Common Drug Review
Clinical Review Report

May 2016

Drug	adalimumab (Humira)
Indication	For the treatment of active moderate to severe hidradenitis suppurativa (HS) in adult patients, who have not responded to conventional therapy (including systemic antibiotics).
Listing request	For the treatment of adult patients with active moderate to severe HS who: • Have a total abscess and nodule count of 3 or greater • Have lesions in at least two distinct anatomic areas, one of which must be Hurley stage II or III • Have had an inadequate response to a 90-day trial of oral antibiotics
Manufacturer	AbbVie Corporation

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ABBREVIATIONS

AE	adverse event
AN	abscess and inflammatory nodule
BMI	body mass index
CI	confidence interval
CSPA	Canadian Skin Patient Alliance
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire
HADS	Hospital Anxiety and Depression Scale
HiSCR	Hidradenitis Suppurativa Clinical Response
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
HSQoL	Hidradenitis Suppurativa Quality of Life
HSS	Hidradenitis Suppurativa Score
IgG1	immunoglobulin G1
ITT	intention-to-treat population
IXRS	interactive voice/Web response system
LOCF	last observation carried forward
LOR	loss of response
MCID	minimal clinically important difference
MCS	mental component summary
MSS	modified Sartorius score
NRI	non-responder imputation
NRS	numerical rating scale
OLE	open-label extension
PCS	physical component summary
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	Short Form (36) Health Survey
TNF	tumour necrosis factor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WOAI	worsening or absence of improvement
WPAI: SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

EXECUTIVE SUMMARY

Introduction

Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory skin disease of the hair follicle that is characterized by painful recurrent nodules and abscesses, most commonly found in the apocrine gland areas of the body.[1,2] The inflamed lesions produce recurrent purulent discharge and unpleasant odour and can lead to sinus tracts, scarring, strictures, or fistulas.[2,3] HS is associated with considerable psychosocial impact and morbidity, including obesity, pain, depression, and a lower health-related quality of life (HRQoL) than other dermatologic diseases.[1,4] The epidemiology of HS is poorly described and variable, with prevalence estimates ranging from 0.05% to 1.0%, depending upon geographic location.[4,5] Typically, HS presents after puberty and affects females two to five times more commonly than males.[4] Genetics, obesity, or cigarette smoking may predispose an individual to HS.[1,3]

Adalimumab (Humira) is a recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody that binds to tumour necrosis factor (TNF) alpha, thus preventing binding to the TNF-alpha receptor and blocking its biological effects.[1,6] Increased levels of TNF are found in HS lesions.[6] Adalimumab is approved in Canada for the treatment of active moderate to severe HS in adults who have not responded to conventional therapy (including systemic antibiotics). Adalimumab is also approved in Canada for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn disease, ulcerative colitis, and chronic moderate to severe psoriasis.[6] It is available as a 40 mg/0.8 mL sterile solution for subcutaneous (SC) injection.[6] Dosage recommendations for the treatment of adult patients with HS are an initial induction dose of 160 mg, followed by 80 mg two weeks later, and then maintenance dosing with 40 mg every week beginning four weeks after the initial dose.[6]

Indication under review
For the treatment of active moderate to severe hidradenitis suppurativa (HS) in adult patients, who have not responded to conventional therapy (including systemic antibiotics).
Listing criteria requested by sponsor[a]
For the treatment of adult patients with active moderate to severe HS who: • Have a total abscess and nodule count of three or greater • Have lesions in at least two distinct anatomic areas, one of which must be Hurley stage II or III • Have had an inadequate response to a 90-day trial of oral antibiotics

[a] The requested listing criteria are identical to the inclusion criteria of the PIONEER I and II trials.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of adalimumab (induction dose 160 mg at week 0, 80 mg at week 2, and 40 mg every week thereafter beginning four weeks after initial dose by SC injection) for the treatment of HS in adult patients.

Results and Interpretation

Included Studies

Two placebo-controlled, double-blind, unpublished, phase 3 randomized controlled trials (RCTs) met the selection criteria for inclusion in the systematic review: PIONEER I (N = 307) and PIONEER II (N = 326). Each study included two periods. In Period A (12 weeks), patients were randomized to adalimumab (160 mg at week 0, 80 mg at week 2, and then 40 mg every week starting at week 4) or matched

placebo. In Period B (24 weeks), patients were re-randomized (regardless of treatment in Period A), to adalimumab 40 mg every week, adalimumab 40 mg every other week, or matched placebo. Period B was considered for exploratory analyses only in both PIONEER trials. The trials enrolled adult patients with a diagnosis of HS and lesions in two or more distinct areas, one of which was Hurley stage II or III; with an abscess and inflammatory nodule (AN) count of 3 or more; and with an inadequate response to a three-month trial of oral antibiotics. Randomization was stratified by Hurley stage at baseline (II versus III) in both PIONEER trials and by baseline antibiotic use (yes versus no) in PIONEER II only. The primary efficacy end point was the proportion of patients who achieved HS clinical response (HiSCR), which was defined as at least a 50% reduction in AN count with no increase in abscess count or draining fistula count relative to baseline at week 12. There were three ranked secondary outcomes: (1) the proportion of patients who achieved an AN count of 0, 1, or 2 among patients stratified as Hurley stage II at baseline, (2) the proportion of patients with baseline numerical rating scale (NRS) of pain of 3 or more who achieved at least 30% reduction and one unit reduction from baseline in the Patient's Global Assessment of Skin Pain (NRS30) at worst (i.e., worst pain in the past 24-hour period), and (3) the change from baseline in modified Sartorius score (MSS), all measured at week 12. An extensive list of other secondary efficacy outcomes was also explored. Results from the two PIONEER trials are reported for all patients and for those patients stratified by Hurley stage II or III at baseline. Key limitations of the included trials are differences in study design and baseline patient characteristics between PIONEER I and II, lack of validation of many outcomes (especially HRQoL) and of identification of minimal clinically important differences (MCIDs) in patients with HS, lack of control for multiplicity in the analyses of non-ranked secondary outcomes, high discontinuation rates in Period B in both trials, and the short duration of the trials for a chronic disease.

Efficacy

Key efficacy outcomes identified in the review protocol were quality of life and health care resource utilization. Other efficacy outcomes included counts of abscesses, nodules, scarring, and draining fistulas, infections, symptoms, mental health/psychological well-being, functional capacity/productivity, caregiver burden, and disease worsening. In this section, results are reported only for efficacy outcomes from Period A, because Period B was considered for exploratory analyses only in both trials.

Quality of life in PIONEER I and II was assessed using the Dermatology Life Quality Index (DLQI) and the Hidradenitis Suppurativa Quality of Life (HSQoL) instrument, which were both non-ranked secondary outcomes. The DLQI is not validated in HS; however, the MCID in a variety of dermatologic conditions is reported to be a reduction of 3.3 points.[7] A reduction in DLQI scores reflects improvement in health-related quality of life (HRQoL).[7] In Period A, the mean DLQI scores at week 12 were reduced, relative to baseline scores, by –5.4 and –5.1 points in adalimumab-treated patients compared with –2.9 and –2.3 points in placebo-treated patients, in PIONEER I and II, respectively. Between-group differences (i.e., –2.5 points in PIONEER I and –2.8 points in PIONEER II) were statistically significant in the all-patient group comparisons in both trials. Between-group differences did not exceed the MCID in any patient group (i.e., [redacted]), but adalimumab-treated patients stratified by [redacted] at baseline in [redacted] did exhibit [redacted] was equivalent to the MCID (i.e., –3.3 points). There is limited information on the validity, reliability, or MCID of the HSQoL, and a focused literature search did not identify any reference for this instrument in the medical literature. It appears that higher scores reflect improvement in HRQoL. At week 12, mean HSQoL scores increased, relative to baseline, in both the adalimumab groups ([redacted] points) and placebo groups ([redacted] points) in the PIONEER I and II trials, respectively. Between-group differences were [redacted] in the all-patient group comparisons in both PIONEER I

([redacted] points) and PIONEER II ([redacted] points), and in patients classified [redacted] ([redacted] points) [redacted] ([redacted] points).

The Short Form (36) Health Survey (SF-36) was included as a non-ranked secondary outcome only in PIONEER I. Although not specifically validated in HS, in general the MCID for either the physical component summary (PCS) or mental component summary (MCS) scores of the SF-36 is between 2.5 and 5 points, with higher scores indicating better health status. At week 12, the mean change from baseline in the PCS score was +4.2 points in adalimumab-treated patients compared with +1.5 points in placebo-treated patients. The between-group difference ([redacted] points) was [redacted] and exceeded the general MCID. The mean change from baseline in the MCS score was +2.3 points in adalimumab-treated patients compared with +1.3 points in placebo-treated patients, [redacted] [redacted] points) [redacted]. For all other domain scores, between-group differences were not statistically significant, with the exception of higher summary scores for bodily pain and general health in the adalimumab group compared with the placebo group.

The EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) was included as a non-ranked secondary outcome only in PIONEER II. The EQ-5D consists of the EQ-5D index score and the EQ-5D visual analogue scale (VAS), and for both measures, higher scores indicate better health status. As with other HRQoL outcomes, the EQ-5D does not appear to have been validated in HS, nor a specific MCID identified, although clinically important differences for the descriptive system are reported to range from 0.033 and 0.074. At week 12, the between-group differences for the mean EQ-5D index score (i.e., 0.1 for all comparisons) was statistically significant in all patients, [redacted] at baseline. For the EQ-5D VAS scores, the between-group mean differences ranged from [redacted].

No data were available for health care resource utilization (i.e., physician visits, surgeries), with the exception of incision and drainage procedures, which were captured as a protocol-allowed intervention. Overall, the number of patients requiring interventions in Period A (i.e., either incision and drainage or intralesional injection of triamcinolone acetonide) was small (≤ 10 patients per treatment group in each trial). Differences between groups were not statistically significant in either of the PIONEER trials.

The primary efficacy end point in the PIONEER trials was the proportion of patients achieving HiSCR at week 12, defined as at least a 50% reduction in AN count with no increase in abscess count or draining fistula count relative to baseline. The HiSCR is validated in patients with HS and, although an MCID has not been established, it is accepted that a 50% or more reduction in AN counts is clinically relevant and meaningful to patients. For all comparisons (i.e., all patients or those stratified by Hurley stage II or III at baseline), between-group differences in the proportion of patients who achieved HiSCR were statistically significantly larger with adalimumab compared with placebo in both trials. The magnitude of the treatment effect appeared to be greater in PIONEER II compared with PIONEER I. For all patients, the proportion of adalimumab-treated patients who achieved HiSCR was 58.9% (PIONEER II) compared with 41.8% (PIONEER I), despite similar proportions of placebo-treated patients reaching HiSCR in the two trials (i.e., 26.0% and 27.6%, respectively). Between-group differences were 31.5% (PIONEER II) and 15.9% (PIONEER I). The proportion of patients achieving HiSCR was statistically significantly greater in adalimumab-treated patients as early as week 2 and remained statistically significant at weeks 4, 8, and 12 in both PIONEER trials.

The proportion of patients who achieved an AN count of 0, 1, or 2 at week 12 in Period A (i.e., the first ranked secondary outcome in the PIONEER trials), [redacted]. Other non-ranked secondary outcomes (e.g., proportion of patients achieving a 50%, 70%, or 100% reduction in AN count relative to baseline [AN50/75/100], mean change from baseline in lesion counts by lesion type, and the proportion of patients with at least one lesion at baseline who achieved complete elimination of lesions at week 12) [redacted].

Change in the MSS from baseline to week 12 was the third ranked secondary outcome in the PIONEER trials. The MSS is based on an assessment of the regions involved, number of lesions, and the distance between and separation of lesions, to obtain an overall score. Higher scores indicate increased severity, and an MCID is not known. In [redacted], the between-group difference in the change in MSS from baseline to week 12 was statistically significant in favour of adalimumab for all-patient comparisons (i.e., [redacted]) whereas in [redacted], the between-group differences [redacted].

The difference in the magnitude of the treatment effect associated with adalimumab in the PIONEER trials may, in part, be due to baseline and study design differences between the trials. In PIONEER I, patients may have had more severe disease due to higher baseline mean counts of draining fistulas, AN counts, and greater mean NRS skin pain compared with patients in PIONEER II. In addition, patients in PIONEER II were able to continue pre-entry antibiotic therapy (i.e., minocycline and doxycycline only) throughout the trial, as opposed to receiving only rescue antibiotic therapy in PIONEER I. In PIONEER II, patients were also stratified by antibiotic use at baseline (yes or no), and results for the primary outcome (HiSCR) were available by baseline antibiotic use versus no antibiotic use. In all-patient group comparisons, the treatment effect with adalimumab was greater in patients who were on antibiotics at baseline compared with those who were not (i.e., 42.6% versus 28.6% in all patients, 38.6% versus 23.5% in patients stratified by Hurley stage II, and 45.0% versus 35.7% in patients stratified by Hurley stage III). During Period A, approximately 20% of patients in PIONEER II compared with 6% of patients in PIONEER I received concomitant minocycline and doxycycline. The clinical expert consulted for this review concurred that antibiotic therapy is effective in HS and that this may have contributed to the difference in the treatment effect of adalimumab observed between the trials. It is also probable that patients would receive concomitant topical and oral antibiotic therapy with biologic therapy in clinical practice.

The NRS30 (i.e., the proportion of patients who achieved at least 30% reduction and at least one unit reduction from baseline in the Patient's Global Assessment of Skin Pain at worst [i.e., worst pain in the past 24-hour period]) at week 12 among patients with baseline NRS ≥ –3 was the second ranked secondary end point in the PIONEER trials. During Period A, the proportion of patients achieving this outcome was [redacted] of adalimumab when compared with [redacted] as early as [redacted] (i.e., [redacted]). [redacted].

Other efficacy outcomes included in the review protocol were physical well-being/mental health and functional capacity/productivity, which were outcomes identified as being important to patients. Based on the results of the Hospital Anxiety and Depression Scale (HADS), which was included in PIONEER I only, mean scores for both the anxiety and depression subscales [redacted]. The Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP) was included as a secondary outcome in both PIONEER trials, although information about this instrument is limited. Mean changes from baseline to week 12 in various subscales of the WPAI: SHP showed that there were [redacted], in PIONEER I and II, respectively. [redacted].

With regard to disease worsening, in the PIONEER trials a flare was defined as an increase of at least 25% and two absolute increases from baseline in lesions. Between-group differences in the reduction in flares of ANs ([redacted]), inflammatory nodules ([redacted]) and draining fistulas ([redacted]) were all [redacted] in both PIONEER I and PIONEER II, respectively. For abscesses, the between-group reduction in flares was [redacted].

Harms

More than half of the patients in each treatment group in Period A experienced adverse events (AEs) (i.e., 52.9% and 57.7% of adalimumab-treated patients and 61.8% and 66.9% of placebo-treated patients in PIONEER I and II, respectively). The most frequent treatment-emergent AEs were HS, headache, and nasopharyngitis. In Period B, similar proportions of patients experienced the same pattern of treatment-emergent AEs (i.e., [redacted] among the re-randomized groups in both trials). The proportions of patients with serious adverse events (SAEs) (i.e., 2.0% and 1.8% of adalimumab-treated patients and 3.3% and 3.7% of placebo-treated patients, respectively) or withdrawals due to adverse events (WDAEs) (i.e., 0.7% and 2.5% of adalimumab-treated patients and 2.0% and 4.3% of placebo-treated patients, respectively) in PIONEER I and II, were low in both adalimumab- and placebo-treated patients in Period A. In Period B, SAEs ranged from [redacted] in adalimumab-treated patients and WDAEs from [redacted] among the re-randomized groups in both trials. There were no deaths in either trial during Period A; [redacted].

The AEs of special interest were injection-site reactions, hypersensitivity, opportunistic infections, and malignancy risk. In Period A, injection-site reactions occurred [redacted] in adalimumab-treated patients ([redacted]) compared with placebo-treated patients ([redacted]) in PIONEER I and II, respectively. There did not appear to be any treatment-related differences in the proportion of patients with allergic reactions or infections, and no patients in either trial experienced an opportunistic infection, nor did any patients report any tuberculosis-related events. There was one malignancy reported in a placebo-treated patient. In Period B, injection-site reactions occurred [redacted] ([redacted]) in the re-randomized groups with the longest duration of exposure to adalimumab (i.e., Placebo/Every Week [PL/EW] and Every Week/Every Week [EW/EW]). [redacted].

[redacted].

Overall, the safety and tolerability profile of adalimumab in HS does not appear to be different from that previously observed with adalimumab in other indications, with the exception of the reporting of HS as an AE in this patient population (which was considered to be an exacerbation of the underlying disease).

Conclusions

Two placebo-controlled, double-blind, unpublished, phase 3 RCTs met the selection criteria for inclusion in the systematic review (PIONEER I and PIONEER II). Data from these trials support the conclusion that, in patients with active moderate to severe HS (i.e., Hurley stage II or III), adalimumab treatment is associated with statistically significant improvements in HRQoL, measured using the DLQI, SF-36 (PCS) and EQ-5D, compared with placebo after 12 weeks. Adalimumab was also associated with statistically significant reductions, compared with placebo, in HiSCR (defined as a reduction of at least a 50% in AN count, with no increase in abscess or draining fistula count relative to baseline), as well as reductions in various lesion counts, skin pain, and improvement in the MSS. In general, the magnitude of improvement in these outcomes was sufficiently large to be clinically meaningful, although, with the exception of the HiSCR and MSS, none of the outcome measures have been validated in patients with HS. A larger treatment effect was observed in PIONEER II than in PIONEER I, likely reflecting greater concomitant use of antibiotics in PIONEER II. Overall, the safety and tolerability profile of adalimumab in HS does not appear to differ from that previously observed with adalimumab in other indications, with the exception of the reporting of HS as an AE in this patient population. The most frequent AEs associated with adalimumab were HS, headache, and nasopharyngitis.

TABLE 1: SUMMARY OF RESULTS

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Quality of Life				
DLQI Mean BL/week 12 Within-group change, LSM (SE)	16.3/10.8 –5.4 (0.50)	16.0/13.1 –2.9 (0.50)	14.1/9.3 –5.1 (0.53)	14.8/12.5 –2.3 (0.53)
LSM Diff (95% CI); *P* value	–2.5 (–3.8 to –1.1); < 0.001		–2.8 (–4.1 to –1.5); < 0.001	
SF-36 (PCS) Mean BL/week 12 Within-group change, LSM (SE)	40.0/44.2 [redacted]	39.6/41.2 [redacted]	NR/NR NR	NR/NR NR
LSM Diff (95% CI); *P* value	2.7 (0.8 to 4.5); 0.005		NA	
SF-36 (MCS) Mean BL/week 12 Within-group change, LSM (SE)	42.3/44.3 [redacted]	40.9/42.5 [redacted]	NR/NR NR	NR/NR NR
LSM Diff (95% CI); *P* value	0.9 (–1.1 to 3.0); 0.370		NA	
EQ-5D Index score Mean BL/week 12 Within-group change, LSM (SE)	NR/NR NR	NR/NR NR	0.6/[redacted] [redacted]	0.5/[redacted] [redacted]
LSM Diff (95% CI); *P* value	NA		[redacted]	
EQ-5D VAS Mean BL/week 12 Within-group change, LSM (SE)	NR/NR NR	NR/NR NR	58.6/[redacted] [redacted]	58.4/[redacted] [redacted]
LSM Diff (95% CI); *P* value	NA		[redacted]	
Abscesses, nodules, and draining fistulas				
Pts with AN count of 0, 1 or 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diff % (95% CI); *P* value	[redacted]		[redacted]	
Pts achieving HiSCR, n (%)	64 (41.8)	40 (26.0)	96 (58.9)	45 (27.6)
Diff % (95% CI); *P* value	15.9 (5.3 to 26.5); 0.003		31.5 (20.7 to 42.2); <0.0001	
Modified Sartorius score Mean BL/week 12 Within-group change, LSM (SE)	151.0/[redacted] [redacted]	146.7/[redacted] [redacted]	107.5/[redacted] [redacted]	122.5/[redacted] [redacted]
LSM Diff (95% CI); *P* value	[redacted]		[redacted]	
Symptoms				
NRS30, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diff % (95% CI); *P* value	[redacted]		[redacted]	
Harms:				
Pts with ≥ 1 AE, n (%)	81 (53.9)	94 (61.8)	94 (57.7)	109 (66.9)
Pts with ≥ 1 SAE, n (%)	3 (2.0)	5 (3.3)	3 (1.8)	6 (3.7)
Pts with ≥ 1 WDAE, n (%)	1 (0.7)	3 (2.0)	0	2 (1.2)
Notable Harms:				
Pts with injection-site reaction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pts with allergic reaction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pts with infection, n (%)	38 (24.8)	43 (28.3)	41 (25.2)	53 (32.5)
Pts with opportunistic infection, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pts with lymphoma, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Pts with non-melanoma skin cancer, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pts with other malignancy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; AN = abscess and inflammatory nodule; BL = baseline; CI = confidence interval; Diff = difference; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire ; HiSCR = Hidradenitis Suppurativa Clinical Response; LSM = least-squares mean; MCS = mental component summary score; NA = not applicable; NR = not reported; NRS30 = numerical rating scale proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from BL in the Patient's Global Assessment of Skin Pain; PCS = physical component summary score; Pts = patients; SAE = serious adverse event; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; WDAE = withdrawal due to AE.
Note: Results are for all patients at week 12 in Period A.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Hidradenitis suppurativa (HS) is a chronic, debilitating, inflammatory skin disease of the hair follicle that is characterized by painful recurrent nodules and abscesses, most commonly found in the apocrine gland–bearing areas of the body (i.e., axillae, inguinal, and anogenital regions).[1,2] The inflamed, deep-seated lesions produce recurrent purulent discharge and unpleasant odour and lead to scarring, strictures, or fistulas.[3] In advanced stages, sinus tracts form, with resulting fibrotic and cribriform scar formation, which can lead to dermal contractures and induration of the affected skin.[2] HS is associated with considerable psychosocial impact and morbidity, including obesity, pain, depression, and a lower health-related quality of life (HRQoL), compared with other dermatologic diseases.[1,4]

The epidemiology of HS is poorly described and variable, with prevalence estimates ranging from 0.05% to 1.0%, depending upon geographic location.[4,5] Typically, HS presents after puberty and affects females two to five times more commonly than males.[4] Various factors, such as genetics, obesity, or cigarette smoking, may predispose an individual to HS.[1,3] HS has also been associated with metabolic syndrome, inflammatory bowel disease (e.g., Crohn disease), and other spondyloarthropathies.[1,3]

The diagnosis of HS is based on clinical presentation, without the need for confirmatory laboratory or histology testing. A positive diagnosis is made if a patient presents with recurrent painful or suppurating lesions more than two to three times in a six-month period in the inverse regions of the body, with the presence of nodules, sinus tracts, abscesses, and/or scarring.[1] The severity of HS is described clinically using the Hurley staging classification system,[10] which defines the levels of severity of HS based on the extent of cicatrization (scarring) and sinus tract involvement as follows:

- Hurley stage I: abscess formation (single or multiple) without sinus tracts and cicatrization
- Hurley stage II: one or more widely separated recurrent abscesses with tract formation and scars
- Hurley stage III: multiple interconnected tracts and abscesses throughout an entire area.

Hurley stage I disease is the most common and is reported in 68% of patients, whereas stage II and III are reported in 28% and 4% of HS patients, respectively.[11] A more detailed and dynamic HS severity scoring system was created by Sartorius and was later modified.[12,13] The modified Sartorius score (MSS) is based on a count of individual abscesses, nodules, and fistulas, as well as the distance between two relevant lesions; thus, it can be used to dynamically measure the clinical severity of HS. The clinical expert consulted for this review advised that the Hurley staging system is used mainly in clinical practice, whereas the MSS, which is more cumbersome, is used mainly in clinical trials.

1.2 Standards of Therapy

Treatment options for HS are limited, and to date (with the exception of adalimumab), there have been no pharmacologic therapies specifically indicated for the treatment of HS in Canada. There are also no Canadian guidelines for the treatment of HS; however, a recent European guideline (2015)[1] recommends a treatment algorithm for HS similar to that currently used in Canadian practice. According to the clinical expert consulted on this review, the treatment goals for HS are to induce disease remission and/or slow progression, reduce the extent of scarring and tract formation, and decrease disability. There is no evidence to suggest that early treatment of HS affects disease progression, and, because most patients tend to hide their disease, they often present at a later stage.

In general, the initial treatment of HS consists of topical antiseptics and topical antibiotic therapies such as clindamycin.[1] Systemic antibiotics (e.g., tetracycline, clindamycin, and rifampicin) may also be used alone or in combination with topical therapies.[1] Intralesional corticosteroids (e.g., triamcinolone acetonide) may be used as monotherapy or as an adjunct to systemic therapies, whereas short-term systemic corticosteroids may provide benefit in reducing inflammation associated with acute flares.[1] Retinoids or anti-androgen agents (e.g., finasteride) may also be tried, as well as immunosuppressant agents such as methotrexate or cyclosporine.[1] Biologics (e.g., adalimumab, infliximab, etanercept, and ustekinumab) have been used in the treatment of moderate to severe HS; however, there is minimal prospective randomized controlled trial (RCT) evidence to support their use.[1] Surgical treatment is also an accepted therapeutic modality for HS, and several methods are used, ranging from excision and incision and/or drainage of lesions, usually in the dermatologist's office, to radical wide excision of an involved region or plastic surgery in a hospital setting.[1] Adjuvant treatment of HS includes pain management, treatment of infections, weight loss, and smoking cessation.[1]

1.3 Drug

Adalimumab is a recombinant, fully human immunoglobulin G1 (IgG1), monoclonal antibody that binds with high affinity and specificity to the soluble and membrane-bound forms of tumour necrosis factor (TNF) alpha.[1,6] In turn, binding to the TNF-alpha receptor is prevented (p55 and p75), and the biological effect of TNF-alpha is blocked. TNF occurs naturally and is involved in normal inflammatory and immune responses. Increased levels of TNF are found in HS lesions.[6]

Adalimumab has also been approved by Health Canada for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, ulcerative colitis, and chronic moderate to severe psoriasis.[6]

Adalimumab is available as 40 mg/0.8 mL sterile subcutaneous (SC) injection. [6] The dosage recommendation for adalimumab for the treatment of adult patients with HS is an initial induction dose of 160 mg, followed by 80 mg two weeks later. [6] The first dose of 160 mg can be administered as four injections in one day or as two injections per day for two consecutive days.[6] The second dose of 80 mg is given as two 40 mg injections in one day.[6] The recommended maintenance dose regimen of adalimumab for the treatment of HS is 40 mg every week, beginning four weeks after the initial dose.[6] In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.[6]

Indication under review
For the treatment of active moderate to severe hidradenitis suppurativa (HS) in adult patients, who have not responded to conventional therapy (including systemic antibiotics).
Listing criteria requested by sponsor[a]
For the treatment of adult patients with active moderate to severe HS who: • Have a total abscess and nodule count of 3 or greater • Have lesions in at least two distinct anatomic areas, one of which must be Hurley stage II or III • Have had an inadequate response to a 90-day trial of oral antibiotics

[a] The requested listing criteria are identical to the inclusion criteria of the PIONEER I and II trials.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of adalimumab (induction dose of 160 mg at week 0, 80 mg at week 2, and 40 mg every week thereafter beginning four weeks after initial dose by SC injection) for the treatment of HS in adult patients.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Additional studies were selected using the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (≥ 18 years) with a diagnosis of HS. Subpopulations: age, gender, disease severity, concomitant antibiotic use, BMI, smoking status
Intervention	Adalimumab (induction dose of 160 mg at week 0, 80 mg at week 2) and 40 mg every week thereafter, beginning four weeks after initial dose by SC injection
Comparators	• Antiseptics (topical) • Antibiotics (topical and oral) • Immunosuppressants (e.g., methotrexate, cyclosporine) • Corticosteroids (intralesional and systemic) • Anti-androgens • Retinoids • Biologics (e.g., etanercept, infliximab, ustekinumab)
Outcomes	**Key efficacy outcomes:** • Quality of life • Health care resource utilization (e.g., physician visits, incision and drainage, surgeries) **Other efficacy outcomes:** • Abscesses, nodules, scarring, and draining fistulas (i.e., counts, severity) • Infections • Symptoms (e.g., pain, bleeding, sleep interruption, fatigue)[a] • Mental health/psychological well-being[a] • Functional capacity/productivity[a] • Caregiver burden[a] • Disease worsening (i.e., recurrence or flares) **Harms outcomes:** • Mortality • AEs • SAEs • WDAEs • AEs of special interest (e.g., injection-site reactions, hypersensitivity, opportunistic infections, malignancy risk)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse events; BMI = body mass index; HS = hidradenitis suppurativa; RCT = randomized controlled trial; SAE = serious adverse events; SC = subcutaneous; WDAE = withdrawal due to adverse events.
[a] Identified in Appendix 1: Patient Input Summary.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Humira (adalimumab) and hidradenitis suppurativa.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2: Literature Search Strategy for the detailed search strategies.

The initial search was completed on December 1, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on April 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2, Included Studies. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

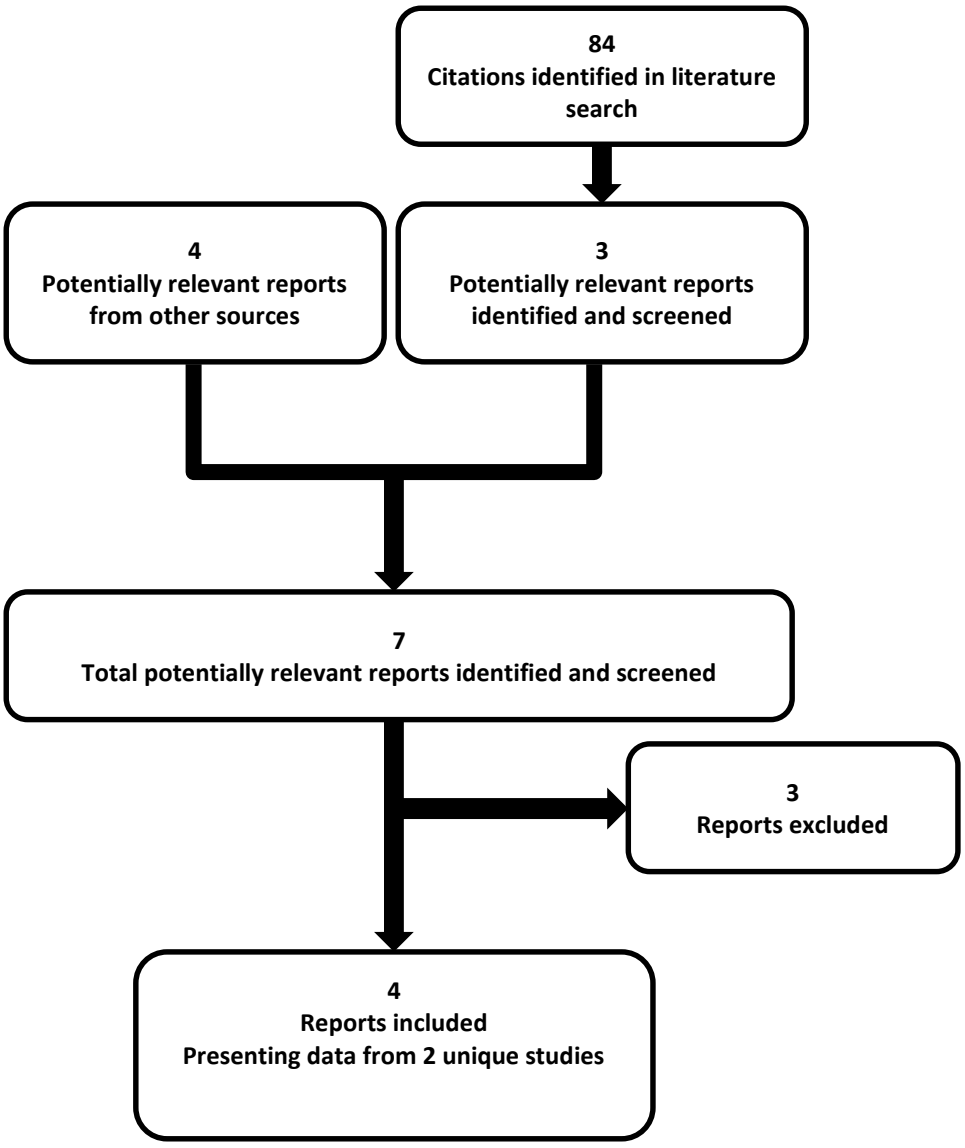


TABLE 3: DETAILS OF INCLUDED STUDIES

		PIONEER I (M11-313)	PIONEER II (M11-810)
DESIGNS & POPULATIONS	**Study Design**	DB, PC, MC, phase 3 RCT	
	Locations	48 sites in Australia, Canada, United States, Czech Republic, Germany, Hungary	53 sites in Australia, Canada, United States, Denmark, France, Greece, Netherlands, Sweden, Switzerland, Turkey
	Randomized (N)	307	326
	Inclusion Criteria	Pts ≥ 18 years with diagnosis of HS for ≥ 1 year, HS lesions in ≥ 2 distinct anatomical areas, one of which was Hurley stage II or III, inadequate response to 3-month trial of oral antibiotics, stable HS for ≥ 2 months, and a total AN count of ≥ 3	
	Exclusion Criteria	Prior txt with adalimumab or other anti-TNF therapy, any other active skin disease or condition, any prior antibiotic, topical therapy, non-biologic therapies for HS or concomitant analgesics for HS within specified timeframes, draining fistula count of > 20	
DRUGS	**Intervention**	Period A: Adalimumab 160 mg adalimumab at week 0, 80 mg at week 2, and 40 mg every week from week 4 to week 11 by SC injection Period B: Adalimumab 40 mg every week or 40 mg every other week for 24 weeks	
	Comparator(s)	Period A and B: Equivalent volumes of placebo SC injection as per intervention	
	Phase		
	Run-in	30-day screening period	
	Double-blind	Period A: 12 weeks Period B: 24 weeks	
	Follow-up	70 days	
OUTCOMES	**Primary End Point**	Proportion of pts achieving HiSCR at week 12	
	Other End Points	Change in AN counts, abscesses, draining fistulas, inflammatory nodules, flares, NRS30, change in modified Sartorius score, DLQI, WPAI:SHP, HADS, HSQoL, and SF-36 (PIONEER I only) and EQ-5D (PIONEER II only)	
NOTES	**Publications**	Not published	Not published

AN = abscess and inflammatory nodule; DB = double-blind; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire; HADS = Hospital Anxiety and Depression Scale; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; HSQoL = Hidradenitis Suppurativa Quality of Life; MC = multi-centre; NRS30 = 30% and 1 unit reduction in Patient's Global Assessment of Skin Pain; PC = placebo-controlled; Pts = patients; RCT = randomized controlled trial; SC = subcutaneous; SF-36 = Short Form 36 item; TNF = tumour necrosis factor; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9] Note: 4 reports were included: Manufacturer's submission,[14] M11-313 CSR,[8] M11-810 CSR,[9] EPAR assessment report.[3]

3.2 Included Studies

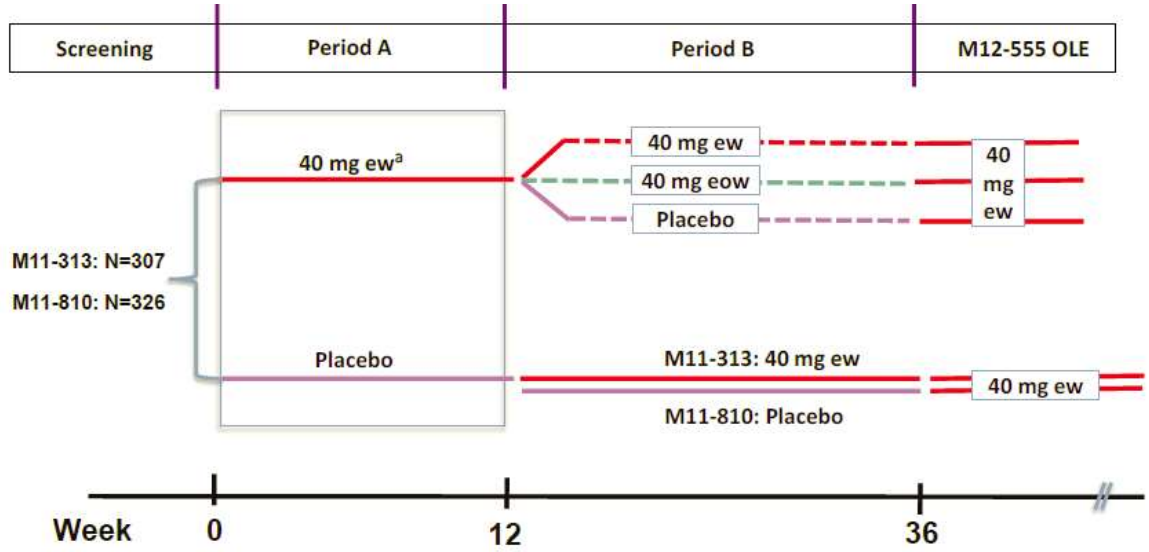
3.2.1 Description of Studies

Two prospective, double-blind, parallel group, multi-centre, placebo-controlled, phase 3 randomized trials of 12-week (Period A) and 24-week (Period B) duration met the selection criteria for inclusion in the systematic review: PIONEER I (N = 307)[8] and PIONEER II (N = 326).[9] Overall, the trials were performed at 101 sites in Australia, North America, and Europe in adult patients with moderate to severe HS.

The primary objective of both trials was to determine the efficacy and safety of adalimumab compared with placebo in patients with moderate to severe HS after 12 weeks of treatment (Period A). A secondary objective in both trials was to evaluate safety and explore efficacy or loss of response (LOR) of adalimumab administered by continuous every week (EW) dosing or every other week (EOW) dosing compared with continuing on, or switching to, placebo in Period B.

The trials were of almost identical design, as illustrated in Figure 2; however, there were some key differences between them. In Period A of both trials, patients were randomized at day 1 in a 1:1 ratio to receive adalimumab 160 mg at week 0, 80 mg at week 2, and then adalimumab 40 mg EW or matching placebo starting at week 4 through week 11. In PIONEER I, randomization was stratified by baseline Hurley stage (II versus III). In PIONEER II, randomization was stratified by baseline Hurley stage (II versus III) and baseline concomitant antibiotic use (yes versus no). In both trials, a patient's Hurley stage was determined by the worst Hurley stage across all affected anatomical regions.

FIGURE 2: STUDY DESIGN SCHEMATIC OF PIONEER I AND PIONEER II TRIALS



eow = every other week; ew = every week; OLE = open-label extension.
Source: PIONEER I (M11-313),[8] PIONEER II (M11-810),[9] and open-label extension study (M12-555).[15]

A key difference between PIONEER I and II was the re-randomization of patients to placebo in Period B. In both trials, all patients, regardless of treatment in Period A, were re-randomized at week 12 to maintain the blind. In PIONEER I, patients randomized to adalimumab in Period A were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg EW, 40 mg EOW, or matching placebo from week 12 to week 35. Patients who received placebo in Period A were assigned (using re-randomization numbers) to

adalimumab 40 mg EW. Patients who had received placebo in Period A and were re-randomized to adalimumab received an induction dose (160 mg at week 12, 80 mg at week 14, and matching placebo at weeks 13 and 15) and then continued on adalimumab 40 mg EW from week 16 to week 35.

Patients who received adalimumab in Period A and were re-randomized to adalimumab received a matching placebo induction dose from weeks 12 to 15. Similarly, in PIONEER II, patients randomized to adalimumab in Period A were re-randomized in a 1:1:1 ratio to receive adalimumab 40 mg EW, 40 mg EOW, or matching placebo in Period B. In contrast to PIONEER I, patients randomized to placebo in Period A were assigned (using re-randomization numbers) to continue on placebo from week 12 to week 35. In both PIONEER I and II, the re-randomization was stratified by week 12 HS clinical response (HiSCR, defined as at least a 50% reduction in abscess and inflammatory nodule [AN] count with no increase in abscess or draining fistula count relative to baseline) (responder versus non-responder) and by baseline Hurley stage (II versus III).

In both PIONEER I and II, all patients, regardless of treatment in Period A, who achieved HiSCR at week 12 continued in Period B through week 36. Those who experienced a LOR, defined as an AN count that was greater than the average of AN counts at baseline and week 12, were discontinued from the study and provided the opportunity to enter the open-label extension (OLE) study M12-555, in which they received open-label adalimumab 40 mg EW. All patients who did not achieve HiSCR at week 12 continued in Period B through week 36. Starting at or after week 16, patients who experienced a worsening or absence of improvement (WOAI), defined as an AN count that was greater than or equal to the AN count at baseline on two consecutive visits (excluding week 12) that occurred at least 14 days apart, were discontinued from the study and provided the opportunity to enter the OLE study M12-555.

In both trials, at week 36, all patients had the opportunity to enter the OLE study M12-555, in which they received adalimumab 40 mg EW.

Another difference between the trials pertained to antibiotic use. In PIONEER I, only rescue antibiotic treatment was permitted (minocycline or doxycycline up to 100 mg twice daily if a patient's AN count was ≥ 150% of the baseline count at week 4 or week 8). In PIONEER II, continuation of baseline antibiotics (minocycline and doxycycline only) was allowed throughout the study.

Different patient-reported HRQoL outcomes were collected in the two trials, although both PIONEER I and II did include the Dermatology Life Quality Index (DLQI) and the Hidradenitis Suppurativa Quality of Life (HSQoL) instruments. In PIONEER I, the Short Form (36) Health Survey (SF-36) was included, whereas in PIONEER II, the EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) index and visual analogue scale (VAS) were reported. Only PIONEER I included the Hospital Anxiety and Depression Scale (HADS).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were identical between the two trials (Table 3). Both trials included adult male and female patients with moderate to severe HS (defined as an AN count ≥ 3 at baseline).

Patients were required to have had an inadequate response to a trial of oral antibiotics of at least a three months (90 days) for the treatment of HS (or to have demonstrated intolerance to, or had a contraindication to, oral antibiotics for the treatment of their HS). An inadequate response or LOR to oral antibiotics was considered to have occurred if, after 90 days, any of the following was seen:

- Progression of Hurley stage (i.e., the Hurley stage of at least one affected anatomical region progressed from I→II, II→III, or I→III)
- Patient required at least one intervention (e.g., incision and drainage or intralesional injection of corticosteroid)
- Patient experienced pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen)
- Patient experienced pain requiring opioids, including tramadol
- Patient experienced drainage interfering with activities of daily living (e.g., multiple dressing changes and/or changes of clothes daily)
- Patient experienced an increase in the number of anatomical regions affected by HS
- Patient experienced at least one new abscess or one new draining fistula.

A patient was defined as intolerant to oral antibiotics when oral antibiotic therapy had been discontinued by a physician as a result of a significant adverse reaction to oral antibiotic administration. A reaction was considered significant if the adverse reaction was at least moderately severe (i.e., the adverse event [AE] causes the patient discomfort and interrupts the patient's usual activities or function).

b) Baseline Characteristics

There was a predominance of female patients in both trials (approximately 60% or more), which is in keeping with the prevalence of HS. The majority of patients (> 75%) were white and obese (mean body mass index [BMI] ranged from 31.3 kg/m^2 to 34.5 kg/m^2 across treatment groups). The majority of patients were also nicotine and alcohol users. Mean age was approximately 35 to 38 years and was similar across treatment groups in both trials.

The median duration of HS was approximately nine years, with an approximately equal distribution of Hurley stages II and III. The majority of patients had an AN count of at least 11 and notable erythema, with moderate red, very red, or bright red coloration in at least one body region. On a scale of 0 to 10, mean numerical rating scale (NRS) daily pain scores at worst (worst pain in the past 24-hour period) were approximately 5.0. Between 8% and 16% of patients had had prior surgery (not including incision and drainage) for HS.

Overall, baseline demographic and disease characteristics were generally well balanced among the adalimumab and placebo treatment groups in the individual trials. A possible exception was baseline AN counts, as a larger proportion of patients randomized to placebo had AN counts of 5 or less and 11 or more at baseline in both trials. An additional difference between the trials was possibly greater disease severity in PIONEER I than in PIONEER II (i.e., considering differences in mean draining fistulas [4.2 versus 3.4], mean AN counts [14.3 versus 11.2], and NRS skin pain [5.0 versus 4.5]). Mean BMI was higher in the PIONEER I study (33.0 kg/m^2 to 34.5 kg/m^2) than in PIONEER II (31.3 kg/m^2 to 32.9 kg/m^2). The proportion of current smokers was higher in PIONEER II (65.8%) than in PIONEER I (56.4%).

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS (ITT_A POPULATION)

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Gender, n (%)				
Female	91 (59.5)	105 (68.2)	108 (66.3)	113 (69.3)
Male	62 (40.5)	49 (31.8)	55 (33.7)	50 (30.7)
Race, n (%)				
White	116 (75.8)	118 (76.6)	143 (87.7)	130 (79.8)
Black	33 (21.6)	29 (18.8)	9 (5.5)	20 (12.3)
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Age				
Mean (SD)	36.2 (10.83)	37.8 (11.33)	34.9 (9.96)	36.1 (12.18)
Median (min, max)	35.0 (19, 65)	35.5 (18, 67)	35.0 (18, 67)	34.0 (19, 69)
< 40 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40 years to ≤ 64 years, n (%)				
≥ 65 years, n (%)				
BMI (kg/m^2)				
Mean (SD)	33.0 (7.62)	34.5 (7.94)	31.3 (7.41)	32.9 (7.94)
Median (min, max)	32.1 (18.3, 54.5)	33.6 (16.4, 69.8)	30.5 (17.4, 54.2)	31.8 (16.7, 60.1)
Nicotine use, n (%)				
User	81 (52.9)	92 (59.7)	105 (64.4)	109 (67.3)
Ex-user	22 (14.4)	22 (14.3)	22 (13.5)	18 (11.1)
Non-user	50 (32.7)	40 (26.0)	36 (22.1)	35 (21.6)
Alcohol use, n (%)				
User	[redacted]	[redacted]	[redacted]	[redacted]
Ex-user				
Non-user				
Hurley stage, n (%)[a]				
II	80 (52.3)	81 (52.6)	86 (52.8)	89 (54.6)
III	73 (47.7)	73 (47.4)	77 (47.2)	74 (45.4)
Family history of HS, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No				
Duration of HS (years)[b]				
< 9.17 (I) or 9.31 (II) (median)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 9.17 (I) or 9.31 (II) (median)				
Baseline AN count, n (%)				
≤ 5	[redacted]	[redacted]	[redacted]	[redacted]
6 to 10				
≥ 11				
Abscess count				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)				
Draining fistula count				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory nodule count Mean (SD) Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Hypertrophic scar count Mean (SD) Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
AN count Mean (SD) Median (min, max)	14.3 (11.92) [redacted]	14.4 (14.80) [redacted]	10.7 (8.10) [redacted]	11.9 (11.02) [redacted]
Erythema[c] No redness Faint but discernible pink coloration Moderate red coloration Very red or bright red coloration	[redacted]	[redacted]	[redacted]	[redacted]
Modified Sartorius score Mean (SD) Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
NRS (daily pain at worst)[d] Mean (SD) Median (min, max)	5.1 (2.51) [redacted]	4.8 (2.68) [redacted]	4.3 (2.62) [redacted]	4.8 (2.73) [redacted]
Prior HS surgery, n (%) Yes No	21 (13.7) 132 (86.3)	13 (8.4) 141 (91.6)	27 (16.6) 136 (83.4)	18 (11.0) 145 (89.0)

AN = abscess and inflammatory nodule; BMI = body mass index; HS = hidradenitis suppurativa; ITT_A = intention-to-treat population in Period A; NRS = numerical rating scale; SD = standard deviation.

[a] Hurley stage in the demographic table may differ from the Hurley stage stratum used for purposes of the efficacy analysis. Hurley stage stratum used for the efficacy analysis was determined at the time of randomization. Subsequent updates to a patient's Hurley stage did not affect the stratum, but are reflected in the demographic information.

[b] Median was 9.17 years in PIONEER I and 9.31 years in PIONEER II.

[c] Worst among all body regions.

[d] Adalimumab n = 151 and placebo n = 146.

Source: M11-313 Clinical Study Report,[8] M11-810 CSR.[9]

3.2.3 Interventions

The intervention was adalimumab administered initially as an induction dose (i.e., 160 mg at week 0 [Period A] or week 12 [Period B] as four injections and 80 mg at week 2 [Period A] or week 14 [Period B] as two injections) followed by a maintenance dose of 40 mg EW or 40 mg EOW given as one injection according to the trial design. The comparator was matched placebo administered in the same manner as the induction and maintenance doses of adalimumab. Study drug was administered by SC injection by the research staff or a designee (e.g., friend, family member, or health care professional) at the study site or at home. The dose of adalimumab was based on findings from a dose-finding phase 2 study M10-467.[4]

All treatments were assigned using an interactive voice/Web response system (IXRS) to maintain blinding.

a) Concomitant Therapies

A summary of concomitant medications taken by 5% or more of study patients during the trials is provided in Table 5. Patients were required to use a daily antiseptic wash on their HS lesions. Allowable antiseptic washes were limited to one of the following: [redacted]. Concomitant use of wound-care dressings on HS wounds was allowed but options were limited to: [redacted].

Concomitant use of oral antibiotic therapy for treatment of HS was generally not allowed, although, as noted in Section 3.2.1, there was a difference between the trials with regard to use of minocycline and doxycycline use. In PIONEER I, only rescue antibiotic treatment was permitted (i.e., minocycline or doxycycline up to 100 mg twice daily [redacted]). The dosing regimen remained stable throughout study participation. In PIONEER II, continuation of pre-entry baseline antibiotics (i.e., minocycline and doxycycline only) was allowed throughout the study.

Most patients were required to wash out all analgesics for 14 days before baseline. This included analgesics for HS-related pain as well as other non–HS-related pain. Nonetheless, if a patient was on a stable dose of a non-opioid analgesic for a non-HS medical condition (e.g., osteoarthritis), the patient was allowed to continue the analgesic, provided the dose was stable for 14 days before baseline and was expected to remain stable throughout the study. If a patient's pain (HS-related or non–HS-related) worsened after baseline, the patient was allowed to initiate analgesic therapy at any time as described below.

For HS-related pain, permitted analgesics were limited to:

- ibuprofen (at a dose of up to 800 mg by mouth every six hours) not to exceed 3.2 g/24 hours; and/or
- acetaminophen as per local labelling; and/or
- if HS-related pain was uncontrolled with ibuprofen or acetaminophen at the above dosing regimens after the baseline visit, patients could be prescribed oral tramadol (at a dose of up to 100 mg every four hours), not to exceed 400 mg/24 hours.

For non–HS-related pain:

- Opioid analgesics were prohibited.
- All other analgesics (including tramadol) were allowed at the recommended or prescribed dose.

TABLE 5: CONCOMITANT MEDICATIONS TAKEN BY ≥ 5% OF PATIENTS (ITT-A POPULATION)

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Any medication, n (%)				
Benzoyl peroxide				
Biseptine				
Chlorhexidine				
Corticosteroids				
Cyteal				
Doxycycline				
Eugynon				
Hydrogen peroxide				
Hypochlorous acid				
Ibuprofen				
Levothyroxine				
Metformin				
Minocycline				
Naproxen				
Paracetamol				
Retinoids (for acne treatment)				
Salbutamol				
Skinsan				
Tramadol				
Triamcinolone				
Triclosan				
Zinc				

ITT_A = intention-to-treat population in Period A; NA = not applicable (i.e., not reported by ≥ 5% of patients).
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

If an acutely painful lesion occurred that required an immediate intervention, physicians had the option to perform protocol-allowed interventions. Only two types of interventions were allowed: injection with intralesional triamcinolone acetonide suspension (at a concentration of up to 5 mg/mL, up to 1 cc) and incision and drainage procedures. If incision and drainage were performed, the required over-the-counter antiseptic wash was used. New systemic and topical therapies following incision and drainage (including antibiotics) were prohibited. Only two protocol-allowed interventions were permissible during Period A (Table 6). If a patient required more than two interventions within the first 12 weeks, then the patient was discontinued from the study. Similarly, during Period B, a maximum of two interventions every four weeks were permitted.

TABLE 6: NUMBER OF INTERVENTIONS DURING PERIOD A (OBSERVED CASES) (ITT-A POPULATION)

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Incision and drainage of lesion				
All patients n Mean no. of interventions Within-group no. of interventions, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group comparison LSM diff (95% CI) *P* value[a]	[redacted]		[redacted]	
Intralesional injection of triamcinolone acetonide suspension				
All patients n Mean no. of interventions Within-group no. of interventions, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group comparison LSM diff (95% CI) *P* value[a]	[redacted]		[redacted]	

CI = confidence interval; diff = difference; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.

[a] *P* values were calculated from analysis of variance (ANOVA) with treatment in the model.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

No data were provided in the Clinical Study Reports of the PIONEER trials for the number of interventions during Period B.

A number of therapies were prohibited for all patients during the trials. These included [redacted] antibiotics (except as allowed for rescue in PIONEER I and as allowed for concomitant treatment in PIONEER II), [redacted] except as outlined in the protocol.

3.2.4 Outcomes

a) Quality of Life

In PIONEER I and II, the HRQoL outcomes were all included as non-ranked secondary end points in Period A. Both trials measured the DLQI and HSQoL; however, SF-36 was included only in PIONEER I and EQ-5D was included only in PIONEER II.

The DLQI is a dermatologic-disease–specific instrument used to assess symptoms and the impact of skin problems on HRQoL by evaluating six areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Patients are asked to respond to the 10 items of the DLQI based on a recall period of "the last week." A score of 30 represents maximum impairment of HRQoL, and decreasing scores reflect improvement in HRQoL (Appendix 6: Validity of Outcome Measures). In a population of patients with a variety of dermatologic conditions, the minimal clinically important difference (MCID) was reported to be 3.3 points,[7] whereas in patients with psoriasis, the MCID is reported to range from 2.3 to 5.7 points.[4] The validity, reliability, or MCID of the DLQI in HS has not been established.

According to the Clinical Study Reports for PIONEER I and II, the HSQoL is an instrument that assesses the quality of life in patients with HS.[8,9] Ratings for the items in the HSQoL range from 0 (worst possible) to 10 (best possible); thus, higher scores indicate an improvement in the HSQoL. No additional information was provided by the manufacturer, and no information on the HSQoL could be located in the medical literature following a focused search. Thus, the validity, reliability, or the MCID of the HSQoL is unknown.

In PIONEER I, patients were also required to complete the SF-36 (version 2). The SF-36 is a generic measure of health status that contains 36 items measuring the following eight domains: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health.[16] For each of the eight categories, a subscale score can be calculated in addition to a physical component summary (PCS) and a mental component summary (MCS). Higher scores on the SF-36 indicate better health status. PCS and MCS scores above or below 50 are considered above or below average for the general US population (Appendix 6: Validity of Outcome Measures).[16] The MCID for either the PCS or MCS is typically between 2.5 and 5 points;[17-19] however, the SF-36 has not been validated in HS, nor has an MCID been established.

In PIONEER II, patients completed the EQ-5D questionnaire, presumably the three-level version, given the timing of the studies, as the version was not specified by the manufacturer. The EQ-5D is a generic, utility-based measure of HRQoL that asks respondents about their current health state "today." It consists of a two-part questionnaire: the EQ-5D descriptive system and the EQ-5D VAS. The descriptive portion of the EQ-5D contains five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For the three-level version of the EQ-5D, the response options reflect three levels of functioning for each dimension. Level 1 is no problems, level 2 is some problems, and level 3 is extreme problems. Based on the responses given for each dimension, a single overall index score is calculated using a utility-function–based scoring algorithm. The EQ-5D VAS asks patients to rate their health on that day on a vertical line based on a range of "worst imaginable health state" equal to 0 and "best imaginable health state" equal to 100. For both the EQ-5D index score and VAS score, higher scores indicate better health states. Additional details on the EQ-5D can be found in Appendix 6: Validity of Outcome Measures; however, it does not appear that the EQ-5D has been validated in HS, nor has an MCID been established, although clinically important differences for the descriptive system are reported to range from 0.033 and 0.074.

Patients were required to complete the HRQoL questionnaires before site personnel performed any clinic assessments or interacted with the patients, to avoid biasing the patients' response.

b) Abscesses, Nodules, Scarring, and Draining Fistulas

The number of inflammatory and non-inflammatory nodules, abscesses, draining and non-draining fistulas, and hypertrophic scars, as well as the physical location (i.e., right and/or left axilla, right and/or left inframammary, intermammary, right and/or left buttock, right and/or left inguinocrural fold, perianal, perineal, other) were recorded at designated study visits. The longest distance between two relevant lesions was measured as well as if the lesions were clearly separated by normal-appearing skin (yes/no). If only one lesion was present, then the lesion diameter was measured.

Identification of representative lesions was a study requirement, and a minimum of three and maximum of six representative lesions in four anatomical regions (i.e., left axilla, right axilla, left inguinocrural fold, and right inguinocrural fold) were identified at baseline and followed over time for progression or resolution. A representative lesion was an inflammatory nodule, abscess, or fistula that was typical of its group and was easily identifiable, discrete, and unlikely to coalesce with a similar nearby lesion. The size, degree of erythema, and tenderness of each representative lesion was assessed and rated by the investigator using severity scores of 0 to 3, where higher scores denoted worse conditions. The investigator also assessed the overall degree of erythema affecting the region on a four-point ordinal scale ranging between 0 (no redness), 1 (faint but discernible pink coloration), 2 (moderate red coloration), and 3 (very red or bright red coloration). Every attempt was made to have the same investigator conduct the assessments throughout the study for each patient. The proportion of patients who achieved an AN count of 0, 1, or 2 at week 12 among patients with Hurley stage II at baseline was a ranked secondary end point in the PIONEER trials.

The change in MSS from baseline to week 12 was the third ranked secondary outcome in the PIONEER trials. The MSS is based on an assessment of the body regions involved, number of lesions, and the distance between and separation of lesions to obtain an overall score. Higher scores indicate greater severity of HS; however, an MCID has not been established in patients with HS. The MSS has been correlated with BMI and the DLQI (Appendix 6: Validity of Outcome Measures).

c) Symptoms

In both PIONEER I and II, the Patient's Global Assessment of Skin Pain NRS was used to assess the worst and average skin pain from HS, from screening through to week 12. Ratings for the two items ranged from 0 (no skin pain) to 10 (skin pain as bad as you can imagine); thus, decreasing scores over time indicated improvement. For the daily assessments from screening to week 12, patients were instructed to complete the assessment before they went to bed, and to respond to the items based on a recall period of the "last 24 hours." A ranked secondary end point in both trials was the proportion of patients with baseline NRS of 3 or more who achieved at least a 30% reduction and at least a one unit reduction from baseline in the NRS (i.e., NRS30) at worst (worst pain in the past 24-hour period) at week 12. To calculate the NRS30, daily assessments were evaluated and the weekly average was used when comparing treatment groups.

d) Mental Health/Psychological Well-Being

In PIONEER I, patients completed the HADS, which was a non-ranked secondary outcome in Period A. The HADS is a questionnaire comprising an anxiety subscale and a depression subscale that was developed to screen for possible and probable cases of anxiety and depression disorders in patients from non-psychiatric hospital clinics.[20] A lower score on the HADS subscales indicates less severity. It

appears to be a valid and reliable instrument that correlates with other commonly used questionnaires and performs well in assessing symptom severity and caseness of anxiety and depression disorders in both somatic, psychiatric and primary care patients, and in the general population.[20] The HADS does not appear to have been validated in patients with HS, nor is the MCID in HS known. In PIONEER I, the HADS questionnaire was not completed by patients in Germany.

e) Functional Capacity/Productivity

In both PIONEER I and II, patients completed the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP), which was included as a non-ranked secondary outcome. According to the Clinical Study Reports for the PIONEER trials,[8,9] the WPAI: SHP evaluates four areas: per cent work time missed due to HS (absenteeism), per cent impairment while working due to HS (presenteeism), per cent overall work impairment due to HS, and per cent activity impairment due to HS. An MCID was reported to be a reduction in the WPAI: SHP of one-half or more of the standard deviation of all patients at baseline.[8,9] No additional information on this instrument was provided by the manufacturer.

f) Disease Worsening

A flare was defined as an increase of at least 25% and two absolute increases from baseline in lesions.

There were no data reported in the PIONEER trials for the efficacy outcomes of health care resource utilization (i.e., physician visits, surgeries), functional capacity, or caregiver burden as identified in the protocol for the systematic review. For the outcome of infections, data are reported from the safety analyses of the trials (Section 3.7, Harms).

g) Harms Outcomes

Safety end points included deaths, serious adverse events (SAEs), AEs, withdrawals due to adverse events (WDAEs), and AEs of special interest (which were injection-site reactions, hypersensitivity, opportunistic infections, and malignancy risk). According to the Clinical Study Reports for the PIONEER trials,[8,9] the reporting of opportunistic infections excluded oral candidiasis and tuberculosis.

h) Outcomes in PIONEER I and II

The primary efficacy variable in the PIONEER I and II trials was the proportion of patients who achieved HiSCR, defined as a reduction of at least 50% in AN count with no increase in abscess count and no increase in draining fistula count relative to baseline at week 12. Please refer to Appendix 6: Validity of Outcome Measures for additional information on the HiSCR, which has been validated in patients with HS.[21,22] While it does not appear that a specific MCID has been identified for the HiSCR, a 50% reduction in AN count is considered to be both clinically appropriate and meaningful to patients.[21]

There were three ranked secondary efficacy variables, as follows:

1. Proportion of patients who achieved an AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline
2. Proportion of patients with baseline NRS of 3 or more who achieved at least 30% reduction and at least one unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) at worst (worst pain in the past 24-hour period) at week 12 (see Section 3.6.3, Symptoms for additional information on this outcome)
3. Change in modified Sartorius score from baseline to week 12.

An extensive number of additional non-ranked secondary efficacy variables were measured in the PIONEER I and II trials. Those pertinent to the outcomes identified in the review protocol (Table 2) are reported in Appendix 4: Detailed Outcome Data.

3.2.5 Statistical Analysis

Both PIONEER I and II were designed to each enrol approximately 300 patients to have sufficient power for the primary efficacy end point (HiSCR). The power calculation was based on the response rates for HiSCR observed in the phase 2 study M10-467 at week 12, which were 61% (adalimumab) and 16% (placebo). A sample size of 150 per treatment group provided more than 90% power to detect the treatment difference with 0.05 two-sided type I error. No power evaluation was performed for Period B, as it was designed for exploratory analysis only.

In both PIONEER I and II, the number of patients with Hurley stage III was not to exceed [redacted] ([redacted]% of the total planned number of patients), and the number of patients with an AN count of 3 or 4 was not to exceed [redacted] ([redacted]% of the total number of patients). In PIONEER II, the number of patients who were on baseline concomitant antibiotics was not to exceed 90 (30% of the total planned number of patients). The per cent limits were not exceeded, based on the total number of enrolled patients in the trials.

All statistical tests were two-sided, with the significance level at 0.05. Descriptive statistics are provided, which include the number of observations, mean, minimum, maximum, and standard deviation for continuous variables, as well as counts and percentages for discrete variables. Categorical variables were analyzed by the Cochran–Mantel–Haenszel test, adjusted for baseline Hurley stage (II versus III). Continuous variables were analyzed by analysis of covariance, with baseline value and baseline Hurley stage (II versus III) in the model.

The intention-to-treat (ITT) population was used for efficacy analyses, and the specific ITT populations used in the trials are defined in Section 3.2.5.1, Analysis populations. Various sensitivity analyses of the primary efficacy end point were also conducted. In addition, analyses of the primary efficacy end point and ranked secondary efficacy end points were repeated using the per-protocol (PP) population defined for Period A.

In both PIONEER I and II, missing data were imputed using the following methods for the efficacy analyses in the ITT populations:

- **Non-responder imputation (NRI)**: Analyses utilizing NRI categorized any patient who had a missing value at a specific visit as not achieving and/or experiencing the end point of interest and assigned the patient as a non-responder for that visit. The NRI was the primary approach in the analysis of categorical variables. Of note, in the ITT population of each period, NRI was applied using evaluations obtained only within the period of interest.
- **Last observation carried forward (LOCF):** Analyses utilizing the LOCF approach used the last observed non-missing evaluation (last completed non-missing evaluation) from the previous visit within the particular period to impute missing data at later visits in the same period. Baseline efficacy evaluations were not carried forward. LOCF was the primary approach in the analysis of continuous variables, and the secondary approach in the analysis of categorical variables.
- **As-observed:** Analyses utilizing the data as observed in the study did not impute values for missing evaluations, and thus a patient who did not have an evaluation at a given visit was excluded from the as-observed analysis for that visit. As-observed analysis was the secondary approach in the analysis of continuous variables.

With regard to multiplicity, the analyses of the primary efficacy variable and the ranked secondary variables were performed in a hierarchical order and using a step-down procedure, with each comparison tested at a significance level of 0.05. A statistically significant result for the comparison in the higher rank (primary, then ranked secondary variables) was required for testing of the next comparison in the lower rank. There did not appear to be any control for multiplicity in the analyses of the other non-ranked secondary end points.

Safety analyses were carried out using the safety population in each period. No interim analysis was planned or performed in any of the trials. Safety data, the primary efficacy end points, and ranked secondary end points in both studies were periodically reviewed by an independent data monitoring committee.

The primary efficacy variable (HiSCR) in both PIONEER I and II was analyzed with respect to pre-specified subgroups based on the following demographic and baseline characteristics:

- Age group (< 40, 40 to 64, ≥ 65; if less than 10% of patients were in the ≥ 65 group, that group was combined with the 40 to 64 group as ≥ 40)
- Sex (male, female)
- Race (white, non-white)
- Duration of HS (by median)
- Weight (by median)
- BMI category: normal (< 25), overweight (25 to < 30), obese (30 to < 40), morbid obesity (≥ 40)
- Current smoking status at baseline (yes, no)
- Baseline C-reactive protein level (by median)
- Baseline AN count (≤ 5, 6 to 10, 11+)
- Baseline AN count (< median, ≥ median)
- Prior HS surgery history (yes, no)
- Smoking habit change (increase, decrease)
- Time from prior HS surgery to the first dose of study drug (< median, ≥ median).

a) Analysis Populations

The ITT population in each period was used for the efficacy analyses. In Period A, the ITT population (ITT_A) was defined as all patients who were randomized at baseline (week 0). The ITT population in Period B (ITT_B) was defined as all patients who were re-randomized in Period B (i.e., received a re-randomization number, regardless of the randomization in Period A).

Three ITT subpopulations for Period B were prospectively defined as follows:

- ITT_B_R: Subjects who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders.
- [redacted]
- [redacted]

The PP population in Period A (PP_A) was used for efficacy analysis of the primary efficacy end point and ranked secondary efficacy end points. [redacted].

The safety population in each period (Safety_A and Safety_B) was defined as all patients who were in the ITT population of the corresponding period and received at least one dose of study drug in the corresponding period. The safety population in each period was used for safety analysis.

3.3 Patient Disposition

Patient disposition data are provided in Table 7 (Period A) and Table 8 (Period B). In PIONEER I, of the total patients randomized, 290 (94.5%) completed Period A and continued to Period B. Of these (i.e., patients re-randomized and dosed in Period B), 170 (58.6%) completed Period B. The majority of patients who discontinued in Period B did so primarily owing to IXRS instruction, which required, as PP requirements, that patients experiencing LOR or WOAI should discontinue the study and enter the OLE M12-555 study. The highest proportion of patients discontinuing for this reason was observed among patients who were re-randomized to the placebo group in Period B (i.e., 23 [46.9%]).

In PIONEER II, of the total patients randomized, 306 (93.9%) completed Period A and continued to Period B. The proportion of patients who discontinued was larger in the placebo group (7.4%) than in the adalimumab group (4.9%), and the primary reason for discontinuation in the placebo group was due to AEs. All patients who completed Period A continued to Period B, and of these 116 (37.9%) completed Period B. As in PIONEER I, the main reason for discontinuation was IXRS instruction that required that upon experiencing LOR or WOAI, the patient was to discontinue and enter the OLE. The highest proportion of patients discontinuing for this reason was observed among patients who were re-randomized to the placebo group in Period B (84 [55.6%] of those in the placebo/placebo [PL/PL] group and 25 [49.0%] in the every week [EW]/PL group).

TABLE 7: PATIENT DISPOSITION FOR PATIENTS IN PERIOD A AND INTENTION-TO-TREAT, PER-PROTOCOL, AND SAFETY POPULATIONS

	PIONEER I		PIONEER II	
	Adalimumab	Placebo	Adalimumab	Placebo
[redacted]				

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 8: PATIENT DISPOSITION FOR RE-RANDOMIZED PATIENTS IN PERIOD B OF PIONEER I AND PIONEER II

	PIONEER I				PIONEER II			
	PL/EW	**EW/PL**	**EW/EOW**	**EW/EW**	**PL/PL**	**EW/PL**	**EW/EOW**	**EW/EW**
Re-randomized, N	145	49	48	48	151	51	53	51
Not treated, N (%)	0	0	0	0	0	0	0	0
Discontinued, N	52 (35.9)	27 (55.1)	21 (43.8)	20 (41.7)	111 (73.5)	28 (54.9)	28 (52.8)	23 (45.1)
(%)	6 (4.1)	1 (2.0)	2 (4.2)	1 (2.1)	3 (2.0)	0	2 (3.8)	1 (2.0)
AE	5 (3.4)	0	0	2 (4.2)	9 (6.0)	1 (2.0)	1 (1.9)	1 (2.0)
Withdrew consent	1 (0.7)	1 (2.0)	0	2 (4.2)	9 (6.0)	2 (3.9)	0	1 (2.0)
Lack of efficacy	5 (3.4)	1(2.0)	0	0	3 (2.0)	0	2 (3.8)	0
Lost to follow-up	30 (20.7)	23 (46.9)	18 (37.5)	13 (27.1)	84 (55.6)	25 (49.0)	22 (41.5)	20 (39.2)
Per IXRS	0	0	0	0	0	0	0	0
instruction[a]	5 (3.4)	1 (2.0)	1 (2.1)	2 (4.2)	3 (2.0)	0	1 (1.9)	0
Protocol violation								
Other								
Completed, N (%)	93 (64.1)	22 (44.9)	27 (56.3)	28 (58.3)	40 (26.5)	23 (45.1)	25 (47.2)	28 (54.9)

AE = adverse event; EOW = every other week; EW = every week; IXRS = interactive voice/Web response system; LOR = loss of response; PL = placebo; WOAI = worsening or absence of improvement.

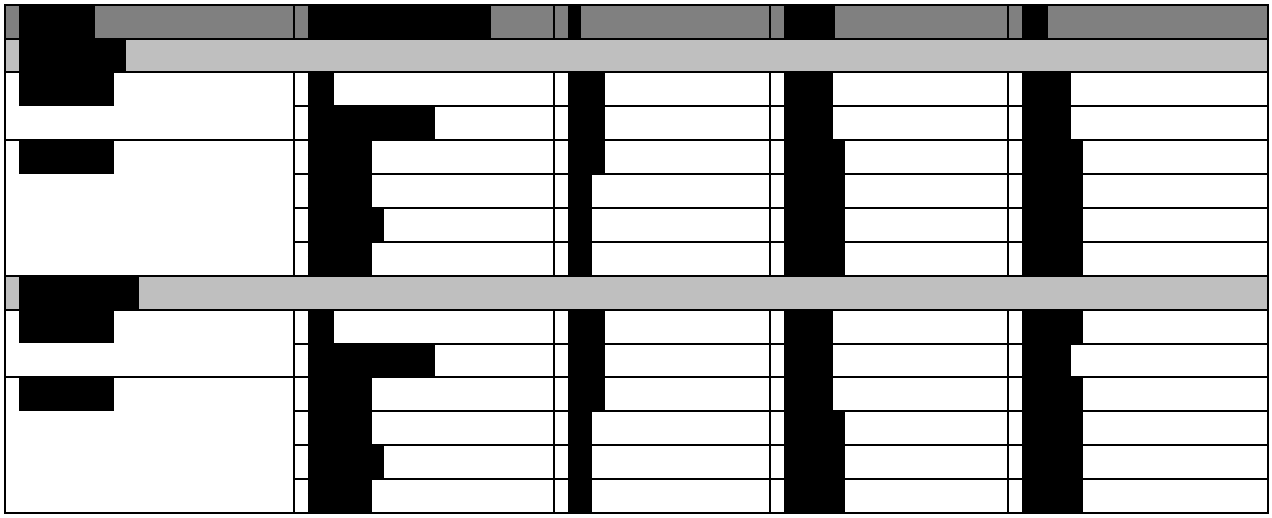
[a] Patients meeting criteria of LOR or WOAI were requested by the IXRS system to discontinue from the study and enter the open-label extension study M12-355.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

3.4 Exposure to Study Treatments

Mean duration of exposure was similar between the adalimumab and placebo treatment groups in Period A of both trials (Table 9). In Period B, mean duration of exposure was longer for patients re-randomized to adalimumab EW or switched from placebo to adalimumab EW in PIONEER I and in patients re-randomized to the EW/EW group compared with the EW/EOW, EW/PL, and PL/PL groups in PIONEER II. The shorter mean duration of exposure observed in the EW/PL and EW/EOW groups was largely due to the higher proportion of patients in these groups who withdrew upon experiencing a WOAI or LOR.

TABLE 9 [redacted]



EOW = every other week; EW = every week; ITT_A or ITT_B = intention-to-treat populations in Period A or Period B; PL = placebo; SD = standard deviation.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

3.5 Critical Appraisal

3.5.1 Internal Validity

- The methods used for randomization (i.e., central IXRS and randomization schedules) are appropriate. Randomization was stratified by Hurley stage (II or III) in both PIONEER trials and by concomitant antibiotic use (yes or no) in PIONEER II. It is appropriate to stratify patients on entry by Hurley stage (i.e., as a measure of HS severity), but it is not useful as a dynamic measure of HS, as the Hurley staging system is based on static disease characteristics and is not quantitative.
- Patients were randomized 1:1 to adalimumab or matched placebo in Period A, and those initially randomized to adalimumab in Period A were re-randomized 1:1:1 to adalimumab EW (continuation with EW treatment), EOW (reduced dosing frequency), or matching placebo (withdrawal of active treatment) upon entry to Period B in order to maintain blinding. Individuals in PIONEER I who were randomized to placebo in Period A were re-randomized to adalimumab EW for Period B, whereas those randomized to placebo in Period A of the PIONEER II trial were re-randomized to placebo in Period B. The results of Period B were considered to be only exploratory in nature, which is unfortunate, as comparisons between the individual treatment groups would have provided useful information to inform appropriate ongoing maintenance treatment with adalimumab.
- In both Periods A and B, the induction and weekly doses of adalimumab were appropriately matched with identical placebo SC injections to prevent performance bias.
- Baseline demographic and disease characteristics were generally balanced among the adalimumab and placebo treatment groups within the individual PIONEER trials. A possible exception is a larger proportion of placebo-treated patients with AN counts of 5 or less and 11 or more at baseline in both trials.
- The inclusion criteria for both PIONEER trials required that patients had an inadequate response to at least a three-month (90 days) trial of oral antibiotics for the treatment of HS (or demonstrated intolerance to, or had a contraindication to, oral antibiotics for the treatment of HS). Despite this, patients in PIONEER II could continue baseline antibiotics (i.e., minocycline or doxycycline only) throughout the study. It is unclear why continued antibiotic therapy was permitted, if, in order to enter the trial, patients would have had to have demonstrated inadequate response to antibiotics.
- While discontinuation rates in Period A were low (4.5% to 7.4% among treatment groups), a large proportion of patients in both PIONEER I and II discontinued the trials in Period B (35.9% to 73.5% among treatment groups). The majority of discontinuations in both trials were due to IXRS instruction, which required, as PP requirements, that patients experiencing LOR or WOAI should discontinue the study and enter the OLE M12-555 study. This may have introduced a systematic bias, as patients who may have experienced a temporary LOR or exacerbation of the underlying disease were removed from Period B with no opportunity to regain a response with continued treatment. Furthermore, it is not known whether the criteria defining LOR or WOAI would be used in clinical practice, as it is likely that physician would adjust the dose, rather than discontinue a patient from treatment, following a temporary LOR or exacerbation of disease. Given that the results from Period B are exploratory in nature and the number of patients in each re-randomization group is small, these results should be interpreted with caution.
- In general, the statistical methods and analyses were appropriate for Period A (i.e., there was adequate sample size and power, stratification factors were taken into account in the analyses, and appropriate imputation methods and sensitivity analyses based on the PP population were conducted). A hierarchical step-wise testing procedure was used to demonstrate superiority of adalimumab over placebo for the primary and three ranked secondary end points to account for multiple comparisons, as detailed in Section 3.2.5, Statistical Analysis). There did not appear to be any control for multiplicity in the analyses of the extensive number of non-ranked secondary end

points that were included in the PIONEER trials. Thus, the results of these end points must be interpreted with caution and largely considered to be only hypothesis-generating.

3.5.2 External Validity

- The PIONEER trials were conducted at 101 sites in Australia, North America, and Europe, including sites in Canada. According to the clinical expert consulted on this review, the patient population in the PIONEER trials is expected to be similar to the target treatment population in Canada.
- There were notable baseline differences between the patient populations in the PIONEER trials, which may, in part, explain the discordant results in the magnitude of the treatment effect with adalimumab between the trials for various outcomes. Patients appeared to have greater disease severity in PIONEER I compared with PIONEER II based on baseline differences in the number of mean draining fistulas, mean AN counts, and NRS skin pain assessment as per Section 3.2.2.2, Baseline Characteristics).
- Design differences in the PIONEER trials may also have contributed to the different magnitude of treatment effects observed with adalimumab between the trials, thus complicating comparison of the trial results. As noted in Section 3.2.1, in PIONEER I, only rescue antibiotic treatment was permitted, whereas in PIONEER II, continuation of pre-entry baseline antibiotics was allowed throughout the study. According to the clinical expert consulted on this review, antibiotics have an important place in the treatment of HS, and this could be a confounding factor, especially since patients in PIONEER I also appeared to have more severe disease, which coupled with lack of concomitant antibiotic therapy, could have resulted in poorer patient outcomes in PIONEER I than in PIONEER II. The trials also differed in how patients who received placebo in Period A were re-randomized in Period B.
- The majority of outcomes included in the PIONEER trials have not been validated in patients with HS, nor have MCIDs been established for these outcomes, especially with regard to the HRQoL instruments used in the trials. The primary outcome in the PIONEER trials (i.e., HiSCR) appears to have been validated for its intended purpose, but an MCID does not appear to have been established in patients with HS, which complicates interpretation of the results. It is acknowledged that a 50% reduction in AN count, per the definition of the HiSCR, is considered clinically relevant and appropriate to define a HiSCR responder.[3] There is also some skepticism regarding the relevance of some outcome measures (e.g., HADS) in an outpatient population, although the HADS has been shown to be useful in determining the caseness of anxiety and depression disorders in the general population.[20]
- The duration of Period A (12 weeks) is insufficient to assess the efficacy and safety of a medication intended for chronic administration. Furthermore, the exploratory nature of Period B (24 weeks), which was also of short duration (especially with regard to safety), and the lack of statistical comparisons between groups precludes drawing meaningful conclusions regarding appropriate ongoing maintenance treatment with adalimumab. The results from an interim analysis of the OLE M12-555 study for up to 72 weeks of treatment are provided in Appendix 7; however, interpretation of the results is limited by the small treatment groups, lack of a control group, possible selection bias, and [redacted].

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Section 2.2, Table 2. See 0 for detailed efficacy data.

3.6.1 Quality of Life

a) Dermatology Life Quality Index

The DLQI was included as a non-ranked secondary end point in Period A and as an exploratory outcome in Period B. Lower scores indicate an improvement in HRQoL, and the MCID for the DLQI in a variety of dermatologic conditions is reported to be a reduction of 3.3 points.[7]

For Period A, the results of the mean change from baseline in DLQI at week 12 are reported in Table 14. In Period A, the mean DLQI score at week 12 was reduced by –5.4 and –5.1 points in adalimumab-treated patients relative to baseline, compared with –2.9 and –2.3 points in placebo-treated patients in PIONEER I and II, respectively. The between-group differences were statistically significant in all patients. Similarly, in patients classified as [redacted] at baseline, the reductions in DLQI scores were [redacted] and [redacted] points in adalimumab-treated patients relative to baseline compared with [redacted] and [redacted] points in placebo-treated patients. Both between-group differences were [redacted]. In patients classified as [redacted] at baseline, the reductions in DLQI were [redacted] and [redacted] points in adalimumab-treated patients relative to baseline, and [redacted] and [redacted] in placebo-treated patients. Only the between-group difference in [redacted]. It appears that, in all adalimumab-treated patients, the MCID (based on a variety of dermatologic conditions) was exceeded relative to baseline by week 12. The between-group differences, however, [redacted] (i.e., [redacted]).

For Period B, the results of the mean change from re-randomization in DLQI at week 36 are shown in Table 37 (ITT_B_R Population), Table 42 (ITT_B_NR Population), and Table 46 (ITT_B_EW Population). Although the majority of patients experienced an [redacted] in mean DLQI score at [redacted] relative to the re-randomization DLQI score, the DLQI scores at [redacted], regardless of treatment. [redacted].

In patients who were randomized to adalimumab in Period A and were week 12 responders (ITT_B_R Population), the mean DLQI score [redacted] compared with the re-randomization score in all groups by [redacted] to [redacted] points in PIONEER I and [redacted] to [redacted] points in PIONEER II (Table 37). In PIONEER I, the smallest increase was in patients who were randomized to the [redacted] ([redacted]), and in PIONEER II, the smallest increase was in patients who were randomized to the [redacted] ([redacted]), although the change in mean DLQI score in patients randomized to the [redacted] ([redacted]).

In patients who were randomized to adalimumab in Period A and were week 12 non-responders (ITT_B_NR Population), the mean DLQI score also [redacted] relative to the re-randomization DLQI score in the [redacted] (i.e., [redacted] points in PIONEER I and [redacted] points in PIONEER II, respectively). In the [redacted] group, however, the mean DLQI score [redacted] relative to the re-randomization DLQI score (i.e., [redacted] in PIONEER I and [redacted] in PIONEER II), [redacted].

In patients who were randomized to placebo in Period A (ITT_B_EW Population), the mean DLQI score [redacted] at [redacted] relative to the baseline DLQI scores (i.e., the re-randomization mean DLQI scores were not reported). The reductions were [redacted] points in PIONEER I and [redacted] points in PIONEER II, [redacted].

b) Hidradenitis Suppurativa Quality of Life

The HSQoL was included as a secondary outcome in Period A. As per Section 3.2.4 (Outcomes), there is limited information available on the validity, reliability, or MCID of the HSQoL instrument other than that higher scores indicate an improvement.

For Period A, the results of the mean change from baseline in HSQoL at week 12 are given in Table 15. The HSQoL scores increased in all treatment groups relative to baseline, and differences between adalimumab- and placebo-treated patients were statistically significant in all patients in both PIONEER I and II, but only in patients classified as [redacted] in PIONEER I and [redacted] in PIONEER III.

c) Short Form (36) Health Survey

The SF-36 was included only in PIONEER I as a secondary outcome in Period A. As per Section 3.2.4 (Outcomes), in general, the MCID for either the PCS or MCS scores of the SF-36 is between 2.5 and 5 points, with higher scores indicating better health status. It does not appear that the SF-36 has been validated in HS, nor has a specific MCID been established for patients with HS.

For Period A, the results of the mean change from baseline in SF-36 scores at week 12 are reported in Table 16. The mean change from baseline in the PCS score was +4.2 points in adalimumab-treated patients compared with +1.5 points in placebo-treated patients. The between-group difference ([redacted] points) was statistically significant and exceeded the general MCID. The mean change from baseline in the MCS score was [redacted] points in adalimumab-treated patients compared with [redacted] points in placebo-treated patients, [redacted]. For all other domain scores, between-group differences were not statistically significant, with the exception of summary scores for bodily pain and general health.

EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire

The EQ-5D was included only in PIONEER II as a secondary outcome in Period A. It comprises the EQ-5D index score and the EQ-5D VAS (as detailed in Section 3.2.4, Outcomes). For both measures, higher scores indicate better health states. It does not appear that the EQ-5D has been validated in HS, nor has a specific MCID been established for patients with HS.

For Period A, the results of the mean change from baseline at week 12 in the EQ-5D index scores are provided in Table 17, and in the EQ-5D VAS scores are shown in Table 18. For the EQ-5D index scores, the between-group mean differences (i.e., [redacted] for all comparisons) were statistically significant in all patients, including those stratified by [redacted] at baseline. For the EQ-5D VAS scores, the between-group mean differences ranged from [redacted].

3.6.2 Health Care Resource Utilization

There were no results available for the efficacy outcome of health care resource utilization (i.e., physician visits, surgeries) identified in the review protocol. Although not reported as an outcome in the PIONEER trials, data on the number of incision and drainage procedures conducted during Period A was captured under the number of interventions performed (Table 6).

Overall, the number of patients requiring interventions during Period A was [redacted] (Table 6). In total, there were [redacted] adalimumab-treated patients compared with [redacted] placebo-treated patients in PIONEER I and [redacted] adalimumab-treated patient compared with [redacted] placebo-treated patients in PIONEER II who required an incision and drainage procedure during Period A. The differences between

groups were [redacted]. Similarly, the number of patients who required an injection of intralesional triamcinolone acetonide was also [redacted] (i.e., [redacted] versus [redacted] patients in PIONEER I and [redacted] versus [redacted] patients in PIONEER II, respectively) [redacted] differences between treatment groups.

3.6.3 Other Efficacy Outcomes

a) Abscesses, Nodules, and Draining Fistulas

The primary efficacy end point in the PIONEER trials was the proportion of patients achieving HiSCR at week 12, which was defined as a reduction in AN count of at least 50%, with no increase in abscess count or draining fistula count relative to baseline. The HiSCR has been validated in patients with HS; although an MCID per se has not been established, it is accepted that a 50% or more reduction in AN counts is clinically relevant and meaningful to patients (see Appendix 6: Validity of Outcome Measures for details). There were no data available on scarring.

For Period A, the proportion of patients achieving HiSCR at week 12 is reported in Table 22. For all-patient comparisons in both PIONEER trials (i.e., all patients or those stratified to Hurley stage II or Hurley stage III at baseline), the differences in the proportion of patients who achieved HiSCR were statistically significant in favour of adalimumab. Overall, the treatment effect appeared to be greater in PIONEER II than in PIONEER I. In the all-patient comparison, the proportion of adalimumab-treated patients who achieved HiSCR was 58.9% (PIONEER II) compared with 41.8% (PIONEER I), whereas the proportion of placebo-treated patients was similar (i.e., 26.0% and 27.6%, respectively). Between-group differences were 31.5% (PIONEER II) compared with 15.9% (PIONEER I). Similarly, between-group differences were also larger in PIONEER II than in PIONEER I when only patients stratified as Hurley stage II (25.5% versus 14.8%) and Hurley stage III (38.1% versus 17.1%) were considered. The proportion of patients achieving HiSCR was statistically significantly greater in adalimumab-treated patients as early as week 2 and remained statistically significant through weeks 4, 8, and 12 (Table 23).

For Period B, in the ITT_B_R Population, the proportions of patients achieving HiSCR at week 36 ranged from [redacted]% to [redacted]% among the treatment groups in PIONEER I and from [redacted]% to [redacted]% in PIONEER II (Table 33). The largest proportions of patients achieving HiSCR in both trials were in the [redacted] treatment groups. In the ITT_B_NR Population, between [redacted]% and [redacted]% of patients among the treatment groups in PIONEER I compared with [redacted]% to [redacted]% of patients in PIONEER II achieved HiSCR at week 36 (Table 39). Similarly, the largest treatment effect was observed in the [redacted] groups in both trials. In the ITT_B_EW Population, at week 36 in PIONEER I, a total of [redacted]% of patients achieved HiSCR in the [redacted] group, whereas [redacted]% of patients in the [redacted] group in PIONEER II achieved HiSCR (Table 43).

For Period A, the proportion of patients who achieved an AN count of 0, 1, or 2 at week 12 (i.e., the first ranked secondary outcome in the PIONEER trials), the treatment effect was also greater in PIONEER II. The between-group difference in all patients was 20.4% (PIONEER II) compared with 7.4% (PIONEER I) (Table 24). The results were statistically significant in favour of adalimumab in all patients and in those stratified by Hurley stage II or III at baseline in PIONEER II, but in PIONEER I, the between-group difference was statistically significant only in those patients stratified as Hurley stage III at baseline.

During Period A, various outcomes related to lesion counts or severity of lesions demonstrated a greater treatment response in PIONEER II than in PIONEER I. The proportion of patients who achieved a 50%/75%/100% reduction in AN counts (AN50/75/100) at week 12 was [redacted] in all-patient comparisons (i.e., all patients or those stratified to Hurley stage II or

III at baseline); [redacted], [redacted] [redacted](Table 25). Mean change from baseline in lesion counts also consistently showed a [redacted] between-group difference in patients treated with [redacted] compared with [redacted]-treated patients in [redacted](Table 26). For all lesions, with the exception of all [redacted] (i.e., [redacted]), [redacted] whereas results were [redacted] in favour of [redacted] only for [redacted] and [redacted] in [redacted](Table 26). The proportion of patients with at least one lesion at baseline who achieved complete elimination of lesions at week 12 also demonstrated that in PIONEER II, between-group differences were [redacted] for [redacted](i.e., [redacted]) whereas in PIONEER I, between-group differences were [redacted]. The mean change from baseline in lesion severity scores at week 12 were all [redacted], with the exception of [redacted] in PIONEER I (Table 28).

For Period B, the mean change from re-randomization in lesion counts (abscesses, draining fistulas, and all fistulas and inflammatory nodules) at week 36 was reported for the various treatment groups in the ITT_B_R population (Table 34). [redacted]. [redacted] ([redacted]). [redacted] (Table 40). [redacted](Table 44).

The change in the MSS from baseline to week 12 was the third ranked secondary outcome in the PIONEER trials. The MSS is based on an assessment of the regions involved, number of lesions, and distance between and separation of lesions to obtain an overall score (see Appendix 6: Validity of Outcome Measures for details). Higher scores indicate increased severity. An MCID has not been established in patients with HS.

In Period A, the between-group difference in the change in MSS from baseline to week 12 was statistically significant in favour of adalimumab for all-patient comparisons (i.e., all patients or those stratified by Hurley stage II or III at baseline) in PIONEER II (Table 29). In PIONEER I, the between-group differences were not statistically significant in any patient group.

[redacted](Table 35). [redacted]. [redacted]([redacted]) [redacted]([redacted]) (Table 45).

b) Symptoms

The NRS30 (i.e., the proportion of patients who achieved at least 30% reduction and at least one unit reduction from baseline in the Patient's Global Assessment of Skin Pain at worst [worst pain in the past 24-hour period] at week 12 among patients with baseline NRS ≥ 3) was the second ranked secondary end point in the PIONEER trials.

For Period A, [redacted] (Table 19). The treatment effect appeared to be [redacted]. A similar pattern is observed at week 12 when [redacted], or those stratified by [redacted] at baseline are considered (Table 20). For patients stratified by Hurley stage III at baseline, between-group differences [redacted]. Results for the change from baseline in NRS on average in patients with baseline NRS ≥ 3 at worst (worst pain in the past 24-hour period) at week 12 are provided in Table 21. In both PIONEER trials, the NRS scores [redacted]; however, between-group differences were [redacted]. For patients stratified by [redacted] at baseline, between-group differences were [redacted].

c) Mental Health/Psychological Well-Being

The HADS scale was included as a secondary outcome in Period A and as an exploratory outcome in Period B of PIONEER I. As detailed in Section 3.2.4, a lower score for the HADS subscales indicates lower severity. The HADS has not been validated in patients with HS, nor is an MCID known.

For Period A, the results for the mean change from baseline at week 12 in the HADS anxiety and depression subscales are reported in Table 31. The mean scores for both the anxiety and depression subscales [redacted] from baseline at week 12 in [redacted].

[redacted] (Table 38). [redacted].

d) Functional Capacity/Productivity

The WPAI: SHP was included as a secondary outcome in Period A in both PIONEER trials, although there is limited information available about this measure (Section 3.2.4, Outcomes). [redacted][8,9] [redacted] Table 32. [redacted]. [redacted] ([redacted]).

e) Disease Worsening

In the PIONEER trials, a flare was defined as an increase of at least 25% and two absolute increases from baseline in lesions. Results for the proportion of patients with flares by lesion type in Period A are

reported in Table 30. Between-group differences in the reduction in flares of ANs ([redacted] inflammatory nodules ([redacted]) and draining fistulas ([redacted]) were [redacted]. For abscesses, the between-group reduction in flares was [redacted] ([redacted]) [redacted] ([redacted]).

3.7 Harms

Only those harms identified in the review protocol are reported below (section 2.2.1, Protocol). See 0 for detailed harms data.

A summary of treatment-emergent AEs are reported in Table 10 (Period A) and Table 11 (Period B).

TABLE 10: HARMS IN PERIOD A (SAFETY_A POPULATION)

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 152	Adalimumab N = 163	Placebo N = 163
Deaths				
Deaths, n (%)	0	0	0	0
AEs				
Pts with ≥ 1 AE, n (%)	81 (52.9)	94 (61.8)	94 (57.7)	109 (66.9)
Most frequent AEs (≥ 5% in any group), n (%)				
Hidradenitis[a]	14 (9.2)	20 (13.2)	7 (4.3)	21 (12.9)
Nasopharyngitis	9 (5.9)	16 (10.5)	9 (5.5)	10 (6.1)
Headache	14 (9.2)	15 (9.9)	21 (12.9)	21 (12.9)
Upper RTI	NA	NA	8 (4.9)	9 (5.5)
Diarrhea	NA	NA	9 (5.5)	4 (2.5)
SAEs				
Pts with ≥ 1 SAE, n (%)	3 (2.0)	5 (3.3)	3 (1.8)	6 (3.7)
SAEs occurring in ≥ 2 pts				
Hidradenitis	1 (0.7)	3 (2.0)	0	2 (1.2)
WDAEs				
Pts with ≥ 1 WDAE, n (%)	1 (0.7)	3 (2.0)	4 (2.5)	7 (4.3)
WDAEs occurring in ≥ 2 pts	NA	NA	NA	NA

AE = adverse event; NA = not applicable (did not occur in specified number or proportion of pts); Pts = patients; RTI = respiratory tract infection; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: More than one AE, SAE, or WDAE could have occurred in one patient.
[a] Refers to exacerbation of underlying disease.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 11: HARMS IN PERIOD B (SAFETY_B POPULATION)

	PIONEER I				PIONEER II			
	PL/EW N = 145	EW/PL N = 49	EW/EOW N = 48	EW/EW N = 48	PL/PL N = 151	EW/PL N = 51	EW/EOW N = 53	EW/EW N = 51
Deaths								
Deaths, n (%)								
AEs								
Pts with ≥ 1 AE, n (%)								
Most frequent AEs (≥ 5% in any group), n (%) Hidradenitis Nasopharyngitis Headache Upper RTI Pyrexia Dermatitis contact Gastroenteritis Influenza Diarrhea Toothache Bronchitis Gastroenteritis, viral								
SAEs								
Pts with ≥ 1 SAE, n (%)								
SAEs occurring in ≥ 2 pts Hidradenitis								
WDAEs								
Pts with ≥ 1 WDAE, n (%)								
WDAEs occurring in ≥ 2 pts Pustular psoriasis								

AE = adverse event; EOW = every other week; EW = every week; NA = not applicable (did not occur in specified number or proportion of pts); PL = placebo; RTI = respiratory tract infection; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: More than one AE, SAE, or WDAE could have occurred in one patient.

[a] Cause of death was cardio-respiratory arrest.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

3.7.1 Adverse Events

In Period A, more than half of the patients in each treatment group experienced AEs (i.e., 52.9% and 57.7% of adalimumab-treated patients and 61.8% and 66.9% of placebo-treated patients in PIONEER I and II, respectively; Table 10). The most frequent treatment-emergent AEs were HS (considered to be an exacerbation of underlying disease), headache, and nasopharyngitis. More patients in the placebo groups experienced HS (13.2% and 12.9%) than those in the adalimumab groups (9.2% and 4.3%) in PIONEER I and II, respectively. More patients experienced nasopharyngitis in the placebo group of

PIONEER I (10.9%) compared with the adalimumab group (5.9%), but in PIONEER II the proportions of patients with nasopharyngitis were similar (6.1% and 5.5%).

[redacted] Table 11. [redacted].

[redacted].

3.7.2 Serious Adverse Events

In Period A, more patients in the placebo groups (3.3% and 3.7%) than in the adalimumab groups (1.8% and 2.0%) experienced SAEs in PIONEER I and II, respectively (Table 10). The most frequent SAE (occurring in two or more patients) was HS.

[redacted] (Table 11). [redacted].

3.7.3 Withdrawals due to Adverse Events

In Period A, WDAEs occurred infrequently in either treatment group in the two trials (Table 10). WDAEs occurred in 0.7% and 2.5% of patients in the adalimumab groups and in 2.0% and 4.3% in the placebo groups in PIONEER I and II, respectively. There was no one type of WDAE that occurred in more than two patients.

[redacted] (Table 11). [redacted].

3.7.4 Mortality

There were no deaths in either PIONEER I or PIONEER II during Period A (Table 10). [redacted] (Table 11). [redacted].

3.7.5 Notable Harms

The AEs of special interest identified in the systematic review protocol were injection-site reactions, hypersensitivity, opportunistic infections, and malignancy risk. A summary of AEs of special interest are reported in Table 12 (Period A) and Table 13 (Period B).

In Period A, injection-site reactions occurred [redacted] (Table 12). There did not appear to be any treatment-related differences in the proportion of patients with [redacted] infections. No patients in either trial or treatment group experienced [redacted]

[redacted], nor did any patients report any [redacted]. There was [redacted].

TABLE 12: NOTABLE HARMS IN PERIOD A (SAFETY_A POPULATION)

	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 152	Adalimumab N = 163	Placebo N = 163
Injection-site reaction AEs, n (%)				
Any injection-site reaction	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity AEs, n (%)				
Any allergic reaction including angioedema and/or anaphylaxis	[redacted]	[redacted]	[redacted]	[redacted]
Infection AEs, n (%)				
Any infection	38 (24.8)	43 (28.3)	41 (25.2)	53 (32.5)
Any serious infection	[redacted]	[redacted]	[redacted]	[redacted]
Any opportunistic infection (excluding candidiasis and TB)	[redacted]	[redacted]	[redacted]	[redacted]
Any TB (active or latent)	[redacted]	[redacted]	[redacted]	[redacted]
Malignancy AEs, n (%)				
Any lymphoma	[redacted]	[redacted]	[redacted]	[redacted]
Any non-melanoma skin cancer	[redacted]	[redacted]	[redacted]	[redacted]
Any malignancy other than lymphoma, HSTCL, leukemia, non-melanoma skin cancer, or melanoma	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; HSTCL = hepatosplenic T-cell lymphoma; TB = tuberculosis.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

[redacted] (Table 13). [redacted].

[redacted].

TABLE 13: NOTABLE HARMS IN PERIOD B (SAFETY_B POPULATION)

	PIONEER I				PIONEER II			
	PL/EW N = 145	EW/PL N = 49	EW/EOW N = 48	EW/EW N = 48	PL/PL N = 151	EW/PL N = 51	EW/EOW N = 53	EW/EW N = 51
Injection-site reaction AEs, n (%)								
Any injection-site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity AEs, n (%)								
Any allergic reaction including angioedema and/or anaphylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection AEs, n (%)								
Any infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any serious infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any opportunistic infection (excluding candidiasis and TB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any TB (active or latent)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignancy AEs, n (%)								
Any lymphoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any non-melanoma skin cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any malignancy other than lymphoma, HSTCL, leukemia, non-melanoma skin cancer, or melanoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; EOW = every other week; EW = every week; HSTCL = hepatosplenic T-cell lymphoma; PL = placebo; TB = tuberculosis.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

4. DISCUSSION

4.1 Summary of Available Evidence

Two placebo-controlled, double-blind, unpublished, phase 3 RCTs of 12 weeks' (Period A) and 24 weeks' (Period B) duration met the selection criteria for inclusion in the systematic review: PIONEER I (N = 307) and PIONEER II (N = 326). In Period A, patients were randomized to adalimumab (160 mg at week 0, 80 mg at week 2, and then 40 mg every week) or matched placebo. In Period B, patients were re-randomized (regardless of treatment in Period A), to adalimumab 40 mg every week, adalimumab 40 mg every two weeks, or matched placebo. The trials enrolled adult patients with a diagnosis of HS and lesions in two or more distinct areas, one of which was Hurley stage II or III; an AN count of three or more; and an inadequate response to a three-month trial of oral antibiotics. The primary efficacy end point was the proportion of patients who achieved HiSCR, which was defined as a reduction at least 50% in AN count, with no increase in abscess count or draining fistula count relative to baseline at week 12. There were three ranked secondary outcomes: the proportion of patients who achieved an AN count of 0, 1, or 2 among patients stratified as Hurley stage II at baseline; the NRS30 or proportion of patients who achieved at least 30% reduction and one unit reduction from baseline in the Patient's Global Assessment of Skin Pain at worst (worst pain in the past 24-hour period) among patients with baseline NRS of 3 or more; and the change from baseline in MSS, all measured at week 12. An extensive number of non-ranked secondary efficacy outcomes were also explored. Key limitations are the differences in study design and baseline patient characteristics between PIONEER I and II, lack of validation of many outcomes (especially HRQoL) in patients with HS, lack of control for multiplicity in the analyses of non-ranked secondary outcomes, high discontinuation rates from Period B, and the short duration of the trials for a chronic disease.

4.2 Interpretation of Results

4.2.1 Efficacy

Quality of life was the key efficacy end point identified in the review protocol and data for this outcome are provided by the DLQI and HSQoL (measured in both PIONEER I and II), SF-36 (PIONEER I only), and the EQ-5D (PIONEER II only). All of the HRQoL outcomes were included in the PIONEER trials as non-ranked secondary outcomes. The MCID for the DLQI in a variety of dermatologic conditions is reported to be a reduction of 3.3 points, although it has not been specifically validated in patients with HS.[7] In Period A, the within-group reduction (indicating improvement) in mean DLQI score from baseline to week 12 exceeded the MCID of 3.3 points in the adalimumab-treated groups in both PIONEER I and II, whereas the change in placebo-treated patients did not. The between-group differences in each trial were statistically significant in favour of adalimumab in all patients, in those stratified by Hurley stage II, and those stratified by Hurley stage III in PIONEER II only. Although the MCID was exceeded relative to baseline by week 12 within the adalimumab groups, the magnitude of the between-group differences did not exceed the MCID in either trial. [redacted]

The HSQoL was included in both PIONEER trials, although there is a paucity of information regarding the validity, reliability, or MCID of this instrument in HS, other than the brief description provided in the Clinical Study Reports.[8,9] In Period A, the HSQoL scores increased (indicating improvement) in all treatment groups relative to baseline in both PIONEER trials. The differences between adalimumab- and

placebo-treated patients were statistically significant in the all-patient groups in both trials, but were only statistically significant in patients [redacted].

The SF-36 was included only in PIONEER I, and, in general, the MCID for either the PCS or MCS scores of the SF-36 is considered to be between 2.5 and 5 points, although it does not appear that the SF-36 has been validated in HS, nor has a specific MCID been established. In Period A, the mean increase in the PCS score from baseline (indicating better health status) exceeded the general MCID in adalimumab-treated patients, but not in placebo-treated patients. The between-group difference was statistically significant and also exceeded the general MCID. In contrast, [redacted]. For all other domain scores of the SF-36, between-group differences were not statistically significant, with the exception of summary scores for bodily pain and general health.

The EQ-5D was included only in PIONEER II. Similar to the other HRQoL outcomes, the EQ-5D has not been validated in HS, nor a specific MCID identified, although clinically important differences for the descriptive system are reported to range from 0.033 and 0.074. In Period A, the EQ-5D health index score increased relative to baseline (indicating better health status) in both adalimumab- and placebo-treated groups. Although the magnitude of the increase at week 12 was small (i.e., [redacted] change from baseline in all patients), the between-group mean differences were statistically significant in all patients, including those [redacted]. For the EQ-5D VAS scores, the between-group mean differences [redacted].

Taken together, these data appear to support an improvement in HRQoL associated with adalimumab; however, interpretation of these data are compromised by a lack of validation of the HRQoL instruments in patients with HS and no establishment of MCIDs for these instruments in this patient population. In addition, the results are limited by a lack of adjustment for multiplicity in the statistical comparisons conducted between treatment groups. According to the natural history of HS (see Appendix 5 for details), HS appears to disproportionately affect patients' HRQoL in comparison with other dermatologic conditions, and may impact HRQoL as much as more serious medical conditions, such as cancer, cardiovascular diseases, and lung diseases.[23]

The second key efficacy outcome in the review protocol was health care resource utilization; however, there were no relevant outcomes (e.g., physician visits, surgeries) reported in the PIONEER trials for this outcome. Data were available on the number of incision and drainage procedures, as well as on intralesional injection of triamcinolone acetonide performed during Period A, as these procedures were captured as protocol-allowed interventions. Nonetheless, the number of procedures performed was [redacted] and there were [redacted]. According to the clinical expert consulted for this review, incision and drainage could have confounded the results of pain assessments, as the procedure typically provides instant pain relief. Based on the small number of procedures performed during Period A, there is no evidence that the NRS30 results were compromised.

The primary efficacy end point in the PIONEER trials was the proportion of patients achieving HiSCR at week 12. The HiSCR has been validated in patients with HS, and, although a specific MCID has not been established, it is accepted that a reduction of 50% or more in AN counts is clinically relevant and meaningful to patients (see Appendix 6: Validity of Outcome Measures for details). In Period A of both

PIONEER trials, the between-group differences in the proportion of patients achieving HiSCR were statistically significant in favour of adalimumab in all patients as well as those stratified by Hurley stage II or III at baseline. It also appears that the treatment effect associated with adalimumab is rapid, as between-group differences in the proportion of patients who achieved HiSCR was statistically significant in both trials as early as week 2. The magnitude of the treatment effect associated with adalimumab appeared to be greater in PIONEER II than in PIONEER I, regardless of the patient group compared.

[redacted]. As with other Period B outcomes, caution should be exercised in interpretation of these results because of the absence of statistical comparisons.

During Period A, many outcomes related to AN or lesion counts demonstrated a similar pattern as with the HiSCR. In Period A, the proportion of patients who achieved an AN count of 0, 1, or 2 at week 12 in patients stratified by Hurley stage II (i.e., the first ranked secondary outcome in the PIONEER trials) was statistically significant in favour of adalimumab compared with placebo in PIONEER II, but not PIONEER I. The proportion of patients who achieved a reduction in AN50/75/100 at week 12 was [redacted], but the treatment effect appeared to be [redacted]. Mean change from baseline in lesion counts at week 12 also [redacted] compared with [redacted]. The proportion of patients with at least one lesion at baseline who achieved complete elimination of lesions at week 12 also showed that in PIONEER II, between-group differences [redacted].

Results for the change from baseline to week 12 in the MSS (the third ranked secondary outcome in the PIONEER trials) is another outcome for which a larger treatment effect was observed with adalimumab in PIONEER II than in PIONEER I. In Period A, the between-group difference in the reduction in MSS (indicating decreased severity) from baseline to week 12 was statistically significant in favour of adalimumab in PIONEER II for all-patient comparisons (i.e., all patients or those stratified by Hurley stage II or III at baseline). In PIONEER I, however, the between-group differences were not statistically significant in any patient group.

The difference in the magnitude of the treatment effect associated with adalimumab in the PIONEER trials for many of the reported outcomes may, in part, be related to baseline patient disease characteristics and study design differences between the trials. In PIONEER I, patients may have had greater disease severity as a result of higher baseline mean counts of draining fistulas, AN counts, and greater mean NRS skin pain compared with patients in PIONEER II. Another important factor is that patients in PIONEER II were able to continue pre-entry baseline antibiotic therapy (i.e., minocycline and doxycycline only) throughout the trial, as opposed to receiving only rescue antibiotic therapy per the design of PIONEER I. In PIONEER II, patients were also stratified by antibiotic use at baseline (yes or no). Results for the primary outcome (HiSCR) were available by baseline antibiotic use versus no antibiotic use. In all-patient group comparisons, the treatment effect with adalimumab was greater in patients who were on antibiotics at baseline compared with those who were not (42.6% versus 28.6% in all

patients, 38.6% versus 23.5% in patients stratified by Hurley stage II, and 45.0% versus 35.7% in patients stratified by Hurley stage III). During Period A, approximately 20% of patients in PIONEER II, compared with 6% of patients in PIONEER I, received concomitant minocycline and doxycycline. The clinical expert consulted on this review concurred that the difference in antibiotic use may have contributed to the difference in the treatment effect of adalimumab observed between the trials; however, the potential for a synergistic treatment effect requires further study.

The NRS30 in the Patient's Global Assessment of Skin Pain was the second ranked secondary end point in the PIONEER trials. Based on the response observed for this outcome [redacted], it appears that adalimumab has a statistically significant and rapid effect on skin pain as compared with placebo. [redacted].

Other efficacy outcomes included in the review protocol were physical well-being/mental health, and functional capacity/productivity, which were outcomes identified as important to patients (see Appendix 1: Patient Input Summary). The only data available to report for the physical well-being/mental health outcome are derived from the HADS scale, which was included as a secondary outcome in Period A and an exploratory outcome in Period B of PIONEER I. The HADS has not been validated in patients with HS, nor is an MCID known in HS patients. In Period A, the mean scores for both the anxiety and depression subscales decreased from baseline at week 12 (indicating improvement) in both the adalimumab- and placebo-treated groups, [redacted]. With regard to functional capacity/productivity, the WPAI:SHP was included as a secondary outcome in Period A in both PIONEER trials, although information about this instrument is limited. Results for the mean change from baseline to week 12 in various subscales of the WPAI: SHP showed that [redacted]. In PIONEER I and II, [redacted].

With regard to the outcome of disease worsening, the only efficacy outcome reported in Period A of the PIONEER trials that may be an indicator of worsening disease was the number of flares (defined as an increase of at least 25% and two absolute increases from baseline in lesions). [redacted].

The clinical expert noted that patients would presumably need to be maintained on adalimumab indefinitely, as there is no known cure for HS. Because of the potential for chronic treatment of HS with adalimumab, it would have been useful to have sufficient numbers of patients enrolled and continued in Period B of the PIONEER trials to permit statistical comparisons between the re-randomized treatment groups to inform appropriate maintenance dosing with adalimumab. The high discontinuation rates of patients from Period B due to the protocol requirement that upon experiencing LOR or WOAI, patients should discontinue the study and enter the OLE M12-555 study may have introduced a serious systematic bias. Patients who may have experienced a temporary LOR or exacerbation of the underlying

disease were removed from Period B with no opportunity to regain a response with continued treatment. It is also not known whether the criteria defining LOR or WOAI used in the PIONEER trials would be the same as those used in clinical practice, where it is likely that a physician would adjust the dose rather than discontinue a patient from treatment following a temporary LOR or exacerbation of disease. Although there are longer-term results available from the unpublished OLE M12-555 study[15] (summarized in Appendix 7: Summary of Other Studies), there are serious limitations to these data; namely, lack of a control group, high discontinuation rates, and the potential for selection bias, which precludes any efficacy conclusions with regard to ongoing adalimumab treatment. There is also a lack of data on the effect of adalimumab on disease remission, and/or slowing of progression, or reduction in the amount of lesion scarring and tract formation, which, according to the clinical expert, are important management goals for the treatment of HS.

4.2.2 Harms

In Period A, more than half of the patients in each treatment group of the PIONEER trials experienced AEs. [redacted]. The proportions of patients with SAEs or WDAEs were low in both PIONEER trials. The most frequent SAE (in two or more patients) in [redacted] was HS. There was no one type of WDAE that occurred in more than two patients. There were [redacted] in either trial during Period A; [redacted].

In the review protocol, AEs of special interest were injection-site reactions, hypersensitivity, opportunistic infections, and malignancy risk. In Period A, injection-site reactions occurred [redacted]. There did not appear to be any treatment-related differences in the proportion of patients with [redacted] or infections, and no patients in either trial or treatment group experienced [redacted].

The results from the OLE M12-555 study (summarized in Appendix 7: Summary of Other Studies) support the conclusion that the safety of adalimumab in the open-label study was similar to that observed in the PIONEER I and II trials. The most frequent AEs included HS, nasopharyngitis, upper respiratory tract infection, and headache. The frequency of SAEs was low and [redacted]. Overall, the safety and tolerability profile of adalimumab in HS does not appear to be different from that previously observed in other indications, with the exception of the reporting of HS as an AE (considered an exacerbation of underlying disease).

4.2.3 Potential Place in Therapy

Treatment gaps for HS patients include access to accurate and timely diagnosis and management. General measures to manage HS patients including managing obesity and encouraging smoking cessation. Pharmacological treatment is directed at patients with active abscesses, nodules, and fistulas. With the exception of adalimumab, there are no Health Canada–approved therapies for this condition. However, readily available and effective treatments, such as incision and drainage, intralesional corticosteroid administration, and topical and oral antibiotics, are used in routine practice. Antibiotic treatment is associated with several potential harms, and long-term oral antibiotics may lead to photosensitivity, recurrent vulvovaginal candidiasis, nausea, vomiting and diarrhea, antibiotic resistance, and, more rarely, *Clostridium difficile* infection. In contrast to antibiotics, adalimumab targets the TNF-alpha pathway, which has been implicated in the pathogenesis of HS. Therefore, adalimumab represents an alternative to antibiotics that could fill the potential treatment gap represented by HS patients who are not adequately controlled or are otherwise inappropriate candidates for antibiotics.

HS patients who would be most appropriate for adalimumab treatment are individuals with active abscesses, nodules, and fistulas. Adalimumab would be used as monotherapy, but antibiotics (topical or oral), incision and drainage, and intralesional corticosteroids could be used as add-on therapy. HS patients should undergo extensive screening before receiving adalimumab, as is the case for other conditions such as psoriasis. Screening would include a baseline history and physical examination, serological testing (for HIV and hepatitis B and C), general blood work, and tuberculosis testing. A manufacturer-sponsored patient support program exists for psoriasis patients who are being treated with adalimumab, and such a program would likely also benefit HS patients.[24] Of note, the manufacturer has confirmed that AbbVie Care, AbbVie's patient support program, which includes a program and tools to help patients with starting and adherence to therapy, is available for patients with HS.

While adalimumab has a role to play in managing and controlling active HS, this role is limited by high cost and the challenge of maintaining patient adherence to ongoing weekly injections. Patients would presumably need to be maintained on adalimumab indefinitely, as there is no known cure for HS. Patient adherence would likely decline over time due to injection burn-out, injection-site reactions, and a suboptimal response. A suboptimal response could be defined as no improvement in quality of life or as disease progression (e.g., appearance of new abscesses, nodules, and/or fistulas in existing or new anatomical regions).

5. CONCLUSIONS

Two placebo-controlled, double-blind, unpublished, phase 3 RCTs met the selection criteria for inclusion in the systematic review (PIONEER I and PIONEER II). Data from these trials support the conclusion that, in patients with active moderate to severe HS (i.e., Hurley stage II or III), adalimumab treatment is associated with statistically significant improvements in HRQoL, measured using the DLQI, SF-36 (PCS) and EQ-5D, compared with placebo after 12 weeks. Adalimumab was also associated with statistically significant reductions, compared with placebo, in HiSCR (defined as a reduction of at least a 50% in AN count, with no increase in abscess or draining fistula count relative to baseline), as well as reductions in various lesion counts, skin pain, and improvement in the MSS. In general, the magnitude of improvement in these outcomes was sufficiently large to be clinically meaningful, although, with the exception of the HiSCR and MSS, none of the outcome measures have been validated in patients with HS. A larger treatment effect was observed in PIONEER II than in PIONEER I, likely reflecting greater concomitant use of antibiotics in PIONEER II. Overall, the safety and tolerability profile of adalimumab in HS does not appear to differ from that previously observed with adalimumab in other indications, with the exception of the reporting of HS as an AE in this patient population. The most frequent AEs associated with adalimumab were HS, headache, and nasopharyngitis.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input
Two patient groups, the Canadian Skin Patient Alliance (CSPA) and Hidradenitis Suppurativa (HS) Aware, submitted input for this submission.

The CSPA is a Canadian non-profit organization that focuses on education and advocacy for patients with dermatologic conditions, diseases, and traumas. They produce a magazine entitled *Canadian Skin* and provide a steady social media community. The CSPA relies on and receives sponsorship and funding from the pharmaceutical industry, particularly AbbVie, Celgene, Eli Lilly, Galderma, GlaxoSmithKline (Stiefel), Janssen, LEO Pharma, Merck, Pfizer, Roche, Novartis, and Valeant.

HS Aware is the sole Canadian patient community that aims to empower patients living with HS through peer support and information. HS Aware does this through sharing stories, experiences, and meaningful and relevant conversations through social media and its website (www.hsaware.com). The managing editor has received honorariums for speaking engagements and educational programs from AbbVie, Sanofi, and Actavis. He also is the Co-Chair of The Beryl Institute's Global Patient and Family Advisory Council and the Executive Director of Patient Commando Productions (which develops educational programming for continuing medical education); both either represent or provide training for a broad spectrum of pharmaceutical companies.

The CSPA declared the following potential conflicts of interest:
- AbbVie provided the CSPA with access to its patient testimonial videos, and
- AbbVie allowed the CSPA to attend and observe an AbbVie-sponsored HS patient meeting, information from helped to inform CSPA's patient input submission.

No conflicts of interest were declared by HS Aware for this submission.

2. Condition-Related Information
Information provided to inform this summary was obtained through a bilingual questionnaire submitted through social media (73 responses were obtained), patient testimonial videos, an HS patient meeting, conversation threads within various social media platforms, website story-submission platforms, and personal interviews.

HS is a chronic and recurring dermatologic condition in which patients experience painful, debilitating, and unsightly boils in the armpits and groin, between the buttocks, or under the breasts. The majority of patients with HS are female, ranging in age from 20 to 45; however, HS has been observed in patients as young as eight and as old as 60.

Pain is one of the primary concerns associated with HS, with most patients finding pain the hardest part of the disease not only to control but also to deal with on a daily basis. Because of the pain associated with the boils, lancing and/or draining of the boils, or abscessing of boils, patients' mobility is often restricted, and can further impede everyday activities that most people take for granted. These include activities such as cleaning, bathing, driving, walking, sitting, working, performing household chores, and taking care of children. Many patients experience problems with sleeping. In addition, patients

commonly experience fatigue due to the constant pain, continual dressing of wounds, and the emotional impact of the disease itself. Psychological impacts of the disease are often brought on by both the pain of the condition and the unsightliness of the boils. Many patients become depressed due to a multitude of factors, including the embarrassment and stigma of leaking or draining, bleeding, and malodorous boils; isolation associated with trying to hide the lesions; loss or fear of intimacy with a partner; restricted mobility affecting their everyday lives; constant pain; fear of flare-ups; ensuing low self-esteem; lack of physician understanding or knowledge regarding HS (including a timely and appropriate diagnosis); and financial burden. As one patient noted, "*HS not only eats away at our bodies, it can take away our self-esteem as well. Having it can also make having intimate relationships almost impossible.*" Major depression and the associated pain in these patients also can lead to thoughts of suicide: *"Pain can be unbearable, make you want to give up."* Many patients also note the intense time constraints, social constraints, and financial hardship associated with both wound care (often having to change wound dressings up to three times per day) and systemic treatments, with one patient stating, *"In Canada we have free access to [doctors] but not meds/treatments. I can go see my dermatologist and she can tell me about the new meds/treatments available, and in the next breath tell me if I don't have $4,000/month, I'm outta luck."* The economic burden and isolation is also further compounded by many patients' inability to maintain constant employment. If the patient is a parent, her or his children are often inadvertently negatively affected, as patients tend to avoid physical and social activities, which can ultimately lead to their children becoming isolated. The lack of intimacy also negatively effects or strains personal relationships, with some patients stating, *"It was a main factor in the demise of my relationship,"* or, *"Sex hasn't happened in over two years because of pain and the look of HS."*

Caregivers of patients with HS are often directly affected on a daily basis, by having to help patients dress their wounds, drive patients to their appointments, and assist with daily chores, including bathing some adult children who have had to return home. Caregivers can experience a financial burden, as they may suffer loss of income due to having to take the patient to the doctor or may need to pay for non-reimbursed treatments or wound-care supplies. In addition, caregivers can also feel an emotional burden because they are unable to help their loved ones, are frustrated when the patient does not follow her or his doctor's advice, or have to take on additional responsibilities. The extent of one caregiver's care for her daughter was exemplified in the following quote, *"I'm thankful for my mom. She is always there for me. Has become my nurse and it's not a profession she wanted, through all my HS surgeries has been there to bandage me up, clean my wounds, and hold my hand. She often helps me cut and drain and pack my HS and bandages me. I don't know what I would do without her."*

3. Current Therapy-Related Information

Treatment options for patients with HS include antiseptics, antibiotics, analgesics, steroids, retinoids, Accutane, hormone blockers, holistic treatments, laser hair removal, photodynamic therapies, weight loss, bleach or Epsom salt baths, exercise, lancing, and surgical removals (often including subsequent skin grafts). Patients have claimed minimal success with weight loss, healthy diets, laser hair removal, and exercise, and generally tend to find systemic treatments or surgery more useful. Antiseptics, antibiotics, and retinoids can work for a period of time but eventually stop being effective. While steroid injections (cortisone) generally work, they are not a long-term solution. Wound care associated with both lancing and surgery is both expensive and time-consuming and is also associated with other adverse events: *"Every tape or bandage hurts me — the only kind that doesn't is too expensive."*

Surgical removal of the boils, with or without subsequent skin graft, appears to be somewhat effective, but only for a period of time, as the boils eventually come back, often in a different spot. It is important

to note that surgery is not a cure for the disease. Some patients have noted that the only time they temporarily have no boils is after surgery; however, most people have substantial scarring, even with skin grafts. There is also a burden on the patient during post-surgery recovery time, as she or he is unable to work while recovering, and an increased burden on caregivers during a very long recovery time. *"Worse are those having skin grafts and multiple surgeries that require weeks of post-surgery care and recovery."* In addition, a proportion of the population is afraid of surgery because of the chance of disfigurement.

4. Expectations About the Drug Being Reviewed

As patients have few options and adalimumab is the only currently-approved treatment for HS in Canada, there is an expectation that adalimumab could have a positive impact on reducing daily wound care, laundry, odour, pain and itching, leaking sores, and scarring associated with surgery. In addition, the potential clinical effectiveness of adalimumab may help patients avoid extensive and potentially disfiguring expensive surgical procedures. Patients believe that there is the potential to lead more normal lives, be free from depression and isolation caused by the disease, and obtain some level of pain relief on adalimumab. There is also the hope that patients would have longer periods of time without pain, fewer medical appointments, and fewer visits to the emergency department. Patients did voice their fears and concerns regarding the side effects and costs associated with adalimumab. In addition, there is some skepticism regarding its effectiveness; however, many patients who have reached a plateau regarding current treatment state that they are willing to try anything for some relief.

For those patients with adalimumab experience, a large number stated that they had better control of their HS, specifically, leaking wounds, red lumps, stinging, pain, cost associated with laundry, and flare-ups. In addition, patients for whom adalimumab has worked have regained their ability to sit, and have reported fewer flare-ups, less painful lesions that go away faster, fewer open tracks, and lesions that do not even drain before going away. Quality of life in these patients has also increased substantially. Some of the side effects in patients on adalimumab include infections, headaches, joint pain, and fatigue post-treatment; however, these patients confirmed that their side effects would not influence their decision to continue treatment.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 1, 2015
Alerts:	Biweekly (twice monthly) updates until April 20, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
Exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kw	Keyword heading word
.rn	CAS registry number
.nm	Name of substance word
.pt	Publication type
.po	Population group [PsycInfo only]
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(331731-18-1 or FYS6T7F842).rn,nm.
2	(humira* or adalimumab* or D2E7 or trudexa* or hsdb 7851 or hsdb7851 or lu200134).ti,ab,ot,kw,hw,rn,nm.
3	or/1-2
4	exp hidradenitis/
5	(Hidradenit* or hydradenit* or hidroadenit* or hydroadenit* or hidrosadenit* or hydrosadenit* or acne inversa*).ti,ab,kw.
6	or/4-5
7	3 and 6
8	7 use pmez
9	*adalimumab/
10	(humira* or adalimumab* or D2E7 or trudexa* or hsdb 7851 or hsdb7851 or lu200134).ti,ab.
11	or/9-10
12	exp hidradenitis/
13	(Hidradenit* or hydradenit* or hidroadenit* or hydroadenit* or hidrosadenit* or hydrosadenit* or acne inversa*).ti,ab,kw.
14	or/12-13
15	11 and 14
16	15 use oemezd
17	conference abstract.pt.
18	16 not 17
19	8 or 18
20	exp animals/
21	exp animal experimentation/ or exp animal experiment/
22	exp models animal/
23	nonhuman/
24	exp vertebrate/ or exp vertebrates/
25	animal.po.
26	or/20-25
27	exp humans/
28	exp human experimentation/ or exp human experiment/
29	human.po.
30	or/27-29
31	26 not 30
32	19 not 31
33	remove duplicates from 32

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2015
Keywords:	Humira (adalimumab), hidradenitis suppurativa
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), were searched:

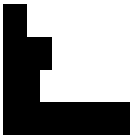
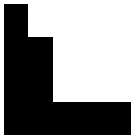
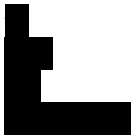
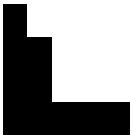
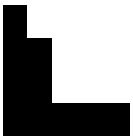
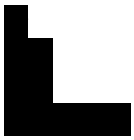
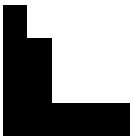
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kimball et al., 2012	Inappropriate study design
Miller et al., 2011	Unapproved dose
Sotiriou et al., 2012	Unapproved dose

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 14: MEAN CHANGE FROM BASELINE IN DERMATOLOGY LIFE QUALITY INDEX AT WEEK 12 IN PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients n BL mean Week 12 mean Within-group change, LSM (SE)	 150 16.3 10.8 –5.4 (0.50)	 151 16.0 13.1 –2.9 (0.50)	 162 14.1 9.3 –5.1 (0.53)	 159 14.8 12.5 –2.3 (0.53)
Between-group change LSM diff (95% CI) *P* value[a]	 –2.5 (–3.8 to –1.1) < 0.001		 –2.8 (–4.1 to –1.5) < 0.001	
Hurley stage II n BL mean Week 12 mean Within-group change, LSM (SE)				
Between-group change LSM diff (95% CI) *P* value[a]				
Hurley stage III n BL mean Week 12 mean Within-group change, LSM (SE)				
Between-group change LSM diff (95% CI) *P* value[a]				

BL = baseline; CI = confidence interval; diff = difference; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.

[a] Across all the strata, *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model. Within each stratum, *P* values were calculated from ANCOVA with BL value and treatment in the model.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 15: MEAN CHANGE FROM BASELINE IN HIDRADENITIS SUPPURATIVA QUALITY OF LIFE AT WEEK 12 IN PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients				
n	152	151	162	160
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change				
LSM diff				
(95% CI)				
P value[a]				
Hurley stage II				
n				
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change				
LSM diff				
(95% CI)				
P value[a]				
Hurley stage III				
n				
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change				
LSM diff				
(95% CI)				
P value[a]				

BL = baseline; CI = confidence interval; diff = difference; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.

[a] Across all the strata, *P* values were calculated from ANCOVA with stratum, BL value, and treatment in the model. Within each stratum, *P* values were calculated from ANCOVA with BL value and treatment in the model.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 16: MEAN CHANGE FROM BASELINE IN THE SHORT FORM (36) HEALTH SURVEY AT WEEK 12 IN PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Item	PIONEER I	
	Adalimumab N = 153	Placebo N = 154
PCS		
n	142	142
BL mean	40.0	39.6
Week 12 mean	44.2	41.2
Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	
MCS		
n	142	142
BL mean	42.3	40.9
Week 12 mean	44.3	42.5
Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	
Physical functioning		
n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	
Role–Physical		
n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	
Bodily pain		
n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change		

Item	PIONEER I	
	Adalimumab N = 153	Placebo N = 154
LSM diff (95% CI) *P* value[a]		
General health n BL mean Week 12 mean Within-group change, LSM (SE)		
Between-group change LSM diff (95% CI) *P* value[a]		
Vitality n BL mean Week 12 mean Within-group change, LSM (SE)		
Between-group change LSM Diff (95% CI) *P* value[a]		
Social functioning n BL mean Week 12 mean Within-group change, LSM (SE)		
Between-group change LSM diff (95% CI) *P* value[a]		
Role–Emotional functioning n BL mean Week 12 mean Within-group change, LSM (SE)		
Between-group change LSM diff (95% CI) *P* value[a]		
Mental health n BL mean Week 12 mean Within-group change, LSM (SE)		

Item	PIONEER I	
	Adalimumab N = 153	Placebo N = 154
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	

BL = baseline; CI = confidence interval; Diff = difference; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; MCS = mental component summary; PCS = physical component summary; SE = standard error.
[a] *P* values were calculated from ANCOVA with stratum, BL value and treatment in the model.
Note: The SF-36 was only measured in PIONEER I
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 17: CHANGE FROM BASELINE IN EQ-5D HEALTH STATE INDEX AT WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Strata	PIONEER II	
	Adalimumab N = 163	Placebo N = 163
All patients n Baseline mean Week 12 mean LSM change within-group (SE)	 156 0.6 [redacted]	 147 0.5 [redacted]
LSM difference, % (95% CI) *P* value[a]	[redacted]	
Hurley stage II n Baseline mean Week 12 mean LSM change within-group (SE)	[redacted]	[redacted]
LSM Difference, % (95% CI) *P* value[a]	[redacted]	
Hurley stage III n Baseline mean Week 12 mean LSM change within-group (SE)	[redacted]	[redacted]
LSM difference, % (95% CI) *P* value[a]	[redacted]	

BL = baseline; CI = confidence interval; EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.
Note: The EQ-5D was measured only in PIONEER II.
[a] *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 18: CHANGE FROM BASELINE IN EQ-5D VAS AT WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Strata	PIONEER II	
	Adalimumab N = 163	Placebo N = 163
All patients		
n	145	139
Baseline mean	58.6	58.4
Week 12 mean	[redacted]	[redacted]
LSM change within group (SE)		
LSM difference, %	[redacted]	
(95% CI)		
P value[a]		
Hurley stage II		
n	[redacted]	[redacted]
Baseline mean		
Week 12 mean		
LSM change within group (SE)		
LSM difference, %	[redacted]	
(95% CI)		
P value[a]		
Hurley stage III		
n	[redacted]	[redacted]
Baseline mean		
Week 12 mean		
LSM change within group (SE)		
LSM difference, %	[redacted]	
(95% CI)		
P value[a]		

BL = baseline; CI = confidence interval; EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.
Note: The EQ-5D was measured only in PIONEER II.
[a] *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 19: PROPORTION OF PATIENTS WHO ACHIEVED NRS30 IN PATIENT'S GLOBAL ASSESSMENT OF SKIN PAIN AMONG PATIENTS WITH BASELINE NRS AT WORST ≥ 3 BY WEEK 12 IN PERIOD A (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 122	Placebo N = 109	Adalimumab N = 105	Placebo N = 111
Week 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Week 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Week 8, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Week 12, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	

CI = confidence interval; ITT_A = intention-to-treat population in Period A; NRS = numerical rating scale.
Notes: NRS30 was defined as the proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from BL in the Patient's Global Assessment of Skin Pain (Non-responder imputation).
[a] 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups.
[b] *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 20: PROPORTION OF PATIENTS WHO ACHIEVED NRS30 IN PATIENT'S GLOBAL ASSESSMENT OF SKIN PAIN AMONG SUBJECTS WITH BASELINE NRS AT WORST ≥ 3 AT WEEK 12 OF PERIOD A (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients, n (%) n Yes No Missing	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Hurley stage II, n/N (%) n Yes No Missing	[redacted]	[redacted]	[redacted]	[redacted]

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Adjusted difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Hurley stage III, n/N (%) n Yes No Missing	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	

CI = confidence interval; ITT_A = intention-to-treat population in Period A; NRS = numerical rating scale.
Notes: NRS30 was defined as the proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from BL in the Patient's Global Assessment of Skin Pain (Non-responder imputation).
[a] Across all strata, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups. Within each stratum, 95% CI for the difference was calculated based on normal approximation to the binomial distribution.
[b] Across all the strata, *P* values were calculated from the Cochran–Mantel–Haenszel test adjusted for strata. Within each stratum, *P* values were calculated based on chi-square test (or Fisher's Exact Test if ≥ 20% of the cells have expected cell count < 5).
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 21: CHANGE WROM BASELINE IN NRS ON AVERAGE AMONG PATIENTS WITH BASELINE NRS AT WORST ≥ 3 AT WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, % LSM diff (95% CI) *P* value[a]	[redacted]		[redacted]	
Hurley stage II n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, % LSM diff (95% CI) *P* value[a]	[redacted]		[redacted]	

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Hurley stage III n BL mean Week 12 mean Within-group change, LSM (SE)				
Between-group change, % LSM diff (95% CI) *P* value[a]				

BL = baseline; CI = confidence interval; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; NRS = numerical rating scale; SE = standard error.
[a] Across all the strata, *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value and treatment in the model. Within each stratum, *P* values were calculated from ANCOVA with BL value and treatment in the model.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 22: PROPORTION OF PATIENTS ACHIEVING HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE AT WEEK 12 OF PERIOD A (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients, n (%)	64 (41.8)	40 (26.0)	96 (58.9)	45 (27.6)
Difference, % (95% CI)[a] *P* value[b]	15.9 (5.3 to 26.5) 0.003		31.5 (20.7 to 42.2) < 0.0001	
Hurley stage II, n/N (%)	37/83 (44.6)	25/84 (29.8)	53/85 (62.4)	32/87 (36.8)
Difference, % (95% CI)[a] *P* value[b]	14.8 (0.3 to 29.3) 0.048		25.5 (10.5 to 40.5) < 0.001	
Hurley stage III, n/N (%)	27/70 (38.6)	15/70 (21.4)	43/78 (55.1)	13/76 (17.1)
Difference, % (95% CI)[a] *P* value[b]	17.1 (22.0 to 32.1) 0.027		38.1 (22.8 to 53.3) < 0.001	

AN = abscess and inflammatory nodule; CI = confidence interval; ITT_A = intention-to-treat population in Period A.
Notes: Hidradenitis Suppurativa Clinical Response defined as at least a 50% reduction in AN count with no increase in abscess count or draining fistula count relative to BL (Non-responder imputation).
[a] In PIONEER I, across all strata, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups; within each stratum of baseline Hurley stage, 95% CI for difference was calculated based on normal approximation to the binomial distribution. In PIONEER II, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic adjusted for baseline Hurley stage (II/III) and baseline antibiotic use (Y/N); for each stratum of baseline Hurley stage, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic adjusted for baseline antibiotics use (Y/N).
[c] In PIONEER I, across all strata, *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata; within each stratum of baseline Hurley stage, *P* value was calculated based on chi-square test (or Fisher's exact test if ≥ 20% of the cells have expected cell count < 5). In PIONEER II, *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for baseline Hurley stage (II/III) and baseline antibiotic use (Y/N); for each stratum of baseline Hurley stage, *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for baseline antibiotics use (Y/N).
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 23: PROPORTION OF PATIENTS ACHIEVING HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE BY VISIT IN PERIOD A OF PERIOD A (ITT_A POPULATION)

Visit	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Week 2	36 (23.5)	22 (14.3)	73 (44.8)	19 (11.7)
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Week 4	45 (29.4)	29 (18.8)	84 (51.5)	36 (22.1)
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Week 8	63 (41.2)	31 (20.1)	89 (54.6)	41 (25.2)
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Week 12	64 (41.8)	40 (26.0)	96 (58.9)	45 (27.6)
Difference, % (95% CI)[a] *P* value[b]	15.9 (5.3 to 26.5) 0.003		31.5 (20.7 to 42.2) < 0.001	

CI = confidence interval; ITT_A = intention-to-treat population in Period A.
Notes: Hidradenitis Suppurativa Clinical Response defined as at least a 50% reduction in AN count with no increase in abscess count or draining fistula count relative to BL (Non-responder imputation).
[a] In PIONEER I, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups. In PIONEER II, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic adjusted for baseline Hurley stage (II/III) and baseline antibiotic use (Y/N); for each stratum of baseline Hurley stage, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic adjusted for baseline antibiotics use (Y/N).
[b] In PIONEER I, across all strata, *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata. In PIONEER II, *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for baseline Hurley stage (II/III) and baseline antibiotic use (Y/N); for each stratum of baseline Hurley stage, *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for baseline antibiotics use (Y/N).
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 24: PROPORTION OF PATIENTS WHO ACHIEVED AN ABSCESS AND INFLAMMATORY NODULE COUNT OF 0, 1, OR 2 AT WEEK 12 OF PERIOD A (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients, n (%) Yes No Missing	[redacted]		[redacted]	
Adjusted difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Hurley stage II, n/N (%) Yes	[redacted]		[redacted]	

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
No Missing	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Hurley stage III, n/N (%) Yes No Missing	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	

CI = confidence interval; ITT_A = intention-to-treat population in Period A.
Note: Non-responder imputation.
[a] Across all strata, 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups. Within each stratum, 95% CI for the difference was calculated based on normal approximation to the binomial distribution.
[b] Across all the strata, *P* values were calculated from the Cochran–Mantel–Haenszel test adjusted for strata. Within each stratum, *P* values were calculated based on chi-square test (or Fisher's Exact Test if ≥ 20% of the cells have expected cell count < 5).
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 25: PROPORTION OF PATIENTS WHO ACHIEVED A REDUCTION IN AN50/75/100 AT WEEK 12 OF PERIOD A (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
AN50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
AN75, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
AN100, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	

AN = abscess and inflammatory nodule; CI = confidence interval; ITT_A = intention-to-treat population in Period A.
Notes: AN 50/75/100 defined as at least 50%/75%/100% reduction in abscess and inflammatory nodule count relative to baseline (Non-responder imputation).
[a] 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups adjusted for strata.
[b] *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 26: MEAN CHANGE FROM BASELINE IN LESION COUNTS AT WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
AN				
n	153	151	163	162
BL mean	14.3	14.2	10.7	11.9
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change, LSM (95% CI)				
P value[b]				
Inflammatory nodule count				
n				
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change, LSM (95% CI)				
P value[b]				
Abscess count				
n				
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change, LSM (95% CI)				
P value[b]				
Draining fistula count				
n				
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change, LSM (95% CI)				
P value[b]				
All fistula count[a]				
n				
BL mean				
Week 12 mean				
Within-group change, LSM (SE)				
Between-group change, LSM (95% CI)				
P value[a]				

AN = abscess and inflammatory nodule; BL = baseline; CI = confidence interval; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.

[a] All fistulas includes draining and non-draining fistulas.

[b] *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 27: PROPORTION OF PATIENTS WITH AT LEAST ONE LESION AT BASELINE WHO ACHIEVED COMPLETE ELIMINATION OF LESIONS BY LESION TYPE AT WEEK 12 OF PERIOD A (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
AN, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Abscesses, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Inflammatory Nodules, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Draining Fistulas, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
All Fistulas, n (%)[c]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	

AN = abscess and inflammatory nodule; CI = confidence interval; ITT_A = intention-to-treat population in Period A.
Note: Non-responder imputation.
[a] 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups.
[b] *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.
[c] All fistulas include draining and non-draining fistulas.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 28: MEAN CHANGE FROM BASELINE IN LESION SEVERITY SCORES BY SCORE TYPE AT WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 151	Placebo N = 150	Adalimumab N = 163	Placebo N = 158
Patient's Lesion Severity Score BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	
Average Lesion Severity Score in Erythema BL mean	[redacted]	[redacted]	[redacted]	[redacted]

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 151	Placebo N = 150	Adalimumab N = 163	Placebo N = 158
Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	
Average Lesion Severity Score in Tenderness BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	
Average Lesion Severity Score in Size BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	

BL = baseline; CI = confidence interval; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.
Note: Severity Scores: the size, degree of erythema and tenderness of each representative lesion was assessed and rated by severity scores of 0 to 3 where higher scores denote worse conditions.
[a] *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 29: CHANGE IN MODIFIED SARTORIUS SCORE FROM BASELINE TO WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
All patients n BL mean Week 12 mean LSM change within group (SE)	 153 151.0 [redacted]	 151 146.7 [redacted]	 163 107.5 [redacted]	 162 122.5 [redacted]
LSM difference, % (95% CI) *P* value[a]	[redacted]		[redacted]	
Hurley stage II n BL mean Week 12 mean LSM change within group (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Strata	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
LSM difference, % (95% CI) *P* value[a]	[redacted]		[redacted]	
Hurley stage III n BL mean Week 12 mean LSM change within group (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference, % (95% CI) *P* value[a]	[redacted]		[redacted]	

BL = baseline; CI = confidence interval; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.

[a] Across all strata, *P* values were calculated from analysis of covariance (ANCOVA) with stratum, baseline value, and treatment in the model. Within each stratum, *P* values were calculated from ANCOVA with baseline value and the treatment in the model.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 30: PROPORTION OF PATIENTS WITH FLARES BY LESION TYPE OVERALL (AT LEAST ONE OCCURRENCE) IN PERIOD A (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
AN, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Abscesses, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Inflammatory nodules, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	
Draining fistulas, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)[a] *P* value[b]	[redacted]		[redacted]	

AN = abscess and inflammatory nodule; CI = confidence interval ITT_A = intention-to-treat population in Period A.

Notes: Flare was defined as at least 25% increase and two absolute increases from baseline in lesions. Non-responder imputation.

[a] 95% CI for adjusted difference was calculated according to the extended Mantel–Haenszel statistic for the comparison of two treatment groups.

[b] *P* value was calculated from the Cochran–Mantel–Haenszel test adjusted for strata.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 31: MEAN CHANGE FROM BASELINE IN HOSPITAL ANXIETY AND DEPRESSION SCALE AT WEEK 12 IN PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Item	PIONEER I	
	Adalimumab N = 153	Placebo N = 154
HADS Anxiety Scale		
n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	
HADS Depression Scale		
n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]
Between-group change LSM diff (95% CI) *P* value[a]	[redacted]	

BL = baseline; CI = confidence interval; Diff = difference; HADS = Hospital Anxiety and Depression Scale; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error.
[a] *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model.
Note: The HADS was measured only in PIONEER I.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 32: MEAN CHANGE FROM BASELINE IN WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT: SPECIFIC HEALTH PROBLEM AT WEEK 12 OF PERIOD A (LAST OBSERVATION CARRIED FORWARD) (ITT_A POPULATION)

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
Absenteeism n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	
Presenteeism n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM	[redacted]		[redacted]	

Variable	PIONEER I		PIONEER II	
	Adalimumab N = 153	Placebo N = 154	Adalimumab N = 163	Placebo N = 163
(95% CI) *P* value[a]	[redacted]		[redacted]	
Overall Work Impairment n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	
Activity Impairment n BL mean Week 12 mean Within-group change, LSM (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group change, LSM (95% CI) *P* value[a]	[redacted]		[redacted]	

BL = baseline; CI = confidence interval; ITT_A = intention-to-treat population in Period A; LSM = least-squares mean; SE = standard error; WPAI:SHP = Work Productivity and Activity Impairment: Specific Health Problem.
[a] *P* values were calculated from analysis of covariance (ANCOVA) with stratum, BL value, and treatment in the model.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 33: PROPORTION OF PATIENTS ACHIEVING HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE BY VISIT IN PERIOD B (ITT_B_R POPULATION)

Visit, n (%)	PIONEER I			PIONEER II		
	EW/PL N = 22	EW/EOW N = 20	EW/EW N = 21	EW/PL N = 31	EW/EOW N = 32	EW/EW N = 31
Entry to Period B	[redacted]					
Week 14	[redacted]					
Week 16	[redacted]					
Week 20	[redacted]					
Week 24	[redacted]					
Week 28	[redacted]					
Week 32	[redacted]					
Week 36	[redacted]					

AN = abscess and inflammatory nodule; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_R = patients who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders; PL = placebo.
Notes: HiSCR defined as a reduction of at least 50% in AN count with no increase in abscess count or draining fistula count relative to BL. One patient in the EW/PL group who was a HiSCR non-responder at entry to Period B was randomized in the HiSCR responder stratum (Non-responder imputation).
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 34: MEAN CHANGE FROM RE-RANDOMIZATION IN LESION COUNTS AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_R POPULATION)

Lesion Type/ Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)
AN EW/PL EW/EOW EW/EW	[redacted]									
Abscesses EW/PL EW/EOW EW/EW	[redacted]									
Draining fistulas EW/PL EW/EOW EW/EW	[redacted]									
All fistulas[a] EW/PL EW/EOW EW/EW	[redacted]									
Inflammatory nodules EW/PL EW/EOW EW/EW	[redacted]									

AN = abscess and inflammatory nodule; BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_R = patients who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders; LSM = least-squares mean; PL = placebo; Re-Rand = re-randomization; SE = standard error.
Note: All fistulas include draining and non-draining fistulas.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 35: MEAN CHANGE FROM BASELINE IN MODIFIED SARTORIUS SCORE AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_R POPULATION)

Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)
EW/PL EW/EOW EW/EW	[redacted]									

BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_R = patients who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders; LSM = least-squares mean; PL = placebo; Re-Rand = re-randomization; SE = standard error.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 36: PROPORTION OF SUBJECTS ACHIEVING NRS30 AT WORST AMONG SUBJECTS WITH BASELINE NRS AT WORST 3 OR MORE IN PERIOD B (ITT_B_R POPULATION)

Visit, n (%)	PIONEER I			PIONEER II		
	EW/PL N = 15	EW/EOW N = 18	EW/EW N = 16	EW/PL N = 20	EW/EOW N = 17	EW/EW N = 19
Entry to Period B	[redacted]					
Week 36						

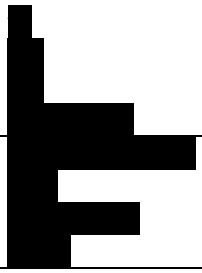
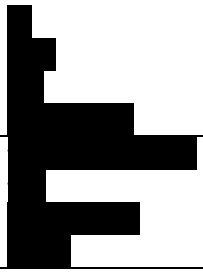
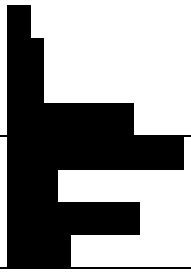
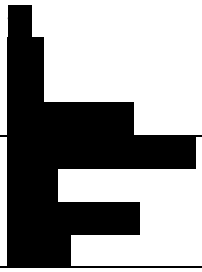
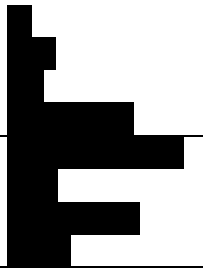
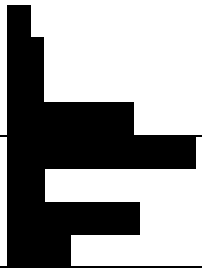
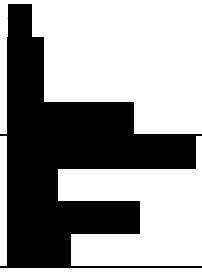
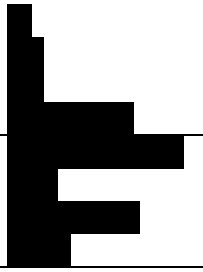
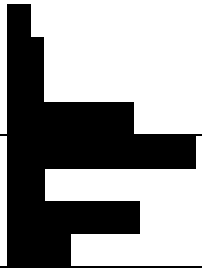
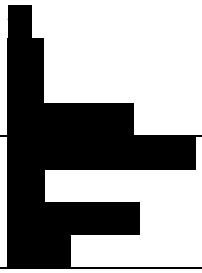
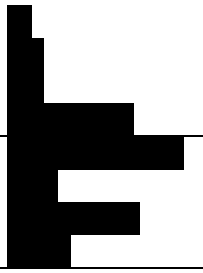
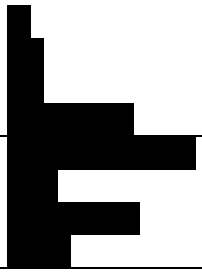
EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_R = patients who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders; NRS = numerical rating scale; PL = placebo.
Note: NRS30 was defined as the proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from BL in the Patient's Global Assessment of Skin Pain.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 37: MEAN CHANGE FROM RE-RANDOMIZATION IN DERMATOLOGY LIFE QUALITY INDEX AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_R POPULATION)

Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)
EW/PL EW/EOW EW/EW	[redacted]									

BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_R = patients who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders; LSM = least-squares mean; PL = placebo; Re-Rand = re-randomization; SE = standard error.
Note: BL mean for the EW/EW group in PIONEER II is based on 28 patients because there is 1 patient who did not have a BL value.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 38: CHANGE FROM BASELINE IN HOSPITAL ANXIETY AND DEPRESSION SCALE IN PERIOD B IN PIONEER I (ITT_B_R POPULATION)

Visit, n (%)	PIONEER I		
	EW/PL N = 22	EW/EOW N = 20	EW/EW N = 21
HADS Anxiety Scale			
Entry to Period B n BL mean Entry to Period B mean Within-group change, LSM (SE)			
Between-group comparisons LSM diff (95% CI) *P* value			
Week 36 n BL mean Week 36 mean Within-group change, LSM (SE)			
Between-group comparisons LSM diff (95% CI) *P* value			
HADS Depression Scale			
Entry to Period B n BL mean Entry to Period B mean Within-group change, LSM (SE)			
Between-group comparisons LSM Diff (95% CI) *P* value			
Week 36 n BL mean Week 36 mean Within-group change, LSM (SE)			
Between-group comparisons LSM Diff (95% CI) *P* value			

BL = baseline; Diff = difference; EOW = every other week; EW = every week; HADS = Hospital Anxiety and Depression Scale; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_R = patients who were randomized to adalimumab in Period A and were week 12 HiSCR responders were re-randomized as HiSCR responders; LSM = least-squares mean; PL = placebo; SE = standard error.

Note: HADS contains both an anxiety scale and a depression scale; a lower score indicates lower severity.

Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 39: PROPORTION OF PATIENTS ACHIEVING HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE BY VISIT IN PERIOD B (ITT_B_NR POPULATION)

Visit, n (%)	PIONEER I			PIONEER II		
	EW/PL N = 27	EW/EOW N = 28	EW/EW N = 27	EW/PL N = 20	EW/EOW N = 21	EW/EW N = 20
Entry to Period B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AN = abscess and inflammatory nodule; BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_NR = patients who were randomized to adalimumab in Period A and were week 12 non-responders were re-randomized as HiSCR non-responders; PL = placebo.
Notes: HiSCR defined as at least a 50% reduction in AN count with no increase in abscess count or draining fistula count relative to BL. Two patients who were HiSCR responders at entry to Period B were randomized in the HiSCR non-responder stratum. Non-responder imputation.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 40: MEAN CHANGE FROM RE-RANDOMIZATION IN LESION COUNTS AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_NR POPULATION)

Lesion Type/ Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)
AN										
EW/PL	[redacted]									
EW/EOW										
EW/EW										
Abscesses										
EW/PL	[redacted]									
EW/EOW										
EW/EW										
Draining fistulas										
EW/PL	[redacted]									
EW/EOW										
EW/EW										

Lesion Type/ Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)
All fistulas[a] EW/PL EW/EOW EW/EW	[redacted]									
Inflammatory nodules EW/PL EW/EOW EW/EW	[redacted]									

AN = abscess and inflammatory nodule; BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_NR = patients who were randomized to adalimumab in Period A and were week 12 non-responders were re-randomized as HiSCR non-responders; LSM = least-squares mean; PL = placebo; Re-Rand = re-randomization; SE = standard error.
[a] All fistulas include draining and non-draining fistulas.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 41: MEAN CHANGE FROM RE-RANDOMIZATION OR BASELINE IN MODIFIED SARTORIUS SCORE AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_NR POPULATION)

Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Week 36 Mean	Change LSM (SE)
EW/PL EW/EOW EW/EW	[redacted]									

BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_NR = patients who were randomized to adalimumab in Period A and were week 12 non-responders were re-randomized as HiSCR non-responders; LSM = least-squares mean; NR = not reported; PL = placebo; Re-Rand = re-randomization; SE = standard error.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 42: MEAN CHANGE FROM RE-RANDOMIZATION IN DERMATOLOGY LIFE QUALITY INDEX AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_NR POPULATION)

Treatment Group	PIONEER I					PIONEER II				
	N	BL Mean	Re-Rand Mean	Visit Mean	Change LSM (SE)	N	BL Mean	Re-Rand Mean	Visit Mean	Change LSM (SE)
Week 36										
EW/PL	[redacted]									
EW/EOW										
EW/EW										

BL = baseline; EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_NR = patients who were randomized to adalimumab in Period A and were week 12 non-responders were re-randomized as HiSCR non-responders; LSM = least-squares mean; NR = not reported; PL = placebo; Re-Rand = re-randomization; SE = standard error.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 43: PROPORTION OF PATIENTS ACHIEVING HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE BY VISIT IN PERIOD B (ITT_B_EW POPULATION)

Visit, n (%)	PIONEER I	PIONEER II
	PL/EW N = 145	PL/PL N = 151
Entry to Period B	[redacted]	[redacted]
Week 14		
Week 16		
Week 20		
Week 24		
Week 28		
Week 32		
Week 36		

AN = abscess and inflammatory nodule; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_EW and ITT_B_PBO = patients who were randomized to placebo in Period A; PL = placebo.
Notes: HiSCR defined as a reduction of at least 50% in AN count with no increase in abscess count or draining fistula count relative to BL. Two patients who were HiSCR responders at entry to Period B were randomized in the HiSCR non-responder stratum. Non-responder imputation. In PIONEER II, this population was also denoted as ITT_B_PBO Population.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 44: MEAN CHANGE FROM RE-RANDOMIZATION IN LESION COUNTS AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_EW POPULATION)

Lesion Type/ Treatment Group	PIONEER I				PIONEER II			
	N	Re-Rand Mean	Visit Mean	Change Mean (SD)	N	Re-Rand Mean	Visit Mean	Change Mean (SD)
AN	[redacted]							
Abscesses	[redacted]							
Draining fistulas	[redacted]							
Inflammatory nodules	[redacted]							

AN = abscess and inflammatory nodule; BL = baseline; Re-Rand = re-randomization; SD = standard deviation.
Note: In PIONEER II, this population was also denoted as ITT_B_PBO Population.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 45: MEAN CHANGE FROM BASELINE IN MODIFIED SARTORIUS SCORE AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_EW POPULATION)

Visit	PIONEER I				PIONEER II			
	N	BL Mean	Visit Mean	Change Mean (SD)	N	BL Mean	Visit Mean	Change Mean (SD)
Entry to Period B	[redacted]							
Week 36	[redacted]							

BL = baseline; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_EW and ITT_B_PBO = patients who were randomized to placebo in Period A; SD = standard deviation.
Note: In PIONEER II, this population was also denoted as ITT_B_PBO Population.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

TABLE 46: MEAN CHANGE FROM RE-RANDOMIZATION IN DERMATOLOGY LIFE QUALITY INDEX AT WEEK 36 (LAST OBSERVATION CARRIED FORWARD) IN PERIOD B (ITT_B_EW POPULATION)

Treatment Group	PIONEER I				PIONEER II			
	N	BL Mean	Visit Mean	Change Mean (SD)	N	BL Mean	Visit Mean	Change Mean (SD)
Week 36	[redacted]							

BL = baseline; HiSCR = Hidradenitis Suppurativa Clinical Response; ITT_B_EW and ITT_B_PBO = patients who were randomized to placebo in Period A; SD = standard deviation.
Note: In PIONEER II, this population was also denoted as ITT_B_PBO Population.
Source: M11-313 Clinical Study Report (CSR),[8] M11-810 CSR.[9]

APPENDIX 5: NATURAL HISTORY OF HIDRADENITIS SUPPURATIVA

Aim

To summarize the natural history, disease characteristics, and patient impact for hidradenitis suppurativa (HS).

Natural History

HS is a dermatologic condition that has, until recently, had a poorly understood natural history. It was first identified in 1854 and was thought to involve the infection of sweat glands.[25] Sometimes referred to as acne inversa,[23] HS has since been identified as an acneiform disorder from which lesions occur as a result of follicular occlusion, rather than originating in the sweat glands.[25] In one study by von der Werth and Williams,[25] who were seeking natural disease information from patients in secondary care (and therefore not necessarily generalizable to the patients in primary care), patients were observed to develop new abscesses at a rate of approximately two per month, with each abscess taking an average of one week to settle. One hundred and 10 patients provided responses in this study, with a high number of these responders (number not provided) being female[25] and having a positive family history of HS (i.e., suggested as an autosomal dominant inheritance pattern).[23,25] The disease predominance in women was further noted by Dufour et al.,[23] who determined the female-to-male ratio to be 3.3 to 1.[23] The onset of HS generally occurs post-puberty, when patients are in their early twenties.[23] In addition, von der Werth and Williams[25] observed a lower proportion of patients who were older than 50 years of age in their study, suggesting the possibility that active disease appears to subside after menopause.

Risk factors associated with HS include tobacco smoking, obesity or an increased body mass index (BMI), and, as previously stated, family history and sex.[23] Disease flare-ups are common and often appear to be the result of stress, tight clothing, friction, sweating, or heat. The flare-ups due to heat and sweating may partially explain why one-third of the patients in the von der Werth and Williams study[25] observed a deterioration of their condition during the warmer summer months.

Possible comorbid conditions associated with HS have been suggested, and these include auto-inflammatory diseases (in particular inflammatory bowel disease and spondyloarthropathies), malignant tumours (including epithelial, non-melanoma skin cancers, buccal cancer, liver cancer, and squamous cell carcinoma), and pyoderma gangrenosum.[23] While these have all been reported to be associated with HS, and some studies have gone even further into looking at risks in terms of standardized incidence ratios, most of these comorbidities were identified in studies with small sample sizes. Therefore, further studies are required for definitive conclusions regarding comorbidities associated with HS.[23]

Disease Characteristics

HS is a chronic, inflammatory, and recurring condition that has a prevalence similar to psoriasis at between 1% and 4% of the industrial nation populations.[23] Patients present primarily with inflammation of the hair follicles, which starts as painful and sore nodules or lesions (the hallmark presentation) that can progress to abscesses, sinus tracts, fistulas, and substantial scarring.[23] These lesions appear in the apocrine, gland-bearing areas of the body, which include the genital areas, perianal region, buttocks, groin, armpits, and inframammary regions.[23] The most common areas for lesions are in the armpit and inguinofemoral regions in both sexes.[23] Lesions in the groin, thighs, and breasts are more likely to occur in women, while in men they are more likely to occur in the buttocks, perianal and perineal areas, as

well as atypical regions such as the ears and chest.[23] Hurley staging (Table 47) is a system to describe the severity of HS with regard to the degree of lesion progression, abscesses, scarring, and sinus tracts.[23] Most patients present with mild (Hurley stage I) or moderate (Hurley stage II) disease, while other recent studies have ascertained that only between 4% and 22% of cases are classified as severe (Hurley stage III).[23]

While HS may be considered a relatively common dermatologic condition, there are suggestions that it is under-recognized, as the primary care physician is usually the first resource for the patient and may not have dermatologic expertise.[23] Reliable diagnoses can be made by an experienced dermatologist who identifies the distinct clinical presentation and asks the proper questions.[23]

TABLE 47: HURLEY STAGING FOR HIDRADENITIS SUPPURATIVA

Stage[a]	Definition[b]
I	*"Abscess formation, single or multiple without sinus tracts and cicatrisation."*
II	*"Recurrent abscesses with sinus tracts and cicatrisation; single or multiple widely spread lesions."*
III	*"Diffuse or almost diffuse involvement, or multiple interconnected tracts and abscess across entire area."*

[a] Degree of involvement.
[b] Verbatim from Dufour et al.;[23] however, originally obtained from Hurley 1996.[26]
Source: Adapted from Dufour DN et al. Hidradenitis suppurativa: a common and burdensome, yet under-recognised, inflammatory skin disease. [23] Commons Attribution Non Commercial (CC BY-NC 3.0) license: https://creativecommons.org/licenses/by-nc/3.0/

Patient Impact

Because of the intense pain associated with the lesions, the chronic and recurring nature of the disease, and the social stigma resulting from both the appearance and malodorous discharge, the health-related quality of life (HRQoL) of patients with HS can be substantially adversely affected.[23] Pain associated with HS has been described as intense, burning, throbbing, aching, sharp, hot, cutting, stretching, and taut, with lesion soreness being the most common complaint by both sexes.[23] Disabling social stigma, low self-esteem and self-worth, and embarrassment are often experienced by these patients due to both the malodorous discharge and unsightliness of the lesions, sinus tracts, and cicatrization. In addition, interpersonal relationships often suffer as a result of the aforementioned reasons, particularly as a consequence of the areas affected by HS and the patients' lack of ability to control their disease.[23] Patients with HS often tend to isolate themselves and experience depression.[23] HS can also affect patients' ability to attend work, thus further reducing HRQoL.[23] For all of these reasons, HS appears to disproportionately affect the patient's HRQoL in comparison with other dermatologic conditions that are perceived to have a greater associated burden and increased disability.[23] Additionally, patients' HRQoL can be affected as much as that of patients who experience more serious medical conditions, such as cancer, cardiovascular diseases, and lung diseases.[23]

APPENDIX 6: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures that have been used in patients with hidradenitis suppurativa (HS) to assess both clinical end points and health-related quality of life (HRQoL):

- Dermatology Life Quality Index (DLQI)
- EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D)
- Hidradenitis Suppurativa Clinical Response (HiSCR) end point
- Short Form (36) Health Survey (SF-36)
- Modified Sartorius score (MSS).

Findings

Dermatology Life Quality Index

The DLQI is a dermatologic-disease–specific quality of life measure applied broadly to all dermatologic conditions. It consists of 10 questions concerning the impact of a dermatologic disease on a patient's quality of life over a one-week period. Items include questions concerning the impact of a dermatologic disease on symptoms, emotions, daily activities, work, school, leisure, and personal relationships. The index also includes a question on the impact of the treatment being used on time and potential messiness of the treatment. Patients answer each question with one of four possible scored choices: 0 = not at all, 1 = a little, 2 = a lot, and 3 = very much. A summed score of 30 represents maximum impairment, 21 to 30 represents an extremely large effect, 11 to 20 a very large effect, 6 to 10 a moderate effect, 2 to 5 a small effect, and 0 to 1 no impairment.[12,27] In general, DLQI is a validated tool,[28] with a recent study determining the minimal clinically important difference (MCID) to be 3.3 in a population of patients with variety of dermatologic conditions; however, HS was not evaluated in this study.[7] In patients with psoriasis, the MCID was reported to range from 2.3 to 5.7 points.[4]

In a study of patients with a confirmed diagnosis of HS in the United Kingdom between 1993 and 1997, von der Werth and Jemec[29] reported a mean DLQI score of 8.9, with a standard deviation (SD) of 8.3, which was observed to be higher than those for other dermatologic conditions (e.g., mean DLQI score for alopecia was 8.3 and for acne was 7.5). In addition, the question regarding how itchy, sore, painful, or stinging the skin condition has been constituted the highest proportion of disability reported by these patients. No information was identified regarding the validity and reliability of the DLQI in patients with HS. In addition, no MCID was identified for the DLQI with regard to patients with HS, and the responsiveness to change in clinical status in patients with HS is unclear.

EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire

The EQ-5D measures the patient's general health status using a descriptive system of five dimensions and a vertical visual analogue scale (VAS). The five dimensions of health status are mobility, self-care, usual activities (i.e., work, study, housework, and family/leisure activities), pain/discomfort, and anxiety/depression. For each dimension, the EQ-5D three-level (3L) includes three possible responses: no problems, some problems, and severe problems. The respondent indicates his or her health state by selecting the most appropriate statement in each of the five dimensions, resulting in a one-digit number expressing the level selected for that dimension. The digits for the five dimensions can be combined in a five-digit profile number describing the respondent's health state.[30] For example, respondents' health state scored as 12231 indicates no problems with mobility, some problems with self-care and usual activities, severe problems with pain/discomfort, and no problems with anxiety/depression.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than death, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported clinically important differences (CIDs) for this scale have ranged from 0.033 to 0.074.[31] The CIDs were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction.[32,33]

The VAS component consists of a 20-centimetre vertical VAS on which a patient provides self-rated health state ranging from "the best imaginable health state," labelled 100 on the VAS, to "the worst imaginable health status," labelled 0 on the VAS.[30] Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day.

A systematic review by Yang et al.[34] noted that significant differences according to the severity groups as defined by the Hurley classification system, were suggested by the EQ-5D, EQ-VAS, and DLQI. In addition, the EQ-5D was reported to have moderate correlation with the DLQI (0.28 to 0.39; $P < 0.05$).[34] However, there were no studies identified that reported the reliability, validity, or responsiveness of the EQ-5D-3L in patients with HS,[34] and no MCID for the EQ-5D-3L in patients with HS has been reported.

Hidradenitis Suppurativa Clinical Response End Point

The HiSCR is a clinical end point that was developed to assess improvement associated with HS disease activity, to increase the sensitivity for the detection of HS-specific lesions during a clinical evaluation, and to facilitate the scoring process in patients with HS.[22] The defining criteria for the HiSCR end point include the comparison of three lesion types: abscesses (described as tender or painful, fluctuant, and with or without drainage), inflammatory nodules (classified as pyogenic granuloma lesions, tender, erythematous), and draining fistulas (described as draining purulent fluid, sinus tracts with communications to the skin surface).[21,22] HiSCR achievers are defined as those patients who achieve the following:

- A reduction in the total count of abscesses and inflammatory nodules (AN) of at least 50% with a baseline AN count of 3 or more; this level was defined as a clinically appropriate level that was meaningful to the patient's HRQoL
- No increase in the number of abscesses from baseline
- No increase in the number of draining fistulas from baseline.[21,22]

Before the development of the HiSCR, the clinical efficacy end points for patients with HS included the Hidradenitis Suppurativa–Physician's Global Assessment (HS-PGA), the MSS (discussed later), and the Hurley staging process. Hurley staging was originally designed for the treatment modality selection process, whereby patients were stratified based on the grading of abscess formation, separation of one abscess from another, and interconnectivity of sinus tracts.[21] However, Hurley staging does not take into account the assessment of the inflammation or its extent within each stage (I, II, and III); therefore, the authors determined that it was not a reliable end point for change associated with treatment and should be used only for staging.[21] The HS-PGA is a six-point scale that assesses treatment effect according to an objective total HS lesion count.[21] The patient must achieve at least a two-grade improvement relative to

baseline (achievement termed minimal, mild, or clear); however, reduced sensitivity associated with the identification of changes associated with treatment effects have been noted.[21]

When originally designing and assessing the responsiveness and utility of the HiSCR, Kimball et al.[22] compared (post hoc to the original study[21]) the HiSCR with the HS-PGA in patients with HS enrolled in a phase 2 placebo-controlled trial involving adalimumab. The HiSCR was reported to be more sensitive to change in disease activity and better able to differentiate response due to treatment effect when compared with the HS-PGA.[22] Although the HiSCR does not focus on the size or severity of the lesion or measure how treatment response affects pain levels or HRQoL, it appears to effectively capture inflammatory changes associated with acute HS disease activity when observing responses at each dose and time point when compared with the HS-PGA and the MSS.[22] In addition, treatment differences were observed consistently between baseline and screening (mean 15.3, SD 8.3 days) owing to its strong test–retest reliability, with intra-class coefficients of 0.91 (95% confidence interval [CI], 0.88 to 0.93), 0.83 (95% CI, 0.77 to 0.88), 0.89 (95% CI, 0.86 to 0.92), and 0.95 (95% CI, 0.93 to 0.96) for AN counts, abscesses, inflammatory nodules, and draining fistulas, respectively.[21] Convergent validity of the HiSCR and other physician- and patient-reported outcomes was reported, with the greatest correlations observed with the HS-PGA and MSS (Spearman's rho of –0.61 and –0.51, respectively).[21] In terms of responsiveness after adjusting for potential confounders, 75% of HiSCR achievers at week 16 were also achievers at week 52.[21] With regard to an MCID, this study supports a threshold of a 50% reduction in ANs (in patients with baseline AN counts of ≥ 3) as both clinically appropriate and, according to the authors, meaningful to patients.[21]

Short Form (36) Health Survey

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[35] The SF-36 consists of eight health domains: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health.[16] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and an SD of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population.[16]

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points;[17-19] however, no MCID has been specified with regard to patients with HS. In addition, this outcome has not been validated in this patient population.

Modified Sartorius Score

The MSS (also termed the modified Hidradenitis Suppurativa Score [HSS]) originated from the Sartorius score and was shortened and further developed for ease of use in clinical settings.[12,36] The MSS score is composed of separate scoring components. First, the dermatologist assigns three points per region for the following anatomical regions: axilla, gluteal (left and/or right), groin, or other region. Second, the dermatologist calculates the scores pertaining to the number of lesions for each of the aforementioned regions, with one point for a nodule and six points for a fistula. Third, the dermatologist provides a score based on the longest distance between two relevant lesions in each region. If there is not more than one, then the size of the single lesion is assigned a number. The scoring (of between-lesion length or for

a single lesion) is as follows: 1 point for less than five centimetres; 3 points for between five and 10 centimetres; or 9 points for greater than 10 centimetres. Fourth, the dermatologist assesses whether all lesions are separated by normal skin, assigning a score of 0 for yes and 9 points for a no (which is equivalent to Hurley grade III). In order to obtain a total score, the patient's regional scores are added, and all are summed. There is an open upper limit to the scale.[12,36] In addition, it is suggested that a supplemental subjective score is obtained from the patient, although it is not included in the actual MSS. This is obtained by the patient scoring the amount of soreness or pain associated with the most symptomatic lesion during a consultation and grading it from 0 to 10 on a VAS.[12,36]

Interobserver reliability was assessed by Sartorius et al.[36] in 61 clinical cases in Sweden in 2009 with a confirmed diagnosis of HS (based on both history and clinical presentation during examination). Eight patients were assessed with the MSS by three experienced dermatologists and one dermatology resident during a training session, and a further 23 patients were individually assessed and scored by all four of the aforementioned specialists to test scoring agreement. The remaining 30 patients were then scored individually by a single observer. The 23 patients scored by the four trained specialists were included in the analysis for interobserver variability, while the full 61 patients were used in the correlation analysis among the DLQI, body mass index (BMI), and smoking habits. All of the 61 patients were required to complete the DLQI. In 23 representative patients (15 women and eight men) with a mean disease duration of 11.2 years (SD 5.6 years) and a BMI of 29.3 kg/m^2 (SD 6.2 kg/m^2), the intra-class coefficients for interobserver reliability were 0.95 and 0.95 using non-parametric analysis (as the HSS was found to be non-linear).[36] Statistically non-significant differences were identified in the HSS between women and men and among non-smokers, former smokers, and smokers. Statistically significant differences were identified in terms of the Hurley classifications of I versus II and III ($P < 0.0001$), and the authors noted that interobserver variability increased in the most severe Hurley stage II and III cases in which large skin areas were affected.[36] A moderate correlation ($r = 0.40$) was reported between the HSS and BMI; however, non-significant differences were reported between the HSS and specific BMI groups (e.g., normal weight, overweight, and obese). A moderate correlation was also reported for the HSS with the DLQI ($r = 0.48$).[36] The authors also highlighted that the DLQI had been reported to correlate poorly with objective disease assessment in previous studies and that some found the DLQI scoring system difficult to use.[36] Additional limitations of the MSS include lack of assessment of the degree of inflammation (which would be useful to assess non-surgical therapies), difficulty in distinguishing between small fistulas and large nodules, lack of an examination regarding the sensitivity to clinical change, and potential for larger variability in clinical settings where specialists have not been formally trained.[36]

TABLE 48: SUMMARY OF THE VALIDITY OF THE OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
DLQI	***Scoring*** • 30 = maximum impairment • 0 = no impairment ***Question values:*** • 0 = not at all • 1 = a little • 2 = a lot • 3 = very much	• Not in HS • Yes in other skin conditions	• Variety of dermatologic conditions = 3.3 • Psoriasis range of 2.3 to 5.7	Kimball et al.,[4] Badia-Tahull et al.,[7] Lewis and Finlay,[27] Basra et al.[28]
EQ-5D-3L	• 5 dimensions of health status:	• Not in HS	• Various conditions: range 0.033 to	Cheung et al.,[30] Melzer and

Instrument	Type	Validated	MCID	References
	○ mobility ○ self-care ○ usual activities (work, study, housework, and family/leisure activities) ○ pain/discomfort ○ anxiety/depression • For each dimension, patient's response could be one of 3 levels: ○ no problems ○ some problems ○ severe problems • The digits for the 5 dimensions can be combined in a 5- digit profiler describing the respondent's health state		0.074 • Not in HS	Meuth,[31] Yang et al.[34]
HiSCR	• ≥ 50% reduction in total AN count with a baseline AN count of ≥3 • No increase in abscesses relative to baseline • No increase in draining fistulas relative to baseline	Yes	≥ 50% reduction in ANs	Kimball et al.,[21] Kimball et al.[22]
MSS	• 3 points if lesions are present in the following anatomical areas: ○ axilla ○ gluteal (left and/or right) ○ groin ○ or other region • number of lesions in each region: ○ 1 for a nodule ○ 6 points for a fistula • scoring between lesions or size of lesion: ○ 1 point < 5 cm ○ 3 points for 5 to 10 cm ○ 9 points > 10 cm • lesions separated by normal skin ○ 0 = yes ○ 9 point = no (= Hurley III)	Yes • interobserver variability and reliability	No	Sartorius et al.,[12] Sartorius et al.[36]
SF-36	• 8 domains: ○ physical functioning ○ role–physical ○ bodily pain ○ general health ○ vitality	• Overall, yes • Not in HS	• PCS or MCS typically between 2.5 and 5 points • No specific one identified for HS	Mease and Mentor,[16] Hays and Morales,[17] Samsa et al., [18] Strand and Singh, [19] Ware and

Instrument	Type	Validated	MCID	References
	○ social functioning ○ role–emotional ○ mental health ***Scoring:*** • 0 to 100 (higher scores indicative of better health) • PCS and MCS have mean of 50 and SD of 10 in US population (therefore, > or < 50 considered > or < avg. for general US population)			Sherbourne[35]

AN = abscess and inflammatory nodule; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol Five-Dimensions Health-Related Quality of Life Questionnaire; HS = hidradenitis suppurativa; MCID = minimal clinically important difference; MCS = mental component summary; MSS = modified Sartorius Score; PCS = physical component summary; SF-36 = Short Form (36) Health Survey.

Conclusion

The DLQI was identified as a potential tool for the measurement of disease activity in patients with HS; however, it has not been officially validated or tested for its reliability in this patient population. Moderate correlation of the EQ-5D with the DLQI has been reported in patients with HS, and significant differences have been suggested when examining severity groups as defined by Hurley staging; however, the EQ-5D has not been formally validated or deemed reliable or responsive in this patient population. The HiSCR has been validated and assessed as a responsive and reliable outcome measure of disease activity in patients with HS, whereas the MSS has been validated and is reliable, but it may have some issues with measuring the inflammatory aspect of disease activity in HS. The SF-36 was not validated in patients with HS.

No MCID was obtained for patients with HS regarding the DLQI, EQ-5D, SF-36, or the MSS; however, the HiSCR supports a threshold of a 50% reduction in ANs as both clinically appropriate (in patients with a baseline AN count of ≥3) and meaningful to patients.

APPENDIX 7: SUMMARY OF OTHER STUDIES

1. Objective

[redacted][15]

[redacted].[15]

2. Findings

Study Design

[redacted].

Assessment

- [redacted]).

[redacted]

- [redacted].

[redacted].

Results

[redacted] Table 49 [redacted].

TABLE 49: PATIENT DISPOSITION FOR THE OPEN-LABEL EXTENSION FOR DIFFERENT ADALIMUMAB TREATMENT GROUPS AND OVERALL

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason:							
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow- up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; AE = adverse event; cont. = continuous; EOW = every other week; EW = every week; OLE = open-label extension; PL = placebo.

[redacted].[15]

[redacted]

[redacted] Table 50.

TABLE 50: BASELINE DISEASE CHARACTERISTICS (AT BEGINNING OF OPEN-LABEL EXTENSION) FOR PATIENTS CONTINUING IN PIONEER-OLE

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age group, n (%)							
< 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40 to 64 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)							
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI group (weight in kg/m^2), n (%)							
Normal (< 25)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overweight (25 to < 30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Obese (30 to < 40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Morbidly obese (≥ 40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nicotine use, n (%)							
Smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ex-smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alcohol use, n (%)							
User	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ex-user	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-user	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hurley stage, n (%)							
II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Family history of HS, n (%)							
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median duration of HS, n (%)							
< 9.42 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 9.42 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AN count							
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AN count, n (%)							
≤ 5							
6 to 10							
≥ 11							
Abscess count							
Mean (SD)							
Draining fistula count							
Mean (SD)							
Inflammatory nodule count							
Mean (SD)							
Erythema,[c] n (%)							
No redness							
Faint but discernible pink coloration							
Moderate red Coloration							
Very red or bright red coloration							
Modified Sartorius score							
Mean (SD)							
NRS (daily pain at worst [worst pain in the past 24-hour period])							
N							
Mean (SD)							

AN = abscess and inflammatory nodule; BMI = body mass index; EOW = every other week; EW = every week; HS = hidradenitis suppurativa; NRS = numeric rating scale; OLE = open-label extension; PL = placebo; SD = standard deviation; yrs = years.

[15]

).

Safety Outcomes

Table 51.

.

TABLE 51: EXPOSURE TO ADALIMUMAB IN DAYS

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; Cont. = continuous; EOW = every other week; EW = every week; min = minimum; max = maximum; PL = placebo; SD = standard deviation.

[redacted].[15]

[redacted] Table 52.

TABLE 52: OVERVIEW OF HARMS

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable AEs, n (%)							
Infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TB (active or latent)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malignancy[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
emyelinating disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths,[c] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; AE = adverse event; Cont. = continuous; EOW = every other week; EW = every week; NMSC = non-melanoma skin cancer; PL = placebo; SAE = serious adverse event; TB = tuberculosis; WDAE = withdrawal due to adverse event.

[redacted][15]

[redacted] Table 53.

TABLE 53: ADVERSE EVENTS (IN ≥ 5% OF PATIENTS) IN TREATMENT GROUPS

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site Erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ADA = adalimumab; AE = adverse event; Cont. = continuous; EOW = every other week; EW = every week; HS = hidradenitis suppurativa; PL = placebo; URTI = upper respiratory tract infection; UTI = urinary tract infection.

[redacted] [15]

[redacted]

Clinical Efficacy Outcomes

Hidradenitis Suppurativa Clinical Response: [redacted] Table 54.

TABLE 54: PROPORTION OF PATIENTS ACHIEVING HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE (LAST OBSERVATION CARRIED FORWARD)

Weeks of Adalimumab Treatment[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline at Entry of OLE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EOW = every other week; EW = every week; HiSCR = Hidradenitis Suppurativa Clinical Response; LOCF = last observation carried forward; OLE = open-label extension; PL = placebo.
Note 'x' denotes extension phase

[redacted].[15]

Abscess and Inflammatory Nodule Counts of 0, 1, or 2: [redacted]

[redacted] Table 55.

TABLE 55: PROPORTION OF PATIENTS ACHIEVING ABSCESS AND INFLAMMATORY NODULE COUNT OF 0, 1, 2 DURING THE OLE (LAST OBSERVATION CARRIED FORWARD)

Weeks of Adalimumab Treatment[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline at Entry of OLE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AN = abscess and inflammatory nodule; EOW = every other week; LOCF = last observation carried forward; OLE = open-label extension; PL = placebo.
Note 'x' denotes extension phase

[redacted].[15]

[redacted].

Change in Lesion Counts (Abscesses, Inflammatory Nodules, Draining Fistulas): [redacted] (Table 56).

TABLE 56: CHANGE FROM BASELINE IN LESION COUNTS OVER TIME FROM FIRST DOSE OF ADALIMUMAB IN THE PRIOR PHASE 3 STUDY (LAST OBSERVATION CARRIED FORWARD)

Weeks of Adalimumab Treatment[a]	[redacted]			
	AN Mean (SD)	Abscess Mean (SD)	IN Mean (SD)	DF Mean (SD)
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 48[b]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60[b]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72[b]	[redacted]	[redacted]	[redacted]	[redacted]

AN = abscess and inflammatory nodule; DF = draining fistulas; EW = every week; IN = inflammatory nodule; LOCF = last observation carried forward; SD = standard deviation.

[redacted].[15]

Health-Related Quality of Life Outcomes

Dermatology Life Quality Index: [redacted] (Table 57). [redacted].

TABLE 57: CHANGE FROM BASELINE IN DERMATOLOGY LIFE QUALITY INDEX OVER TIME FROM FIRST DOSE OF ADALIMUMAB (LAST OBSERVATION CARRIED FORWARD)

Weeks of Adalimumab Treatment[a]	[redacted]		
	Visit Mean	Baseline Mean	Change From Baseline Mean (SD)
Week 4	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]
Week 48[b]	[redacted]	[redacted]	[redacted]
Week 72[b]	[redacted]	[redacted]	[redacted]

DLQI = Dermatology Life Quality Index; EW = every week; LOCF = last observation carried forward; SD = standard deviation.

[redacted].[15]

Modified Sartorius Score: [redacted] Table 58.

TABLE 58: CHANGE FROM BASELINE IN MODIFIED SARTORIUS SCORE OVER TIME DURING THE OPEN-LABEL EXTENSION (LAST OBSERVATION CARRIED FORWARD)

Weeks of Adalimumab Treatment[a]	Change From Baseline[b] Mean (SD)				Change From Baseline[e] Mean (SD)
	[redacted]				
Start of OLE					
Week 4x					
Week 8x					
Week 12x					
Week 24x[c]					
Week 36x[c]					
Week 48x[c]					

EOW = every other week; EW = every week; LOCF = last observation carried forward; OLE = open-label extension; PL = placebo; SD = standard deviation.
Note 'x' denotes extension phase

[redacted] [15]

Limitations: [redacted]

[redacted].

3. Summary

[redacted].

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