ORIGINAL ARTICLE

# Secukinumab in Plaque Psoriasis — Results of Two Phase 3 Trials

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## ABSTRACT

### BACKGROUND

Interleukin-17A is considered to be central to the pathogenesis of psoriasis. We evaluated secukinumab, a fully human anti–interleukin-17A monoclonal antibody, in patients with moderate-to-severe plaque psoriasis.

### METHODS

In two phase 3, double-blind, 52-week trials, ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis), we randomly assigned 738 patients (in the ERASURE study) and 1306 patients (in the FIXTURE study) to subcutaneous secukinumab at a dose of 300 mg or 150 mg (administered once weekly for 5 weeks, then every 4 weeks), placebo, or (in the FIXTURE study only) etanercept at a dose of 50 mg (administered twice weekly for 12 weeks, then once weekly). The objective of each study was to show the superiority of secukinumab over placebo at week 12 with respect to the proportion of patients who had a reduction of 75% or more from baseline in the psoriasis area-and-severity index score (PASI 75) and a score of 0 (clear) or 1 (almost clear) on a 5-point modified investigator's global assessment (coprimary end points).

### RESULTS

The proportion of patients who met the criterion for PASI 75 at week 12 was higher with each secukinumab dose than with placebo or etanercept: in the ERASURE study, the rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo; in the FIXTURE study, the rates were 77.1% with 300 mg of secukinumab, 67.0% with 150 mg of secukinumab, 44.0% with etanercept, and 4.9% with placebo ($P<0.001$ for each secukinumab dose vs. comparators). The proportion of patients with a response of 0 or 1 on the modified investigator's global assessment at week 12 was higher with each secukinumab dose than with placebo or etanercept: in the ERASURE study, the rates were 65.3% with 300 mg of secukinumab, 51.2% with 150 mg of secukinumab, and 2.4% with placebo; in the FIXTURE study, the rates were 62.5% with 300 mg of secukinumab, 51.1% with 150 mg of secukinumab, 27.2% with etanercept, and 2.8% with placebo ($P<0.001$ for each secukinumab dose vs. comparators). The rates of infection were higher with secukinumab than with placebo in both studies and were similar to those with etanercept.

### CONCLUSIONS

Secukinumab was effective for psoriasis in two randomized trials, validating interleukin-17A as a therapeutic target. (Funded by Novartis Pharmaceuticals; ERASURE and FIXTURE ClinicalTrials.gov numbers, NCT01365455 and NCT01358578, respectively.)

Psoriasis is a chronic, immune-mediated inflammatory skin disease that is associated with substantial impairment of physical and psychological quality of life.[1,2] Our understanding of the pathogenesis of psoriasis was advanced by the discovery of the class of type 17 helper T (Th17) cells, which regulates innate and adaptive immunity. The proinflammatory cytokine interleukin-17A is the primary effector of Th17 cells, but it is also produced by other cell types in psoriatic lesions, including γδ T cells, neutrophils, and possibly mast cells.[3-7] Interleukin-17A stimulates keratinocytes to secrete chemokines and other proinflammatory mediators that recruit additional inflammatory cells, including neutrophils, Th17 cells, dendritic cells, and innate lymphoid cells.[8-10] Interleukin-17A thus potentially acts as a master cytokine in the pathogenesis of psoriasis. In addition, a substantial body of genetic research and early data from clinical trials of therapeutic inhibitors of interleukin-17A has shown that this cytokine plays a crucial role in the pathogenesis of several other immune-mediated diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and multiple sclerosis.[10,11]

Secukinumab (Novartis Pharmaceuticals) is a recombinant, high-affinity, fully human immunoglobulin G1κ monoclonal antibody that selectively binds and neutralizes interleukin-17A. To confirm the findings of basic research and early clinical studies regarding the crucial role of interleukin-17A in psoriasis, we conducted two randomized, phase 3 trials to assess the efficacy and safety of secukinumab, at a dose of 300 mg or 150 mg, administered as induction therapy (with assessment at week 12) and maintenance therapy (with assessment at week 52) in patients with moderate-to-severe plaque psoriasis. The ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) study compared secukinumab with placebo, and the FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) study compared secukinumab with placebo and etanercept, the first tumor necrosis factor (TNF) inhibitor approved by the Food and Drug Administration for moderate-to-severe plaque psoriasis.[12]

## METHODS

### STUDY POPULATION

The eligibility criteria were similar in the two studies. Patients were 18 years of age or older with moderate-to-severe plaque psoriasis that had been diagnosed at least 6 months before randomization and that was poorly controlled with topical treatments, phototherapy, systemic therapy, or a combination of these therapies. In addition, patients had a score of 12 or higher on the psoriasis area-and-severity index (PASI; on a scale from 0 to 72, with higher scores indicating more severe disease),[13] a score of 3 or 4 on the modified investigator's global assessment (on a scale from 0 to 4, with higher scores indicating more severe disease),[14] and involvement of 10% or more of the body-surface area. Patients with forms of psoriasis other than chronic plaque-type psoriasis or with drug-induced psoriasis were excluded.

The use of medications that might confound efficacy was not allowed (see the Supplementary Appendix, available with the full text of this article at NEJM.org). In the FIXTURE study, patients who had used etanercept at any time before screening were excluded.

### STUDY OVERSIGHT

Both studies were sponsored by Novartis Pharmaceuticals and designed by the scientific steering committee and Novartis Pharmaceuticals personnel. The site investigators collected the data, Novartis Pharmaceuticals conducted the data analyses, and all the authors had access to the data. All the authors vouch for the completeness and accuracy of the data and analyses for their respective studies and vouch for the fidelity of this report to the study protocols. Agreements between Novartis Pharmaceuticals and the investigators included provisions relating to confidentiality of the study data. The initial draft of the manuscript was written by a medical writer paid by Novartis Pharmaceuticals, with subsequent revisions by all the authors. All the authors made the decision to submit the manuscript for publication.

The study protocols, available at NEJM.org, were approved by the institutional review board or ethics committee at each participating site, and the studies were conducted in accordance

with the ethical principles of the Declaration of Helsinki. U.S. sites maintained compliance with Health Insurance Portability and Accountability Act regulations. Eligible patients provided written informed consent.

### STUDY DESIGN

Both studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials; the FIXTURE study was also active-controlled. The ERASURE study was conducted from June 2011 through April 2013 at 88 sites worldwide; the FIXTURE study was conducted from June 2011 through June 2013 at 231 sites. The participating study sites are listed in the Supplementary Appendix.

Each study consisted of a screening period of 1 to 4 weeks, a 12-week induction period, a 40-week maintenance period, and an 8-week follow-up period (Fig. S1 and S4 in the Supplementary Appendix). Patients in the ERASURE study were randomly assigned in a 1:1:1 ratio to receive secukinumab at a dose of 300 mg, secukinumab at a dose of 150 mg, or placebo; those in the FIXTURE study were randomly assigned in a 1:1:1:1 ratio to receive secukinumab at a dose of 300 mg or 150 mg, etanercept, or placebo (see the Supplementary Appendix).

Patients randomly assigned to secukinumab in either study received either two 150-mg subcutaneous secukinumab injections (i.e., 300 mg total) or one 150-mg injection plus one placebo injection, with both injections administered once weekly at baseline and at weeks 1, 2, 3, and 4 and then every 4 weeks until week 48. Patients randomly assigned to etanercept received 50 mg administered subcutaneously twice weekly from baseline until week 12 and then once weekly through week 51, in accordance with the standard dosing regimen.[15] In the FIXTURE study, the placebo group received placebo injections corresponding to the secukinumab and the etanercept regimens, and the secukinumab and etanercept groups received placebo injections corresponding to the other active-drug regimen, in order to maintain a double-dummy design. In the ERASURE study, patients randomly assigned to placebo received placebo injections corresponding to the secukinumab regimens.

In each study, patients in the placebo group who did not meet the criteria for a reduction of 75% or more in the baseline PASI score (PASI 75) at week 12 underwent randomization again in a 1:1 ratio to receive secukinumab at a dose of either 300 mg or 150 mg (see the Supplementary Appendix); those who met the criteria for PASI 75 at week 12 continued to receive placebo. The efficacy data for the patients who underwent randomization twice (i.e., first to placebo and subsequently to one of two doses of secukinumab) are not reported here.

### ASSESSMENTS

Efficacy assessments were conducted throughout each study, with key assessments at the end of the induction period before the week-12 dose was administered and at the end of the maintenance period at week 52 (i.e., 1 week after the last dose of etanercept or its matching placebo and 4 weeks after the last dose of secukinumab or its matching placebo). Disease activity was assessed with the use of PASI (a composite evaluation instrument for psoriasis severity, with subscores for erythema, induration, scaling, and percentage of body-surface area affected)[13] and the modified investigator's global assessment (a static, 5-point instrument for rating the clinician's impression of the overall severity of the psoriasis, on a scale from 0 [clear skin] to 4 [severe disease]) (Table S1 in the Supplementary Appendix).[14] A response on the modified investigator's global assessment was defined as a score of 0 (clear) or 1 (almost clear) and a reduction from baseline of at least 2 points. Patients performed a self-assessment of symptoms using the validated Psoriasis Symptom Diary[16] and reported on quality of life with the Dermatology Life Quality Index (DLQI), a validated instrument for dermatologic conditions (scores range from 0 to 30 points, with higher scores indicating a greater effect on quality of life).[17]

We evaluated safety by monitoring adverse events, including the severity of the event and the relationship of the event to study drug, and by obtaining clinical laboratory measurements, assessing vital signs, and performing physical examinations at each study visit. An independent cardiovascular and cerebrovascular safety adjudication committee was established to review and adjudicate major adverse cardiovascular events, which were reported in a blinded manner. Blood samples were obtained at baseline and at weeks 12, 24, 52, and 60 for an assessment of

the immunogenicity of secukinumab with the use of a homogeneous Meso Scale Discovery bridging assay (see the Supplementary Appendix) and a three-tiered approach (screening, confirmation, and quasiquantification by means of titration).[18]

### OBJECTIVES AND END POINTS

The objective in each study was to assess the superiority of secukinumab over placebo with respect to the coprimary efficacy end points of PASI 75 and a response of 0 or 1 on the modified investigator's global assessment at week 12. Key secondary efficacy objectives in the ERASURE study were to determine the superiority of secukinumab over placebo with respect to the proportion of patients who met the criteria for a reduction of 90% or more in the PASI score from baseline at week 12 (PASI 90); the superiority of secukinumab over placebo with respect to patient-reported psoriasis-related itching, pain, and scaling on the Psoriasis Symptom Diary at week 12; maintenance of PASI 75 from week 12 through week 52; and maintenance of a response of 0 or 1 on the modified investigator's global assessment from week 12 through week 52. Other end points included PASI 50, PASI 100 (reductions of 50% and 100%, respectively, in the baseline PASI score), PASI 75, PASI 90, and a response of 0 or 1 on the modified investigator's global assessment at each study visit until week 52 and a score of 0 or 1 on the DLQI at weeks 12 and 52. Each end point was assessed by means of a between-group comparison of the proportion of patients who met the criterion for that end point.

The key secondary objectives in the FIXTURE study included assessments of the superiority of secukinumab over placebo with respect to the proportion of patients who met the criteria for PASI 90 at week 12; the superiority of secukinumab over etanercept with respect to the proportion of patients who met the criteria for PASI 75 at week 12; the noninferiority of secukinumab to etanercept with respect to the proportion of patients who met the criteria for PASI 75 at week 12; the superiority of secukinumab over etanercept with respect to the proportion of patients who met the criteria for a response of 0 or 1 on the modified investigator's global assessment at week 12; the superiority of secukinumab over etanercept with respect to the proportion of patients who met the criteria for PASI 75 or a response of 0 or 1 on the modified investigator's global assessment at week 12 and who continued to have that response at week 52; and the superiority of secukinumab over placebo with respect to patient-reported, psoriasis-related itching, pain, and scaling scores on the Psoriasis Symptom Diary at week 12. Other end points included PASI 50, PASI 75, PASI 90, PASI 100, and the response of 0 or 1 on the modified investigator's global assessment until week 52 and a DLQI score of 0 or 1 at weeks 12 and 52.

### STATISTICAL ANALYSIS

In each study, the analyses of the efficacy end points included all the patients who underwent randomization according to the treatment assigned at randomization. Closed testing procedures[19] (see the Supplementary Appendix) were used to evaluate the study hypotheses. Under these procedures, hypotheses regarding the 300-mg and 150-mg doses of secukinumab were evaluated independently, each at the 0.025 significance level, to control the family-wise error rates (Fig. S2 and S5 in the Supplementary Appendix). For the coprimary efficacy end points, between-group comparisons were made with the use of the stratified Cochran–Mantel–Haenszel test, with geographic region and body weight as strata. Missing values for the PASI score and the score on the modified investigator's global assessment were conservatively imputed as nonresponses, regardless of the reason for the missing data.

Per the study protocols, the PASI score was calculated with the use of the percentage of the affected body-surface area rounded to integers; these results are reported here. For both studies, a sensitivity analysis was performed for the coprimary end point of PASI 75 with the use of nonrounded numbers for the body-surface area.

We calculated sample sizes such that the studies would have more than 99% power to show response rates of 55.0% for PASI 75 and 30.0% for the modified investigator's global assessment score of 0 or 1 in each secukinumab-dose group, assuming response rates of 5.0% for both PASI 75 and the modified investigator's global assessment score of 0 or 1 in the placebo group, on the basis of a two-group Fisher's exact test of equal proportions (see the Supplementary Appendix). Safety end points were evaluated for all the patients who

received at least one dose of study drug; these end points were summarized descriptively.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

The demographic and baseline clinical characteristics of the patients in each study were well balanced across the study groups (Table 1). In the ERASURE study, 738 patients underwent randomization at baseline. A total of 700 patients (94.9%) completed the 12-week induction period, and 623 (84.4%) completed the entire 52-week treatment period (Fig. S3 in the Supplementary Appendix). A total of 737 patients were included in the efficacy analyses; 1 patient signed the informed-consent

**Table 1. Demographic and Baseline Clinical Characteristics of the Patients.***

| Characteristic | ERASURE | | | FIXTURE | | | |
|---|---|---|---|---|---|---|---|
| | Secukinumab, 300 mg (N=245) | Secukinumab, 150 mg (N=245) | Placebo (N=248) | Secukinumab, 300 mg (N=327) | Secukinumab, 150 mg (N=327) | Etanercept (N=326) | Placebo (N=326) |
| Age — yr | 44.9±13.5 | 44.9±13.3 | 45.4±12.6 | 44.5±13.2 | 45.4±12.9 | 43.8±13.0 | 44.1±12.6 |
| Male sex — no. (%) | 169 (69.0) | 168 (68.6) | 172 (69.4) | 224 (68.5) | 236 (72.2) | 232 (71.2) | 237 (72.7) |
| Race — no. (%)† | | | | | | | |
| White | 171 (69.8) | 171 (69.8) | 176 (71.0) | 224 (68.5) | 219 (67.0) | 219 (67.2) | 218 (66.9) |
| Asian | 52 (21.2) | 54 (22.0) | 46 (18.5) | 73 (22.3) | 72 (22.0) | 74 (22.7) | 72 (22.1) |
| Other or unknown | 22 (9.0) | 20 (8.2) | 26 (10.5) | 30 (9.2) | 36 (11.0) | 33 (10.1) | 36 (11.0) |
| Weight — kg | 88.8±24.0 | 87.1±22.3 | 89.7±25.0 | 83.0±21.6 | 83.6±20.8 | 84.6±20.5 | 82.0±20.4 |
| Body-mass index‡ | 30.3±7.2 | 29.8±6.8 | 30.3±7.8 | 28.4±6.4 | 28.4±5.9 | 28.7±5.9 | 27.9±6.1 |
| Time since psoriasis diagnosis — yr | 17.4±11.1 | 17.5±12.0 | 17.3±12.4 | 15.8±12.3 | 17.3±12.2 | 16.4±12.0 | 16.6±11.6 |
| PASI score§ | 22.5±9.2 | 22.3±9.8 | 21.4±9.1 | 23.9±9.9 | 23.7±10.5 | 23.2±9.8 | 24.1±10.5 |
| Body-surface area involved — % | 32.8±19.3 | 33.3±19.2 | 29.7±15.9 | 34.3±19.2 | 34.5±19.4 | 33.6±18.0 | 35.2±19.1 |
| Modified investigator's global assessment score — no. (%)¶ | | | | | | | |
| 3 | 154 (62.9) | 161 (65.7) | 151 (60.9) | 203 (62.1) | 206 (63.0) | 195 (59.8) | 202 (62.0) |
| 4 | 91 (37.1) | 84 (34.3) | 97 (39.1) | 124 (37.9) | 121 (37.0) | 131 (40.2) | 124 (38.0) |
| Psoriatic arthritis — no. (%) | 57 (23.3) | 46 (18.8) | 68 (27.4) | 50 (15.3) | 49 (15.0) | 44 (13.5) | 49 (15.0) |
| Previous systemic treatment — no. (%) | | | | | | | |
| Any | 163 (66.5) | 156 (63.7) | 146 (58.9) | 206 (63.0) | 212 (64.8) | 214 (65.6) | 204 (62.6) |
| Conventional agent‖ | 128 (52.2) | 125 (51.0) | 108 (43.5) | 195 (59.6) | 198 (60.6) | 204 (62.6) | 199 (61.0) |
| Biologic agent | 70 (28.6) | 73 (29.8) | 73 (29.4) | 38 (11.6) | 45 (13.8) | 45 (13.8) | 35 (10.7) |
| TNF inhibitor | 48 (19.6) | 44 (18.0) | 51 (20.6) | 12 (3.7) | 15 (4.6) | 21 (6.4) | 12 (3.7) |
| Anti–interleukin-12 and anti–interleukin-23 agent | 32 (13.1) | 37 (15.1) | 31 (12.5) | 23 (7.0) | 23 (7.0) | 22 (6.7) | 21 (6.4) |
| No response to previous use of TNF inhibitor — no. (%) | 17 (6.9) | 18 (7.3) | 21 (8.5) | 10 (3.1) | 9 (2.8) | 10 (3.1) | 3 (0.9) |

* Plus–minus values are means ±SD. In each study, there were no significant between-group differences in the baseline characteristics listed. ERASURE denotes Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis, FIXTURE Full Year Investigative Examination of Secukinumab versus Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis, and TNF tumor necrosis factor.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Scores on the psoriasis area-and-severity index (PASI) range from 0 to 72, with higher scores indicating more severe disease.[13]

¶ Scores on the modified investigator's global assessment range from 0 (clear skin) to 4 (severe disease); a score of 3 indicates moderate disease.[14]

‖ Conventional systemic agents included methotrexate, cyclosporine, glucocorticoids, and fumaric acid esters.

form after starting study procedures and as a result of the protocol deviation was excluded from efficacy and safety analyses. In the FIXTURE study, 1306 patients who had not received etanercept previously underwent randomization, of whom 1233 (94.4%) completed the induction period and 1100 (84.2%) completed the maintenance period (Fig. S6 in the Supplementary Appendix). A total of 1305 patients were included in the efficacy analyses; 1 patient signed the informed-consent form after starting the study procedures and was excluded from the efficacy and safety analyses.

### COPRIMARY EFFICACY END POINTS IN BOTH STUDIES

In both studies, secukinumab was shown to be superior to the comparators (or noninferior, when noninferiority was assessed) with respect to all the coprimary and key secondary end points that were evaluated in the testing procedures (Tables S2 and S7 in the Supplementary Appendix). The criteria for the coprimary end points — PASI 75 response and the response of 0 or 1 on the modified investigator's global assessment at week 12 — were met by significantly greater proportions of patients in each secukinumab-dose group than in the placebo group in each study (P<0.001 for all comparisons) (Tables 2 and 3). Across all efficacy end points, the 300-mg dose of secukinumab was associated with rates of response that were numerically superior to the rates observed with the 150-mg dose.

### SECONDARY EFFICACY END POINTS

#### *ERASURE Study*

Secukinumab at the 300-mg and 150-mg doses was shown to be superior to placebo with respect to the key secondary end point of PASI 90 response at week 12 (P<0.001 for both comparisons) (Table 2). The proportion of patients who met the criteria for PASI 100 at week 12 was also significantly greater with each secukinumab dose than with placebo (P<0.001 for both comparisons).

Each dose of secukinumab was superior to placebo with respect to patient reports of itching, pain, and scaling on the Psoriasis Symptom Diary at week 12, another prespecified key secondary end point (P<0.001 for all comparisons) (Table S3 in the Supplementary Appendix). The proportion of patients with a DLQI score of 0 or 1, indicating no impairment of health-related quality of life, was significantly higher at week 12 in each secukinumab-dose group than in the placebo group (P<0.001 for both comparisons) (Table 2, and the Supplementary Appendix).

#### *FIXTURE Study*

Secukinumab was superior to etanercept and placebo with respect to all key secondary end points (Table 3, and Table S8 in the Supplementary Appendix). The proportion of patients with a DLQI score of 0 or 1 at week 12 was significantly higher in each secukinumab-dose group than in the etanercept or placebo group (P<0.001 for all comparisons) (Table 3, and the Supplementary Appendix). As specified per protocol, the percentage change from baseline in the PASI score was assessed according to study visit and treatment group. The median time to a 50% reduction from baseline in the mean PASI score was significantly shorter with secukinumab at the doses of 300 mg and 150 mg than with etanercept (3.0 weeks and 3.9 weeks, respectively, vs. 7.0 weeks; P<0.001 for both comparisons) (Fig. 1).

### RESPONSE OVER TIME

Inspection of the curves showing response over time suggests that the rates of response on the PASI and the modified investigator's global assessment increased during the period from week 12 to week 16 and then stabilized after week 16 (Fig. 2). In the FIXTURE study, the rates of response according to PASI 75, PASI 90, PASI 100, and a score of 0 or 1 on the modified investigator's global assessment were higher with secukinumab than with etanercept through week 52 (Fig. 2B).

### SAFETY

During the induction period in the ERASURE study, the proportion of patients who had at least one adverse event was higher in the secukinumab groups (55.1% in the 300-mg group and 60.4% in the 150-mg group) than in the placebo group (47.0%) (Table S4 in the Supplementary Appendix). There were also higher proportions of patients with infections and infestations in the secukinumab groups (29.4% in the 300-mg group and 26.9% in the 150-mg group) than in the placebo group (16.2%) during the induction period. The most common adverse events in the induction period and the entire treatment period in this study were nasopharyngitis, headache, and upper respiratory tract infection (Table S4 in the Supplementary Appendix). The incidence of ad-

**Table 2. Efficacy End Points in ERASURE.***

| End Point | Secukinumab, 300 mg | Secukinumab, 150 mg | Placebo |
|---|---|---|---|
| Coprimary efficacy end points at wk 12 — no./total no. (%) | | | |
| PASI 75 | 200/245 (81.6)† | 174/243 (71.6)† | 11/246 (4.5) |
| Response of 0 or 1 on modified investigator's global assessment‡ | 160/245 (65.3)† | 125/244 (51.2)† | 6/246 (2.4) |
| Key secondary efficacy end points | | | |
| PASI 90 at wk 12 — no./total no. (%) | 145/245 (59.2)† | 95/243 (39.1)† | 3/246 (1.2) |
| Maintenance of PASI 75 from wk 12 to wk 52 — no./total no. (%) | 161/200 (80.5) | 126/174 (72.4) | NE |
| Maintenance of 0 or 1 response on modified investigator's global assessment from wk 12 to wk 52 — no./total no. (%)‡ | 119/160 (74.4) | 74/125 (59.2) | NE |
| Other efficacy end points | | | |
| PASI 100 at wk 12 — no./total no. (%) | 70/245 (28.6)† | 31/243 (12.8)† | 2/246 (0.8) |
| DLQI — mean score§ | | | |
| Baseline | 13.9 | 13.4 | 12.0 |
| Wk 12 | 2.5 | 3.3 | 10.9 |
| Absolute change | –11.4 | –10.1 | –1.1 |

* In the statistical analyses, missing data were imputed as nonresponses. PASI 75, PASI 90, and PASI 100 responses indicate reductions from baseline in the PASI score of 75% or more, 90% or more, and 100%, respectively. NE denotes not evaluated.
† P<0.001 for the comparison with placebo.
‡ A response on the modified investigator's global assessment was defined as a score of 0 (clear) or 1 (almost clear) and an improvement of 2 or more points from baseline.
§ Scores on the Dermatology Life Quality Index (DLQI) range from 0 to 30, with higher scores indicating a greater effect of the disease on quality of life.[17]

**Table 3. Efficacy End Points in FIXTURE.***

| End Point | Secukinumab, 300 mg | Secukinumab, 150 mg | Etanercept | Placebo |
|---|---|---|---|---|
| Coprimary efficacy end points at wk 12 — no./total no. (%) | | | | |
| PASI 75 | 249/323 (77.1)†‡ | 219/327 (67.0)†‡ | 142/323 (44.0) | 16/324 (4.9) |
| Response of 0 or 1 on modified investigator's global assessment | 202/323 (62.5)†‡ | 167/327 (51.1)†‡ | 88/323 (27.2) | 9/324 (2.8) |
| Key secondary efficacy end points — no./total no. (%) | | | | |
| PASI 90 at wk 12 | 175/323 (54.2)†‡ | 137/327 (41.9)†‡ | 67/323 (20.7) | 5/324 (1.5) |
| Maintenance of PASI 75 from wk 12 to wk 52 | 210/249 (84.3)† | 180/219 (82.2)§ | 103/142 (72.5) | NE |
| Maintenance of 0 or 1 response on modified investigator's global assessment from wk 12 to wk 52 | 161/202 (79.7)† | 113/167 (67.7)¶ | 50/88 (56.8) | NE |
| Other efficacy end points | | | | |
| PASI 100 at wk 12 — no./total no. (%) | 78/323 (24.1)†‖ | 47/327 (14.4)†‖ | 14/323 (4.3) | 0/324 |
| DLQI — mean score | | | | |
| Baseline | 13.3 | 13.4 | 13.4 | 13.4 |
| Wk 12 | 2.9 | 3.7 | 5.5 | 11.5 |
| Absolute change | –10.4 | –9.7 | –7.9 | –1.9 |

* In the statistical analyses, missing data were imputed as nonresponses. The criteria for the noninferiority of secukinumab to etanercept with regard to PASI 75 at week 12, one of the key secondary end points, were met for each secukinumab dose.
† P<0.001 for the comparison with etanercept.
‡ P<0.001 for the comparison with placebo.
§ P=0.009 for the comparison with etanercept.
¶ P=0.002 for the comparison with etanercept.
‖ No comparison with placebo was performed because there were no patients with a response in the placebo group.

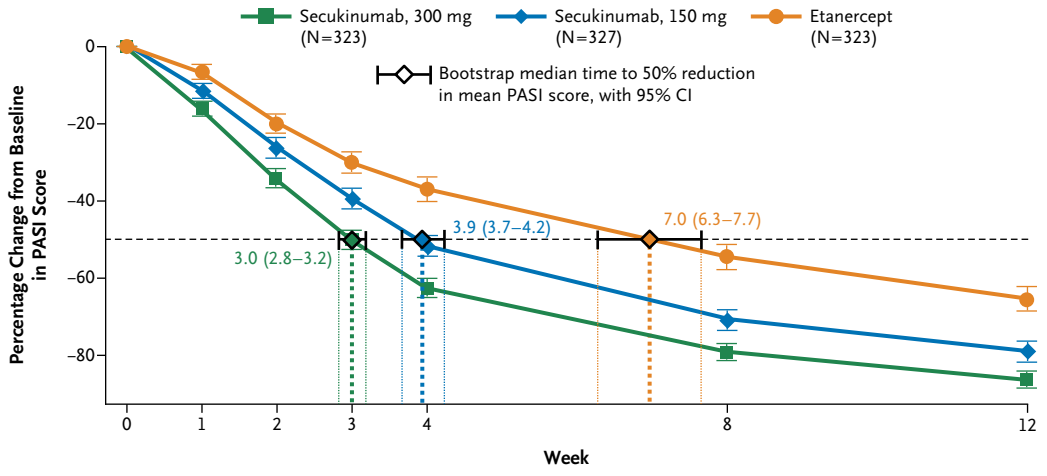


**Figure 1. Speed of Response.**

The speed of response among patients in the Full Year Investigative Examination of Secukinumab versus Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis (FIXTURE) study was evaluated according to the median time to a 50% reduction from baseline in the mean score on the psoriasis area-and-severity index (PASI; scores range from 0 to 72, with higher scores indicating more severe disease). A repeated-measures, mixed-effects model was used to analyze the mean percentage change from baseline in the PASI score. Symbols without black outlining indicate the least-squares means, and I bars the 95% confidence intervals (CIs). The median time to a 50% reduction in the mean PASI score (dashed line) was estimated from parametric bootstrap samples with the use of linear interpolation between time points. A 50% reduction in the mean PASI score was not observed in the placebo group, so an analysis of the median time to 50% reduction was not conducted.

verse events in other system organ classes was similar among the study groups. Additional data on adverse events in this study are provided in the Supplementary Appendix.

The incidences of adverse events during the induction period and the entire treatment period in the FIXTURE study were similar in the secukinumab and etanercept groups (Table 4). The most common adverse events in the secukinumab groups during induction and the entire treatment period were nasopharyngitis, headache, and diarrhea. The incidence of injection-site reactions during the entire study was lower in the combined secukinumab groups than in the etanercept group (7 patients [0.7%] vs. 36 patients [11.1%]), although the difference was not assessed for significance.

The proportions of patients in the FIXTURE study who had infections and infestations during the induction period were 26.7% with the 300-mg dose of secukinumab, 30.9% with the 150-mg dose of secukinumab, 24.5% with etanercept, and 19.3% with placebo (Table 4). Candida infections were more common with secukinumab than with etanercept during the entire treatment period: 22 patients in the 300-mg secukinumab group (4.7%) and 11 in the 150-mg secukinumab group (2.3%) reported mild or moderate candida infection. None of the infections resulted in chronic mucocutaneous candidiasis or discontinuation of the study drug, and all resolved on their own or with standard therapy. In the etanercept group, 4 patients (1.2%) had candida infection, 2 of whom had an infection that was graded as severe. Grade 3 neutropenia occurred in 9 patients (1.0%) in the combined secukinumab-dose groups and in no patients in the etanercept group; no infections or any other adverse events were reported in these patients. Grade 4 neutropenia occurred in no patient who received secukinumab and in 1 patient (0.3%) in the etanercept group (see the Supplementary Appendix). Results for candida infection and neutropenia were similar in the two studies (see the Supplementary Appendix).

There were no deaths during the treatment period in either study, although there was one death unrelated to psoriasis (suicide) during the screening period in the FIXTURE study. In the ERASURE study, the rates of serious adverse

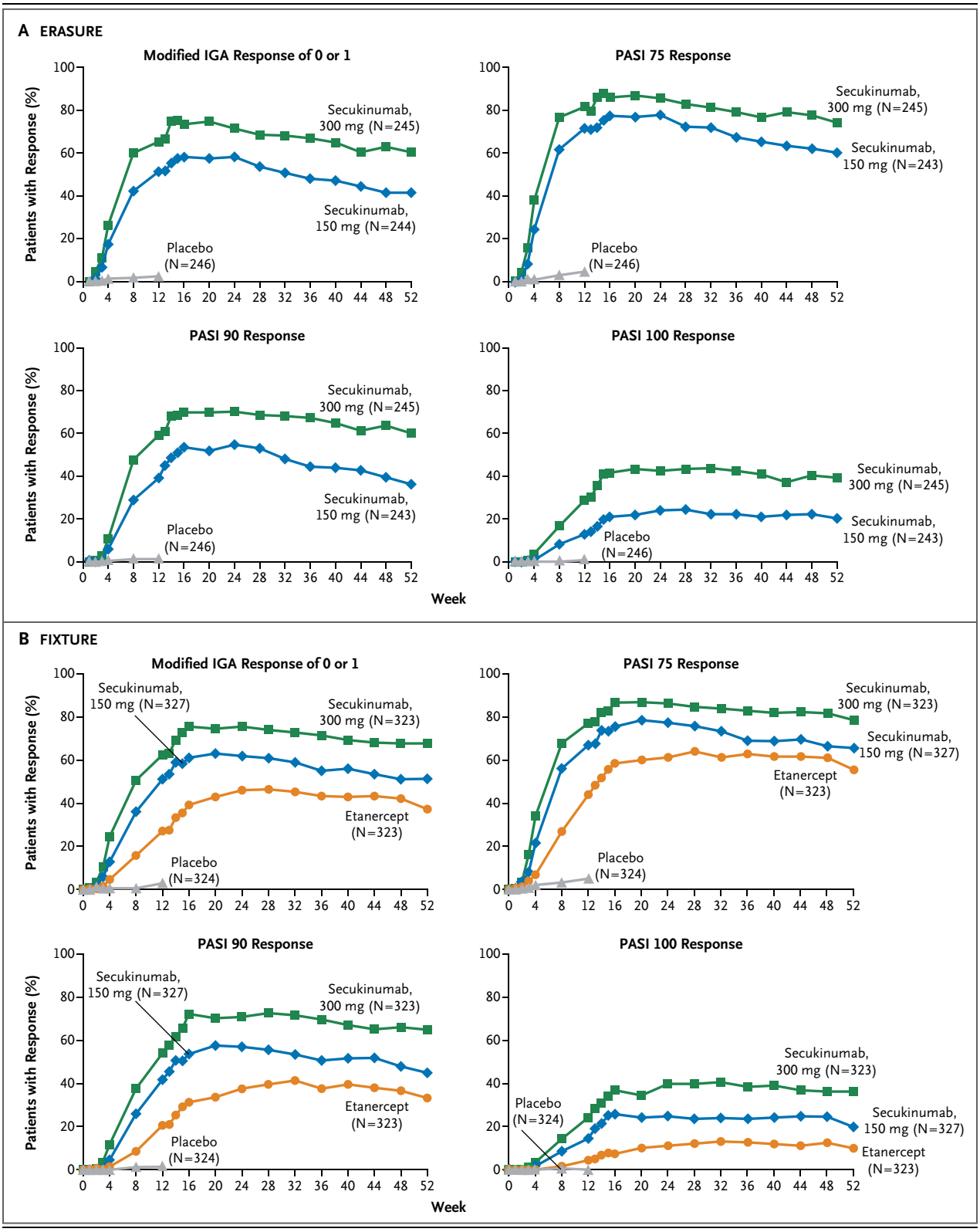

**Figure 2 (facing page). Efficacy over Time.**
Panel A shows the results in the Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis (ERASURE) study, and Panel B the results in the FIXTURE study. Shown are the proportions of patients who met the criteria for prespecified efficacy end points at each visit to week 52. The PASI 75, PASI 90, and PASI 100 responses indicate reductions from baseline in the PASI score of 75% or more, 90% or more, and 100%, respectively. Missing values were imputed as nonresponses. Only patients who could be evaluated for a response were included. IGA denotes investigator's global assessment.

events during the entire treatment period were 6.3 events per 100 patient-years in the 300-mg secukinumab group, 6.4 events per 100 patient-years in the 150-mg secukinumab group, and 7.4 events per 100 patient-years in the placebo group. In the FIXTURE study, the rates of serious adverse events were 6.8 events per 100 patient-years in the 300-mg secukinumab group, 6.0 events per 100 patient-years in the 150-mg secukinumab group, 7.0 events per 100 patient-years in the etanercept group, and 8.3 events per 100 patient-years in the placebo group (Table 4). There were no clinically apparent differences in the type of serious adverse events among the various study groups (Tables S5 and S9 in the Supplementary Appendix). Rates of cancer, serious infection, and major adverse cardiovascular events are shown in Tables S6 and S10 in the Supplementary Appendix. Discontinuations due to adverse events were more frequent in the etanercept group than in either secukinumab group in the FIXTURE study.

Anti-secukinumab antibodies were detected in 4 patients after the start of secukinumab treatment in the FIXTURE study (0.4% of the 980 secukinumab-treated patients tested). No patient had neutralizing antibodies, and there was no association with adverse events or loss of efficacy. Samples from 19 patients were positive for anti-secukinumab antibodies at baseline (before treatment), and antibodies persisted after baseline in 7 of these patients. Samples from 2 patients who received placebo and 4 who received etanercept were positive for new-onset anti-secukinumab antibodies after baseline. No testing was performed for anti-etanercept antibodies. In the ERASURE study, anti-secukinumab antibodies that developed during treatment were detected in 2 of 702 (0.3%) secukinumab-treated patients tested; additional immunogenicity data from this study are provided in the Supplementary Appendix.

## DISCUSSION

The results of these phase 3 studies validate interleukin-17A as an important therapeutic target in moderate-to-severe plaque psoriasis, confirming earlier findings from basic research and phase 2 trials of secukinumab that suggested that interleukin-17A plays a role in the pathogenesis of psoriasis.[11,20,21] The superiority (or the noninferiority, when that was assessed) of secukinumab over the comparators was shown with respect to the coprimary efficacy end points and all key secondary end points in both studies. Secukinumab was associated with a rapid reduction in psoriasis symptoms, elicited significantly greater PASI 75 rates and higher rates of 0 or 1 responses on the modified investigator's global assessment than placebo at week 12, and with continued treatment was associated with sustained high response rates in a majority of patients through week 52. The FIXTURE study showed the superior efficacy of secukinumab over the TNF inhibitor etanercept over a period of 52 weeks, a duration that exceeds the 12-week study duration in a previous phase 3, blinded, direct comparison of biologic therapies for psoriasis.[22]

Responses at week 12 were sustained in the majority of patients through week 52 with continued secukinumab therapy every 4 weeks. The maintenance of response was rigorously evaluated, given that missing data were imputed as nonresponses, providing a conservative assessment.[23]

Clinical response (i.e., a 50% reduction in the mean PASI score) occurred more rapidly with each secukinumab dose (median, 3.0 weeks with 300 mg and 3.9 weeks with 150 mg) than with etanercept (median, 7.0 weeks) in the FIXTURE study. The investigator-assessed reduction in signs and symptoms in each study was accompanied by a reduction in patient-reported itching, pain, and scaling on the Psoriasis Symptom Diary and an improvement in the health-related quality of life on the DLQI.

These studies were not designed to statistically differentiate efficacy between the two secu-

**Table 4. Adverse Events during the Induction Period and the Entire 52-Week Study Period in FIXTURE.***

| Variable | Induction Period | | | | Entire Study Period† | | | |
|---|---|---|---|---|---|---|---|---|
| | Secukinumab, 300 mg (N=326) | Secukinumab, 150 mg (N=327) | Etanercept (N=323) | Placebo (N=327) | Any Secukinumab, 300 mg (N=467) | Any Secukinumab, 150 mg (N=469) | Etanercept (N=323) | Placebo (N=327) |
| Exposure to study treatment — days | 82.8±9.8 | 83.3±11.6 | 82.6±9.4 | 81.7±11.4 | 320.7±75.3 | 317.5±75.4 | 331.9±89.7 | 95.3±61.0 |
| | *no. of patients with event (percent)* | | | | *no. of patients with event (no. of cases per 100 patient-yr)* | | | |
| Any adverse event | 181 (55.5) | 191 (58.4) | 186 (57.6) | 163 (49.8) | 376 (252.0) | 364 (236.4) | 253 (243.4) | 168 (329.7) |
| Death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nonfatal serious adverse event | 4 (1.2) | 7 (2.1) | 3 (0.9) | 6 (1.8) | 27 (6.8) | 24 (6.0) | 20 (7.0) | 7 (8.3) |
| Discontinuation due to adverse event‡ | 4 (1.2) | 2 (0.6) | 6 (1.9) | 3 (0.9) | 14 | 10 | 12 | 3 |
| Infection or infestation | 87 (26.7) | 101 (30.9) | 79 (24.5) | 63 (19.3) | 269 (105.4) | 240 (91.9) | 170 (91.4) | 65 (89.5) |
| Common adverse event§ | | | | | | | | |
| Nasopharyngitis | 35 (10.7) | 45 (13.8) | 36 (11.1) | 26 (8.0) | 122 (35.2) | 108 (31.4) | 86 (35.7) | 26 (32.8) |
| Headache | 30 (9.2) | 16 (4.9) | 23 (7.1) | 23 (7.0) | 58 (15.7) | 47 (12.4) | 40 (15.2) | 24 (29.6) |
| Diarrhea | 17 (5.2) | 12 (3.7) | 11 (3.4) | 6 (1.8) | 38 (9.9) | 36 (9.3) | 22 (7.9) | 7 (8.4) |
| Pruritus | 8 (2.5) | 12 (3.7) | 8 (2.5) | 11 (3.4) | 16 (4.0) | 21 (5.3) | 16 (5.7) | 11 (13.2) |
| Arthralgia | 5 (1.5) | 14 (4.3) | 12 (3.7) | 10 (3.1) | 24 (6.0) | 33 (8.5) | 23 (8.2) | 10 (12.1) |
| Upper respiratory tract infection | 7 (2.1) | 10 (3.1) | 7 (2.2) | 3 (0.9) | 26 (6.6) | 26 (6.6) | 18 (6.4) | 3 (3.5) |
| Back pain | 8 (2.5) | 8 (2.4) | 9 (2.8) | 6 (1.8) | 31 (7.9) | 20 (5.1) | 26 (9.3) | 6 (7.1) |
| Cough | 11 (3.4) | 5 (1.5) | 4 (1.2) | 4 (1.2) | 30 (7.6) | 15 (3.7) | 12 (4.2) | 4 (4.8) |
| Hypertension | 5 (1.5) | 10 (3.1) | 5 (1.5) | 4 (1.2) | 20 (5.0) | 22 (5.6) | 14 (4.9) | 4 (4.7) |
| Nausea | 8 (2.5) | 6 (1.8) | 4 (1.2) | 7 (2.1) | 11 (2.7) | 10 (2.5) | 7 (2.4) | 7 (8.3) |
| Oropharyngeal pain | 9 (2.8) | 5 (1.5) | 4 (1.2) | 7 (2.1) | 25 (6.3) | 20 (5.0) | 10 (3.5) | 7 (8.3) |

* Plus–minus values are means ±SD. The induction period was defined as the period from baseline through week 12, and the entire study period as the period from baseline through week 52.

† Patients in the placebo group who did not meet the criteria for PASI 75 at week 12 underwent randomization again to secukinumab at a dose of 300 mg or 150 mg. In the analysis for the entire study period, the placebo group includes all the patients who received placebo during the induction period, which includes the 16 patients who met the criteria for PASI 75 at week 12, who continued to receive placebo during the maintenance period (week 13 through week 52).

‡ Exposure-adjusted incidence rates were not calculated for discontinuations due to adverse events.

§ The most common adverse events are expressed according to the preferred term in the *Medical Dictionary for Regulatory Activities*, version 16.0, and were events that occurred in at least 2.0% of the patients in the combined secukinumab groups during the induction period or events that had an incidence rate of at least 5.0 cases per 100 patient-years in the combined secukinumab groups during the entire treatment period. Adverse events are listed in decreasing order of frequency in the combined secukinumab groups during the induction period.

kinumab doses. However, the results suggest that the 300-mg dose may have been more effective than the 150-mg dose, a finding that was consistent across efficacy end points.

Secukinumab had a safety profile consistent with that observed in previous phase 2 trials. In both of our studies, the incidences of adverse events, notably infectious adverse events, were higher in the secukinumab groups than in the placebo group during the induction period. The incidences of adverse events in the secukinumab groups during induction and the entire 52-week treatment period in the FIXTURE study were similar to the incidence with etanercept. There were no apparent dose-related differences between the secukinumab groups with respect to adverse events, with the exception of mild and moderate candida infections.

Interleukin-17A plays a key role in host defense, specifically in mucocutaneous microbial surveillance.[24] Continued vigilance with respect to the potential for candida infection will be necessary for interleukin-17A inhibitors. Neutropenia may also be of potential concern because of the reported role of interleukin-17A in the stimulation of granulopoiesis and neutrophil trafficking.[25]

Anti-secukinumab antibodies were detected during treatment in 2 of 702 patients (0.3%) receiving secukinumab in the ERASURE study and in 4 of 980 (0.4%) in the FIXTURE study. The presence of anti-secukinumab antibodies was not associated with adverse events or reduced efficacy. The assay used in these studies is highly sensitive and therefore capable of detecting very low levels of antibodies that can bind to secukinumab. Consequently, non–treatment-related, naturally occurring antidrug antibodies may lead to a confirmed positive response. The observations of anti-secukinumab antibodies in some patients at baseline or while they were receiving placebo or etanercept were not considered to be clinically relevant, because the antidrug antibodies were not associated with secukinumab treatment; therefore, they were not explored further.

A limitation of these studies was that few patients continued to receive placebo after week 12, which limited the comparisons with this group during the maintenance periods. In addition, the trial populations, although sufficient for assessing efficacy and common adverse events, may have been too small to detect rare adverse events. Extension studies evaluating long-term efficacy are ongoing.

In conclusion, these phase 3 studies showed the efficacy of secukinumab over a period of 52 weeks in patients with moderate-to-severe plaque psoriasis.

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