Modified full analysis set (seven patients who did not receive any study medication were not included). BD 2, β-defensin 2; GM, Geometric mean; *N*, total number of subjects in the treatment arm; n, number of subjects with non-missing data; nb-UVB, narrow-band ultraviolet B; PASI, Psoriasis Area and Severity Index; *r*, Pearson correlation coefficient.

Results from previous clinical trials and real-world observation suggest that the proportion of PASI 90 responders at Week 52 with secukinumab treatment in biologic-naive patients with a longer than 1 year history of psoriasis, is around 70%–80%.[51,52] In this study, over 90% of patients achieved a PASI 90 response at Week 52 in the secukinumab arm. Since the patients enrolled in the STEPIn study had new-onset psoriasis (all of whom were biologic-naive), while the biologic-naive patients in previous studies had an established psoriasis with disease duration of around 15–17 years since diagnosis,[51,52] this indicates that biologic treatment for psoriasis may be more effective if used early in the disease course.

The high and sustained PASI 90 response observed in the STEPIn study with secukinumab treatment was also associated with significant benefits for patients in terms of patient-reported outcomes, with 80% of patients in the secukinumab arm experiencing little to no impact of psoriasis on quality of life at Week 52. Mean SAPIS scores in the secukinumab arm were all reduced below 1 (on a scale of 0–10, with higher

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TABLE 2 Adverse events (safety set)

	Secukinumab 300 mg, *N* = 77 *n* (%)	nb-UVB, *N* = 76 *n* (%)
Any AE	47 (61.0)	24 (31.6)
Most common AEs[a]		
Infections and infestations (SOC)	27 (35.1)	12 (15.8)
Nasopharyngitis (PT)	8 (10.4)	5 (6.6)
Upper respiratory tract infection (PT)	5 (6.5)	2 (2.6)
Influenza (PT)	1 (1.3)	3 (3.9)
Oral herpes (PT)	3 (3.9)	0 (0.0)
Gastrointestinal disorders[b] (SOC)	7 (9.1)	2 (2.6)
Musculoskeletal and connective tissue disorders (SOC)	9 (11.7)	0 (0.0)
Arthralgia (PT)	6 (7.8)	0 (0.0)
Skin and subcutaneous tissue disorders (SOC)	5 (6.5)	4 (5.3)
Nervous system disorders (SOC)	8 (10.4)	1 (1.3)
Headache (PT)	6 (7.8)	1 (1.3)
Injury, poisoning and procedural complications (SOC)	4 (5.2)	2 (2.6)
General disorders and administration site conditions (SOC)	3 (3.9)	3 (3.9)
Investigations (SOC)	5 (6.5)	0 (0.0)
Vascular disorders (SOC)	4 (5.2)	1 (1.3)
Hypertension (PT)	4 (5.2)	1 (1.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps; SOC)	3 (3.9)	0 (0.0)
Any AE possibly related to study treatment	16 (20.8)	3 (3.9)
Any AE leading to discontinuation	0 (0.0)	2 (2.6)
Application site burn (PT)	0 (0.0)	1 (1.3)
Deterioration of psoriasis (PT)	0 (0.0)	1 (1.3)
Most common[c] AEs possibly related to study treatment		
Infections and infestations (SOC)	11 (14.3)	0 (0.0)
Oral herpes (PT)	3 (3.9)	0 (0.0)
Nasopharyngitis (PT)	2 (2.6)	0 (0.0)
Gastrointestinal disorders (SOC)	5 (6.5)	0 (0.0)
General disorders and administration site conditions (SOC)	2 (2.6)	1 (1.3)
Skin and subcutaneous tissue disorders (SOC)	1 (1.3)	2 (2.6)
Any treatment-emergent SAE	4 (5.2)	1 (1.3)
Any SAE possibly related to study treatment	0 (0.0)	0 (0.0)

Note: In total, seven patients did not receive any study medication and were not included in the safety set. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. The median (Q1, Q3) duration of secukinumab exposure was 365.0 (364.0, 367.0) days. In the nb-UVB arm in Cycle 1, 71.1% (54/76) of patients had 24–36 sessions, while 28.9% (22/76) of patients had <24 sessions; in Cycle 2, 14.5% (11/76) of patients had 24–36 sessions, while 9.2% (7/76) of patients had <24 sessions.

Abbreviations: AE, adverse event; nb-UVB, narrow band ultraviolet B; PT, preferred term; SAE, serious adverse event; SOC, system organ class.

[a]Occurring in ≥3% of patients in either treatment arm.

[b]No cases of inflammatory bowel disease were reported.

[c]Occurring in ≥2% of patients in either treatment arm.

scores representing worse condition), indicating minimal patient-reported impact of pain, itching and scaling at Week 52. Percent activity impairment, impairment while working or work time missed due to psoriasis were all reduced to below 5% at Week 52 in the secukinumab arm, indicating a minimal impact of psoriasis on ability to work and perform regular activities.

Greater reductions in β-defensin 2 levels, a biomarker for psoriasis skin clearance, were observed with secukinumab versus nb-UVB at Weeks 16 and 52. Change in PASI score with secukinumab, but not nb-UVB, significantly correlated with change in β-defensin 2 level. These data support the clinical findings which demonstrate the superior efficacy of secukinumab versus nb-UVB in patients with new-onset psoriasis over 52 weeks.

The safety data in this study were consistent with the safety profile of secukinumab in the adult population across psoriasis, psoriatic arthritis and axial spondyloarthritis[9,43] and the established safety profile for nb-UVB.[50] No new or unexpected safety signals were identified. The incidence of infections and infestations was similar to that seen in trials of patients with chronic moderate to severe plaque psoriasis.[9,43] Consistent with real life data,[53] high drop-out rates mainly driven by lack of efficacy were observed in the nb-UVB arm.

The speed at which psoriasis disease severity progresses is highly variable, many patients live with mild disease for several years before developing moderate to severe disease.[19,54,55] An important feature of this study was that all patients enrolled had moderate to severe plaque psoriasis and an average of 6 months since diagnosis. Potential triggers or clinical risk factors for the early and rapid progression to moderate to severe disease in the patient population enrolled in this study could not be identified.

Due to the study design and nature of the treatments, the authors consider absence of blinding as a limitation of the study. Another possible limitation is the higher proportion of patients in the nb-UVB arm with a baseline IGA score of

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4 compared with the secukinumab arm. This indicates that patients in the nb-UVB arm may have had a more severe psoriasis, although baseline PASI score and BSA affected were similar in both groups.

In this study, nb-UVB was selected as a comparator for secukinumab as it represents the standard of care for patients with new-onset plaque psoriasis in many geographies. However, secukinumab is a continuous, systemic treatment, while nb-UVB is applied in schedules of 12 weeks. Although there was the possibility of receiving additional schedules, another limitation of the study is that not all patients in the nb-UVB arm may have been receiving active treatment during the timepoints of evaluation.

Early intervention with biologics represents an emerging paradigm shift to improve outcomes in immune-mediated diseases and evidence to determine its utility in psoriasis is needed.[19] The high level of sustained skin clearance observed in this study with secukinumab versus standard of care, nb-UVB, provides evidence for the potential benefit of treating early with biologics in order to achieve complete skin clearance and normalization of quality of life, work life and daily activities and may support a change in treatment strategy for patients with new-onset moderate to severe plaque psoriasis.

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CONFLICT OF INTEREST

L. Iversen has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Almirall, Amgen, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen Cilag, Kyowa, Leo Pharma, MSD, Novartis, Pfizer, Regranion, Samsung, Union Therapeutics UCB. C. Conrad served as a scientific adviser and/or clinical study investigator and/or paid speaker for AbbVie, Actelion, Almirall, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Galderma, Incyte, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Samsung, Sanofi, and UCB. L. Eidsmo has received consultancy fees from Galderma, Leo Pharma, Novartis and Pfizer and investigator-initiated research grants from MSD, Novartis and Pfizer. A. Costanzo has served as a scientific adviser and/or clinical study investigator and/or paid speaker for AbbVie, Amgen, BMS, Celgene, Galderma, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, and UCB. J. Narbutt has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Almirall, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen Cilag, Sanofi, Regeneron, Sandoz, Leo Pharma, MSD, Novartis, Pfizer, Samsung, Union Therapeutics, and UCB. A. Pinter has worked as an investigator and/or speaker and/or advisor for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Boehringer-Ingelheim, Celgene, GSK, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi-Genzyme, Schering-Plough, and UCB. K. Kingo has received fees for serving as an investigator in studies sponsored by Celgene, Merck, Mitsubishi Tanabe Pharma, Novartis, Regeneron Pharmaceuticals, and Sandoz. R. Rivera Diaz has worked as an investigator/speaker and/or advisor for: Abbvie, Boehringer Ingelheim, Celgene, Janssen, Leo-Pharma, Lilly, MSD, Pfizer, and Novartis. F. Kolbinger, M. Nanna, J. Frueh and P. Jagiello are employed by Novartis.

DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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