ORIGINAL ARTICLE

Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis

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ABSTRACT

BACKGROUND

Two phase 3 trials (UNCOVER-2 and UNCOVER-3) showed that at 12 weeks of treatment, ixekizumab, a monoclonal antibody against interleukin-17A, was superior to placebo and etanercept in the treatment of moderate-to-severe psoriasis. We report the 60-week data from the UNCOVER-2 and UNCOVER-3 trials, as well as 12-week and 60-week data from a third phase 3 trial, UNCOVER-1.

METHODS

We randomly assigned 1296 patients in the UNCOVER-1 trial, 1224 patients in the UNCOVER-2 trial, and 1346 patients in the UNCOVER-3 trial to receive subcutaneous injections of placebo (placebo group), 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg (2-wk dosing group), or 80 mg of ixekizumab every 4 weeks after a starting dose of 160 mg (4-wk dosing group). Additional cohorts in the UNCOVER-2 and UNCOVER-3 trials were randomly assigned to receive 50 mg of etanercept twice weekly. At week 12 in the UNCOVER-3 trial, the patients entered a long-term extension period during which they received 80 mg of ixekizumab every 4 weeks through week 60; at week 12 in the UNCOVER-1 and UNCOVER-2 trials, the patients who had a response to ixekizumab (defined as a static Physicians Global Assessment [sPGA] score of 0 [clear] or 1 [minimal psoriasis]) were randomly reassigned to receive placebo, 80 mg of ixekizumab every 4 weeks, or 80 mg of ixekizumab every 12 weeks through week 60. Coprimary end points were the percentage of patients who had a score on the sPGA of 0 or 1 and a 75% or greater reduction from baseline in Psoriasis Area and Severity Index (PASI 75) at week 12.

RESULTS

In the UNCOVER-1 trial, at week 12, the patients had better responses to ixekizumab than to placebo; in the 2-wk dosing group, 81.8% had an sPGA score of 0 or 1 and 89.1% had a PASI 75 response; in the 4-wk dosing group, the respective rates were 76.4% and 82.6%; and in the placebo group, the rates were 3.2% and 3.9% ($P<0.001$ for all comparisons of ixekizumab with placebo). In the UNCOVER-1 and UNCOVER-2 trials, among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks, 80 mg of ixekizumab every 12 weeks, or placebo, an sPGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively. Patients in the UNCOVER-3 trial received continuous treatment of ixekizumab from weeks 0 through 60, and at week 60, at least 73% had an sPGA score of 0 or 1 and at least 80% had a PASI 75 response. Adverse events reported during ixekizumab use included neutropenia, candidal infections, and inflammatory bowel disease.

CONCLUSIONS

In three phase 3 trials involving patients with psoriasis, ixekizumab was effective through 60 weeks of treatment. As with any treatment, the benefits need to be weighed against the risks of adverse events. The efficacy and safety of ixekizumab beyond 60 weeks of treatment are not yet known. (Funded by Eli Lilly; UNCOVER-1, UNCOVER-2, and UNCOVER-3 ClinicalTrials.gov numbers NCT01474512, NCT01597245, and NCT01646177, respectively.)

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*A complete list of investigators in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 Study Groups is provided in the Supplementary Appendix, available at NEJM.org.

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Psoriasis is a chronic inflammatory disease that is mediated by aberrant immune responses and driven by self-perpetuating cytokine networks.[1,2] Advances in understanding the pathogenic cytokine network of psoriasis have led to the development of new treatments[3-5] that provide greater efficacy in terms of complete skin clearance.[6-9] The motivation to completely clear psoriasis plaques from the skin of patients has grown in response to accumulating evidence that residual skin disease can affect a patient's health-related quality of life[10-12] similar to that associated with chronic conditions such as type 2 diabetes.[13]

Ixekizumab, a recombinant, high-affinity, humanized, IgG4-κ monoclonal antibody, selectively binds and neutralizes interleukin 17A (IL-17A), the proinflammatory and primary effector cytokine of type 17 helper T (Th17) cells.[5] The UNCOVER-2 and UNCOVER-3 trials showed that after a 12-week induction period, ixekizumab was superior to placebo and to twice-weekly etanercept for the treatment of moderate-to-severe psoriasis.[9] Here we report the 12-week efficacy data from the UNCOVER-1 trial, the maintenance of response up to week 60 in all three UNCOVER trials, and the integrated safety data from the cumulative UNCOVER data set that included data from 3736 patients, representing 3458 patient-years of exposure to ixekizumab.

Methods

Trial Oversight

The trials were sponsored by Eli Lilly and were designed by the scientific steering committee and Eli Lilly personnel. The site investigators collected the data, Eli Lilly personnel performed the data analyses, and all the authors had access to the data. All the authors take responsibility for the accuracy and completeness of the reported data and analyses for the trials in which they were involved and vouch for the fidelity of the trials to the protocols, available with the full text of this article at NEJM.org. The agreements between Eli Lilly and the investigators included provisions relating to confidentiality of the trial data. The initial draft of the manuscript was written by a medical writer paid by Eli Lilly, and subsequent revisions were made by all the authors. A second medical writer paid by Eli Lilly provided writing support during the review of the manuscript. The trial protocols were approved by the institutional review board or ethics committee at each participating site, and the trials were conducted in accordance with the ethical principles of the Declaration of Helsinki. Eligible patients provided written informed consent.

Trial Population

The eligibility criteria were similar for all three trials. Eligible patients were 18 years of age or older; had moderate-to-severe plaque psoriasis that had been diagnosed at least 6 months before randomization; and were candidates for phototherapy, systemic therapy, or both, with 10% or more of their body-surface area affected by psoriasis, a static Physician's Global Assessment (sPGA) score of 3 or higher (on a scale of 0 to 5, with higher scores indicating more severe disease),[14] and a Psoriasis Area and Severity Index (PASI) of 12 or higher (on a scale from 0 to 72, with higher scores indicating more severe disease)[14] at both the screening and baseline visits.

Patients were excluded if they had forms of psoriasis other than chronic plaque psoriasis (such as drug-induced psoriasis or guttate, erythrodermic, or pustular psoriasis) or if the psoriasis did not meet the criterion of chronicity as defined by the investigator (i.e., the patient had had a clinically significant flare of psoriasis within 12 weeks before baseline). The use of medications that might confound efficacy was not allowed. In the UNCOVER-2 and UNCOVER-3 trials, patients who had used etanercept at any time before screening were excluded. (Details of the prohibited medications and exclusion criteria, as well as the treatments permitted during the trials, are provided in the Methods section in the Supplementary Appendix, available at NEJM.org.)

Trial Design

Overview

The trials were multicenter, randomized, double-blind, placebo-controlled phase 3 trials; an active drug control was also included in the UNCOVER-2 and UNCOVER-3 trials. Overall, the trials were conducted at 100 sites worldwide. A list of the participating sites and the patient flow charts for each of the three UNCOVER trials are provided in Table S1 and Figures S1, S2, and S3 in the Supplementary Appendix.

Induction Period (UNCOVER-1)

During the induction period in the UNCOVER-1 trial, the patients were randomly assigned, in a 1:1:1 ratio, to receive subcutaneous injections of placebo (placebo group), 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg at week 0 (2-wk dosing group), or 80 mg of ixekizumab every 4 weeks after a starting dose of 160 mg at week 0 (4-wk dosing group). For all trials and trial periods, placebo was given to match all active treatment dosing regimens. The placebo group comprised 431 patients, the 2-wk dosing group 433 patients, and the 4-wk dosing group 432 patients. The designs of the induction periods in the UNCOVER-2 and UNCOVER-3 trials were published previously.[9]

Long-Term Extension Period (UNCOVER-3)

In the UNCOVER-3 trial, the patients who completed the 12-week induction period entered the long-term extension period at the discretion of the investigator and the patient. All patients received ixekizumab every 4 weeks; the patients who had received placebo during the 12-week induction period received a starting dose of 160 mg of ixekizumab at week 12, followed by 80 mg every 4 weeks, and the patients who had received etanercept during the induction period had a 4-week washout period before receiving 80 mg of ixekizumab every 4 weeks starting at week 16.

Randomized Withdrawal Period (UNCOVER-1 and UNCOVER-2)

The UNCOVER-1 and UNCOVER-2[9] trials had similar induction designs. At week 12, the patients who received ixekizumab were classified as either having had a response (defined as an sPGA score of 0 [clear] or 1 [minimal psoriasis]) or not having had a response (defined as an sPGA score >1). Patients who had had a response entered a randomized withdrawal period (weeks 12 through 60) in which they were randomly reassigned (stratified according to ixekizumab-regimen group during the induction period), in a 1:1:1 ratio, to receive subcutaneous injections of placebo (402 patients), 80 mg of ixekizumab every 4 weeks (416 patients), or 80 mg of ixekizumab every 12 weeks (408 patients). Patients who had an sPGA score of 3 or higher (indicating relapse in the trials) during weeks 12 through 60 were classified as not having a response at all later time points; among these patients, those who were already receiving the every-4-week regimen maintained that regimen and those who were receiving the every-12-week regimen or placebo were switched to the every-4-week regimen.

END POINTS AND ASSESSMENTS

The primary objective in the UNCOVER-1 trial was to assess whether ixekizumab would be superior to placebo with respect to the coprimary efficacy end points of a 75% or greater reduction from baseline in PASI (PASI 75) and an sPGA score of 0 (clear) or 1 (minimal psoriasis) at week 12.[14] Secondary objectives were to assess whether ixekizumab would be superior to placebo with respect to the major secondary efficacy end points of a 90% or greater reduction from baseline in PASI (PASI 90) and complete resolution of psoriasis plaques (sPGA score of 0 and a 100% reduction from baseline in PASI [PASI 100]). The objectives in the UNCOVER-2 and UNCOVER-3 trials at week 12 have been published previously.[9] Major secondary efficacy end points for the randomized withdrawal periods in the UNCOVER-1 and UNCOVER-2 trials included the percentage of patients who maintained an sPGA score of 0 or 1 at week 60. The sPGA and PASI end points in the long-term extension period in the UNCOVER-3 trial were reported through week 60 (details of the end-point assessments are provided in the Supplementary Appendix.)

We evaluated safety by monitoring adverse events, including the severity of the event and the relationship of the event to the use of the study drug or placebo, and by obtaining clinical laboratory measurements through 60 weeks. An independent, external cardiovascular and cerebrovascular safety adjudication committee was established to review and adjudicate major adverse cardiovascular or cerebrovascular events, which were reported in a blinded manner. Adverse events that occurred during the treatment periods, which included the induction period (weeks 0 to 12), the maintenance period (weeks 12 through 60), and the combined period (weeks 0 through 60), were defined as those that appeared or worsened during the period from immediately after the first injection through the date of the last visit in that treatment period.

Adverse events of special interest included serious infections, candidal infections, neutropenia, inflammatory bowel disease, cardiovascular or cerebrovascular events and major adverse cardiovascular or cerebrovascular events, and cancer.

STATISTICAL ANALYSIS

Unless otherwise specified, all analyses of efficacy during the induction period were performed according to the intention-to-treat principle. Missing values for the PASI and the sPGA score were imputed conservatively as nonresponses, regardless of the reason for the missing data. In the primary-analysis population, comparisons of efficacy among the study groups with respect to categorical variables during the induction period were performed with the use of logistic-regression analysis. Secondary analyses of efficacy with respect to categorical variables were performed with the use of Fisher's exact test. A gatekeeping testing strategy for primary and major secondary analyses was implemented to control the overall type I error rate at a two-sided alpha level of 0.05. The gatekeeping procedure was based on the Bonferroni test and used an intuitive, stepwise testing algorithm. The alpha levels for the P values associated with the results of the primary and secondary analyses were computed at each step, depending on the results of the preceding tests of significance. (The order in which the primary and major secondary objectives were tested, along with additional details of the statistical analysis, is provided in the Supplementary Appendix.)

The analyses of efficacy during the randomized withdrawal periods were performed with the use of integrated data from the UNCOVER-1 and UNCOVER-2 trials. Comparisons of efficacy among the study groups with respect to categorical variables were performed with the use of the Cochran–Mantel–Haenszel test, stratified according to trial. In the long-term extension period in the UNCOVER-3 trial, efficacy was summarized by descriptive statistics.

Safety analyses included all patients who received at least one dose of the study drug or placebo. The rates of adverse events were compared among the study groups and analyzed with the use of the Cochran–Mantel–Haenszel test, stratified according to trial. Exposure-adjusted incidence rates were calculated for common adverse events and serious adverse events that occurred during each treatment period (the induction period, the maintenance period, and the combined period); exposure-adjusted incidence rates were calculated as the total number of patients who had an adverse event or serious adverse event during each treatment period, divided by the total of all patients' exposure during the same treatment period (per 100 patient-years). A Poisson regression model was used to analyze exposure-adjusted incidence rates.

RESULTS

PATIENT CHARACTERISTICS

In the UNCOVER-1 trial, the mean age of the patients was 46 years, the mean weight was 92 kg, and the mean duration of psoriasis was 20 years. Two thirds of the patients were men. The mean body-surface-area involvement was greater than 25%, and the mean PASI was approximately 20. Approximately 40% of the patients in the UNCOVER-1 trial had received prior biologic therapy, as compared with 24% in the UNCOVER-2 trial and 16% in the UNCOVER-3 trial, probably because the UNCOVER-2 and UNCOVER-3 trials excluded patients who had prior use of etanercept (Table 1).[9]

EFFICACY

Induction Period (UNCOVER-1)

During the induction period in the UNCOVER-1 trial, all primary and major secondary end points were met, with significantly greater improvements with both ixekizumab regimens than with placebo (Fig. 1). For all efficacy end points, the rates of response were higher in the 2-wk dosing group than in the 4-wk dosing group. Among the patients in the 2-wk dosing group, 89.1% had a PASI 75 response, 70.9% had a PASI 90 response, and 35.3% had a PASI 100 response at week 12 (Fig. 1). The results of the analyses of efficacy during the induction period were consistent in the three UNCOVER trials (Fig. S4 and Table S2 in the Supplementary Appendix).[9]

Long-Term Extension Period (UNCOVER-3)

The high rates of response observed during the induction period were generally maintained during the long-term extension period in UNCOVER-3 (Fig. 2). Most patients had maintained or attained near-complete resolution (PASI 90) or complete

Table 1. Baseline Demographics and Clinical Characteristics in All UNCOVER Trials.*

Variable	UNCOVER-1			UNCOVER-2[9]				UNCOVER-3[9]			
	Placebo (N=431)	Ixekizumab Every 4 wk (N=432)	Ixekizumab Every 2 wk (N=433)	Placebo (N=168)	Etanercept (N=358)	Ixekizumab Every 4 wk (N=347)	Ixekizumab Every 2 wk (N=351)	Placebo (N=193)	Etanercept (N=382)	Ixekizumab Every 4 wk (N=386)	Ixekizumab Every 2 wk (N=385)
Age — yr†	46±13	46±13	45±12	45±12	45±13	45±14	45±13	46±12	46±14	46±13	46±13
Male sex — no. (%)	303 (70.3)	289 (66.9)	291 (67.2)	120 (71.4)	236 (65.9)	244 (70.3)	221 (63.0)	137 (71.0)	269 (70.4)	258 (66.8)	254 (66.0)
White race — no./total no. (%)‡	401/431 (93.0)	397/432 (91.9)	401/433 (92.6)	149/168 (88.7)	331/354 (93.5)	315/343 (91.8)	330/350 (94.3)*	176/193 (91.2)	351/382 (91.9)	360/386 (93.3)	361/385 (93.8)
Weight — kg§	92±25	92±24	92±23	92±22	93±22	93±23	89±22*	91±21	92±24	91±24	90±23
<100 kg — no. (%)	289 (67.1)	290 (67.1)	288 (66.5)	111 (66.9)	232 (65.0)	227 (65.6)	256 (72.9)*	138 (71.9)	256 (67.0)	274 (71.9)	275 (71.6)
≥100 kg — no. (%)	142 (32.9)	142 (32.9)	145 (33.5)	55 (33.1)	125 (35.0)	119 (34.4)	95 (27.1)*	54 (28.1)	126 (33.0)	107 (28.1)	109 (28.4)
Duration of psoriasis — yr	20±12	19±12	20±12	19±13	19±12	19±13	18±12	18±13	18±12	18±12**	18±12
Percent of body-surface area involved	27±18	27±16	28±18	27±18	25±16	27±17	25±16	29±17	28±17	28±16**	28±17
sPGA score ≥4 — no. (%)¶	227 (52.7)	235 (54.4)	202 (46.7)	82 (48.8)	172 (48.0)	181 (52.2)	173 (49.3)	101 (52.3)	192 (50.3)	177 (46.2)**	178 (46.2)
PASI score‖	20±9	20±7	20±8	21±8	19±7*	20±7	19±7	21±8	21±8	21±8**	21±8
Previous therapy — no. (%)	418 (97.0)	419 (97.0)	424 (97.9)	164 (97.6)	344 (96.1)	338 (97.4)	340 (96.9)	181 (93.8)	368 (96.3)	360 (93.3)	361 (93.8)
Phototherapy	185 (42.9)	205 (47.5)	201 (46.4)	74 (44.0)	173 (48.3)	160 (46.1)	163 (46.4)	60 (31.1)	157 (41.1)*	154 (39.9)*	151 (39.2)
Nonbiologic systemic	224 (52.0)	213 (49.3)	247 (57.0)	80 (47.6)	170 (47.5)	178 (51.3)	178 (50.7)	82 (42.5)	182 (47.6)	181 (46.9)	170 (44.2)
Biologic	181 (42.0)	168 (38.9)	173 (40.0)	43 (25.6)	76 (21.2)	85 (24.5)	84 (23.9)	33 (17.1)	60 (15.7)	58 (15.0)	58 (15.1)

* Plus–minus values are means ±SD. The following baseline variables differed significantly between the groups: white race (UNCOVER-2: ixekizumab every 2 weeks [80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg] vs. placebo, P=0.02); mean weight (UNCOVER-2: ixekizumab every 2 weeks vs. etanercept, P=0.03); <100-kg group and ≥100-kg group (UNCOVER-2: ixekizumab every 2 weeks vs. etanercept, P=0.02); baseline Psoriasis Area Severity Index (PASI) score (UNCOVER-2: etanercept vs. placebo, P=0.03); and phototherapy (UNCOVER-3: ixekizumab every 4 weeks [80 mg of ixekizumab every 4 weeks after a starting dose of 160 mg] vs. placebo and etanercept vs. placebo, P<0.05 for both comparisons).

† Data were not available for 1 patient in the placebo group, the etanercept group, and the ixekizumab-every-2-week group in the UNCOVER-2 trial, and were not available for 4 patients in the ixekizumab-every-4-week group and 1 patient in the ixekizumab-every-2-week group in the UNCOVER-3 trial.

‡ Race was self-reported.

§ Data were not available for 2 patients in the placebo group, 1 patient in the etanercept group, and 1 patient in the ixekizumab-every-4-week group in the UNCOVER-2 trial, and were not available for 1 patient in the placebo group, 5 patients in the ixekizumab-every-4-week group, and 1 patient in the ixekizumab-every-2-week group in the UNCOVER-3 trial.

¶ Scores on the static Physician's Global Assessment (sPGA) range from of 0 (clear) to 5 (very severe); a score of 3 indicates moderate disease.

‖ Overall PASI ranges from 0 (clear skin) to 72 (worst possible psoriasis); a score of 12 indicates moderate disease.

** Data were available for 383 patients.

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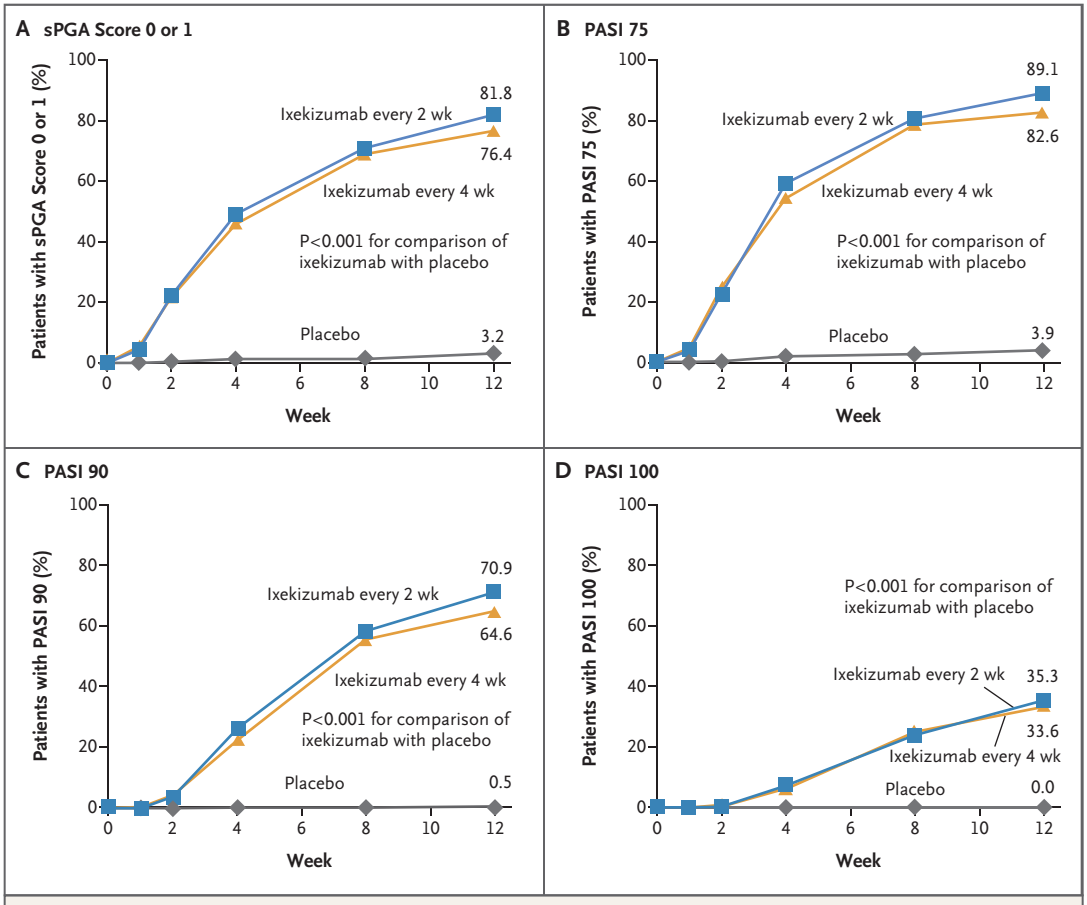

Figure 1. Response to Ixekizumab During the Induction Period in the UNCOVER-1 Trial.

The induction period lasted for 12 weeks. The patients in the two active-treatment groups received a starting dose of 160 mg of ixekizumab followed by 80 mg of ixekizumab every 2 weeks (433 patients) or 80 mg of ixekizumab every 4 weeks (432 patients); a total of 431 patients received placebo. Panel A shows the percentage of patients with a static Physician's Global Assessment (sPGA) score of 0 or 1. Scores on the sPGA range from 0 (clear) to 5 (very severe); a score of 3 indicates moderate disease. Panel B shows the percentage of patients with a 75% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) (PASI 75). The overall score on the PASI ranges from 0 (clear skin) to 72 (worst possible psoriasis); a score of 12 indicates moderate disease. Panel C shows the percentage of patients with 90% or greater reduction from baseline in PASI (PASI 90), and Panel D shows the percentage of patients with 100% reduction from baseline in PASI (PASI 100). P values were calculated with the use of a logistic-regression model unless the placebo value was equal to zero, in which case a Fisher's exact test was used. Missing values were imputed as nonresponse.

resolution (PASI 100) of psoriasis plaques through week 60.

Randomized Withdrawal Period (UNCOVER-1 and UNCOVER-2)

Among the patients who had an sPGA score of 0 or 1 at week 12 and entered the randomized withdrawal periods in the UNCOVER-1 and UNCOVER-2 trials, 73.8% of the patients who were randomly reassigned to ixekizumab every 4 weeks maintained an sPGA score of 0 or 1 at week 60; the corresponding rates for those randomly reassigned to ixekizumab every 12 weeks or to placebo were 39.0% and 7.0%, respectively. When the patients were analyzed separately according to the ixekizumab regimen during the induction period, an sPGA score of 0 or 1 through week 60 was consistently maintained by 78.3% of the patients in the 2-wk dosing group who went on to receive the every-4-week regimen in the randomized withdrawal period and by 68.7% of those in the 4-wk dosing group who

continued to receive the every-4-week regimen in the randomized withdrawal period; none of these patients had an observed exacerbation of psoriasis that resulted in an sPGA score of 3 or higher at any point between week 12 and week 60 (Fig. 3A). Similarly, high rates were also maintained or attained between weeks 12 and 60 for other measures of high-level responses (PASI 75 [Fig. 3B] and PASI 90 and PASI 100 [Fig. S5 in the Supplementary Appendix]).

SAFETY IN THE POOLED DATA SET

During the 12-week induction period in all the UNCOVER trials, the patients who received either regimen of ixekizumab had a higher rate of adverse events during this treatment period than did the patients who received placebo (Table 2). Among the patients who received ixekizumab during the induction period, the most common adverse events that occurred during the treatment period included nasopharyngitis, upper respiratory tract infection, injection-site reaction, injection-site erythema, and headache; among the patients who received placebo during the induction period, the most common adverse events during the induction period included nasopharyngitis, upper respiratory tract infection, psoriasis, headache, and pruritus (Table 2, and Table S3 in the Supplementary Appendix). The exposure-adjusted incidence rates of at least one serious adverse event and of discontinuation of the study regimen because of an adverse event were similar in the patients who received ixekizumab and those who received placebo. The most common serious adverse event during weeks 0 to 12 among the patients who received ixekizumab was cellulitis, which occurred in 3 patients; no serious adverse event was reported more than once among the patients who received placebo. The integrated safety data set included pooled data from 3736 patients, accounting for 3458 patient-years of exposure to ixekizumab. Nasopharyngitis remained the most common adverse event that occurred during the treatment period, from week 0 through week 60.

During the induction period, oral candidiasis occurred significantly more frequently in the 2-wk dosing group than in the placebo group and occurred at a higher frequency in the 2-wk dosing group than in the 4-wk dosing group (Table 2, and Fig. S6 in the Supplementary Appendix). The exposure-adjusted incidence rate of candidal infections during weeks 0 through 60 was similar to the rate during weeks 0 to 12. No candidal infection met the criteria for a serious adverse event, but in the UNCOVER-2 trial, one patient reported severe candidal otitis externa during the induction period and two patients reported severe oral candidiasis during weeks 12 through 60.

Incidences of neutropenia of grades 1 and 2 were more common among the patients who received ixekizumab than among the patients who received placebo during the induction period. Two patients who received ixekizumab and one

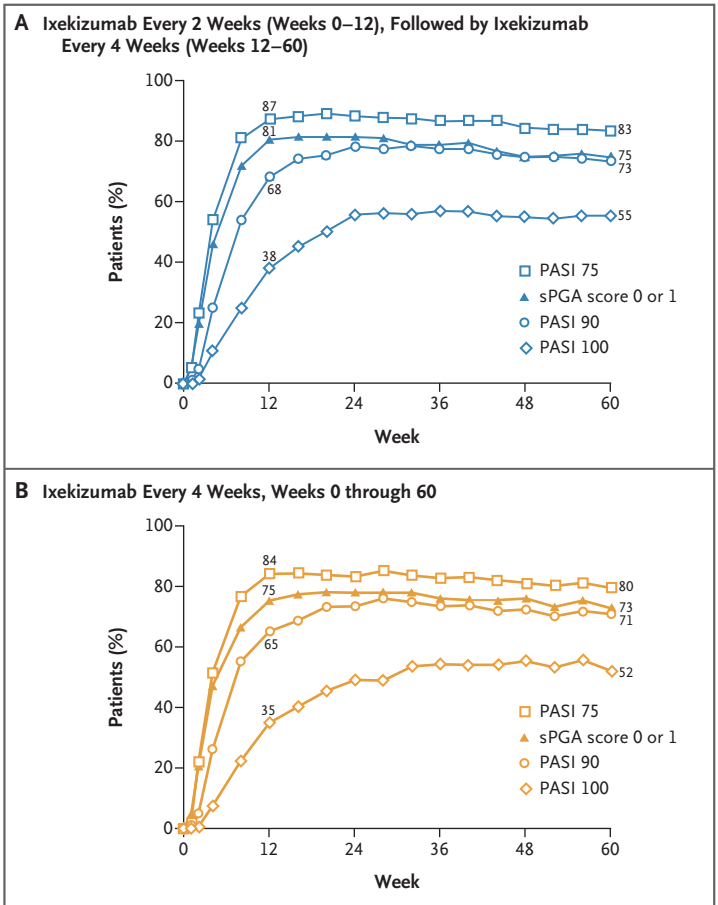

Figure 2. Maintenance of Response to Ixekizumab during Weeks 0 through 60 (UNCOVER-3).

Shown is the maintenance of response to ixekizumab, at a dose of 80 mg, during the long-term extension period (weeks 12 through 60) among the 385 patients who had received ixekizumab every 2 weeks during the induction period (Panel A) and the 386 patients who had received ixekizumab every 4 weeks during the induction period (Panel B). The responses that were measured were an sPGA score of 0 or 1, PASI 75, PASI 90, and PASI 100. Missing values were imputed as nonresponse.

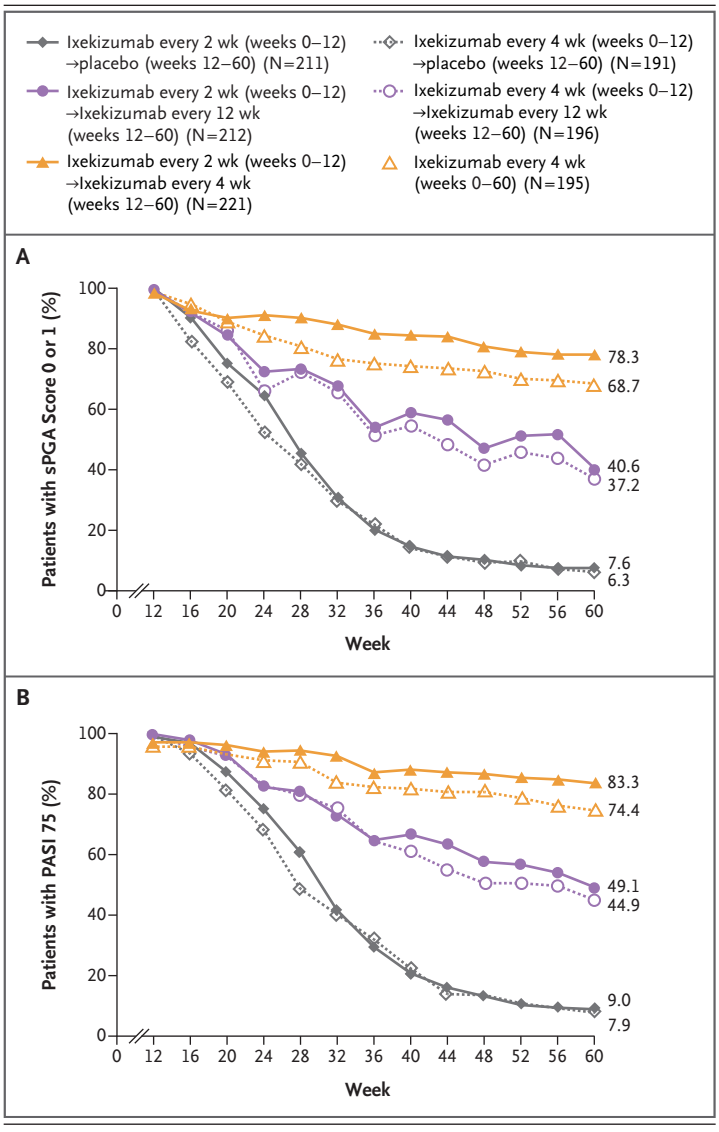

Figure 3. Consistency of Response during Maintenance Weeks 12 through 60 among Patients Who Had an sPGA 0 or 1 Response at Week 12 (UNCOVER-1 and UNCOVER-2).

Patients who had an sPGA score of 0 or 1 at the end of the induction period (week 12) of the UNCOVER-1 and UNCOVER-2 trials were randomly reassigned to receive 80 mg of ixekizumab every 4 weeks, 80 mg of ixekizumab every 12 weeks, or placebo. Shown are the percentages of patients who had an sPGA score of 0 or 1 at week 12 in the pooled UNCOVER-1 and UNCOVER-2 trials, who maintained or attained an sPGA score of 0 or 1 (Panel A) and who maintained or attained a PASI 75 response (Panel B) during the randomized withdrawal period (weeks 12 through 60). Patients who had an sPGA score of 0 or 1 at the end of the induction period were randomly reassigned for the randomized withdrawal period to receive 80 mg of ixekizumab every 4 weeks, 80 mg of ixekizumab every 12 weeks, or placebo. Missing values were imputed as nonresponse. The percentage of patients who had a consistent response to ixekizumab through week 60 (those who maintained an sPGA score of 0 or 1 or a PASI 75 response) was significantly higher in the group that continued to receive ixekizumab during weeks 12 through 60 than in the group that received placebo during weeks 12 through 60 ($P<0.001$ for all comparisons). This analysis excludes subsequent results for patients who had an sPGA score of 3 or higher at any visit but may have subsequently regained response while continuing to receive ixekizumab every 4 weeks.

patient who received placebo had neutropenia of grade 3, and one patient who received ixekizumab had neutropenia of grade 4 (Table 2). Overall, among all the patients who were exposed to ixekizumab during weeks 0 through 60, eight had neutropenia of grade 3 and two had neutropenia of grade 4.

The exposure-adjusted incidence rates of major adverse cardiovascular and cerebrovascular events during the induction period were similar in the placebo group and the 4-wk dosing group (0.6 and 0.8, respectively); no patients in the 2-wk dosing group had a major adverse cardiovascular or cerebrovascular event before week 12 (Table 2, and Fig. S6 in the Supplementary Appendix). During weeks 12 through 60, two patients in the 2-wk dosing group who were randomly reassigned to receive ixekizumab every 4 weeks during the randomized withdrawal period died from vascular causes: one patient had a myocardial infarction and the other had an ischemic stroke.

Among all patients who were treated with ixekizumab during the combined treatment period (weeks 0 through 60), ulcerative colitis was reported in seven patients and Crohn's disease was reported in four patients. Three patients who were randomly reassigned to placebo during the randomized withdrawal period also reported Crohn's disease after 23, 70, and 134 days of receiving placebo (Table 2, and Fig. S6 in the Supplementary Appendix).

During the induction period, no significant differences were observed between the placebo group and either ixekizumab group or between the 2-wk dosing group and the 4-wk dosing

group with respect to the exposure-adjusted incidence rates of nonmelanoma skin cancer and cancers other than nonmelanoma skin cancers. The rates remained stable during weeks 0 through 60 (Table 2, and Fig. S6 in the Supplementary Appendix).

Antidrug antibodies against ixekizumab developed in 103 of 1150 patients (9.0%) in the 2-wk dosing group in the three UNCOVER trials during the induction period; 19 patients (1.7%) had high titers of antidrug antibodies (≥1:1280), accompanied by a lower clinical response than that of patients who had no or low-to-moderate titers of antidrug antibodies (Fig. S7A in the Supplementary Appendix). The patients in the 2-wk dosing group who had a response at week 12 and were randomly reassigned to receive ixekizumab every 4 weeks during weeks 12 through 60 did not have high titers of antidrug antibodies and maintained high-level clinical responses, with no significant differences among the patients with no, low, or moderate titers (Fig. S7B in the Supplementary Appendix).

DISCUSSION

Neutralization of IL-17A with ixekizumab was effective in the treatment of moderate-to-severe plaque psoriasis in three phase 3 trials involving 3736 patients; ixekizumab was superior to placebo with respect to all primary and major secondary end points. In addition, 34 to 37% of the patients who received treatment with ixekizumab had complete resolution (PASI 100 or sPGA score of 0) of their psoriasis plaques at week 12 (UNCOVER-1). The high levels of clinical response were maintained with continued exposure to ixekizumab every 4 weeks through week 60, with at least 50% of patients maintaining or attaining complete resolution of their psoriasis (PASI 100). Among the patients in the 2-wk dosing group and the 4-wk dosing group who had an sPGA score of 0 or 1 at week 12 and were randomly reassigned to receive ixekizumab every 4 weeks during the randomized withdrawal period, 78.3% and 68.7%, respectively, maintained an sPGA score of 0 or 1 through week 60, with no exacerbation of their disease that resulted in an sPGA score of 3 or higher at any visit. All patients with an sPGA score of 0 or 1 at week 12 could continue topical therapies as approved in the protocol, including those who were randomly reassigned to ixekizumab every 12 weeks or to placebo; still, the majority of patients who were randomly reassigned to ixekizumab every 12 weeks or to placebo did not maintain an sPGA score of 0 or 1 through week 60. Patients who had an sPGA score of 3 or higher at any visit began treatment with ixekizumab every 4 weeks at that visit and may have subsequently regained a response during the course of the every-4-week regimen. The analyses in this report excluded the subsequent results for those patients.

With more than 100 sites in 21 countries, the UNCOVER program represented a large, globally diverse population. Candidal infections occurred more frequently among the patients treated with ixekizumab than among those who received placebo, a finding that is consistent with the role of IL-17A in the mucocutaneous defense against fungal infections.[15]

Although low serum levels of IL-17 have been associated with repeat myocardial infarctions and may affect atherosclerotic plaque stability,[16] the role of neutralizing IL-17 in cardiovascular disease is complex and should be defined by careful monitoring and long-term studies involving large numbers of patients.[17] During the 12-week induction periods in these three trials, the risk of adverse cardiovascular events did not differ between the patients who received placebo and those who received ixekizumab. Among all patients in the UNCOVER trials who received ixekizumab during weeks 0 through 60, there were two confirmed deaths from vascular causes. The third death in the UNCOVER program was reported as being due to unknown causes (the patient had received ixekizumab every 4 weeks in both the induction and maintenance periods).

In the UNCOVER trials, 11 patients reported inflammatory bowel disease while receiving ixekizumab, and 3 additional patients reported inflammatory bowel disease while receiving placebo during the randomized withdrawal period after they had received ixekizumab during the induction period. The results from the UNCOVER trials suggest that further evaluation is needed to understand the relationship between IL-17A inhibitors and inflammatory bowel disease.

Ixekizumab provided high levels of clinical response at week 12 and through week 60. How-

Table 2. Adverse Events during the Induction Periods and the Total Ixekizumab Exposure in the Three UNCOVER Trials.*

Adverse Event	Weeks 0–12						Weeks 0–60	
	Placebo (N=791)		Ixekizumab Every 4 wk (N=1161)		Ixekizumab Every 2 wk (N=1167)		All Patients with Ixekizumab Exposure (N=3736)	
	no. of patients (%)	*incidence rate/100 patient-yr*	*no. of patients (%)*	*incidence rate/100 patient-yr*	*no. of patients (%)*	*incidence rate/100 patient-yr*	*no. of patients (%)*	*incidence rate/100 patient-yr*
Any adverse event†	370 (46.8)	205.5	683 (58.8)	256.8	681 (58.4)	253.6	3021 (80.9)	87.4
Serious adverse event	12 (1.5)	6.7	26 (2.2)	9.8	20 (1.7)	7.4	250 (6.7)	7.2
Discontinuation of study regimen because of an adverse event	9 (1.1)	5.0	24 (2.1)	9.0	25 (2.1)	9.3	165 (4.4)	4.8
Death	0	0.0	0	0.0	0	0.0	3 (0.1)	0.1
Common adverse events‡								
Nasopharyngitis	69 (8.7)	38.3	104 (9.0)	39.1	111 (9.5)	41.3	733 (19.6)	21.2
Upper respiratory tract infection	28 (3.5)	15.6	45 (3.9)	16.9	51 (4.4)	19.0	372 (10.0)	10.8
Injection-site reaction	9 (1.1)	5.0	89 (7.7)	33.5	117 (10.0)	43.6	387 (10.4)	11.2
Arthralgia	17 (2.1)	9.4	22 (1.9)	8.3	29 (2.5)	10.8	196 (5.2)	5.7
Headache	23 (2.9)	12.8	50 (4.3)	18.8	51 (4.4)	19.0	243 (6.5)	7.0
Selected adverse events of special interest								
Infection or infestation	181 (22.9)	100.5	318 (27.4)	119.6	315 (27.0)	117.3	2064 (55.2)	59.7
Candidal§	4 (0.5)	2.2	7 (0.6)	2.6	16 (1.4)	6.0	128 (3.4)	3.7
Oral	0	0.0	2 (0.2)	0.8	9 (0.8)	3.4	63 (1.7)	1.8
Vulvovaginal¶	3 (1.3)	1.7	5 (1.3)	1.9	3 (0.7)	1.1	40 (3.3)	3.6
Skin	1 (0.1)	0.6	0	0.0	2 (0.2)	0.7	20 (0.5)	0.6
Esophageal	0	0.0	0	0.0	1 (0.1)	0.4	2 (0.1)	0.1
Nail	0	0.0	0	0.0	0	0.0	1 (<0.1)	0.0
Unspecified	0	0.0	0	0.0	0	0.0	9 (0.2)	0.3
Major adverse cardiovascular and cerebrovascular events‖	1 (0.1)	0.6	2 (0.2)	0.8	0	0.0	23 (0.6)	0.7
Crohn's disease	0	0.0	1 (0.1)	0.4	1 (0.1)	0.4	4 (0.1)	0.1
Ulcerative colitis	0	0.0	0	0.0	2 (0.2)	0.7	7 (0.2)	0.2
Cancer, excluding nonmelanoma skin cancer	1 (0.1)	0.6	2 (0.2)	0.8	1 (0.1)	0.4	14 (0.4)	0.4
Nonmelanoma skin cancer	1 (0.1)	0.6	1 (0.1)	0.4	2 (0.2)	0.7	20 (0.5)	0.6
Selected serious adverse events of special interest								
Infection	3 (0.4)	1.7	8 (0.7)	3.0	5 (0.4)	1.9	51 (1.4)	1.5
Major adverse cardiovascular and cerebrovascular events‖	1 (0.1)	0.6	2 (0.2)	0.8	0	0.0	22 (0.6)	0.6
Crohn's disease	0	0.0	1 (0.1)	0.4	1 (0.1)	0.4	3 (0.1)	0.1

Table 2. (Continued.)

Adverse Event	Weeks 0–12						Weeks 0–60	
	Placebo (N=791)		Ixekizumab Every 4 wk (N=1161)		Ixekizumab Every 2 wk (N=1167)		All Patients with Ixekizumab Exposure (N=3736)	
	no. of patients (%)	*incidence rate/100 patient-yr*	*no. of patients (%)*	*incidence rate/100 patient-yr*	*no. of patients (%)*	*incidence rate/100 patient-yr*	*no. of patients (%)*	*incidence rate/100 patient-yr*
Ulcerative colitis	0	0.0	0	0.0	0	0.0	1 (<0.1)	0.0
Cancer, excluding nonmelanoma skin cancers	1 (0.1)	0.6	1 (0.1)	0.4	0	0.0	10 (0.3)	0.3
Nonmelanoma skin cancer	0	0.0	0	0.0	0	0.0	2 (0.1)	0.1
Other serious adverse event**	9 (1.1)	5.0	16 (1.4)	6.0	15 (1.3)	5.6	179 (4.8)	5.2
Neutropenia††								
Grade 1	23 (2.9)	–	76 (6.6)	–	81 (7.0)	–	321 (8.6)	–
Grade 2	2 (0.3)	–	22 (1.9)	–	25 (2.1)	–	97 (2.6)	–
Grade 3	1 (0.1)	–	0	–	2 (0.2)	–	8 (0.2)	–
Grade 4	0	–	1 (0.1)	–	0	–	2 (0.1)	

* The placebo group represented 180.0 patient-years; the group that received ixekizumab every 4 weeks, 265.9 patient-years; the group that received ixekizumab every 2 weeks, 268.6 patient-years; and the combined groups with ixekizumab exposure, 3458.4 patient-years.
† Adverse events included here are those that appeared or worsened during the treatment periods.
‡ Common adverse events occurring during treatment were defined as those that had an incidence rate of at least 5% among all the patients with ixekizumab exposure and occurred in a greater number of patients who received ixekizumab than patients who received placebo during the induction period.
§ A list of specific terms included in each category of candidal infection is provided in the Methods section in the Supplementary Appendix.
¶ Because this event was sex-specific for females, the denominator was adjusted to 232 for the placebo group, 374 for the group that received ixekizumab every 4 weeks, 401 for the group that received ixekizumab every 2 weeks, and 1207 for all the patients with ixekizumab exposure.
‖ Major adverse cardiovascular and cerebrovascular events were included only if they were confirmed after adjudication.
** A list of other serious adverse events is provided in Table S4 in the Supplementary Appendix.
†† The number of patients with a least one postbaseline value for neutrophil level was 787 in the placebo group, 1152 in the group that received ixekizumab every 4 weeks, 1163 in the group that received ixekizumab every 2 weeks, and 3716 among all the patients with ixekizumab exposure. Neutropenia data include patients with postbaseline neutrophil counts that worsened from a normal level or from the grade at baseline. Neutropenia of grade 1 was defined as an absolute neutrophil count of 1500 to less than 2000 per cubic millimeter (from a normal level at baseline); grade 2, as a count of 1000 to less than 1500 per cubic millimeter (from a normal level or grade 1 at baseline); grade 3, as a count of 500 to less than 1000 per cubic milliliter (from a normal level or grade 1 or 2 at baseline); and grade 4, as a count of less than 500 per cubic millimeter (from a normal level or grade 1, 2, or 3 at baseline).

ever, as with any treatment, the benefits need to be weighed against the adverse events, and the safety profile of longer-term treatment with ixekizumab should be examined.

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APPENDIX

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