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Indication Review: Humira® (adalimumab) for Hidradenitis Suppurativa

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Purpose for Indication Review: To evaluate evidence for Humira® (adalimumab) in the setting of hidradenitis suppurativa (HS) as requested by the Health Evidence Review Commission (HERC). Medical therapy for HS is currently not funded by the Oregon Health Authority (OHA).[1]

Research Questions:

1. What is the efficacy and effectiveness of adalimumab in treating HS?
2. What are the comparative harms of adalimumab in patients with HS?

Conclusions:

- Evidence for adalimumab in HS comes from two phase 3 trials[2] and a systematic review from the Cochrane Collaboration.[3] A technology appraisal of adalimumab in HS was also completed by the National Institute for Health and Care Excellence (NICE).[4] The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed.
- There is low quality evidence from 2 randomized controlled trials (RCT) that adalimumab 40 mg weekly improves the proportion of patients achieving a Hidradenitis Suppurativa Clinical Response (HiSCR), defined as at least a 50% reduction in total abscess and inflammatory nodule count from baseline with no increase in the abscess or draining-fistula count, compared to placebo at 12 weeks (41.8% vs. 26.0%, respectively, number needed to treat [NNT] 7; and 58.9% vs. 27.6%, NNT 4).[2]
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with a 0-2 total abscess and inflammatory-nodule count at week 12 for patients with Hurley stage 2 disease at baseline compared to placebo (28.9% vs. 28.6%, respectively, p=0.96; and 51.8% vs. 32.2%, respectively, p=0.01, NNT 6).[2] The Hurley staging system ranges from stage 1 (least severe) to stage 3 (most severe), with stage 2 indicating recurrent abscesses with tract formation and cicatrization, single or multiple, and widely separated lesions.[5]
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly increases the proportion of patients with at least 30% reduction and at least 1 unit reduction in pain score from baseline compared to placebo at week 12 (27.9% vs. 24.8%, respectively, p=0.63; and 45.7% vs. 20.7%, respectively, p<0.001, NNT 4).[2] Clinical significance of a 30% reduction is unclear and it has been suggested that a 50% reduction in baseline pain is considered clinically meaningful.[4]
- There is insufficient evidence from 2 conflicting RCTs that adalimumab 40 mg weekly improves the mean change in modified Sartorius score compared to placebo from baseline to week 12 (-24.4 points vs. -15.7 points, respectively, p=0.12; and -28.9 points vs. -9.5 points, respectively, p<0.001).[2] Points for this scale are assigned in categories which include anatomical regions involved (3 points per region involved), number and scores of lesions (2 points for nodules,

4 for fistulas, 1 for scars, and 1 for others), the longest distance between two relevant lesions (<5 cm, 2 points; <10 cm, 4 points; ≥10 cm, 8 points), and if all lesions are clearly separated by normal skin (for each region: yes, 0 points; no, 6 points).[6,7] There is no upper limit and a larger score indicates more severe disease, but the definition of a minimum clinically significant change is unclear.[8]

- Differences in efficacy outcome results between the two trials may be due to differences in baseline characteristics, antibiotic use, and geographic distribution of patients.[2] A greater benefit for several outcomes was seen in PIONEER 2, in which the patients had less severe disease and were able to continue on stable doses of tetracycline antibiotics.[2]
- There is moderate quality evidence that adalimumab 40 mg weekly improves the Dermatology Life Quality Index (DLQI) score compared to placebo in moderate to severe HS at week 12 and week 16. Evidence from 2 RCTs found decreases of 5.4 points and 5.1 points with adalimumab compared with decreases of 2.9 points and 2.3 points with placebo at 12 weeks.[2] The differences between placebo and adalimumab group changes do not meet the suggested minimum clinically significant difference of 4-5 points.[2,4] Additionally, another RCT assessed in the Cochrane review found a benefit with adalimumab compared to placebo at 16 weeks in DLQI score (mean difference 4 points; 95% confidence interval [CI], 6.5 to 1.5 points lower).[3,9] The DLQI questionnaire consists of 10 quality of life questions each ranked from 0 to 3, with a max score of 30 indicating the skin disease has a very large impact on the patient's quality of life.[10] A change of 0-1 points indicates no effect; 2-5 points a small effect; 6-10 points a moderate effect; 11-20 points a large effect; and 21-30 an extremely large effect.[11]
- There is insufficient evidence to determine the effect of adalimumab on the need for surgery from clinical trials. However, NICE guidance based on post-hoc analyses of draining fistulas and non-draining fistulas concludes there is a decreased need for some types of surgical procedures (likely minor surgeries such as narrow margin excisions and incision and drainage procedures).[4] No definite conclusions could be made on the effect of adalimumab on surgical-inpatient admissions.[4] The post hoc analysis assessed by NICE found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; p<0.001; NNT 8) and non-draining fistulas (15% vs. 9%; p=0.017; NNT 17).[4,12]
- There is low quality evidence that adalimumab 40 mg weekly and placebo have similar risks of serious adverse events [SAEs] (1.3%-1.8% vs. 1.3%-3.7%, respectively; RCT = 2), infections (24.8%-25.2% vs. 28.3%-32.5%, respectively; RCT = 2), and serious infections (0.6-0.7% vs. 0-1.2%, respectively; RCT = 2) through 12 weeks.[2]
- There is low quality of evidence from patients who remained continuously on the respective treatment that adalimumab-treated patients have a similar risk of SAE at 12-36 weeks of therapy compared to placebo (2.1-3.9% vs. 4.6%, respectively; RCT=2 for adalimumab and 1 for placebo).[2] Similarly, there is low quality of evidence in the same time frame that adalimumab- and placebo-treated patients have similar risk for serious infections (0-2.0% vs. 1.3%; RCT=2 for adalimumab and 1 for placebo).[2] This evidence is limited by a high rate of overall attrition (41.3% and 52.8% for the two RCTs).[2]
- There is insufficient evidence to determine the long-term safety of adalimumab for HS beyond 36 weeks. However, the safety profile of adalimumab dosed every other week for other conditions has been well characterized since the drug's initial U.S. approval in 2002.[13] Like other immunosuppressants, adalimumab has FDA boxed warnings for serious infections and malignancies.[13]
- NICE guidance recommend adalimumab as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4] It is recommended to assess response to treatment after 12 weeks of treatment, and only continue treatment if there is a reduction of 25% or more in total abscess and inflammatory nodule count and no increase in abscesses and draining fistulas.[4]

Recommendations:

- Modify PA criteria (**Appendix 2**) for adalimumab to include moderate to severe HS treatment if OHA policy for HS changes. Modify as follows:
    - Require trial and failure, intolerance, or contraindication to conventional therapy (such as oral antibiotics) and

- Require evidence of response (a reduction of 25% or more in the total abscess and inflammatory nodule count and no increase in abscesses and draining fistulas) for renewal of authorization.

Background:
Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease which has a prevalence of 1-4% worldwide and is 3 times more common in women than men.[7,14] The mean age of onset is 22 years.[14] It is characterized by inflamed nodules which occur most frequently in the axillary, inguinal, and anogenital regions of the body.[7,14] These nodules are painful, recurrent, and can result in abscesses, chronic draining sinus tracts, scarring, disfigurement, and disability.[14] Genetic predisposition, hormonal factors, immune factors, medications such as lithium and medroxyprogesterone acetate, obesity, and smoking all are potential contributors to the etiology.[14]

There are multiple staging systems that evaluate symptoms and severity of HS. The Hurley clinical staging system describes disease severity by 3 stages: stage 1 indicates abscess formation, single or multiple, without sinus tracts and cicatrization (scar formation); stage 2 indicates recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions; and stage 3 indicates diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.[5] About 69% of patients have stage 1 disease, while approximately 28% and 4% of patients have more severe stage 2 and 3 disease.[5] The minimum clinically significant change in Hurley staging is unclear.[15]

The modified Sartorius score is another method of determining severity in which individual nodules and fistulas are counted.[5] Points are assigned in categories which include anatomical regions involved (3 points per region involved), number and scores of lesions (2 points for nodules, 4 for fistulas, 1 for scars, and 1 for others), the longest distance between two relevant lesions (<5 cm, 2 points; <10 cm, 4 points; ≥10 cm, 8 points), and if all lesions are clearly separated by normal skin (for each region: yes, 0 points; no, 6 points).[6,7] There is no upper limit as scoring depends on the individual patient's lesions, and a larger score indicates more severe disease.[8] The definition of a minimum clinically important change in this score is unclear.[15]

The Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) is another scale utilized which stages severity as clear (no inflammatory or non-inflammatory nodules), minimal (only non-inflammatory nodules), mild (<5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules), moderate (<5 inflammatory nodules or one abscess or draining fistula and ≥1 inflammatory nodules or 2-5 abscesses or draining fistulas and <10 inflammatory nodules), severe (2-5 abscesses or draining fistulas and ≥10 inflammatory nodules), or very severe (more than 5 abscesses or draining fistulas).[5,16]

The Hidradenitis Suppurativa Clinical Response (HiSCR) measure incorporates the status of lesions: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulas (sinus tracts, with communications to skin surface, draining purulent fluid).[17] A responder is identified as having a 50% or greater reduction in abscesses and inflammatory nodules, no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline.[17] However, the minimum clinically important difference is unclear.[4] A 25% reduction in total abscess and inflammatory nodules may also reflect a partial response to treatment.[4]

The Dermatology Life Quality Index (DLQI) can be used to determine quality of life. The questionnaire consists of 10 quality of life questions, each ranked from 0 to 3, with a maximum score of 30 indicating the skin disease has a very large negative impact on the patient's quality of life.[10] A change of 0-1 points indicates no effect; 2-5 points a small effect; 6-10 points a moderate effect; 11-20 points a large effect; and 21-30 points an extremely large effect.[11] It has been suggested that a change of 4 or 5 points may be the minimum clinically important difference, but this scale may underestimate effects of treatment in patients who have

developed coping mechanisms for the disease.[2,4] Patient-reported pain scales are also used to determine disease severity and effects of treatment, and a reduction of 50% from baseline in pain scores may be considered clinically meaningful.[4]

Nonpharmacological treatments for HS include local hygiene and cleansing, reducing heat, humidity, and friction in the area, weight loss to ideal weight, and smoking cessation.[14] Surgical treatment may also be an option for Hurley stage 2 and 3 patients.[14] Pharmacological treatments for HS include antibiotics, retinoids, corticosteroids, and immunosuppressive agents such as tumor necrosis factor (TNF)-alpha inhibitors.[5,14] However, the most commonly used treatments are topical and oral antibiotics.[4] Antibiotics can be used both for the acute treatment of an infected area as well as for maintenance treatment.[7,14,18] The most commonly used oral antibiotic treatments are tetracyclines.[4] The next most commonly utilized therapies are acitretin, isotretinoin, dapsone, and cyclosporine.[4]

TNF-alpha inhibitors are often reserved for patients with moderate to severe HS.[5,14] Guidance from NICE recommends the use of adalimumab for active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4] Continuation of therapy beyond 12 weeks is recommended only if there is a reduction of 25% or more in the total abscess and inflammatory nodule count as well as no increase in abscesses or draining fistulas at that time.[4]

Adalimumab was approved for moderate to severe HS in September 2015 and is the only medication FDA-approved for this condition.[13] Adalimumab is administered with a loading dose of 160 mg subcutaneously followed by a second dose of 80 mg two weeks later (Day 15) and then 40 mg for the third (Day 29) and subsequent weekly doses.[13] Medical therapy for HS currently appears in the unfunded region of the Oregon Health Authority's Prioritized List of Health Services. [1]

Randomized Controlled Trials:
A total of 26 citations were manually reviewed from the initial literature search for the HS indication review. After further review, 25 citations were excluded because of wrong study design (e.g., observational or phase 2 trial when phase 3 trials available), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or already being included in a systematic review within the indication review. The one included citation was the PIONEER 1 and PIONEER 2 study manuscript, described below.

Clinical Efficacy:
Clinical Trials
Adalimumab, a TNF-alpha inhibitor, is approved by the FDA for the treatment of moderate to severe HS.[13] Two phase 3 trials (PIONEER 1 and PIONEER 2) provide efficacy and safety data for adalimumab in HS compared to placebo.[2] Both trials were manufacturer-funded and the manufacturer participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval.[2] Additionally, all of the authors disclosed potential conflicts of interest including conflicts specific to the manufacturer (such as employment, consulting fees, grant support, honoraria, etc.).[2]

The methods and trial design for PIONEER 1 and PIONEER 2 were similar.[2] Both trials were composed of 2 periods which compared adalimumab to placebo. In the first period, adalimumab was dosed at 160 mg at week 0, 80 mg at week 2, and 40 mg weekly at 4 through 12 weeks.[2] In the second period, patients who had been randomized to adalimumab in the first period underwent re-randomization to either adalimumab weekly, adalimumab 40 mg every other week, or placebo.[2] Patients randomized to placebo in the first period were reassigned in a blinded fashion in period 2 to either adalimumab 160 mg at week 12, 80 mg at

week 14, followed by 40 mg weekly starting at week 16 (in PIONEER 1) or placebo beginning at week 12 (in PIONEER 2).[2] The second period lasted for a duration of 24 weeks, resulting in a total study duration of 36 weeks for period 1 and period 2 combined.[2] However, the primary and secondary efficacy endpoints were all determined at week 12 which marked the end of period 1.[2] Patients enrolled in both PIONEER 1 (n=307) and PIONEER 2 (n=326) had moderate to severe HS and a duration of disease of at least one year.[2]

The primary efficacy endpoint was the proportion of patients with a HiSCR response, defined as at least a 50% reduction from baseline in total abscess and inflammatory nodule count, with no increase in the abscess or draining-fistula count.[2] Three ranked secondary endpoints included the proportion of patients with a total abscess and inflammatory-nodule count of 0, 1, or 2 for patients with Hurley stage 2 disease at baseline, at least 30% reduction and at least 1-unit reduction from baseline in pain score, and the change from baseline in modified Sartorius score.[2]

In PIONEER 1, HiSCR response at week 12 was achieved by a statistically significant greater proportion of adalimumab-treated patients compared to placebo-treated patients (41.8% vs. 26%, respectively; ARR 15.8%; NNT 7; p=0.003).[2] However, no statistically significant results were seen in the three ranked secondary endpoints.[2] No statistically significant difference was found between the number of adalimumab-treated and placebo-treated patients in the proportion of patients with a total abscess and inflammatory nodule count of 0, 1, or 2 at week 12 (28.9% vs. 28.6%, respectively; ARR 0.3%; 95% CI -13.4 to 14.1; p=0.96).[2] Similarly, no statistically significant difference was found in the proportion of patients with at least 30% reduction and at least 1-unit reduction from baseline in pain score between adalimumab and placebo groups at week 12 (27.9% vs. 24.8%, respectively; ARR 3.1%; 95% CI -8.6 to 14.2; p=0.63).[2] Finally, no statistically significant difference was found for the change in mean score from baseline in modified Sartorius score for either adalimumab or placebo group at week 12 (-24.4 points vs. -15.7 points, respectively; mean difference: -8.7 points; 95% CI -19.7 to 2.4; p=0.12).[2]

In PIONEER 2, HiSCR response at week 12 was achieved by a statistically significant greater proportion of adalimumab-treated patients compared to placebo-treated patients (58.9% vs 27.6%, respectively; ARR 31.3%; NNT 4; p<0.001).[2] In contrast to PIONEER 1, a statistically significant benefit was seen with adalimumab compared to placebo in the three ranked secondary outcomes.[2] A statistically significant difference was also found in the proportion of adalimumab- and placebo-treated patients with a total abscess and inflammatory nodule count of 0, 1, or 2 at week 12 (51.8% vs. 32.2%, respectively; ARR 19.6%; 95% CI 4.7 to 34.2; p=0.01; NNT 6).[2] Similarly, a statistically significant difference was found in the proportion of patients with at least 30% reduction and at least 1 unit reduction from baseline in pain score between adalimumab and placebo groups at week 12 (45.7% vs. 20.7%, respectively; ARR 25.1%; 95% CI 12.7 to 37.6; p<0.001; NNT 4).[2] A statistically significant difference was also found for the change in mean score from baseline in modified Sartorius score for either adalimumab or placebo group at week 12 (-28.9 points vs. -9.5 points, respectively; mean difference: -19.4 points; 95% CI -28.6 to -10.1; p<0.001).[2]

Differences in the results of the three ranked secondary endpoints, all non-statistically significant in PIONEER 1 yet all statistically significant in PIONEER 2, may be due to differences in baseline characteristics, antibiotic use, and geographic distribution of patients.[2] Patients in PIONEER 1 had higher mean abscess count (2.75 vs. 2.2, respectively), inflammatory nodule count (11.55 vs. 9, respectively) and draining fistula count (4.2 vs. 3.35, respectively) as well as higher mean modified Sartorius scores (149.1 vs. 115.1 points, respectively) compared to patients in PIONEER 2.[2] While patients were required to stop oral antibiotic treatment in PIONEER 1, patients who were on stable doses of tetracycline antibiotics were allowed to continue them in PIONEER 2.[2] Concomitant oral antibiotics were used by 19% of patients in PIONEER 2.[2] Approximately 50% of patients in PIONEER 1 were from the U.S., while only 27% of patients in PIONEER 2 were from the U.S., which limits applicability to the Oregon Medicaid population.[2] Other countries of origin for patients in PIONEER 1 included Australia, Canada, Czech Republic, Germany, and Hungary.[2] Other countries of origin for patients in PIONEER 2 included Australia, Canada, Denmark, France, Greece, the Netherlands, Puerto Rico, Sweden, Switzerland, and Turkey.[2]

Quality of life, as assessed by DLQI, was a non-ranked secondary endpoint for both PIONEER 1 and PIONEER 2.[2] Patients treated with adalimumab experienced greater improvements in DLQI score compared to placebo in both PIONEER 1 (-5.4 vs. -2.9, respectively) and PIONEER 2 (-5.1 and -2.3, respectively).[2] The minimum clinically significant difference is suggested to be around 4-5 points.[2,4] Among patients with a baseline score of greater than or equal to 5 (>90% of patients in period 1), a decrease of 5 points was seen with a greater proportion of patients in the adalimumab groups compared to the placebo groups in both PIONEER 1 (50.7% vs. 33.8%, p=0.004, respectively) and PIONEER 2 (49% vs. 34%, p=0.011, respectively).[2]

Both PIONEER 1 and PIONEER 2 were rated as poor quality due to manufacturer involvement and attrition. There was low attrition in period 1 which encompassed the primary and ranked secondary endpoints (5.5% and 6.1%, respectively) but high attrition occurred with longer follow-up in period 2 (41.3% and 52.8%, respectively).[2] A majority of the attrition in period 2 for both trials was due to loss of response, worsening of symptoms, or absence of improvement.[2]

Systematic Reviews

A 2017 Cochrane review on treatments for HS evaluated RCTs through August 2015 for all interventions.[3] Five of the eleven authors disclosed conflicts of interest related to the manufacturer of adalimumab (including advisory fees, honorarium, or acting as an investigator for a manufacturer-funded study).[3] As the PIONEER 1 and PIONEER 2 trials discussed above were published in 2016, these were not included in this review.[2,3] The review found moderate quality evidence that adalimumab 40 mg weekly improved the DLQI score compared to placebo in moderate to severe HS (difference: 4 points; 95% CI 6.5 to 1.5 points lower; studies = 1).[3] However, the lower end of the 95% CI (1.5 points) may not be clinically significant and the overall effect (4 points) was small.[3] This study of weekly adalimumab dosing was limited by not being powered to detect rare or delayed AEs.[3] For adalimumab every other week dosing, a meta-analysis of two trials (n=124) found no difference between adalimumab and placebo in quality of life or secondary outcomes such as pain score, HS scoring systems, PGA, or duration of remission.[3] The review concluded that results from the PIONEER studies may improve confidence in the effect size and safety of weekly adalimumab therapy.[3]

Guidelines

National Institute for Health and Care Excellence

In June 2016, NICE published a technology appraisal guidance for adalimumab in treating moderate to severe HS.[4] This guidance evaluated both the clinical and cost effectiveness and provided recommendations for place in therapy.[4] Clinical effectiveness was determined from the PIONEER 1 and 2 trials (described above).[4] It was concluded that adalimumab provides a significant benefit for symptom improvement and quality of life compared to placebo in the short term, but have not been shown long term.[4] The recommendations for use of adalimumab in HS were as follows:

- Adalimumab is recommended as an option for treating active moderate to severe HS in adults whose disease has not responded to conventional systemic therapy.[4]
- After 12 weeks of treatment, assess the response to adalimumab and only continue if there is clear evidence of response as defined as
    - a reduction of 25% or more in total abscess and inflammatory nodule count and
    - no increase in abscesses and draining fistulas.[4]

The definition of response in the recommendations based on a 25% or more reduction in total abscess and inflammatory nodule count differs from the 50% reduction in the PIONEER 1 and 2 primary endpoints.[2,4] However, the clinical experts determined that the 50% reduction threshold was too high, and instead

determined that a 25% reduction in total abscess and inflammatory nodule count with no increase in abscesses or draining fistulas would reflect a treatment response.[4]

While the recommendations do not specify which conventional systemic therapies must be tried, the most commonly used treatments are topical and oral antibiotics.[4] The most commonly used oral antibiotic is tetracycline, followed by a combination of clindamycin and rifampicin.[4] The next most commonly utilized conventional therapies are acitretin, isotretinoin, dapsone, and cyclosporine.[4]

In the cost effectiveness analysis, the cost of surgical-inpatient admissions was a key consideration.[4] However, there was a lack of data regarding surgeries in the PIONEER trials as surgery was not permitted in the trials per protocol.[4,12] In response to a request from the evidence review group for outcome data on surgical procedures, the manufacturer completed a post-hoc analysis of pooled PIONEER 1 and 2 data.[4,12] The post hoc analysis found that a greater proportion of patients treated with adalimumab as compared to placebo had improvement in draining fistulas (33% vs. 19%; p<0.001; NNT 8) and non-draining fistulas (15% vs. 9%; p=0.017; NNT 17).[4,12] These outcomes would likely be associated with minor surgeries, such as narrow margin excisions and incision and drainage procedures, and therefore, the committee concluded that adalimumab reduces the need for some types of surgical procedures.[4] However, based on the lack of robust evidence, no conclusions could be made on adalimumab's effect on surgical-inpatient admissions.[4]

Clinical Safety:
In PIONEER 1 and PIONEER 2 through week 12 (period 1), the proportions of patients with any adverse event (AE) were similar for adalimumab- and placebo-treated patients (50.3% vs. 58.6%, respectively in PIONEER 1; 57.1% vs. 63.2%, respectively in PIONEER 2).[2] The two AEs which occurred by week 12 in at least 10% of patients in either the adalimumab or placebo groups of either trial included headache (9.2% vs. 9.9%, respectively in PIONEER 1; 12.9% vs. 12.9%, respectively in PIONEER 2) and nasopharyngitis (5.9% vs. 10.5%, respectively in PIONEER 1; 5.5% vs. 6.1%, respectively in PIONEER 2).[2] SAEs reported by week 12 were similar or lower with adalimumab compared to placebo (1.3% vs. 1.3%, respectively for PIONEER 1; 1.8% vs. 3.7%, respectively for PIONEER 2).[2] Infections occurred at a lower rate by week 12 for adalimumab-treated patients compared to placebo-treated patients in both trials (24.8% vs. 28.3%, respectively for PIONEER 1; 25.2% vs. 32.5%, respectively for PIONEER 2) and rates of serious infections were also low and similar between groups (0.7% vs. 0%, respectively; 0.6% vs. 1.2%, respectively).[2]

Safety outcomes from period 2 (weeks 12-36) of PIONEER 1 and 2 are presented in **Table 1**.[2] For period 2 of both trials, high attrition was seen (41.3% and 52.8% for PIONEER 1 and PIONEER 2, respectively).[2]

Table 1: Selected Safety Outcomes in Period 2 (weeks 12-36) of PIONEER 1 and PIONEER 2.[2]

	PIONEER 1				PIONEER 2			
Safety Outcome	**Adalimumab Weekly (n=145; reassigned from placebo in Period 1)**	**Placebo (n=49)**	**Adalimumab Every Other Week (n=48)**	**Adalimumab Weekly (n=48)**	**Placebo (n=151; reassigned from placebo in Period 1)**	**Placebo (n=51)**	**Adalimumab Every Other Week (n=53)**	**Adalimumab Weekly (n=51)**

Any adverse event	90 (62.1%)	28 (57.1%)	22 (45.8%)	28 (58.3%)	68 (45.0%)	33 (64.7%)	30 (56.6%)	29 (56.9%)
Serious adverse events	3 (2.1%)	0 (0%)	1 (2.1%)	1 (2.1%)	7 (4.6%)	0 (0%)	2 (3.8%)	2 (3.9%)
Adverse events leading to study drug discontinuation	5 (3.4%)	1 (2.0%)	0 (0%)	0 (0%)	3 (2.0%)	0 (0%)	1 (1.9%)	1 (2.0%)
Infections	43 (29.7%)	16 (32.7%)	12 (25.0%)	14 (29.2%)	35 (23.2%)	13 (25.5%)	19 (35.8%)	18 (35.3%)
Serious infections	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)	1 (2.0%)

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Improvement in symptoms
2) Improvement in quality of life (DLQI)
3) Reduction in complications and surgeries
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Clinical response per HiSCR measure at week 12 (>50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count)

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Kimball et al.[2] (PIONEER I) MC Phase 3, RCT with 2 DB, PC periods 36 weeks (period 1: 12 weeks; period 2: 24 weeks)	Period 1 1. Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4 2. Placebo Period 2 *Pts previously assigned to adalimumab*	Demographics: • Mean age: 37 y • Female: 64% • White: 76% • Median duration of HS: 9.1 y • Previous systemic therapy: 43% • Prior surgery for HS: 11% • Total number of abscesses & inflammatory nodules: 14	ITT: *Period 1* Total: 307 1. 153 2. 154 *Period 2* Total: 290 1. 48 2. 48 3. 49 4. 145 Attrition: *Period 1:*	Primary Endpoint: Clinical response per HiSCR measure at week 12 (≥50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count) 1. 41.8% 2. 26.0% P=0.003 RR & CI NR Secondary Endpoint:	15.8%/7	*Period 1* Serious AEs 1. 2 (1.3%) 2. 2 (1.3%) AEs Leading to DC 1. 0 (0%) 2. 2 (1.3%) Infection 1. 38 (24.8%) 2. 43 (28.3%) Serious Infection 1. 1 (0.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized centrally and treatments assigned by IVRS. Balanced characteristics at baseline. Performance Bias: Low. Matching placebo was used. Protocol was approved at each site. Detection Bias: Low. Investigator and study site personnel blinded. Attrition Bias: High. Overall high attrition for Period 2 (41.3%). Low attrition for Period 1 (5.5%) which was utilized for primary and ranked secondary outcomes. ITT used for efficacy analysis. LOCF utilized for analysis of missing continuous variables. Non-responder

	1. Adalimumab 40 mg weekly 2. Adalimumab 40 mg every other week 3. Placebo *Pts previously assigned to placebo* 4. Adalimumab 160 mg at week 12, 80 mg at week 14, followed by 40 mg weekly starting at week 16	• Modified Sartorius score: 149.1 <u>Key Inclusion Criteria</u>: • Age ≥18 y • HS ≥1 y • Moderate to severe HS (total abscess & inflammatory nodule count ≥3) at baseline • Inadequate response to oral antibiotics • Anti-TNF-a naïve <u>Key Exclusion Criteria</u>: • Prior anti-TNF therapy • Any active skin disease or condition that could interfere with assessment of HS • Antibiotic treatment within 28 days of baseline • Receipt of prescription topical therapies for HS ≤14 days prior to baseline • Receipt of systemic non-biologic therapies with potential impact on HS <28 days prior to baseline	Total: 17 (5.5%) 1. 8 (5.2%) 2. 9 (5.8%) *Period 2:* Total: 120 (41.3%) 1. 20 (41.6%) 2. 21 (43.8%) 3. 27 (55.1%) 4. 52 (35.9%)	Total abscess and inflammatory-nodule count of 0, 1, or 2 in patients with Hurley stage II disease at week 12 1. 24/83 (28.9%) 2. 24/84 (28.6%) Difference: 0.3 (95% CI -13.4 to 14.1) P=0.96 ≥30% reduction and ≥1 unit reduction from baseline in pain score at week 12 1. 34/122 (27.9%) 2. 27/109 (24.8%) Difference: 2.8 (95% CI -8.6 to 14.2) P=0.63 Change in mean score from baseline in modified Sartorius score at week 12 1. -24.4 2. -15.7 Difference: -8.7 (95% CI -19.7 to 2.4) P=0.12	NA NA NA	2. 0 (0%) <u>Cancer</u> 1. 0 (0%) 2. 1 (0.7%) *Period 2* <u>Serious AEs</u> 1. 1 (2.1%) 2. 1 (2.1%) 3. 0 (0%) 4. 3 (2.1%) <u>AEs Leading to DC</u> 1. 0 (0%) 2. 0 (0%) 3. 1 (2.0%) 4. 5 (3.4%) <u>Infection</u> 1. 14 (29.2%) 2. 12 (25.0%) 3. 16 (32.7%) 4. 43 (29.7%) <u>Serious Infection</u> 1. 0 (0%) 2. 0 (0%) 3. 0 (0%) 4. 1 (0.7%) p-values, RR, 95% CI were NR		imputation utilized for analysis of missing categorical values. <u>Reporting Bias</u>: Unclear. Protocol available. Pre-specified primary and ranked secondary outcomes reported. Confidence intervals not reported for primary endpoint. <u>Other Bias:</u> High. Funded by AbbVie who participated in data collection, data analysis, data interpretation, and manuscript writing, review, and approval. **Applicability**: <u>Patient</u>: Moderate to severe HS at baseline appropriate for utilizing second-line therapies such as TNF-a inhibitors. <u>Intervention</u>: Adalimumab dosing appropriate and approved by FDA. <u>Comparator</u>: Placebo appropriate to establish efficacy. No other TNF-a inhibitor agents approved for this condition. <u>Outcomes</u>: Clinically meaningful symptom endpoints used appropriate for HS. However, minimum clinically important difference for this outcome is unclear. Majority of attrition in period 2 due to loss of response, worsening of symptoms, or absence of improvement. <u>Setting</u>: 50.5% of patients from the U.S. Other countries of origin included Australia, Canada, Czech Republic, Germany, and Hungary.

		• Receipt of oral concomitant analgesics for HS pain ≤14 days prior to baseline						
2. Kimball et al.[2] (PIONEER II) MC Phase 3, RCT with 2 DB, PC periods 36 weeks (period 1: 12 weeks; period 2: 24 weeks)	Period 1 1. Adalimumab 160 mg at week 0, 80 mg at week 2, followed by 40 mg weekly starting at week 4 2. Placebo Period 2 *Pts previously assigned to adalimumab* 1. Adalimumab 40 mg weekly 2. Adalimumab 40 mg every other week 3. Placebo *Pts previously assigned to placebo* 4. Placebo	Demographics: • Mean age: 35 y • Female: 68% • White: 84% • Median duration of HS: 9.5 y • Previous systemic therapy: 48% • Prior surgery for HS: 14% • Total number of abscesses & inflammatory nodules: 11 • Modified Sartorius score: 115.1 Key Inclusion Criteria: • See PIONEER 1 Key Exclusion Criteria: • Prior anti-TNF therapy • Any active skin disease or condition that could interfere with assessment of HS • Receipt of prescription topical therapies for HS ≤14 days prior to baseline	ITT: *Period 1* Total: 326 1. 163 2. 163 *Period 2* Total: 306 1. 51 2. 53 3. 51 4. 151 Attrition: *Period 1:* Total: 20 (6.1%) 1. 8 (4.9%) 2. 12 (7.4%) *Period 2:* Total: 190 (52.8%) 1. 23 (45.1%) 2. 28 (52.8%) 3. 28 (54.9%) 4. 111 (73.5%)	Primary Endpoint: Clinical response per HiSCR measure at week 12 (≥50% reduction from baseline in total abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula count) 1. 58.9% 2. 27.6% P<0.001 RR & CI NR Secondary Endpoint: Total abscess and inflammatory-nodule count of 0, 1, or 2 in patients with Hurley stage II disease at week 12 1. 44/85 (51.8%) 2. 28/87 (32.2%) Difference: 19.5 (95% CI 4.7 to 34.2) P=0.01 ≥30% reduction and ≥1 unit reduction from baseline in pain score at week 12 1. 48/105 (45.7%) 2. 23/111 (20.7%) Difference: 25.1 (95% CI 12.7 to 37.6) P<0.001 Change in mean score from baseline in modified Sartorius score at week 12	31.3%/4 19.6%/6 25%/4	Outcome: *Period 1* Serious AEs 1. 3 (1.8%) 2. 6 (3.7%) AEs Leading to DC 1. 4 (2.5%) 2. 6 (3.7%) Infection 1. 41 (25.2%) 2. 53 (32.5%) Serious Infection 1. 1 (0.6%) 2. 2 (1.2% Cancer 1. 0 (0%) 2. 0 (0%) *Period 2* Serious AEs 1. 2 (3.9%) 2. 2 (3.8%) 3. 0 (0%) 4. 7 (2.0%) AEs Leading to DC 1. 1 (2.0%) 2. 1 (1.9%) 3. 0 (0%) 4. 3 (2.0%) Infection 1. 18 (35.3%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. See PIONEER 1. Performance Bias: Low. See PIONEER 1. Detection Bias: Low. See PIONEER 1. Attrition Bias: High. Overall high attrition for Period 2 (52.8%). Low attrition for Period 1 (6.1%) which was utilized for primary and ranked secondary outcomes. ITT used for efficacy analysis. LOCF utilized for analysis of missing continuous variables. Non-responder imputation utilized for analysis of missing categorical values. Reporting Bias: Unclear. See PIONEER 1. Other Bias: High. See PIONEER 1. **Applicability**: Patient: See PIONEER 1. Intervention: See PIONEER 1. Comparator: See PIONEER 1. Outcomes: See PIONEER 1. Setting: 27.3% of patients from the U.S. Other countries of origin included Australia, Canada, Denmark, France, Greece, the Netherlands, Puerto Rico, Sweden, Switzerland, and Turkey.

		• Receipt of systemic non-biologic therapies with potential impact on HS <28 days prior to baseline • Receipt of oral concomitant analgesics for HS pain ≤14 days prior to baseline		1. -28.9 2. -9.5 Difference: -19.4 (95% CI -28.6 to -10.1) P<0.001	NA	2. 19 (35.8%) 3. 13 (25.5%) 4. 35 (23.2%) Serious Infection 1. 1 (2.0%) 2. 0 (0%) 3. 0 (0%) 4. 2 (1.3%) p-values, RR, 95% CI were NR		

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; DC = discontinuation; FDA = Food and Drug Administration; HiSCR = Hidradenitis Suppurativa Clinical Response; HS = hidradenitis suppurativa; ITT = intention to treat; IVRS = interactive voice-response system; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; Pts = patients; RCT = randomized controlled trial; RR = relative risk; TNF-a = tumor necrosis factor-alpha; U.S. = United States; y = years.

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Appendix 1: Search Strategy

Medline search on 8/2/2018 for hidradenitis suppurativa indication review
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Hidradenitis Suppurativa/ 1234
2 exp Adalimumab/ 4338
3 1 and 2 69
4 limit 3 to (English language and humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 26

Appendix 2: Proposed Prior Authorization Criteria to be Implemented if OHA Policy for HS Changes

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

- 12 weeks to ~~Up to~~ 12 months

Requires PA:

- All biologics for autoimmune diseases (both pharmacy and physician-administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Approved and Funded Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira); HS (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Baricitinib (OLUMIANT)						≥18 yo		
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo

								TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (Tremfya)				≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	≥18 yo			
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo	≥18 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS = hidradenitis suppurativa; MKD = Mevalonate Kinase Deficiency; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5
5. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. If the request is for a non-preferred agent, has the patient failed to respond to a Humira® product or an Enbrel® product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Has the patient failed to respond to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #16

Approval Criteria		
13. Has the patient failed to respond to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® product or an Enbrel® product for at least 3 months?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for tofacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months.
15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months.
16. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #17	**No:** Go to #18

Approval Criteria		
17. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • For Crohn's Disease patients only: has the patient tried and failed a 3 month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment.	**No:** Go to #19
19. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #20	**No:** Go to #21~~Pass to RPh. Deny; medical appropriateness.~~
20. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
21. Is the diagnosis moderate to severe hidradenitis suppurativa and the requested drug is adalimumab?	**Yes:** Go to #22	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
22. Has the patient failed to respond to, is intolerant of, or has a contraindication to conventional therapy (such as oral antibiotics)?	**Yes:** Approve for up to 12 weeks.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for adalimumab for hidradenitis suppurativa?	**Yes:** Go to #3	**No:** Go to #2
~~1.~~2. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Renewal Criteria		
3. Is there clear evidence of response, defined as: • A reduction of 25% or more in the total abscess and inflammatory nodule count, and • No increase in abscesses and draining fistulas?	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *11/18 (JP); 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *TBD; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/21/13*