Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study

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Background: The optimal long-term dosing strategy for adalimumab (ADA) in hidradenitis suppurativa/acne inversa (HS) was evaluated by pooling the results of the PIONEER phase 3 trials and an open-label extension (OLE) study.

Objective: To assess the response to and tolerability of long-term administration of ADA in HS.

Methods: The durations of the PIONEER I/II periods A, B, and OLE were 12, 24, and 52 or more weeks, respectively. Patients who entered the OLE and received ADA (40 mg every week continuously) and responders plus partial responders (PRRs) were evaluated. Primary efficacy assessments included measurement of HS clinical response (HiSCR), lesion counts, skin pain, and Dermatology Life Quality Index (DLQI). Treatment-emergent adverse events were assessed.

Results: At week 12, 52.3% of those receiving ADA weekly and 73.0% of PRRs achieved HiSCR. Achievement of HiSCR was maintained through week 168 in 52.3% of patients who received ADA weekly and 57.1% of PRRs. Sustained improvement in lesion counts, skin pain, and DLQI score were also observed. The safety profile throughout the OLE was similar to the profiles observed in the PIONEER studies.

Limitations: The OLE was uncontrolled.

Conclusion: Continuous weekly dosing with ADA, 40 mg, is a reasonable treatment option for long-term control of moderate-to-severe HS. (J Am Acad Dermatol 2019;80:60-9.)

Key Words: acne inversa; adalimumab; continuous; dose; hidradenitis suppurativa; longitudinal; long-term; weekly.

CAPSULE SUMMARY

- Adalimumab is approved for moderate-to-severe hidradenitis suppurativa/acne inversa.
- A sustained response is seen through week 168 in 52.3% of patients treated with adalimumab, 40 mg weekly, with no additional safety issues identified.
- Adalimumab can be considered for long-term control of moderate-to-severe hidradenitis suppurativa.

Hidradenitis suppurativa/acne inversa (HS) is a chronic, inflammatory, recurrent debilitating skin disease of the terminal hair follicle that usually occurs after puberty and presents as painful, deep-seated, inflamed lesions in the apocrine gland–bearing areas of the body, most commonly, the axillae, inguinal, and anogenital regions.[1] Approximately 0.1% to 1% of the general populations in North America and Europe are affected by HS.[2] HS lesions include inflammatory nodules and abscesses, tunnel (fistula and sinus) formation with purulent drainage, and subsequent scarring, all of which can affect patient health and quality of life.[2-8]

Adalimumab (ADA) is a monoclonal antibody against tumor necrosis factor-α that has been approved in Europe, Australia, and North America to treat moderate-to-severe HS, making it the only currently approved medication for this indication.[9-11] In 2 pivotal phase 3 randomized controlled trials, PIONEER I and II, ADA, 40 mg weekly, resulted in significantly higher clinical response rates than with placebo in patients with moderate-to-severe HS.[12]

The PIONEER I and II trials were similarly designed phase 3, multicenter trials with 2 double-blind, placebo-controlled periods.[12] A phase 3, open-label extension (OLE) trial (NCT01635764) designed to assess the long-term tolerability of and response to ADA in patients with moderate-to-severe HS followed both PIONEER trials. This analysis reports the long-term results for patients who received ADA, 40 mg weekly, throughout PIONEER I and II (36 weeks) and onward through the OLE trial to at least week 60.

METHODS

Patients

The PIONEER I and II patient eligibility criteria are described in detail elsewhere.[12] Briefly, patients were eligible if they were at least 18 years of age, had not previously received anti–tumor necrosis factor-α treatment, and had moderate-to-severe HS (total abscess and inflammatory nodule [AN] count of $\geq$3 at baseline and HS lesions in 2 distinct body areas, 1 of which was classified as Hurley stage II or III) with inadequate response to oral antibiotic treatment. In PIONEER I, patients receiving oral

Abbreviations used:

ADA:	adalimumab
AN:	abscess and inflammatory nodule
DLQI:	Dermatology Life Quality Index
HiSCR:	hidradenitis suppurativa clinical response
HS:	hidradenitis suppurativa
OLE:	open-label extension
PRRs:	responders plus partial responders

antibiotic agents for HS were required to discontinue treatment for at least 28 days before the baseline visit. In PIONEER II, patients could continue treatment with antibiotics (doxycycline or minocycline only) in stable doses.

To be eligible for the OLE trial, patients must have participated in and completed periods A and B of PIONEER I or II. Two populations were evaluated in this study: (1) the population that received ADA treatment weekly, which included all patients who received continuous weekly ADA treatment in PIONEER I or PIONEER II and the OLE trial, and (2) the population of responders plus partial responders (PRRs), a subset of patients in the population of those receiving ADA weekly who either achieved HiSCR at week 12 (responders) or did not achieve HiSCR but achieved at least a 25% reduction in AN count relative to baseline (partial responders) at the end of period A in PIONEER I or II.[13]

Study design and treatment

PIONEER I and PIONEER II and the OLE trial were conducted in accordance with Good Clinical Practice Guidelines as defined by the International Conference on Harmonization, the Declaration of Helsinki, and/or all applicable federal and local regulations.[12] 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 study designs for PIONEER I and II are described in detail elsewhere (Fig 1).[12,13] In period A, patients were randomized to receive ADA, 40 mg weekly, or placebo for 12 weeks. In period B, patients who were randomized to receive ADA in period A were reassigned to receive ADA, 40 mg weekly or every other week, or placebo for 24 weeks. Patients who were randomized to receive placebo in period A were reassigned to continue receiving placebo (PIONEER II) or receive ADA, 40 mg weekly, in period B (PIONEER I).[12] In the OLE trial, all patients received ADA, 40 mg weekly, for at least 60 weeks or until marketing authorization or permanent withdrawal of the marketing application in the patient's country of residence.

Assessments

The primary objective of this study was to assess the long-term safety, tolerability, and response to continuous weekly ADA in patients with moderate-to-severe HS.

Efficacy assessment. Several efficacy variables were measured at specified weeks throughout the OLE study. Achievement of a hidradenitis suppurativa clinical response (HiSCR), which was defined as at least a 50% reduction from baseline in the total AN count with no increase in abscess or draining fistula count relative to baseline of the prior phase 3 study (determined at each visit), was assessed from week 2 through week 168.[14] Mean improvements from baseline in abscess, fistula (draining and nondraining), nodule (inflammatory and noninflammatory), and AN counts were also determined for each patient from week 2 through week 168, as was the incidence of flare, which was defined as a 25% or greater increase in the total AN count with an increase of at least 2 relative to baseline. The Patient Global Assessment of Skin Pain (numeric rating scale of 0 to 10) and modified Sartorius score[15] (with higher scores [no upper limit] indicating increasingly severe disease) were assessed from week 2 through week 168. Mean improvement in Dermatology Life Quality Index (DLQI) score and achievement of a DLQI score of 0 or 1 were assessed from week 4 through week 72.

Safety assessment. Safety assessments included recording of treatment-emergent adverse events, clinical laboratory tests, physical examinations, and vital sign measurements. All treatment-emergent adverse events were summarized by using the Medical Dictionary for Regulatory Activities (version 19.0).

Statistical analysis

The PRR population was defined post hoc to identify the most clinically appropriate population for continuous weekly ADA dosing in period B. Multiple predictive models were applied to search for the subpopulation of interest by evaluating candidate variables, including stratification factors, patient initial response at the end of period A, and key demographic variables. The final PRR subpopulation was proposed on the basis of a threshold-based model,[16,17] which showed highly stable performance through a rigorous cross-validation framework.[13] Other predictive models were used as sensitivity analyses and

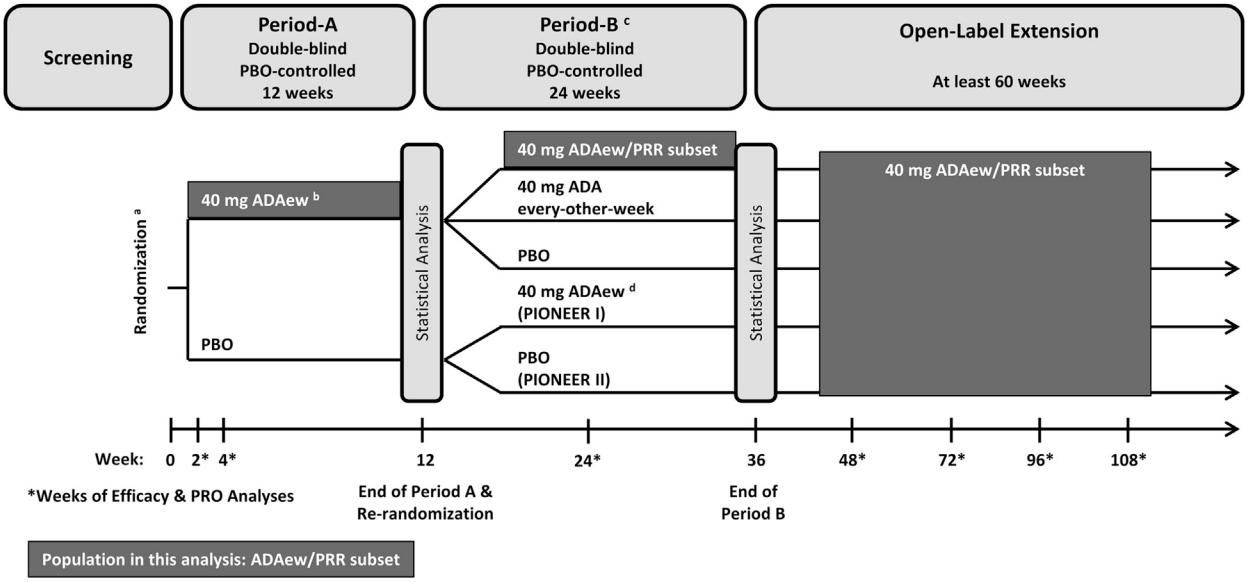

Fig 1. Hidradenitis suppurativa. Study design for PIONEER I, PIONEER II, and the open-label extension. [a]Stratified by baseline Hurley Stage II versus III (PIONEER I and II) and baseline concomitant antibiotic use (PIONEER II). [b]Dosing strategy: 160 mg at week 0; 80 mg at week 2; 40 mg from week 4. [c]Re-randomization at entry to period B, stratified by week 12 hidradenitis suppurativa clinical response (HiSCR) status and baseline Hurley stage II versus III. [d]Dosing strategy: 160 mg at week 12; 80 mg at week 14; 40 mg from week 16. *ADAew*, Adalimumab every week; *PBO*, placebo; *PRO*, patient-reported outcomes; *PRRs*, responders plus partial responders (a subset of patients in the population treated with ADA weekly who either achieved HiSCR at week 12 [responders] or did not achieve HiSCR but did achieve a ≥25% reduction in abscess and inflammatory nodule count relative to baseline [partial responders] at the end of period A in PIONEER I or II).

identified similar subpopulations that support the validity of our final results.[13]

This was an OLE trial, and no formal inferential statistical tests were conducted; descriptive statistics are provided. Continuous variables were summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum; discrete variables were summarized in terms of counts and percentages. The analysis was performed with SAS statistical software (SAS Institute Inc, Cary, NC). Missing values for categoric variables were handled by nonresponder imputation in periods A and B of PIONEER I and II. The nonresponder imputation analysis categorized any patient who had a missing value at a specific visit as a nonresponder for that visit. Last observation carried forward analyses, which used the completed evaluation from the previous visit to impute missing data at later visits, was performed. Results were reported in terms of study weeks, which consisted of PIONEER I or PIONEER II and OLE study weeks, shown consecutively.

RESULTS

Patients

In this analysis of results across PIONEER I and II (pooled data) into the OLE trial, 88 patients comprised the ADA weekly population and 63 comprised the PRR population. All patients were followed for at least 96 weeks (36 weeks in PIONEER I or PIONEER II and at least 60 weeks in the OLE), but follow-up time varied depending on when patients entered the OLE. Key demographics are summarized in Table I. The population treated with ADA weekly was mostly female (64%) and white (92%), with a median age of 36 years and median duration of HS of 10 years. The PRR population was similar to the population treated with ADA weekly, but with a numerically lower median C-reactive protein level. The median AN, abscess, inflammatory nodule, and draining fistula counts were 9, 1, 7, and 2, respectively, and the level of patient-reported daily pain was 4.6 in the population treated with ADA weekly and 4.7 in the PRR population.

In all, 51 patients in the population treated with ADA weekly discontinued study treatment: 22

Table I. Baseline characteristics of the population treated with ADA weekly and the PRR population

Characteristic	ADA qwk (n = 88)	PRR population (n = 63)
Sex, n (%)		
Female	56 (63.6)	41 (65.1)
Male	32 (36.4)	22 (34.9)
Race; n (%)		
White	81 (92.0)	57 (90.5)
Black	4 (4.5)	3 (4.8)
Other*	3 (3.4)	3 (4.8)
Median age, y (min, max)	35.5 (18.0, 64.0)	36.0 (18.0, 64.0)
Median BMI, kg/m^2 (min, max)	31.4 (20.3, 54.5)	31.6 (20.3, 49.6)
Current nicotine use, n (%)	52 (59.1)	40 (63.5)
Hurley stage, n (%)		
II	42 (47.7)	32 (50.8)
III	46 (52.3)	31 (49.2)
Median modified Sartorius score (min, max)	103.0 (20, 1093)	102.0 (27, 1093)
Family history of HS. n (%)	27 (30.7)	20 (31.7)
Median duration of HS, y (min, max)	10.34 (1.0, 40.4)	10.10 (1.0, 40.4)
HS lesions; median (min, max)		
AN	9.0 (3, 71)	9.0 (3, 49)
Abscess	1.0 (0, 13)	1.0 (0, 13)
Draining fistula	2.0 (0, 19)	2.0 (0, 16)
Inflammatory nodule	7.0 (0, 69)	7.0 (0, 48)
Median daily pain at worst (min 0, max 10)	4.6 (0.0, 9.7)	4.7 (0.0, 9.7)
Median hs-CRP level, mg/L (min, max)	6.50 (0.2, 189.0)	4.8 (0.2, 66.6)

ADA, Adalimumab; *AN*, sum of abscesses and inflammatory nodules; *BMI*, body mass index; *HS*, hidradenitis suppurativa; *hs-CRP*, high-sensitivity C-reactive protein; *max*, maximum; *min*, minimum; *PRRs*, responders plus partial responders; *qwk*, every week.
*Other includes Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, multirace, and other races.

primarily because of adverse events or lack of efficacy, 8 because of protocol deviations or loss to follow-up, and 21 because of withdrawn consent or for other reasons (eg, pregnancy).

Efficacy

HiSCR. For the 316 patients who were randomized to receive ADA weekly in the double-blind, placebo-controlled period A of the 2 PIONEER trials, the pooled data indicated achievement of HiSCR at week 12 in 50.6% of patients (160 of 316), which was significantly higher than the rate for the 317 patients randomized to receive placebo (26.8% [85 of 317]) ($P < .001$).

Among the 88 patients who entered the OLE trial and were included in the population treated with ADA weekly, the percentage achieving HiSCR during period A (52.3% at week 12) was maintained throughout period B (62.5% at week 36) and the OLE trial period (52.3% at week 168) (Fig 2). The achieved HiSCR rate during period A in the PRR population (73.0% at week 12) was reduced after week 36, but the result was generally maintained throughout period B (68.3% at week 48) and the OLE trial period (57.1% at week 168 [Fig 2]).

Additional end points

The AN count, draining fistula count, inflammatory nodule count, and total fistula count (sum of the draining fistulas and nondraining fistulas) improved from baseline in both populations, and the response was maintained through study week 168 (Fig 3, *A-D*). The rates of flare (Fig 4) and a 25% or greater increase in total fistula count (Supplemental Fig 1; available at http://www.jaad.org) were low and stable. In addition, there was an improvement from baseline in pain, which was indicated by a mean percent decrease in numeric rating scale scores and remained generally stable in both populations through week 168 (Fig 5).

In both populations, there was also a clinically meaningful improvement (defined as a 4-point improvement by Basra et al)[18] in DLQI score from baseline through week 72 (5.1-6.8 points in the population treated with ADA weekly and 6.0-7.6 points in the PRR population, respectively) (Fig 6, *A*). The percentage of patients who achieved

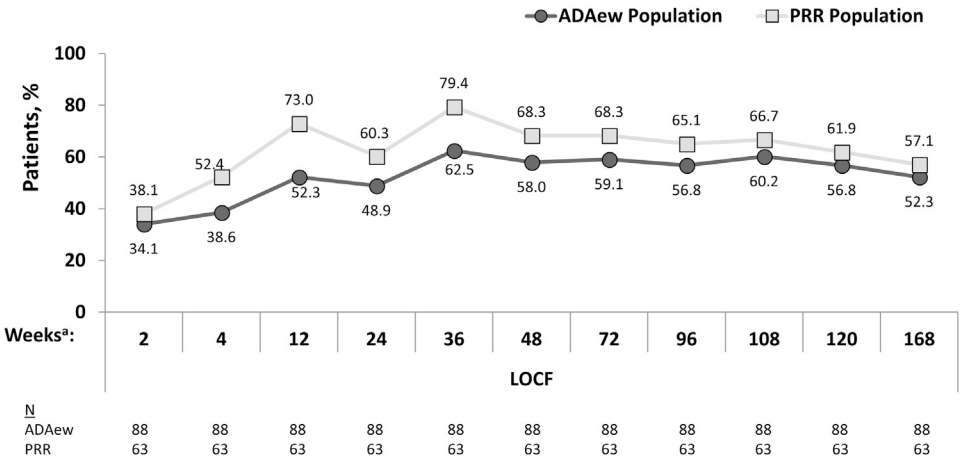

Fig 2. Hidradenitis suppurativa. Achievement of a hidradenitis suppurativa clinical response. [a]Weeks include PIONEER I or PIONEER II and the open-label extension, listed consecutively. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *PRRs*, responders plus partial responders.

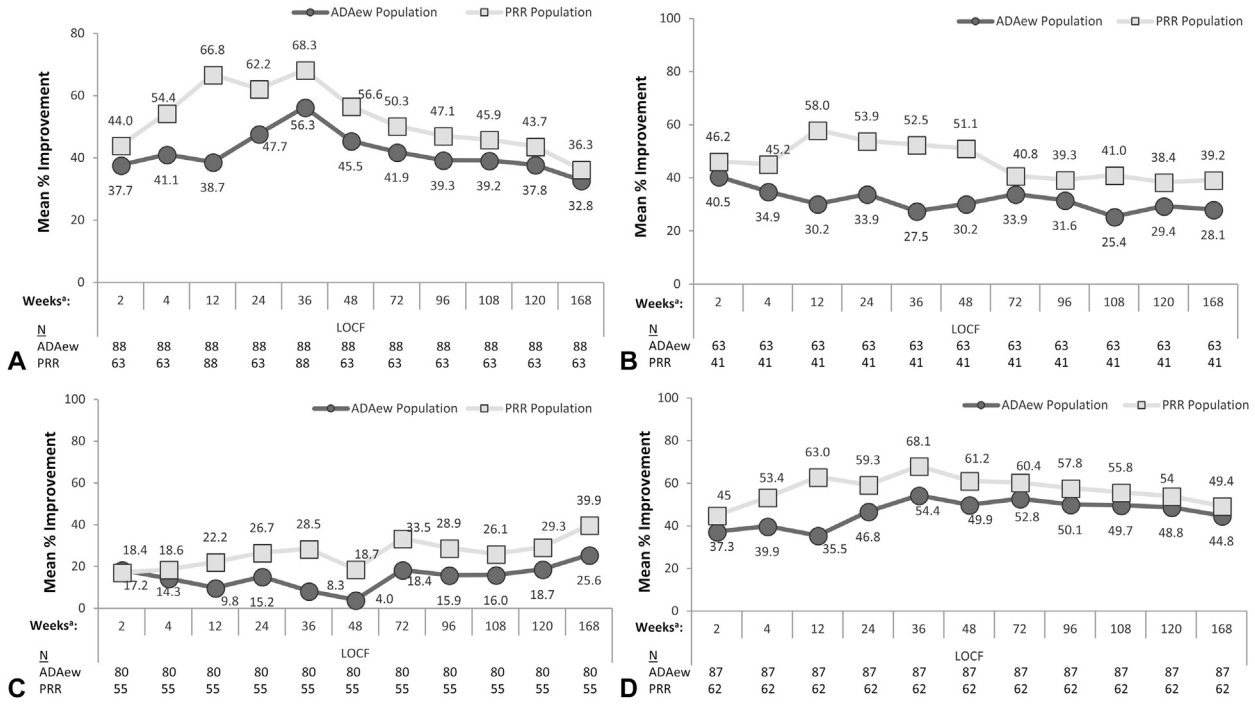

Fig 3. Hidradenitis suppurativa. Improvement in lesion count: abscesses and inflammatory nodules (**A**), draining fistulas (**B**), total fistulas (**C**), and inflammatory nodules (**D**). [a]Weeks include PIONEER I or PIONEER II and the open-label extension, listed consecutively. Mean improvement is relative to baseline. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *PRRs*, responders plus partial responders.

a DLQI score of 0 or 1 increased from baseline through week 48 and was generally maintained through week 72 (Fig 6, *B*). Similar results were observed with modified Sartorius scores (Supplemental Fig 2; available at http://www.jaad.org).

Safety assessments. The mean patient-years of exposure were 2.21 in the population treated with ADA weekly and 2.26 in the PRR population. There were no adverse events of opportunistic infections, excluding oral candidiasis; no events of active tuberculosis, lymphoma, nonmelanoma skin

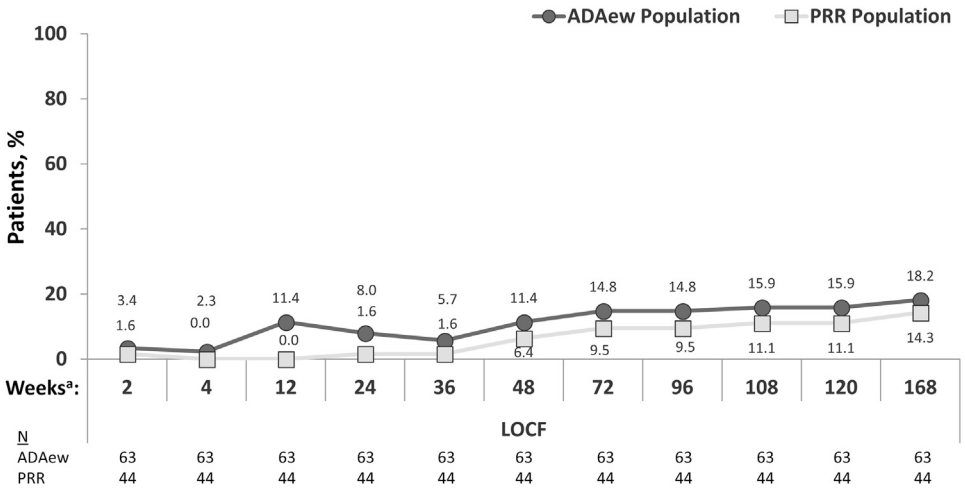

Fig 4. Hidradenitis suppurativa. Incidence of flare (a ≥25% increase in the total count of abscesses and inflammatory nodules with an increase of ≥2 relative to baseline). [a]Weeks include PIONEER I or PIONEER II and the open-label extension, listed consecutively. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *PRRs*, responders plus partial responders.

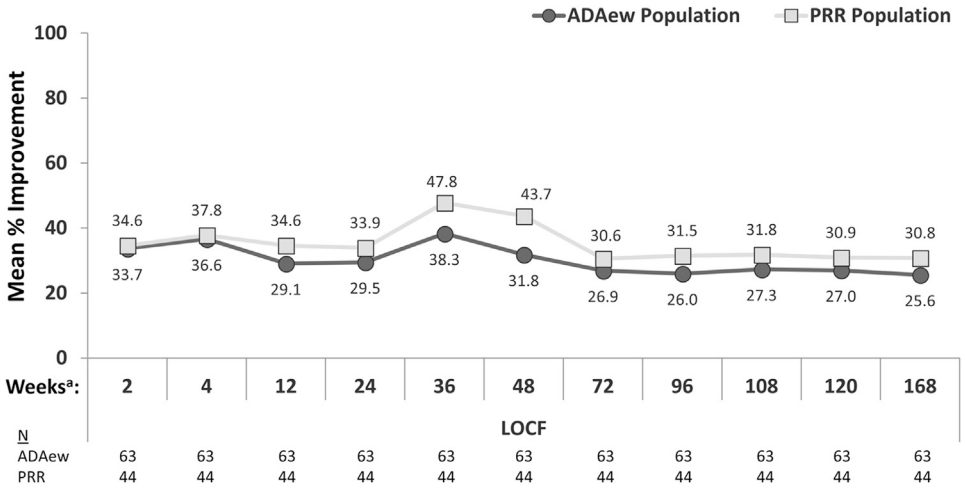

Fig 5. Hidradenitis suppurativa. Improvement in skin pain. [a]Weeks include PIONEER I or PIONEER II and the open-label extension, listed consecutively. Mean changes are relative to baseline. Change in numeric rating scale at worst at each visit among patients with a baseline numeric rating scale score of 3 or higher. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *PRRs*, responders plus partial responders.

cancer, malignancy, or demyelinating disorder; and no deaths. Three serious infections were reported in the population treated with ADA weekly; 1 (pneumonia) was considered probably related to the treatment. The most frequently reported treatment-emergent adverse events (a rate of ≥10% in either population) were hidradenitis, upper respiratory tract infection, headache, nasopharyngitis, arthralgia, influenza, diarrhea, urinary tract infection, sinusitis, bronchitis, dizziness, and nausea (Table II).

DISCUSSION

Efficacy and safety results derived from pooling the pivotal phase 3 trials with the OLE trial confirm that ADA sustains efficacy and has an acceptable safety profile following a strategy of continuous weekly treatment. Pooling of the data from the 2 PIONEER trials was prespecified in the protocol for period A and period B results. The combined analysis was appropriate on the basis of the similarities in study design and provided a more robust assessment by combining the somewhat

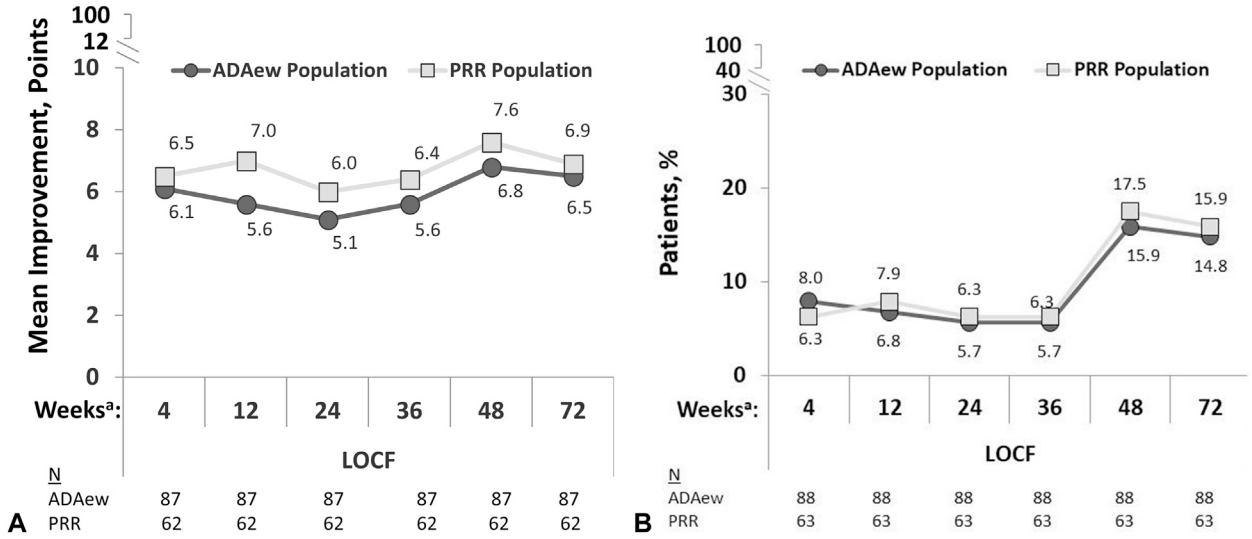

Fig 6. Hidradenitis suppurativa. Improvement in dermatology-specific quality of life: mean improvement in Dermatology Life Quality Index from baseline (**A**) and achievement of a Dermatology Life Quality Index score of 0 or 1 (no effect of skin disease on quality of life) (**B**). [a]Weeks include PIONEER I or PIONEER II and the open-label extension, listed consecutively. Mean changes are relative to baseline. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *PRRs*, responders plus partial responders.

Table II. Treatment-emergent adverse events

Adverse events, n (%)	ADA qwk population n = 88	PRR population n = 63
Any event	76 (86.4)	55 (87.3)
Leading to discontinuation of the study drug	13 (14.8)	10 (15.9)
Serious	12 (13.6)	9 (14.3)
Infections	63 (71.6)	45 (71.4)
Serious infections	3 (3.4)*	2 (3.2)†
Latent tuberculosis	2 (2.3)	2 (3.2)
Most frequently reported TEAEs (≥10%)‡		
Hidradenitis	21 (23.9)	16 (25.4)
Upper respiratory tract infection	17 (19.3)	15 (23.8)
Headache	17 (19.3)	13 (20.6)
Nasopharyngitis	16 (18.2)	13 (20.6)
Arthralgia	12 (13.6)	10 (15.9)
Influenza	13 (14.8)	9 (14.3)
Diarrhea	7 (8.0)	7 (11.1)
Urinary tract infection	9 (10.2)	4 (6.3)
Sinusitis	8 (9.1)	6 (9.5)
Bronchitis	6 (6.8)	6 (9.5)
Dizziness	6 (6.8)	6 (9.5)
Nausea	6 (6.8)	6 (9.5)

ADA, Adalimumab; *PRRs*, responders plus partial responders; *qwk*, every week; *TEAE*, treatment-emergent adverse event.
*Includes pneumonia (n = 2) and cellulitis of the right leg (n = 1).
†Includes pneumonia (n = 1) and cellulitis of the right leg (n = 1).
‡In either population.

limited sample sizes in period B of each study. The data for the populations of patients with HS who received weekly ADA treatment spanning the PIONEER I and II studies and the OLE trial confirm that weekly ADA treatment maintained long-term responses, as demonstrated by achievement of HiSCR and improvements in lesion counts, skin pain, and DLQI score. HiSCR was achieved by at

least half of the patients in both the population treated with ADA weekly and the PRR population at week 12 (the primary end point of PIONEER I and II), and the HiSCR was maintained through week 168 (OLE). Study closure was at the same time for all patients, and those who enrolled later did not have the opportunity to reach the later time points.

Improvements from baseline in skin lesions, including in AN count, draining fistulas, total fistulas, inflammatory nodules, and skin pain, were observed as early as week 2, also detected at week 12, and maintained through week 168. The natural history of untreated HS is chronic and progressive in some patients.[19-21] Although the data presented here are uncontrolled, the mean improvement in total fistula count suggests that some patients with HS who were treated with continuous weekly ADA may have experienced a halt in progression of HS, suggesting that ADA may be disease modifying. Additionally, a clinically meaningful improvement in DLQI score was observed through week 72.

Results from the PRR population demonstrate the effect of continuous weekly dosing because findings indicate that patients who had even a partial response at week 12 were likely to achieve HiSCR if they continued treatment with ADA. Continuous weekly dosing in patients who achieved at least a 25% reduction in AN count relative to baseline at week 12 is also supported by the outcomes of other end points, including reduced levels of skin pain and lower lesion counts. Given the current absence of alternative therapies, the burden of disease in the target population, and the observation of late achievement of some of the benefits in pain relief and improved scores on DLQI assessments (weeks 48 and 72), continuation of therapy may be considered even in patients with an initial partial response after short-term treatment.

The safety profile of long-term weekly administration of ADA therapy in this analysis was similar to that observed in PIONEER I and II, demonstrating the longitudinal safety of ADA in the treatment of patients with moderate-to-severe HS. The results were consistent with the known ADA safety profile.[12-22] ADA was generally well tolerated, and no new safety risks were identified in this patient population.

In conclusion, on the basis of the data from the studies that have been reported here and elsewhere,[12] ADA dosing of 40 mg weekly is effective and safe for long-term treatment of patients with moderate-to-severe HS.

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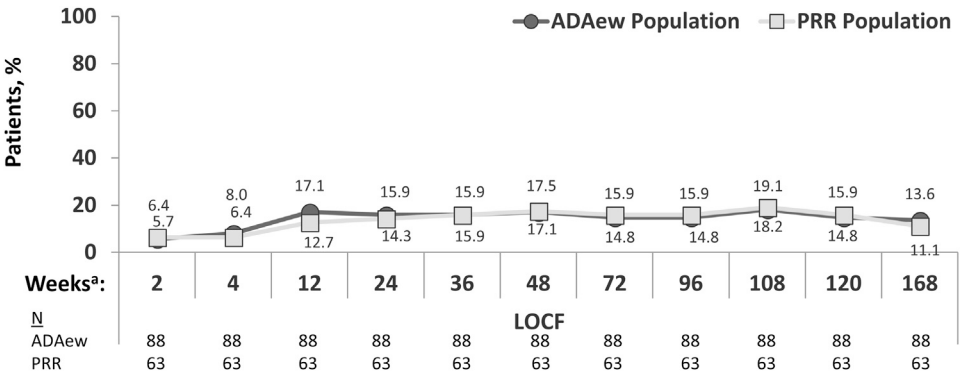
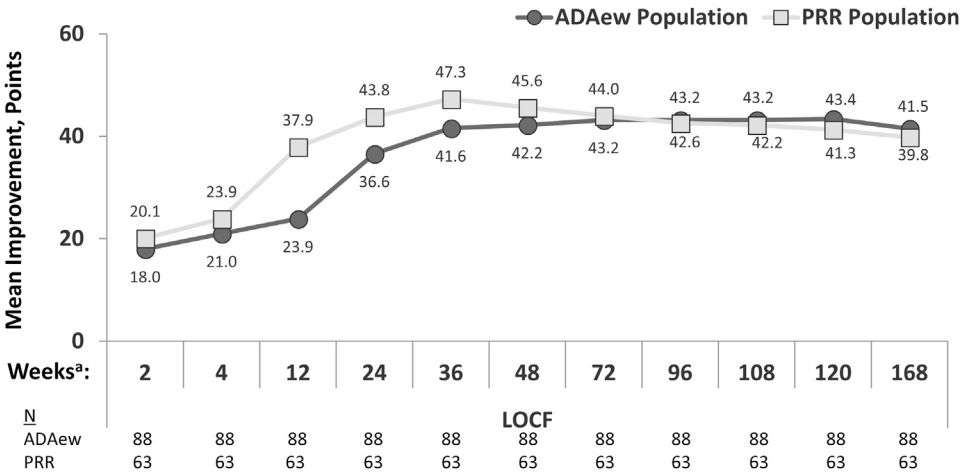


Supplemental Fig 1. Hidradenitis suppurativa. Incidence of ≥25% increase in total fistula count. [a]Weeks include PIONEER I or II and the open-label extension, listed consecutively. Mean improvement is relative to baseline. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *N*, number of patients in the population; *PPR*, responders plus partial responders.



Supplemental Fig 2. Hidradenitis suppurativa. Mean improvement from baseline in modified Sartorius scores. [a]Weeks include PIONEER I or II and the open-label extension, listed consecutively. Mean improvement is relative to baseline. *ADAew*, Adalimumab every week; *LOCF*, last observation carried forward; *N*, number of patients in the population; *PPR*, responders plus partial responders.