ORIGINAL ARTICLE

Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa

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ABSTRACT

BACKGROUND

Hidradenitis suppurativa is a painful, chronic inflammatory skin disease with few options for effective treatment. In a phase 2 trial, adalimumab, an antibody against tumor necrosis factor α, showed efficacy against hidradenitis suppurativa.

METHODS

PIONEER I and II were similarly designed, phase 3 multicenter trials of adalimumab for hidradenitis suppurativa, with two double-blind, placebo-controlled periods. In period 1, patients were randomly assigned in a 1:1 ratio to 40 mg of adalimumab weekly or matching placebo for 12 weeks. In period 2, patients were reassigned to adalimumab at a weekly or every-other-week dose or to placebo for 24 weeks. The primary end point was a clinical response, defined as at least a 50% reduction from baseline in the abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula counts, at week 12.

RESULTS

We enrolled 307 patients in PIONEER I and 326 in PIONEER II. Clinical response rates at week 12 were significantly higher for the groups receiving adalimumab weekly than for the placebo groups: 41.8% versus 26.0% in PIONEER I ($P=0.003$) and 58.9% versus 27.6% in PIONEER II ($P<0.001$). Patients receiving adalimumab had significantly greater improvement than the placebo groups in rank-ordered secondary outcomes (lesions, pain, and the modified Sartorius score for disease severity) at week 12 in PIONEER II only. Serious adverse events in period 1 (excluding worsening of underlying disease) occurred in 1.3% of patients receiving adalimumab and 1.3% of those receiving placebo in PIONEER I and in 1.8% and 3.7% of patients, respectively, in PIONEER II. In period 2, the rates of serious adverse events were 4.6% or less in all the groups in both studies, with no significant between-group differences.

CONCLUSIONS

Treatment with adalimumab (40 mg weekly), as compared with placebo, resulted in significantly higher clinical response rates in both trials at 12 weeks; rates of serious adverse events were similar in the study groups. (Funded by AbbVie; ClinicalTrials.gov numbers, NCT01468207 and NCT01468233 for PIONEER I and PIONEER II, respectively.)

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Hidradenitis suppurativa, also known as acne inversa, is a painful, chronic inflammatory skin disease[1-3] characterized by multifocal, recurrent nodules, abscesses, and fistulas, predominantly affecting the axillary, inguinal, breast-fold, and anogenital regions.[4] The prevalence of self-reported disease is 1% in Western Europe.[1,5] The average interval from the onset of symptoms to diagnosis is 7.2 years.[6] Women are affected 2 to 5 times as frequently as men, and the disease may be more common in blacks than in whites.[1,7] Disease severity ranges from mild (localized lesions) to severe (multiple areas of widely dispersed lesions, including interconnected sinus tracts and hypertrophic scars).[8] Pain, drainage, and range-of-motion limitations from scarring can decrease the quality of life.[9,10] Immunologic abnormalities are hypothesized to have a causal role in the disease[11]; significant elevations in levels of the proinflammatory cytokines interleukin-1β and tumor necrosis factor α (TNF-α) and the anti-inflammatory cytokine interleukin-10 have been detected in hidradenitis suppurativa lesions.[12]

Adalimumab, a fully human, IgG1 monoclonal antibody specific for TNF-α, is currently approved for the treatment of a wide range of inflammatory diseases, including moderate-to-severe plaque psoriasis and moderate-to-severe hidradenitis suppurativa; the latter indication resulted from the trials reported here. No other medical treatments for hidradenitis suppurativa have been approved by regulatory agencies, and the few available treatment algorithms are based primarily on expert opinion, case reports, and case series.[13,14] In a phase 2 dose-ranging trial involving 154 patients, weekly dosing with adalimumab as compared with placebo showed significant efficacy in controlling objective signs of disease and reducing pain.[15] We conducted two phase 3 trials to further determine the clinical safety and efficacy of adalimumab as compared with placebo, to compare continuation of a weekly dose with a dose reduction, and to assess the maintenance of a clinical response after treatment has been discontinued.

METHODS

PATIENTS

We enrolled a total of 633 patients at 101 sites in 14 countries and randomly assigned them to receive placebo or adalimumab (PIONEER I: 154 patients and 153 patients, respectively; PIONEER II: 163 patients in each group) (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Men and women who had not received previous anti–TNF-α treatment were eligible if they had moderate-to-severe hidradenitis suppurativa (total abscess and inflammatory-nodule count, ≥3) at baseline and an inadequate response to oral antibiotic treatment. In PIONEER I, patients receiving oral antibiotic agents for hidradenitis suppurativa were required to stop treatment for at least 28 days before baseline; in PIONEER II, patients were allowed to continue treatment with antibiotics (tetracycline class) in stable doses. A detailed description of the eligibility criteria is provided in the Supplementary Appendix.

STUDY OVERSIGHT

The two studies were similarly designed and were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations, and the principles of the Declaration of Helsinki. The studies were designed jointly by the study investigators and the sponsor (AbbVie). The study protocols were approved by the independent ethics committee or institutional review board at each study site. All patients provided written informed consent before enrollment.

The site investigators gathered the data. The sponsor participated in data collection, analysis, and interpretation, as well as in writing, reviewing, and approving the manuscript. All the authors had full access to the data and signed confidentiality agreements with the sponsor before the data were provided for their review. The first draft of the manuscript was written by a medical writer employed by the sponsor, with input from all the authors, who reviewed and provided feedback on all subsequent versions, approved the final version, and in conjunction with the sponsor, made the decision to submit the manuscript for publication. All authors vouch for the completeness and accuracy of the data and analyses presented and affirm that the study was conducted and reported with fidelity to the protocol (available at NEJM.org).

STUDY DESIGN

Both studies were multicenter, 36-week, phase 3 trials with two double-blind, placebo-controlled periods (12-week period 1 and 24-week period 2).

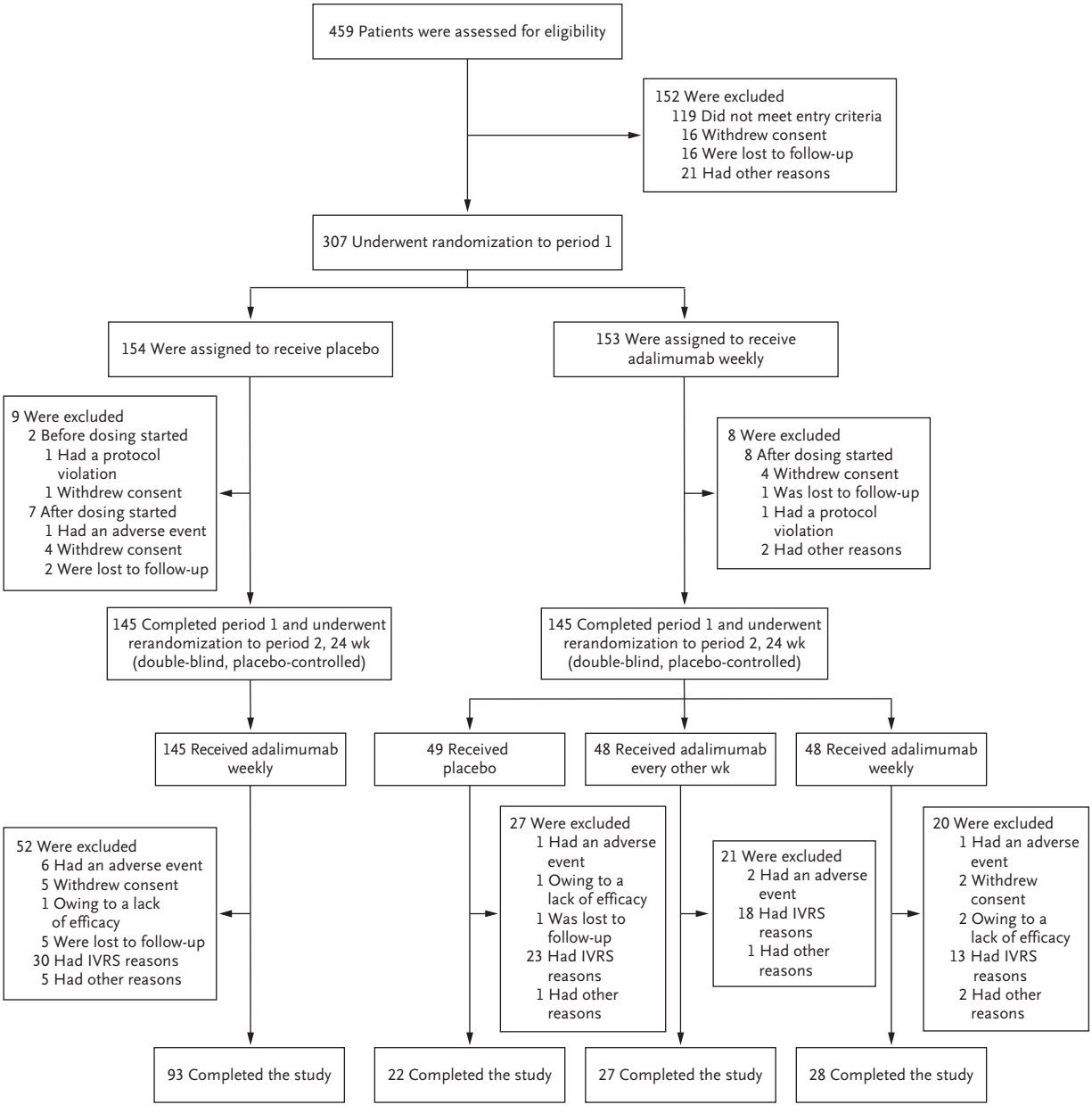

Figure 1. Study Design for PIONEER I.

After assessment for eligibility, patients could have more than one reason for being excluded. Randomization in period 1 was stratified according to the baseline Hurley stage (II vs. III). (Hurley stages are defined as follows: stage I, localized formation of single or multiple abscesses, without sinus tracts or scarring; stage II, single or multiple recurrent abscesses, with sinus tract formation and scarring; and stage III, multiple abscesses, with extensive, interconnected sinus tracts and scarring.) All patients were to continue into the 24-week period 2. To maintain blinding, patients who were randomly assigned in period 1 to 160 mg of adalimumab at week 0 and 80 mg at week 2, followed by 40 mg weekly starting at week 4, were randomly assigned again in period 2 (with stratification according to baseline Hurley stage and Hidradenitis Suppurativa Clinical Response [HiSCR] status at entry to period 2) in a 1:1:1 ratio to 40 mg of adalimumab weekly or every other week or to matching placebo; patients randomly assigned to placebo in period 1 were reassigned in a blinded fashion to 160 mg of adalimumab at week 12 and 80 mg at week 14, followed by 40 mg weekly starting at week 16. Treatments were assigned by means of an interactive voice-response system (IVRS) to maintain blinding. The IVRS instructed patients with loss of response, worsening of symptoms, or absence of improvement to discontinue the study and enter an open-label extension trial (shown in the figure as "IVRS reasons" for exclusion).

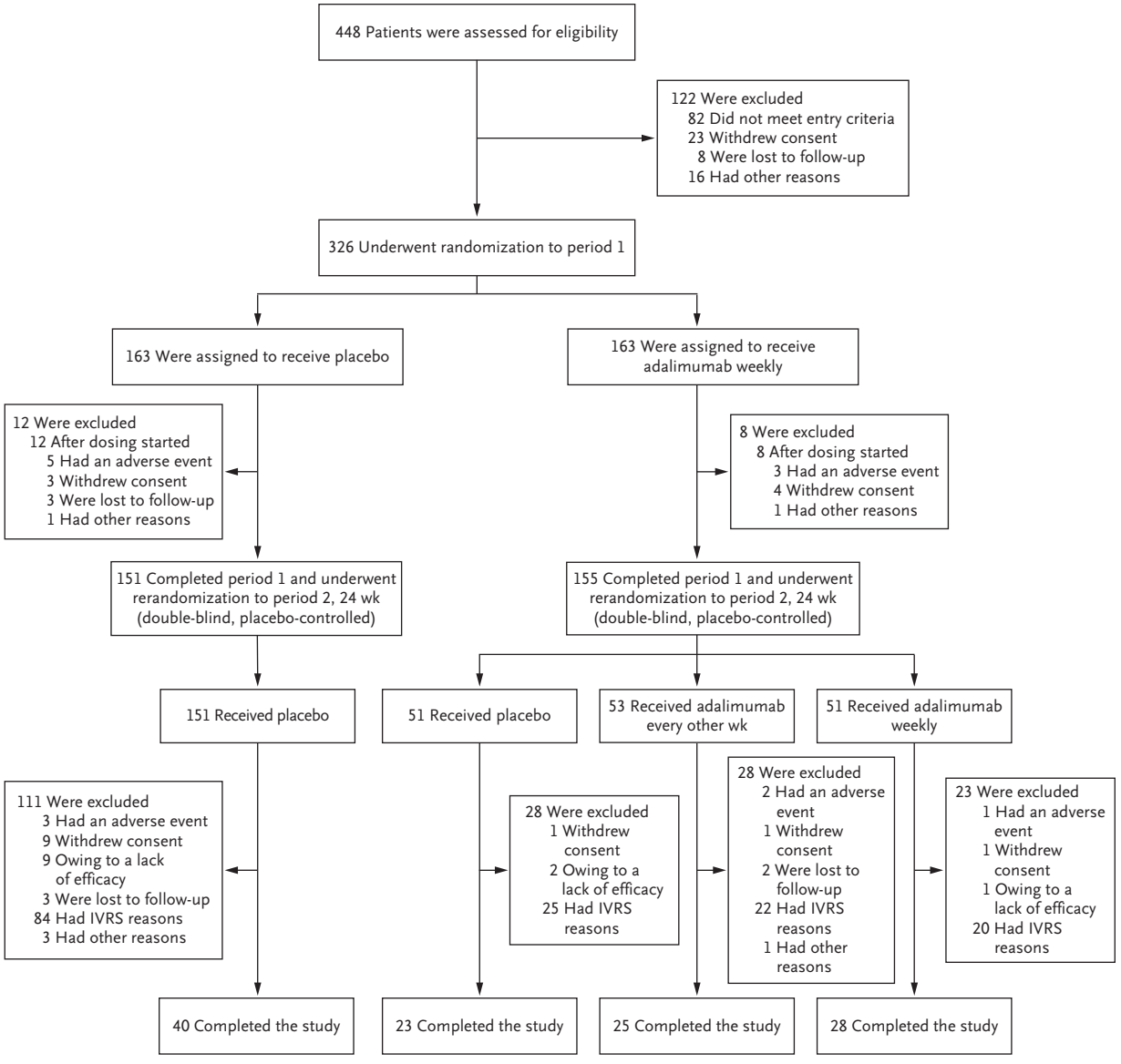

Figure 2. Study Design for PIONEER II.

After assessment for eligibility, patients could have more than one reason for being excluded. Randomization in period 1 was stratified according to the baseline Hurley stage (II vs. III) and status with respect to concomitant use of baseline antibiotics. All patients were to continue into the 24-week period 2. To maintain blinding, patients who were randomly assigned in period 1 to 160 mg of adalimumab at week 0 and 80 mg at week 2, followed by 40 mg weekly starting at week 4, were randomly assigned again in period 2 (with stratification according to baseline Hurley stage and HiSCR status at entry to period 2) in a 1:1:1 ratio to 40 mg of adalimumab weekly or every other week or to matching placebo; patients randomly assigned to placebo in period 1 were reassigned in a blinded fashion to continued placebo. Treatments were assigned by means of an IVRS to maintain blinding. The IVRS instructed patients with loss of response, worsening of symptoms, or absence of improvement to discontinue the study and enter an open-label extension trial (shown in the figure as "IVRS reasons" for exclusion).

PIONEER I was conducted from November 29, 2011, through January 28, 2014, and PIONEER II from December 28, 2011, through April 28, 2014. Study design and dosing details are shown in Figures 1 and 2. Patients were required to use a daily antiseptic wash on their lesions. In period

1, patients were randomly assigned in a 1:1 ratio to 40 mg of adalimumab weekly or matching placebo for 12 weeks. All patients who received adalimumab in period 1 and continued to period 2 underwent a second randomization at week 12 (Figs. 1 and 2); patients who received placebo in period 1 were reassigned to adalimumab weekly (in PIONEER I) or to placebo (in PIONEER II) in a blinded fashion and received that regimen for 24 weeks. During period 2, patients discontinued the study treatment and had the opportunity to enter an open-label extension study if they met the primary efficacy end point and subsequently lost 50% or more of the improvement gained in period 1 or if they did not meet the primary efficacy end point and subsequently had a total abscess and inflammatory-nodule count on two consecutive visits that was greater than or equal to the count at baseline.

ASSESSMENTS

The primary efficacy end point was the proportion of patients with a clinical response at week 12 (end of period 1), defined according to the Hidradenitis Suppurativa Clinical Response (HiSCR) measure as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in the abscess or draining-fistula count; these changes have been identified as clinically meaningful by patients.[16-18] Three secondary end points were rank-ordered at week 12. First was a total abscess and inflammatory-nodule count of 0, 1, or 2 among patients with Hurley stage II disease (defined as recurrent abscesses, single or multiple, with sinus tract formation and scarring) at baseline (Table S2 in the Supplementary Appendix). Second was at least a 30% reduction and at least a 1-unit reduction from baseline in the pain score (on a numerical rating scale of the patient's global assessment of skin pain, with 0 indicating no pain and 10 indicating the worst pain imaginable), on the basis of 24-hour recall of the worst pain, among patients with a baseline score of 3 or higher. Third was the change from baseline in the modified Sartorius score[19] (a score of 4 indicates the least severe disease, and higher scores [no upper limit] indicate increasingly severe disease). Additional, nonranked secondary outcome measures were also assessed at each visit in each period (see the protocol); outcomes in period 1 for all nonranked secondary end points are provided in the Supplementary Appendix. All period 1 assessments were also performed in period 2. The period 2 analyses were exploratory.

Adverse events that emerged during treatment were monitored throughout the studies until 70 days after discontinuation of the study drug. Clinical laboratory measurements, assessment of vital signs, and physical examinations were also performed. Bacteriologic culturing is not a routine diagnostic test for hidradenitis suppurativa and was not performed in these trials. Assessment of serum anti-adalimumab antibody levels is described in the Supplementary Appendix.

STATISTICAL ANALYSIS

Efficacy outcomes were analyzed in the intention-to-treat population according to the randomized group assignments. For the primary outcome, the number and percentage of patients who had a clinical response according to HiSCR were calculated for each study group. The between-group difference in response rates (adalimumab vs. placebo) was analyzed with the use of the Cochran–Mantel–Haenszel test, stratified according to the baseline Hurley stage (stage II vs. stage III [multiple abscesses, with extensive, interconnected sinus tracts and scarring]) (Table S2 in the Supplementary Appendix) in PIONEER I and according to the baseline Hurley stage and use or nonuse of oral antibiotics at baseline in PIONEER II. Statistical comparisons for the primary and rank-ordered secondary efficacy end points were carried out in a hierarchical order — that is, significant results ($P<0.05$) for the comparison in the higher rank (primary end point, then rank-ordered secondary end points) were necessary to conclude significance in the next comparison in the lower rank. For other end points, no adjustment was made for multiple comparisons.

Missing assessments were handled with the use of nonresponse imputation (primary approach to handling missing data), last observation carried forward (sensitivity analysis), multiple imputation (sensitivity analysis for the primary end point) for categorical efficacy variables, and last observation carried forward (primary approach to handling missing data) and as observed without adjustment for missing data (sensitivity analysis) for continuous efficacy variables. Baseline evaluations were not carried forward. In period 2, patients who discontinued the study early and entered the open-label extension study

Table 1. Demographic and Baseline Clinical Characteristics of the Study Populations in Period 1.*

Characteristic	PIONEER I (N=307)		PIONEER II (N=326)	
	Placebo (N=154)	ADA Weekly (N=153)	Placebo (N=163)	ADA Weekly (N=163)
Female sex — no. (%)	105 (68.2)	91 (59.5)	113 (69.3)	108 (66.3)
Race — no. (%)†				
White	118 (76.6)	116 (75.8)	130 (79.8)	143 (87.7)
Black	29 (18.8)	33 (21.6)	20 (12.3)	9 (5.5)
Other	7 (4.5)	4 (2.6)	13 (8.0)	11 (6.7)
Age — yr	37.8±11.3	36.2±10.8	36.1±12.2	34.9±10.0
Body-mass index‡				
No. of patients	154	152	161	163
Mean value	34.5±7.9	33.0±7.6	32.9±7.9	31.3±7.4
Hurley stage — no. (%)§				
II	81 (52.6)	80 (52.3)	89 (54.6)	86 (52.8)
III	73 (47.4)	73 (47.7)	74 (45.4)	77 (47.2)
Previous systemic treatment — no. (%)	63 (40.1)	71 (46.4)	76 (46.6)	82 (50.3)
Median disease duration (range) — yr	9.4 (1.0–43.0)	8.8 (1.1–40.4)	9.9 (1.2–68.5)	9.0 (1.0–43.5)
Prior surgery for hidradenitis suppurativa — no. (%)	13 (8.4)	21 (13.7)	18 (11.0)	27 (16.6)
Lesion counts				
Total no. of abscesses and inflammatory nodules	14.4±14.8	14.3±11.9	11.9±11.0	10.7±8.1
No. of abscesses	2.7±3.7	2.8±3.5	2.4±3.3	2.0±2.6
No. of inflammatory nodules	11.6±13.9	11.5±10.9	9.4±9.6	8.6±6.9
No. of draining fistulas	3.8±4.4	4.6±5.2	3.7±5.2	3.0±4.1
Modified Sartorius score¶	147.3±97.2	151.0±131.2	122.6±88.0	107.5±80.0
Patient's global assessment of skin pain‖				
No. of patients	109	122	111	105
Mean score	6.0±2.0	6.0±1.8	6.2±1.9	5.7±1.9
High-sensitivity C-reactive protein**				
No. of patients	151	152	163	163
Mean value — mg/liter	17.4±20.2	20.3±25.0	18.3±30.7	13.3±18.0
Dermatology Life Quality Index††				
No. of patients	153	151	162	162
Mean score	16.0±7.1	16.3±6.6	14.9±7.3	14.1±7.7

* Plus–minus values are means ±SD. ADA denotes adalimumab. There were no significant between-group differences for the listed baseline characteristics.

† Race was self-reported. In PIONEER I, the "other" category included Asian (4 patients, 1.3%), American Indian or Alaskan native (2 patients, 0.7%), multiple races (1 patient, 0.3%), and other (4 patients, 1.3%). In PIONEER II, the "other" category included Asian (10 patients, 3.1%), American Indian or Alaskan native (1 patient, 0.3%), Native Hawaiian or other Pacific Islander (1 patient, 0.3%), multiple races (3 patients, 0.9%), and other (9 patients, 2.8%).

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

§ Data for the Hurley stage[8] reflect actual assessments, not the Hurley stage stratification factor. A patient's overall Hurley stage was documented as the highest stage across all affected anatomical regions. Stage I is defined as localized formation of single or multiple abscesses, without sinus tracts or scarring; stage II as recurrent abscesses (single or multiple), with sinus tract formation and scarring; and stage III as multiple abscesses, with extensive, interconnected sinus tracts and scarring.

¶ A score of 4 indicates the least severe disease, and higher scores indicate increasingly severe disease; there is no upper limit.

‖ Patients rated skin pain on a numerical rating scale, with scores ranging from 0 (no skin pain) to 10 (the worst pain imaginable); the data shown are for patients who had a baseline score of 3 or higheron the basis of the worst pain in the previous 24 hours.

** Higher values indicate a higher level of systemic inflammation.

†† The Dermatology Life Quality Index measures the effect of skin disease on the patient's quality of life. A score of 0 or 1 indicates no effect, 2 to 5 a small effect, 6 to 10 a moderate effect, 11 to 20 a very large effect, and 21 to 30 an extremely large effect.[20]

according to protocol were classified as not having a response at week 36. Additional details are provided in the Supplementary Appendix. Safety was analyzed for all patients who received at least one dose of the study drug. All statistical tests were two-tailed at a significance level of 0.05.

RESULTS

STUDY PARTICIPANTS

We enrolled 307 patients in PIONEER I and 326 in PIONEER II. The numbers of patients who were assessed for eligibility, who underwent randomization in periods 1 and 2, and who completed the study are shown in Figures 1 and 2. Baseline characteristics (Table 1), including coexisting medical conditions, were generally similar across study groups, except that body weight in PIONEER II was significantly higher in the placebo group than in the adalimumab group (P=0.04) (Table S3 in the Supplementary Appendix). Participants in PIONEER I had a higher weight and greater disease burden (higher mean abscess, inflammatory-nodule, and draining-fistula counts and mean modified Sartorius scores) at baseline than those in PIONEER II. In PIONEER II, 19% of patients received concomitant oral antibiotics.

EFFICACY

In period 1 of each study, a significantly higher proportion of patients in the adalimumab group than in the placebo group met the primary efficacy end point of a clinical response (according to HiSCR) at week 12 (PIONEER I: 41.8% vs. 26.0%, P=0.003; PIONEER II: 58.9% vs. 27.6%, P<0.001) (Fig. 3). Responses to adalimumab were similar regardless of whether baseline antibiotic therapy was continued (in PIONEER II) and regardless of the baseline Hurley stage (Fig. S1 in the Supplementary Appendix). All sensitivity analyses of the primary end point at week 12 yielded similar results (P<0.05). For rank-ordered secondary end points, adalimumab treatment resulted in greater improvements than placebo in PIONEER II (P=0.01 for total abscess and inflammatory-nodule count of 0, 1, or 2 for patients with Hurley stage II disease at baseline, P<0.001 for 30% reduction from baseline in the score for skin pain, and P<0.001 for mean improvement in the modified Sartorius score) but did not have a significant effect in PIONEER I (Table 2, and Table S4 in the Supplementary Appendix). Results for nonranked secondary outcomes are shown in Table S5 in the Supplementary Appendix.

Figure 3 (facing page). Rates of Clinical Response.
The proportions of patients with HiSCR, defined as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula counts, are shown according to the study visit for all patients in period 1 of PIONEER I and II (Panels A and B, respectively), for patients in period 2 of the two studies who had a response at week 12 (Panels C and D, respectively), for patients in period 2 of the two studies who did not have a response at week 12 (Panels E and F, respectively), for patients in PIONEER I who received placebo in period 1 and were reassigned to adalimumab weekly in period 2 (Panel G), and for patients in PIONEER II who received placebo in period 1 and were reassigned to placebo in period 2 (Panel H). Patients who withdrew from the study were classified as not having a response to the study treatment. For the comparison between the adalimumab and placebo groups in period 1, one asterisk denotes P<0.05, two asterisks P<0.01, and three asterisks P<0.001.

Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time (Fig. 3). During period 2, there were no significant differences in clinical-response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.

SAFETY

The proportions of patients who had any adverse event, a serious adverse event, or an infectious event or who discontinued the study drug owing to an adverse event were generally similar between treatment groups in each period (Table 3). Rates of adverse events excluded rates of worsening of underlying disease. The majority

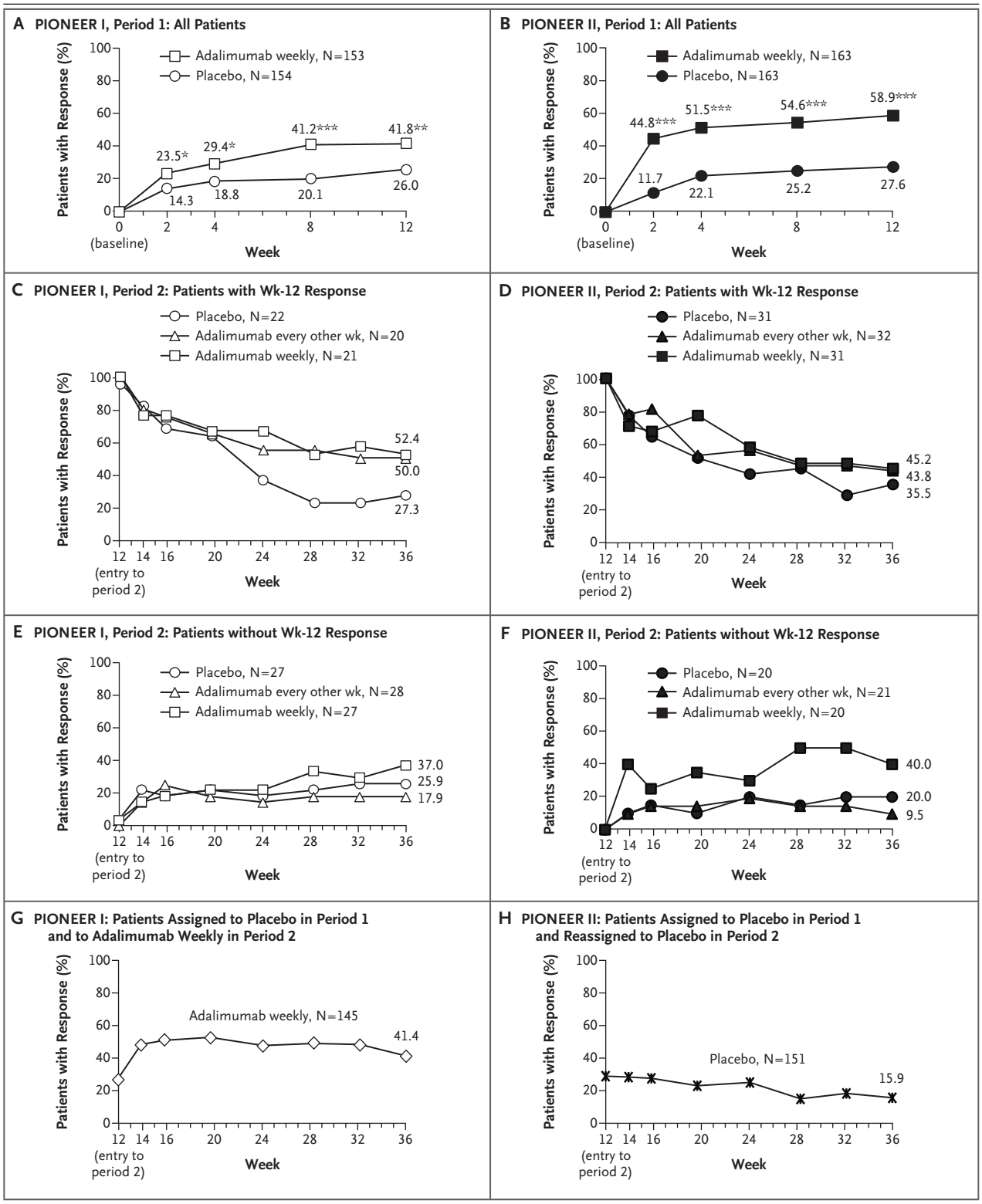

Table 2. Adjusted Between-Group Differences in Rank-Ordered Secondary End Points at Week 12.*

End Point	PIONEER I				PIONEER II			
	Placebo	ADA Weekly	Difference (95% CI)	P Value	Placebo	ADA Weekly	Difference (95% CI)	P Value
Total abscess and inflammatory-nodule count of 0, 1, or 2 — no./total no. (%)†	24/84 (28.6)	24/83 (28.9)	0.3 (−13.4 to 14.1)	0.96	28/87 (32.2)	44/85 (51.8)	19.5 (4.7 to 34.2)	0.01
≥30% Reduction and ≥1-unit reduction in pain score — no./total no. (%)‡	27/109 (24.8)	34/122 (27.9)	2.8 (−8.6 to 14.2)	0.63	23/111 (20.7)	48/105 (45.7)	25.1 (12.7 to 37.6)	<0.001
Improvement in modified Sartorius score§								
Mean score	130.5	125.8			115.2	81.4		
Change in mean score from baseline	−15.7	−24.4	−8.7 (−19.7 to 2.4)	0.12	−9.5	−28.9	−19.4 (−28.6 to −10.1)	<0.001

* Statistical comparisons for the primary and ranked secondary efficacy end points were carried out in a hierarchical order — that is, significant results (P<0.05) for the comparison in the higher rank (primary end point followed by rank-ordered secondary end points) were necessary to conclude the significance in the next comparison in the lower rank. No adjustment was made for multiple comparisons for other end points.

† Total abscess and inflammatory-nodule count was assessed for patients with Hurley stage II disease at baseline. Between-group differences are expressed as percentage-point differences. A nonresponse was imputed for patients with missing data.

‡ This end point was assessed for patients with a score of 3 or higher at baseline on a numerical rating scale of the patient's global assessment of skin pain. Between-group differences are expressed as percentage-point differences. A nonresponse was imputed for patients with missing data.

§ For this end point, 151 patients in the placebo group and 153 in the adalimumab group were assessed in PIONEER I; 162 patients and 163 patients, respectively, were assessed in PIONEER II. A negative value for change indicates improvement. Between-group differences for improvement in the modified Sartorius score are expressed as differences in the means. The last observation was carried forward for patients with missing data.

Table 3. Adverse Events Emerging during Treatment.*

Variable	PIONEER I		PIONEER II	
	Placebo (N=152)†	ADA Weekly (N=153)	Placebo (N=163)	ADA Weekly (N=163)
	number of patients (percent)			
Period 1				
Any adverse event	89 (58.6)	77 (50.3)	103 (63.2)	93 (57.1)
Serious adverse events‡	2 (1.3)	2 (1.3)	6 (3.7)	3 (1.8)
Adverse event leading to study drug discontinuation	2 (1.3)	0	6 (3.7)	4 (2.5)
Infection	43 (28.3)	38 (24.8)	53 (32.5)	41 (25.2)
Serious infection§	0	1 (0.7)	2 (1.2)	1 (0.6)
Cancer¶	1 (0.7)	0	0	0

Any adverse event in ≥10% of patients in either group of either trial								
Headache	15 (9.9)		14 (9.2)		21 (12.9)		21 (12.9)	
Nasopharyngitis	16 (10.5)		9 (5.9)		10 (6.1)		9 (5.5)	
	ADA Weekly (N=145)	Placebo (N=49)	ADA Every Other Week (N=48)	ADA Weekly (N=48)	Placebo (N=151)	Placebo (N=51)	ADA Every Other Week (N=53)	ADA Weekly (N=51)
	number of patients (percent)							
Period 2								
Any adverse event	90 (62.1)	28 (57.1)	22 (45.8)	28 (58.3)	68 (45.0)	33 (64.7)	30 (56.6)	29 (56.9)
Serious adverse event‡	3 (2.1)	0	1 (2.1)	1 (2.1)	7 (4.6)	0	2 (3.8)	2 (3.9)
Adverse event leading to study drug discontinuation	5 (3.4)	1 (2.0)	0	0	3 (2.0)	0	1 (1.9)	1 (2.0)
Infection	43 (29.7)	16 (32.7)	12 (25.0)	14 (29.2)	35 (23.2)	13 (25.5)	19 (35.8)	18 (35.3)
Serious infection§	1 (0.7)	0	0	0	2 (1.3)	0	0	1 (2.0)
Nonmelanoma skin cancer	0	0	0	0	0	0	1 (1.9)	0
Psoriasis-related event‖	5 (3.4)	1 (2.0)	0	1 (2.1)	0	0	1 (1.9)	2 (3.9)
Adverse event leading to death**	0	0	0	0	0	0	1 (1.9)	0
Any adverse event in ≥10% of patients in any group of either trial: Nasopharyngitis	11 (7.6)	9 (18.4)	1 (2.1)	3 (6.3)	5 (3.3)	1 (2.0)	3 (5.7)	3 (5.9)

* Adverse events do not include worsening of underlying disease.

† Two patients in PIONEER I, both randomly assigned to placebo in period 1, did not receive the study drug and are not included in the safety analysis.

‡ In PIONEER I, period 1, the serious adverse events were effusion, intervertebral disk calcification, tendonitis, and breast cancer (one event each in the placebo group), and chronic obstructive pulmonary disease and pyelonephritis (one event each in the adalimumab-weekly group). In PIONEER II, period 1, the serious adverse events were accidental overdose, anemia, inadequate control of diabetes mellitus, dizziness, fatigue, gastroenteritis, increased international normalized ratio, presyncope, suicide attempt, and viral infection (one event each in the placebo group), and infection, acute renal failure, sexual abuse, and tendon rupture (one event each in the adalimumab-weekly group). In PIONEER I, period 2, the serious adverse events were abdominal pain, ectopic pregnancy, positive test for hepatitis A antibody, abnormal liver-function test, and pneumonia (one event each in the group receiving placebo followed by adalimumab weekly), and induced abortion (one event in the group receiving adalimumab weekly followed by adalimumab every other week). In PIONEER II, period 2, the serious adverse events were induced abortion, appendicitis, atrial fibrillation, *Clostridium difficile* infection, depression, intraabdominal hematoma, renal colic, and suicide attempt (one event each in the group receiving placebo followed by placebo); atrial fibrillation, lymphadenitis, and acute myocardial infarction (one event each in the group receiving adalimumab weekly followed by adalimumab every other week); and pneumonia and rash (one event each in the group receiving adalimumab weekly followed by adalimumab weekly).

§ The following eight serious infections occurred: in PIONEER I, pyelonephritis in period 1 (one event in the adalimumab-weekly group) and pneumonia in period 2 (one event in the group receiving placebo followed by adalimumab weekly); in PIONEER II, in period 1, gastroenteritis and viral infection (one event each in the placebo group) and an unspecified infection (one event in the adalimumab-weekly group), and in period 2, appendicitis and *C. difficile* infection (one event each in the group receiving placebo followed by placebo) and pneumonia (one event in the group receiving adalimumab weekly followed by adalimumab weekly).

¶ Included in this category were malignant conditions other than lymphoma, hepatosplenic T-cell lymphoma, leukemia, nonmelanoma skin cancer, and melanoma.

‖ Events of worsening or new onset included psoriasis (two mild events and two that were moderate in severity), dermatitis psoriasiform (two mild and two moderate events), and pustular psoriasis (one moderate and one severe event). One patient with severe pustular psoriasis had a history of psoriasis; the other nine events were of new onset.

** One death owing to cardiorespiratory arrest occurred 42 days after the last dose of adalimumab in a 35-year-old man with a history of diabetes mellitus and smoking and a family history of coronary heart disease.

of adverse events were mild or moderate in severity. Ten psoriasis-related adverse events were reported among patients receiving adalimumab in period 2; none were reported in period 1. During period 1, the rates of serious adverse events were 1.3% and 1.3% in the adalimumab group and the placebo group, respectively, in PIONEER I and 1.8% and 3.7% in the two groups, respectively, in PIONEER II. During period 2, the rates were 4.6% or less in all the groups in both studies (Table 3). In PIONEER II, period 2, squamous-cell carcinoma of the nose was diagnosed on day 85 in a patient assigned to receive adalimumab weekly in period 1 and every other week in period 2, and in PIONEER I, period 1, a breast carcinoma was diagnosed on day 52 in a patient assigned to receive placebo. In PIONEER II, there was one death owing to cardiorespiratory arrest, which occurred 42 days after the last dose of adalimumab in a 35-year-old man with a history of diabetes mellitus and smoking and a family history of coronary heart disease. No deaths were reported in PIONEER I. No clinically meaningful negative changes in laboratory measures or vital signs (i.e., no adverse events of grade 2 or higher, according to the National Institutes of Health Common Terminology Criteria for Adverse Events, version 3.0, for which grades range from 1 to 5, with higher grades indicating more severe adverse events) were noted in the adalimumab-treated patients.

DISCUSSION

In both of these phase 3 studies, the results at week 12 confirmed the finding in the phase 2 trial[15] that 40 mg of adalimumab weekly was efficacious for the treatment of moderate-to-severe hidradenitis suppurativa, and the majority of adverse events were mild or moderate, with no evidence of an increased risk of serious adverse events with adalimumab as compared with placebo. The proportion of patients with a clinical response at week 12 was significantly higher in the group assigned to weekly adalimumab than in the placebo group. The magnitude of improvement with adalimumab treatment in our patients was relatively modest as compared with adalimumab treatment in patients with other diseases,[21,22] and our patients were unlikely to have complete resolution of their symptoms. However, in PIONEER II, although not in PIONEER I, significant improvement was noted in the rank-ordered secondary outcomes of lesion count, pain score, and disease severity.

Smaller randomized trials of other anti–TNF-α agents for the treatment of hidradenitis suppurativa, in which nonvalidated efficacy measurements were used, did not show a significant benefit. These included a trial of infliximab (a dosing regimen of 5 mg per kilogram of body weight) administered at weeks 0, 2, 6, and 8, in which efficacy was assessed with the Hidradenitis Suppurativa Severity Index,[23] and a trial of etanercept (50 mg twice weekly) administered for 12 weeks, in which efficacy was based on the physician's global assessment of disease.[24] In the current studies, we used a scoring system that could detect clinically meaningful change.[16]

Baseline differences in the study populations may have contributed to the difference in the observed treatment effect in period 1 between the two PIONEER studies. The higher disease burden at baseline for patients in PIONEER I (higher mean abscess, inflammatory-nodule, and draining-fistula counts and a higher mean modified Sartorius score) may have led to lower responsiveness to therapy at week 12, thereby contributing to between-study differences in outcomes for the rank-ordered secondary end points. Treatment-effect differences may also have resulted from factors related to the difference in the geographic distribution of patients between the studies (Table S1 in the Supplementary Appendix).

Neither study was powered to establish the best dosing strategy after week 12. Period 2 response rates were higher in each study with continued adalimumab treatment (vs. placebo), but among the patients who had a clinical response at week 12, there were no significant differences between those who continued to receive active treatment and those who received placebo in period 2 or between those who continued to receive adalimumab weekly and those who received adalimumab every other week. The decline in response rates during period 2 for patients with a response at week 12 is partly attributable to the protocol-specified discontinuation of treatment in period 2 for patients with a 50% loss of the improvement in period 1, even if the loss of response was due to a temporary disease fluctuation.

An increased risk of serious infections and of nonmelanoma skin cancers has been associated

with anti–TNF-α treatment.[25] Although the small sample and brief follow-up period limited our ability to detect rare events, we observed only nonmelanoma skin cancer (a squamous-cell carcinoma of the nose in an adalimumab-treated patient in PIONEER II); we observed no serious skin or soft-tissue infections among adalimumab-treated patients, despite the presence of open, suppurating wounds and scars. The observation of new psoriasiform eruptions and psoriasis in 10 patients treated with adalimumab is consistent with reports on anti–TNF-α treatment in patients with rheumatoid arthritis or Crohn's disease and suggests shared immunologic mechanisms in these diseases. An understanding of the long-term risks of adalimumab treatment in patients with hidradenitis suppurativa awaits longer-term studies.

In conclusion, these two randomized trials involving patients with moderate-to-severe hidradenitis suppurativa showed that adalimumab substantially increased the likelihood of a clinically significant response at week 12, as defined by at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count and no increase in abscess or draining-fistula counts, with or without continued antibiotic treatment. Adalimumab also improved rank-ordered secondary outcomes (inflammatory-lesion counts, pain score, and disease severity) in PIONEER II but not in PIONEER I. Rates of serious events were similar in the study groups.

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