NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Contents:

1. **Pre-Meeting Briefing**

2. **Final Scope and Final Matrix of Consultees and Commentators**

3. **Company submission** from AbbVie

4. **Patient Access Scheme** submission from AbbVie

5. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification
   - Company response to the ERG's additional clarification questions

6. **Patient group, professional group and NHS organisation submission** from:
   - Hidradenitis Suppurativa Trust
   - British Association of Dermatologists, *endorsed by the Royal College of Physicians*

7. **Expert statements** from:
   - Dr Anthony Bewley, Dermatology Consultant – clinical expert, nominated by AbbVie
   - Mrs Tara Burton – patient expert, nominated by The Hidradenitis Suppurativa Trust
   - Miss Ceri Harris – patient expert, nominated by The Hidradenitis Suppurativa Trust

8. **Evidence Review Group report** prepared by School of Health and related Research (ScHARR)

9. **Evidence Review Group report – factual accuracy check**

10. **Erratum to Evidence Review Group report** prepared by School of Health and Related Research (ScHARR**)**

11. **Evidence Review Group addendum report** prepared by School of Health and Related Research (ScHARR)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Adalimumab for treating moderate to severe hidradenitis suppurativa

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report, addendum and errata.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

Clinical effectiveness

Generalisability

- Are results from the adalimumab PIONEER trials generalisable to patients seen in clinical practice in England?
  - The trials recruited people with moderate to severe hidradenitis suppurativa who were intolerant, or whose disease had not responded, to oral antibiotics. People who had received TNF-inhibitors were excluded.
  - There was no requirement for trial patients to have tried other treatments for their hidradenitis suppurativa. Average duration of disease was approximately 12 years.
  - PIONEER I excluded people taking oral antibiotics but permitted rescue therapy; PIONEER II allowed concomitant treatment with oral or topical antibiotics.

  - Surgery was not permitted during the trials (intralesional corticosteroid injection, and incision and drainage of lesions, were permitted).
  - "Supportive care" interventions, such as tobacco cessation or weight control counselling were not permitted.
  - No-one was recruited from UK sites.
  - Hidradenitis suppurativa is more common in people of African family origin.
- What are the most clinically meaningful endpoints in hidradenitis suppurativa?
  - Is the Hidradenitis Suppurativa Clinical Response (HiSCR) used? Is it used alone or alongside other instruments and tools?

Treatment pathway

- What is the relevant comparator for adalimumab based on current clinical practice?
  - Should infliximab be considered a comparator? Is there a subgroup for which infliximab would be more appropriate than adalimumab?
  - Will antibiotics and surgery be used alongside adalimumab?

Effectiveness

- Is it appropriate to pool results from the PIONEER I and II trials?
- Evidence for efficacy for up to 72 weeks was from a single non randomised, non-controlled, unblended open-label extension study. Is this sufficient for a drug that might be taken for many years?
- Is there robust evidence to show that adalimumab improves health-related quality of life relative to placebo?

Assessing response to treatment and implementing stopping rules

- The Summary of Product Characteristics (SmPC) recommends adalimumab for people with hidradenitis suppurativa "with an inadequate response to conventional systemic HS therapy". How is an inadequate response to treatment defined in clinical practice?
- The SmPC for adalimumab recommends "continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period." What constitutes "no improvement" in clinical practice?

  - Would treatment be continued beyond 12 weeks in people who have a partial HiSCR response to treatment (defined as at least a 25% reduction in total Abscess and inflammatory Nodule [AN] count)?
- If someone on long-term treatment with adalimumab (longer than 36 weeks) was not responding to treatment, would treatment be stopped immediately or after a period of reassessment?

Cost effectiveness

Generalisability and robustness

- Is the model, which is based on depth of HiSCR, appropriate, since it does not reflect the primary endpoint in the clinical trials? Does it reflect what happens in clinical practice?
- Are the utility estimates in the company model appropriate and robust, given that EQ-5D data were only collected in the PIONEER II trial?
- Was it appropriate for the company to exclude adverse-event related disutilities from the model?

Costs and resource use

- Was it appropriate for the company to exclude the cost of concomitant medications from the model?
- Was it appropriate for the company to model resource use according to depth of HiSCR response, and independently of treatment received?
- Estimation of surgical inpatient admissions was a key cost driver in the model.
  - How many surgeries do people receiving supportive care require over their lifetime? What proportion involve extensive surgery (that is, wide excisions) or inpatient stays, and for how long?
- The company model assumed that adalimumab reduced the number of inpatient admissions relative to supportive care.
  - Is there evidence to show that adalimumab reduces surgical procedures, particularly those requiring an inpatient stay, relative to supportive care?

Treatment discontinuation

- In the company model, people who had at least a partial response (at least a 25% reduction in total AN count) after 12 weeks of treatment continued treatment. Is this reflective of the evidence base and clinical practice?
- Have the company modelled long-term discontinuation rates (beyond 36 weeks) accurately?

Long-term projections

- How reliable are the company estimates of long-term transition probabilities (beyond 36 weeks)?
- Were the company's methods for imputing missing data appropriate?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of adalimumab within its marketing authorisation for treating moderate to severe hidradenitis suppurativa. Table 1 summarise the decision problem.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the Evidence Review Group (ERG)
Population	Adults with active moderate to severe HS which has not responded to conventional therapy	As in the scope	-	-
Intervention	Adalimumab	As in the scope	Antibiotics can also be used alongside adalimumab	-
Comparator	Established clinical management without adalimumab	As in the scope where data allows	Adalimumab would be used after all conventional systemic treatments (antibiotics, dapsone, retinoids and immunomodulators), therefore the appropriate comparator is supportive care (including surgery and non-surgery related hospital visits and A&E attendances) represented by the placebo trial arms.	Infliximab could be an appropriate comparator, because it is used interchangeably with adalimumab. The company did not perform mixed/indirect treatment comparisons for any outcome and did not compare adalimumab with any specific pharmacological agent or surgical procedure.
Outcomes	• Disease severity • Clinical response • Inflammation and fibrosis • Discomfort and pain • AEs of treatment • Health-related quality of life	As in the scope	New endpoint developed for phase III trials (HiSCR) and validated against other measures of response in HS (Hurley stage, Modified Sartorius Score and HS-Physician's Global Assessment).	See sections 5.3 and 5.10 for the ERG's critique of how the company modelled HiSCR response and treatment continuation based on response.
Abbreviations: AE, Adverse Effect; AN, Abscess and inflammatory Nodule; HiSCR, HS Clinical Response; HS, Hidradenitis Suppurativa				

2 The technology and the treatment pathway

2.1 There is no standard treatment pathway for hidradenitis suppurativa and NICE has not published guidelines on its management. Local or mild disease is usually managed with topical antibiotics, and systemic (oral) antibiotics are typically used for widespread or severe disease. The severity of hidradenitis suppurativa is assessed using a variety of instruments, including the Hurley staging system, the Modified Sartorius Score (MSS) and the 6-point Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) (Table 2).

Table 2 Assessing the severity of Hidradenitis Suppurativa

Instrument	Detail
Hurley staging system	• **Stage I (mild):** single or multiple isolated abscesses; without scarring, fibrosis or sinus tracts • **Stage II (moderate):** recurrent abscesses, single or multiple widely separated lesions; with scarring, fibrosis and sinus tracts • **Stage III (severe):** diffuse or broad involvement, with multiple interconnected sinus tracts and abscesses across entire area
Modified Sartorius Score (MSS)	Counts involved regions, nodules and sinus tracts (a higher score reflects more severe disease) • **Anatomic region involved (7 regions):** 3 points per region involved • **Number and severity of lesions:** 1 points for each nodule, 3 points for each fistula • **Longest distance between 2 relevant lesions**: 1 point for <5 cm; 3 points for 5–10 cm; 9 points for >10 cm • **Lesions clearly separated by normal skin in each region:** 0 points if yes; 9 points if no
Hidradenitis Suppurativa Physician Global Assessment (HS-PGA)	• **Clear:** 0 abscesses, 0 draining fistulas, 0 inflammatory nodules and 0 non-inflammatory nodules • **Minimal:** 0 abscesses, 0 draining fistulas, 0 inflammatory nodules and presence of non-inflammatory nodules • **Mild:** 0 abscesses, 0 draining fistulas, and 1–4 inflammatory nodules; OR 1 abscess or draining fistula and 0 inflammatory nodules • **Moderate:** 0 abscesses, 0 draining fistulas, and ≥5 inflammatory nodules; OR 1 abscess or draining fistula and ≥1 inflammatory nodule; OR 2–5 abscesses or draining fistulas and <10 inflammatory nodules • **Severe:** 2–5 abscesses or draining fistulas and ≥10 inflammatory nodules • **Very severe:** >5 abscesses or draining fistulas

2.2 There is currently no known effective monotherapy for treating hidradenitis suppurativa, and therefore a combination of different treatment types is often used. The company that manufactures adalimumab surveyed UK clinicians about current clinical management of hidradenitis suppurativa and found that, after topical antibiotics, the most commonly used treatments in the UK are oral tetracycline antibiotics, followed by a combination of clindamycin and rifampicin. The duration of treatment depends on how the condition responded to treatment. The third, fourth, fifth and sixth choice interventions were acitretin, isotretinoin, dapsone, and ciclosporin. None of these treatments have a marketing authorisation in the UK for hidradenitis suppurativa. The company submission suggested that adalimumab, and other tumour necrosis factor (TNF)-inhibitors such as infliximab and etanercept, are used only if the condition has not responded to all of the treatment options listed above. That is, adalimumab is used after all other conventional treatment options. Surgery may be considered if the condition does not respond to pharmacological treatments, and might involve simple local incision and drainage to treat an acute flare up of the disease (rather than to control the disease or reduce recurrence), narrow margin excision or wide margin excision for people with advanced disease. The company suggested, in its response to clarification, that adalimumab can be used before or after surgery.

Table 3 Technology: Adalimumab (Humira, AbbVie)

Marketing authorisation	The treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic hidradenitis suppurativa therapy.
Administration method	Subcutaneous injection. **Day 1:** 160 mg (4 X 40 mg injections in 1 day or 2 X 40 mg injections per day for 2 consecutive days) **Day 15:** 80 mg (2 X 40 mg injections) **Day 29 onwards:** 40 mg every week. Antibiotics may be continued. People should use a topical antiseptic wash on their hidradenitis suppurativa lesions on a daily basis. Continued therapy beyond 12 weeks should be carefully reconsidered in someone with no improvement within this time period. The benefit and risk of continued long-term treatment should be periodically evaluated. Source: summary of product characteristics
Cost	£352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial (excluding VAT, British national formulary [BNF] online December 2015). There are no administration costs because adalimumab will be provided via AbbVie Care (home care company) and administered in the patient's home (source: company submission page 27). When the patient access scheme was incorporated, the drug costs for adalimumab was [redacted] for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial.
See summary of product characteristics for details on adverse reactions and contraindications	

3 Comments from consultees

3.1 Patient experts reported that moderate to severe hidradenitis suppurativa has a substantial impact on quality of life and activities of daily living. The painful abscesses severely impact mobility, meaning that simple everyday tasks like getting dressed or walking up the stairs are very difficult, or even impossible. This has an impact on family life, for example making it difficult to take care of children. In addition, self-care is time consuming; patient experts reported needing to take a shower up to 3 or 4 times a day, after which they must dress all open wounds. If leakage from open

wounds is severe, dressings need to be changed 3 or 4 times a day. As a result, people may need to give up work. People with hidradenitis suppurativa experience pain on a daily basis and can have severe scarring and disfigurements as a result of the condition. Patients often report low self-esteem, low body image and depression. Relationships can also break down because intimacy becomes problematic, and people with the condition often become isolated from friends and family.

3.2 Patient experts expressed frustration at the lack of awareness of hidradenitis suppurativa and the length of time it takes to be diagnosed; the limited support from the medical community and family and friends; and the absence of treatment guidelines. Clinical experts agreed that many non-dermatologists have limited experience of treating people with hidradenitis suppurativa. Patient experts noted that treatment plans are generally trial and error, and change frequently, which is both upsetting and time consuming. Some treatments can make symptoms worse, or introduce new symptoms and side effects, and can include frequent travel to hospital. Patient experts explained that people with less severe disease (Hurley stage I–II) generally still maintain a good quality of life without the need for intense treatment.

3.3 The key outcomes for patients are to gain control over current disease activity, prevent future flare ups and reduce pain. Reducing scarring, disability, and odour or leakage from open wounds is also important. Some patients might be concerned about the potential adverse effects of adalimumab; patient experts cited an increased risk of cancer or infections as examples. But they felt that the self-administration of adalimumab was an advantage and would promote self-awareness and self-management of the condition.

3.4 Clinical experts reported that hidradenitis suppurativa does not respond to conventional treatment in about 10% of people with the condition, and suggested that adalimumab can be effective for these people. They stated that treatment with adalimumab can be “revolutionary” in the management

of both the physical symptoms and the emotional impact of disease. Professional groups noted that there is a lack of long-term safety data for adalimumab every week, however the existing data do not indicate any safety concerns.

3.5 The submission from a professional group presented a similar treatment pathway to that described in the company submission (see section 2.2), and agreed with the company's position of adalimumab after all other conventional treatments. It noted that the main alternative to adalimumab is infliximab, but suggested that the evidence base for infliximab was weaker, and its intravenous route of administration is less convenient, than adalimumab.

3.6 The professional group's submission suggested that the rules for starting and stopping adalimumab treatment should be based on both physician and patient-reported outcome measures, because there are limited validation data for the measure used in adalimumab clinical trials (Hidradenitis Suppurativa Clinical Response [HiSCR]). It suggested that, if using the HiSCR, a 50% reduction in AN count (that is, a complete response) represents treatment success. It noted that the physician's global assessment (PGA) is an alternative measure that is quicker to perform. The professional group provided an indication of how to define response using patient-reported outcomes and suggested that the disease's response to treatment with adalimumab should be assessed after 16 weeks:

- the minimal clinically important difference on the Dermatology Life Quality Index (DLQI) is 4 points
- a 50% reduction in baseline pain (which can be measured on a visual analogue scale [VAS]) is usually considered an adequate response.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The clinical evidence for adalimumab in hidradenitis suppurativa came from 3 randomised double-blind trials, comprising 2 phase III trials (PIONEER I [n=307] and PIONNER II [n=326]) and a phase II trial (M10-467 [n=154]). All 3 trials compared adalimumab with placebo in adults aged 18 years or older with moderate to severe hidradenitis suppurativa who were intolerant to, or whose disease had not responded to, oral antibiotics. The inclusion criteria for the trials is summarised in Table 4. People who had received TNF-inhibitors were excluded. The primary outcome differed between the phase II and phase III trials:

- **M10-467**: proportion of people with a Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) score of clear, minimal or mild, with at least a 2 grade improvement relative to baseline at week 16.
- **PIONEER I and II:** proportion of people with a Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12. HiSCR is defined as at least a 50% reduction in the total Abscess and inflammatory Nodule (AN) count with no increase in abscess count or draining fistula count. HiSCR was an endpoint developed by the company in consultation with regulatory health authorities and was been validated against other measures of response in hidradenitis suppurativa.

Table 4 Inclusion criteria for trials of adalimumab for hidradenitis suppurativa

	M10-467	**PIONEER I and II**
Duration of disease	≥6 months	≥1 year
Presence of lesions	≥2 distinct anatomic regions	
Instrument(s) used to assess disease severity (see Table 2)	HS-PGA score of moderate or worse	• Hurley stage II or III in ≥1 affected anatomic region • AN count >3
Previous treatment with antibiotics	Patient is intolerant to, or disease has not responded to, oral antibiotics (after ≥90 days). Inadequate response defined as any of the following: • worsening of Hurley Stage in ≥1 affected anatomic region • increased number of affected anatomic regions • ≥1 new abscess or one new draining fistula requirement for intervention (such as incision and drainage or local corticosteroid injection) • pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics • pain requiring opioids • discharge from lesions interfering with activities of daily living.	
Ongoing antibiotic treatment	Concomitant treatment with oral or topical antibiotics permitted	• PIONEER I: rescue therapy permitted. • PIONEER II: concomitant treatment with oral or topical antibiotics permitted
Abbreviations: AN, Abscess and Inflammatory Nodule; HS-PGA, Hidradenitis Suppurativa Physician Global Assessment **Source:** company submission pages 57–67 and response to clarification question A16		

4.2 The phase II (dose-finding) M10-467 trial compared 2 dosing regimens for adalimumab for 16 weeks (period 1); patients were randomised to either adalimumab 40 mg every week (n=51), adalimumab 40 mg every other week (n=52), or placebo (n=51). All patients who completed period 1 of the trial continued in a 36-week open-label extension of adalimumab every other week. The dosing frequency could increase to 40 mg every week for the rest of the study in patients with a HS-PGA score of moderate or worse (a score greater than 3) at weeks 28 or 31. The trial allowed concomitant treatment with oral (tetracycline, doxycycline, or minocycline) or topical (clindamycin) antibiotic treatment if the patient had received a stable dose for at least 4 weeks before the first study visit, and stayed on a stable dose during the study. The trial was conducted in 26 centres in the USA and Europe (Germany, Denmark, the Netherlands).

4.3 PIONEER I and PIONEER II had very similar methodology but differed in the countries involved, the concomitant treatments permitted, and the method for re-randomising people in the placebo arm. Both trials included 2 study periods and an open-label extension study.

- **Period A (12 weeks 'induction'):** people were randomised to adalimumab 40 mg every week or placebo.
- **Period B (24 weeks 'maintenance'):** people who received adalimumab 40 mg every week in period A were re-randomised to either adalimumab 40 mg every week, adalimumab 40 mg every other week or placebo. In PIONEER I, people who received placebo in period A were re-randomised to adalimumab 40 mg every week, whereas in PIONEER II people who received placebo in period A remained on placebo for period B.

Eligibility for period B depended on clinical response at the end of period A. People who had a clinical response (HiSCR) at week 12 were enrolled in period B until the end of week 36, but were excluded from the study if their condition stopped responding to treatment with adalimumab. People who did not have an HiSCR response at week 12 were enrolled in period B until week 16; if the severity of their hidradenitis suppurativa worsened or did not improve after week 16 they were excluded from the study. The open-label extension study included people who:

- completed PIONEER I or II (whose disease responded to treatment)
- had an HiSCR response at the start of period B then experienced loss of response (defined as AN count greater than the average AN counts at baseline and week 12)
- did not have an HiSCR response at the start of period B, then experienced worsening or absence of improvement (WOAI) on or after week 16 (defined as an AN count greater than the baseline AN count at 2 consecutive visits at least 14 days apart, excluding week 12).

4.4 In PIONEER II, people were allowed to take oral antibiotic treatment (doxycycline or minocycline) for their hidradenitis suppurativa if they had received a stable dose for at least 4 weeks before the first study visit, and stayed on a stable dose during the study. People were excluded from PIONEER I people if they had received oral antibiotics for hidradenitis suppurativa within 4 weeks of the trial starting, but were allowed rescue therapy with doxycycline or minocycline. Supportive care interventions (such as tobacco cessation or weight control counselling) were not given to anyone in the trials, but everyone was instructed to use a daily antiseptic wash on the areas affected by hidradenitis suppurativa. The company stated during clarification, and after checking the ERG report for factual inaccuracies, that extensive surgical procedures were not permitted during the trials, and that only 2 types of acute surgical interventions were permitted:

- corticosteroid injection (triamcinolone acetonide suspension) directly into the lesion
- incision and drainage of lesions.

4.5 PIONEER I and II both had study centres in Australia, Canada, Europe, and the USA, but the European countries involved differed:

- PIONEER I was conducted in Denmark, France, Greece, the Netherlands, Sweden, Switzerland, and Turkey
- PIONEER II was conducted in Czech Republic, Germany, and Hungary.

4.6 EuroQol (EQ-5D) data were only collected in PIONEER II. Other quality of life instruments used in the PIONEER studies included the Short Form-36 Health Status Survey (SF-36; PIONEER I only), the Hospital Anxiety and Depression Scale (HADS; PIONEER I only), the Dermatology Life Quality Index (DLQI), Hidradenitis Suppurativa Quality of Life (HSQOL), and the Patient Global Assessment of Skin Pain.

4.7 The company indicated that baseline characteristics were generally similar in the different arms of the trials (see table 11 on page 73 of the company submission). However, people in PIONEER I had more severe disease than in PIONEER II; as demonstrated by higher:

- mean Modified Sartorius Score (MSS) score: 149.1 compared with 115
- Abscess and Inflammatory Nodule (AN) count: 14.3 compared with 11.3
- worst pain score: 5.0 compared with 4.5.

The average duration of hidradenitis suppurativa in the trials was 11.5 years in PIONEER I, 11.6 years in PIONEER II and 10.9–13.4 years in M10-467. There were more women than men in the trials.

4.8 The company acknowledged that none of the clinical trials recruited people from the UK. The company funded a study to compare the baseline characteristics of the adalimumab trials with data from 142 people across 10 UK hospitals (see pages 121–2 and table 37 of the company submission). The company reported that in the study, people from the UK:

- were slightly older (41 years compared with 36.2 years in the overall PIONEER population)
- were less likely to smoke (45% compared with 62%)
- had shorter disease duration (9 years compared with 11.5 years)
- were more likely to have had surgery (41% compared with 12.5%).

The company suggested that the higher levels of prior surgery in the UK study were a reflection of the cohort recruited, which were people who have been seen in secondary care.

ERG comments

4.9 The ERG considered that the company's review of clinical evidence was generally sound but poorly reported. However it criticised the company's

collection of safety evidence and non-randomised or non-controlled studies because it was not systematic.

4.10 The ERG disagreed with some of the company's risk of bias assessments for period B of the PIONEER trials, and the open-label extension study (see section 4.1.4 on pages 23–30 of the ERG report). The ERG considered that:

- period 1 of the M10-467 trial as at a low risk of bias across all domains
- period A of the PIONEER trials was generally at low risk of bias
- there was a moderate or unclear risk of selection and attrition bias for the results of period B in the PIONEER trials, and a low-to-moderate risk of reporting

Clinical trial results

4.11 The primary outcomes from the trials of adalimumab are presented in Table 5. In all 3 studies, more people treated with adalimumab had a clinical response (defined using HS-PGA in M10-467 and HiCSR in PIONEER) than patients receiving placebo; these differences were statistically significant in all 3 trials. The company did a post-hoc analysis of M10-467 to assess the number of people with a clinical response at week 16 based on HiSCR:

- 59.1% of people receiving adalimumab every week
- 16.3% of people receiving placebo (difference 42.8%, $p<0.007$).

Secondary outcomes are presented on pages 77–8 (M10-467) and 81–4 (PIONEER) of the company submission. The differences between adalimumab and placebo were statistically significant for all secondary outcomes at week 12 in PIONEER II (showing a benefit in favour of adalimumab). None of the differences were significant at week 12 in PIONEER I, although some outcomes showed numerical differences in

favour of adalimumab which were statistically significant at earlier time points (weeks 2, 4 and 8).

Table 5 Primary outcomes for adalimumab 40 mg every week, from phase II and phase III randomised controlled trials

Trial	Intervention	People with clinical response, n (%)	Difference (95% CI)	p value
M10-467[a]	Adalimumab[c] (n=51)	9 (17.6%)	13.7% (1.7% to 25.7%)	<0.025
	Placebo (n=51)	2 (3.9%)		
PIONEER I[b]	Adalimumab (n=153)	64 (41.8%)	15.9% (5.3% to 26.5%)	0.003
	Placebo (n=154)	40 (26.0%)		
PIONEER II[b]	Adalimumab (n=163)	96 (58.9%)	31.5% (20.7% to 42.2%)	<0.001
	Placebo (n=163)	45 (27.6%)		

[a] M10-467 definition of clinical response: proportion of people with a Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) score of clear, minimal or mild, with at least a 2 grade improvement relative to baseline at week 16
[b] PIONEER definition of clinical response: proportion of people with a Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12
[c] Results for the 40 mg every week (licensed) dose of adalimumab; results for the every other week dose of adalimumab from M10-467 can be found in the company submission
Source: company submission pages 76–81

4.12 Subgroup analysis of the PIONEER trials showed that the difference between adalimumab and placebo was significant regardless of Hurley status (post-hoc analysis of PIONEER I and II) and antibiotic use (pre-planned analysis of PIONEER II only; PIONEER I did not allow concomitant antibiotics) (see table 14 of the company submission). Pre-planned subgroup analyses according to other demographic and baseline characteristics (including age, sex, race, duration of disease, smoking) showed that treatment by subgroup interactions were not significant in either of the PIONEER studies. A consistent treatment effect was observed across most subgroups, with a few exceptions in subgroups with small sample sizes (see pages 95–98, including figures 19 and 20, of the company submission).

4.13 The company stated that the benefits observed with adalimumab at 12 weeks were maintained up to 36 weeks (period B) in the PIONEER studies, but did not report whether differences were statistically significant. The company provided an interim analysis of the primary endpoint from the open-label extension study, noting that patient numbers were small. It reported that, among people who received the adalimumab every week dose throughout the trial, the proportion with a complete HiSCR clinical response was [redacted], [redacted] and [redacted] at weeks 48, 60, and 72 (see page 106 of the company submission for full results).

4.14 A post-hoc analysis of pooled data from the PIONEER studies and the open-label extension study showed that the continued benefit of adalimumab was observed in people with a partial response (defined as at least a 25% reduction in the total AN count with no increase in abscess count or draining fistula count), as well as people with a complete HiSCR clinical response (see table 20 on page 90 of the company submission). The proportion of people with a response decreased over time in all arms (see figure 17 on page 89 of the company submission). The company suggested that the apparent reduction in HiSCR over time in period B was probably because of study design: people discontinued if their disease stopped responding to treatment, and they were classified as a non-responder even though they could have a clinical response at a later date (captured in the open-label extension study).

4.15 In PIONEER I and II, adalimumab was associated with significant improvements in health-related quality of life compared with placebo after 12 weeks, as measured by the EQ-5D, the physical components of SF-36, DLQI and the HSQOL. The difference between adalimumab and placebo in the mental component of the SF-36 was not significant. See pages 84–88 of the company submission.

ERG comments

4.16 The ERG noted that adalimumab appeared to be more effective, relative to placebo, in people with Hurley Stage III than in people with Hurley Stage II disease (Table 6).

Table 6 Primary outcome in PIONEER studies: difference between adalimumab and placebo

	Proportion of people with HiSCR: difference between adalimumab and placebo arms	
	Hurley Stage II	**Hurley Stage III**
PIONEER I	14.8%	17.1%
PIONEER II	25.5%	38.1%
Abbreviations: HiSCR, Hidradenititis Suppurativa Clinical Response **Source:** company submission table 14		

4.17 The ERG noted that the benefit with adalimumab was greater in PIONEER II than PIONEER I: the difference in clinical response between arms in PIONEER II was double that of the PIONEER I trial (31.5% compared with 15.9%, see Table 5). The effect of adalimumab on the secondary outcomes was also greater in PIONEER II. The ERG suggested this might be because PIONEER II participants appear to have had less severe disease than people in PIONEER I (see section 4.7), and had potentially received higher levels of systemic antibiotics due to the study inclusion criteria. The ERG suggested that any relationship between level of clinical response and Hurley Stage or other measures of disease severity (Table 6) is therefore uncertain. The ERG noted that the company acknowledged these uncertainties in its submission.

4.18 The ERG had concerns about the company's assertion that adalimumab may delay or reduce the need for surgery (see page 118 of the company submission), because this potential treatment benefit was not substantiated by empirical evidence in the company submission. In response to clarification (see question B5), the company did a post-hoc analysis using pooled data from the PIONEER studies to assess the use of incision and drainage procedures and steroid injections as surrogate

markers for surgical interventions. The results of the company's analysis showed that at week 12, a greater proportion of people who received adalimumab, compared with placebo, experienced elimination of both draining fistulas (33% compared with 19%; p<0.001) and non-draining fistulas (15% compared with 9%; p=0.017). But the ERG was unclear whether this fully reflected an overall reduction in surgery, particularly inpatient surgical admissions, which were a key cost driver in the company's model (see section 5.20).

Meta-analyses

4.19 The company concluded a network meta-analysis was not feasible for the following reasons (see appendix 5 of the company submission):

- the networks of evidence for all outcomes of interest were small (fewer than 4 nodes)
- there was variation in baseline characteristics which were potential treatment effect modifiers, and insufficient trials to adjust for these characteristics to produce unbiased estimates of treatment effects
  - some variation in age, gender, race, and proportion of smokers at baseline across trials
  - substantial differences in C-reactive protein levels and disease severity at baseline between studies of adalimumab and infliximab
- accounting for bias would not be feasible because of the poor reporting of baseline characteristics.

ERG comments

4.20 The ERG noted that the company had not found any evidence that the specified subgroups were treatment effect modifiers in PIONEER I and that AN count was the only potential treatment effect modifier in PIONEER II. However, the ERG recognised that other trial characteristics may have been treatment effect modifiers. The ERG noted that there are methods available which may have enabled the company to compare the clinical trials of different treatments, for example, matching-adjusted treatment

comparisons or simulated treatment comparisons. However, the ERG acknowledged that the value of using such comparisons to inform the company's model would be limited (or an entirely different model would be required), because only the adalimumab trials assessed response according to the HiSCR measure.

Adverse effects of treatment

4.21 The company reported that the most common adverse events with adalimumab were exacerbation of hidradenitis suppurativa, nasopharyngitis and headache. These were typically of mild to moderate severity. The company noted that during the first 12 weeks of both PIONEER studies (period A), adverse events were less common in people treated with adalimumab than in people treated with placebo (PIONEER I: 52.9% of people in the adalimumab arm compared with 61.8% of people in the placebo arm had adverse events; PIONEER II: 57.7% in the adalimumab arm compared with 66.9% in the placebo arm). Discontinuation due to adverse events was less common with adalimumab than placebo in the first 12 weeks of treatment (see table 31 on page 111 of the company submission). The company reported that the open-label extension study did not identify any new safety risks for adalimumab (see pages 114–5 of the company submission for the results)

ERG comments

4.22 The ERG stated that there were no obvious tolerability concerns associated with adalimumab treatment. It suggested that longer-term data are required to determine whether reported adverse events rates are maintained for people who continue to receive adalimumab, whether or not certain subgroups of people are at higher risk of certain events, and to confirm whether or not there are any changes to tolerability if treatment is interrupted.

5 Cost-effectiveness evidence

Model structure

5.1 The company provided a Markov model to assess the cost effectiveness of adalimumab compared with supportive care in adults with moderate to severe hidradenitis suppurativa whose disease has not responded to conventional treatment (see Figure 1). The model used a lifetime horizon (66 years), with a cycle length of 4 weeks (except for the first 2 cycles which were 2 weeks each). The company discounted costs and benefits at 3.5% per year and applied a half cycle correction. The company stated that costs were from the perspective of the NHS and Personal Social Services.

5.2 All patients enter the model in the non-response health state and then transition between 5 health states based on their responses to treatment and natural mortality rate. Four of the health states were defined according to varying levels of response to treatment based on the primary efficacy measure in the PIONEER I and II studies (the Hidradenitis Suppurativa Clinical Response [HiSCR]):

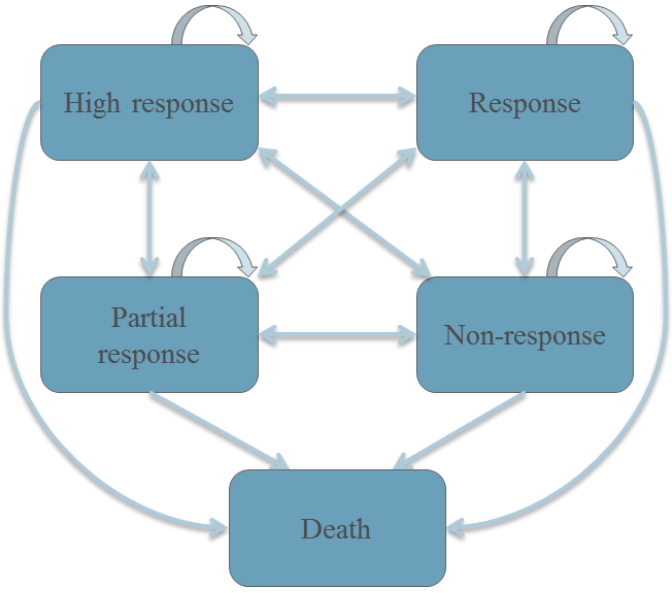
- **High response:** ≥75% reduction in total Abscess and inflammatory Nodule (AN) count with no increase in abscess count or draining fistula count
- **Response:** 50–74% reduction in total AN count with no increase in abscess count or draining fistula count
- **Partial response:** 25–49% reduction in total AN count
- **Non-response**: <25% reduction in total AN count
- **Death**

The high response and response health states together constitute the complete HiSCR response. People in the partial response and non-response health states would have been classified as HiSCR

non-responders in the PIONEER trials. The company provided a number of justifications for splitting the HiSCR into 4 health states:

- there was a statistically significant difference in the utility values between the high response and response health states (p=0.036), and between the utility values of the partial response and non-response health states (p=0.034)
- the difference in the response rates between adalimumab and placebo were statistically significant across 3 of the 4 response health states (high response, response and non-response; see table 13 on page 28 of the company response to clarification)
- resource use differed across the 4 health states (see table 51 on page 29 of the company response to clarification)
- a post-hoc analysis of the PIONEER studies identified a population where continued treatment with adalimumab could be beneficial (that is, people with a partial response or higher).

Figure 1 Diagram of the company's model (figure 22 on page 134 of the company submission)



High response: ≥75% reduction in total Abscess and inflammatory Nodule (AN) count with no increase in abscess count or draining fistula count (HiSCR responder)
Response: 50–74% reduction in total AN count with no increase in abscess count or draining fistula count (HiSCR responder)
Partial response: 25–49% reduction in total AN count (HiSCR non-responder)
Non-response: <25% reduction in total AN count (HiSCR non-responder)

ERG comments

5.3 Given that the HiSCR is a dichotomous outcome (that is, either a person has a clinical response or does not), the ERG had concerns about the company's decision to model 4 health states according to the depth of HiSCR response. The ERG noted that primary endpoint in the PIONEER trials of adalimumab was complete HiSCR response (defined as at least a 50% reduction in total AN count, with no increase in abscesses or draining fistulas from baseline), and therefore considered that the company's modelling approach represented a post-hoc analysis of a pre-planned endpoint. The ERG noted that the company's approach results in inconsistency in the interpretation of data from the PIONEER trials, because people who would be classed as partial responders in the model would have been considered to be non-responders in the clinical analysis. The ERG also reported that the company's 4-state model is not consistent with the findings of the validation study of the HiSCR measure by Kimball (2014), which related only to complete HiSCR response (see pages 102–3 of the ERG for full details). The ERG noted that it could be argued that the 50% AN reduction threshold determined in the validation study has been set at the wrong level for clinical practice. The ERG was also concerned that dividing the efficacy data across 4 rather than 2 health states resulted in small sample sizes for the calculation of some transition probabilities, which could be considered as a matter of structural uncertainty.

5.4 Following clarification, the company produced the results of an analysis with 2, rather than 4, response states: HiSCR response and non-response (see company response to clarification question B2). The ERG reported inconsistencies in the company analysis and stated that the results had limited value (see company response to clarification question B2 and pages 103–104 of the ERG report); the ERG undertook its own exploratory analyses to address these issues, although these did not form

part of its preferred base case (analysis 7 and 8, see section 5.24 for the assumptions and Table 13 for the results).

Model details

5.5 The company based the efficacy of adalimumab on pooled data from the PIONEER I and II trials (using an integrated arm-based summary), using results from the adalimumab 40 mg every week dosing regimen to be consistent with the marketing authorisation. The company compared adalimumab with supportive care; efficacy data for supportive care were based on the placebo arms in PIONEER clinical trials (see pages 140–141 of the company submission for details). The company stated that it was not appropriate to compare adalimumab with any active pharmacological agents, because adalimumab would be used after all conventional systemic treatments (including antibiotics, dapsone, retinoids and immunomodulators). It noted that antibiotics can also be used alongside adalimumab, and that this was reflected in the clinical trials which allowed concomitant use (PIONEER II) or rescue therapy (PIONEER I). The company stated that surgery was not an appropriate comparator because adalimumab does not represent an alternative choice to surgery; the company noted that people in the adalimumab clinical trials were allowed to have acute surgical procedures (intralesional corticosteroid injection, and incision and drainage of lesions) for symptom control.

5.6 The depth of HiSCR response at 12 weeks determined whether patients continued receiving adalimumab. People who had at least a partial response (at least a 25% reduction in total AN count) after 12 weeks continued treatment. For patients who continued receiving adalimumab after 12 weeks, there was an ongoing chance of stopping treatment at any time point:

- **Weeks 12–36:** the company used discontinuation rates from the PIONEER studies, based on people who had a response at 12 weeks, to estimate 4-week discontinuation rates for the model. The company

applied the same discontinuation rate to everyone receiving adalimumab, regardless of their response state.

- **Long term discontinuation (beyond 36 weeks):** the company used data from the open-label extension studies to estimate discontinuation rates specific to each response state (Table 7). The company's application of discontinatuion rates intended to reflect its assumption that people in the non-response health state at 36 weeks would continue treatment for an additional 12 weeks, not stopping until 48 weeks, based on clinical advice and recommendations in the adalimumab Summary of Product Characteristics.

People who stopped adalimumab treatment (at either 12 weeks, or later) were assumed to move on to supportive care.

Table 7 Discontinuation rates for adalimumab after 12 weeks

	Annual rate	4-week rate
Maintenance period (week 12–36)		
All states	20.48%	1.75%
Maintenance period (after week 36)		
High response, response or partial response	7.47%	0.60%
Non-response	44.99%	4.49%

5.7 The company estimated the transition probabilities between health states for the first 36 weeks of treatment using the distribution of people across the 4 response health states in the PIONEER clinical trials. The transition probabilities were estimated separately for each arm and each cycle, based on the distribution of people across the health states at each trial assessment visit. The company imputed missing values using the same imputation method specified in the clinical trial protocol for analysis of the primary endpoint (non-responder imputation). The company considered an alternative imputation method (last observation carried forward [LOCF]) in sensitivity analyses. To extrapolate data beyond what was available from clinical trials (that is, beyond 36 weeks), the company used

separate generalised logit models from different sources depending on the treatment received:

- for people who continued receiving adalimumab, the company used data from the open-label extension study
- for people who stopped adalimumab treatment and people receiving supportive care, separate models were fitted using data from period B of the PIONEER trials.

The company used LOCF for missing data.

5.8 The company assigned utility values to each health state in the model using EQ-5D data collected in the PIONEER II clinical trial (Table 8). The model did not incorporate reductions in utility values (disutilities) from treatment-related adverse events. The company stated that this was likely to have minimal impact on the results because the adverse event rates were similar between people who received adalimumab and people who received placebo in the PIONEER clinical trials.

Table 8 EQ-5D derived utility values in the company model

Model health state	Utility value	95% confidence interval	P value[a]
High response	0.782	0.746 to 0.816	0.036
Response	0.718	0.667 to 0.766	
Partial response	0.576	0.512 to 0.639	0.034
Non-response	0.482	0.402 to 0.542	

[a] p values reflect the significant differences in utility values between the high response and response health states, and the difference between the partial- and non-response states
Source: company response to clarification, page 28

5.9 The company included the following costs in its model:

- treatment costs
- adverse event-related costs, for adverse events with an incidence of 5% or more in the PIONEER trials

- resource use costs: in-patient stays, outpatient visits, visits to wound-care (each divided into surgery-related and non-surgery related) and A&E visits; assigned to each health state independent of the treatment received
- one-off set up costs (£0.70 per patient) and ongoing operational costs (£8.21 per 4-week cycle) associated with the patient access scheme (see the company's PAS submission for the derivation of these costs).

Adalimumab costs were taken from the British National Formulary 2015 and the average cost of adalimumab was £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial. When the patient access scheme was incorporated, the drug cost for adalimumab was [redacted] for a 40 mg pre-filled pen or pre-filled syringe. The cost of adalimumab was based on the dosing schedule and unit cost, and took into account compliance rates in the PIONEER clinical trials. The company did not include any drug costs for supportive care because it considered that any of the conventional treatments taken by people receiving supportive care would also be taken, less frequently, by people receiving adalimumab. The company considered that adding the cost of these therapies would improve the cost effectiveness of adalimumab. The company estimated resource use based on the results of a survey of 40 physicians who treat people with moderate to severe hidradenitis suppurativa in the UK. The company obtained costs associated with each type of resource use from NHS reference costs 2013–2014 (Table 9).

Table 9 Company estimates of resource use, according to health state

Type of visit (unit cost per day/visit)	Resource use by health state (average number of units per year)			
	High response	Response	Partial response	Non-response
A&E visits (£123.67)	0.12	0.20	0.47	0.57
Surgery-related				
Hospitalisations (£5488.32)	0.13	0.22	0.54	0.80
Outpatient visits (£97.63)	0.22	0.35	0.67	0.94
Visits to wound-care (£97.63)	0.12	0.17	0.40	0.85

Type of visit (unit cost per day/visit)	Resource use by health state (average number of units per year)			
	High response	Response	Partial response	Non-response
Not surgery-related				
Hospitalisations (£2202.14)	0.11	0.23	0.29	0.45
Outpatient visits (£97.63)	3.10	3.51	4.44	4.68
Visits to wound-care (£97.63)	0.67	0.47	0.64	0.45

According to the ERG (see page 106 of the ERG report) the company model predicted an average of 33.87 inpatient surgical admissions for people receiving supportive care, and 29.78 for people receiving adalimumab; the average surgery-related hospital stay lasted 5.1 days (see page 106 of the ERG report).

ERG comments

Treatment continuation rules

5.10 The ERG highlighted that the Summary of Product Characteristics (SmPC) for adalimumab does not define "improvement" in its recommendation that "continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period". The ERG questioned whether the company's assumption that people continued treatment if they had at least a 25% reduction in total AN count after 12 weeks (a partial response or higher; see section 5.6) reflects what would happen in clinical practice, suggesting that this is not consistent with the primary endpoint in the trials. During clarification (see question B2), the company explained that a post-hoc analysis of the PIONEER trials indicated that people with a partial response after 12 weeks continued to benefit from treatment. The ERG assessed the impact of changing treatment continuation rules after week 12 in an exploratory analysis, although this did not form part of its preferred base case (analysis 6 and 8, see section 5.24 for the assumptions and Table 13 for the results).

5.11 The ERG raised some issues with the company's assumption that adalimumab treatment is not stopped immediately if the disease is not responding to treatment after 36 weeks (see section 5.6). The model allowed for a further 12 weeks (3 model cycles) of treatment, in line with the SmPC recommendation that "the benefit and risk of continued long-term treatment should be periodically evaluated". The ERG was satisfied that people may continue to receive treatment for some time after response is lost, but it was concerned that the SmPC does not define how to assess the benefits and risks of continued long-term treatment, and considered that using only the HiSCR may not be sufficient (see also comments from professional groups in section 3.6). The ERG also identified an error in the way that the company had implemented this assumption in the model; it did not consider the company's method to be mathematically correct (see pages 112–116 of the ERG report for the details). The ERG explained that the impact of the company's approach is that people stop adalimumab more quickly than the rate observed in the open-label extension study, thereby substantially reducing the total adalimumab treatment costs and improving its cost effectiveness when compared with supportive care. The ERG suggested that the mathematically correct approach would be to incorporate memory into the model by using additional health states (tunnel states), which it did in its preferred base case (analysis 2 and 3, sections 5.22–5.25).

Transition probabilities

5.12 The ERG had concerns about the uncertainty in transition probability estimates beyond week 12, attributed to the small sample sizes in the maintenance period of the trials and lack of long-term data (see table 50 on page 107 of the ERG report), and noted that the company model was sensitive to altering these estimates (see section 5.20).

5.13 The ERG considered that the company used an inappropriate method to pool data from PIONEER I and II trials, in order to inform the transition probabilities in the model, and noted that the ICER for adalimumab

increased in the company's scenario analysis using only PIONEER II data. The ERG explained that the company's method of synthesising arm-based data from different trials was not appropriate because it breaks the randomisation within the trials. In addition, there were differences in baseline characteristics between PIONEER I and PIONEER II that were potential treatment effect modifiers, and differences in study design with respect to concomitant antibiotics, which the company should have addressed by conducting a random effects meta-analysis. The ERG used data from only PIONEER II in an exploratory analysis, although this did not form part of its preferred base case (analysis 4, sections 5.22–5.25).

5.14 The ERG considered that there was a risk of bias and confounding in the model as a result of the company using data from the open-label extension study to model long-term outcomes for people whose disease responds to adalimumab, because the open-label phase was un-blinded and un-randomised. The ERG also raised the following issues with the company's extrapolation of open-label trial data:

- the data from the open-label study and used in the model included people whose disease stopped responding to treatment, which did not reflect the modelled population (people whose response is maintained up to week 36)
- the data used in the model were immature
- the company used LOCF to account for missing data in the open-label study, which the ERG suggested may produce optimistic estimates of treatment effect.

The company model was sensitive to changes in long-term transition probabilities beyond week 36 (see section 5.20), and the ERG used alternative assumptions in an exploratory analysis, although this did not form part of its preferred base case (analysis 5, sections 5.22–5.25).

Costs and resource use

5.15 The ERG's main issue with respect to costs in the model related to the estimation of surgical inpatient admissions (see section 5.9), because this was a key cost driver in the model (see section 5.20). Based on clinical advice, the ERG generated alternative estimates and assumptions (detailed on pages 107–8 of the ERG report), which suggest that the company overestimated the mean cost of inpatient surgical admissions in the model, for both the supportive care and adalimumab groups. The ERG noted that reducing inpatient costs in both arms would increase the ICER for adalimumab because the company model assumed that adalimumab will reduce the number of inpatient admissions relative to supportive care. The ERG used alternative assumptions about the cost of surgical inpatient admission in its preferred base case (see section 5.23 for the assumptions and Table 13 for the results). However the ERG remained concerned that the company had not provided evidence showing that adalimumab reduces the requirement for overall surgical admissions relative to supportive care, and noted that clinical experts suggested surgery might increase after successful adalimumab treatment (see page 100 of the ERG report).

5.16 The ERG highlighted issues with the company's calculation of the costs and benefits associated with supportive care (see section 5.9). The ERG had concerns about the company using one source to model the benefits of treatment (the clinical trials) and another source to model the resource-use required to achieve these benefits (the physician survey). The ERG was concerned that the company had not included costs of other concomitant pharmacological therapies. The company claimed that fewer pharmacological therapies would be taken by people receiving adalimumab, and in response to clarification it provided trial data showing that concomitant medication was similar across trial arms for the first 12 weeks, but the ERG noted that there were no long term data supporting this assumption. These issues were not explored in either the company's or the ERG's scenario analyses. The ERG was also unsure about the

appropriateness of specifying resource use according to depth of HiSCR response, and used alternative assumptions in an exploratory analysis, although this did not form part of its preferred base case (analysis 7, sections 5.22 –5.25).

Other issues

5.17 In addition to the issues listed above, the ERG also identified some minor errors in the company's model:

- Inconsistent handling of time: in the QALY calculations the company correctly assumed 365.25 days per year, but in other calculations the company assumed 364 days per year.
- Incorrect implementation of cost of adalimumab: the first cycle correctly included health state and adverse event costs, but incorrectly excluded the costs of adalimumab.
- Incorrect implementation of half cycle correction: the QALYs and costs were not adjusted properly in the first cycle.

The ERG corrected these model errors in all of its exploratory analyses (see sections 5.22–5.25).

5.18 The NICE technical team noted that there was no requirement for people in the PIONEER trials to have tried other treatments (such as dapsone, retinoids or immunomodulators) for their hidradenitis suppurativa before starting the trial. The company did not present data on previous treatments taken by study participants, but noted that the average duration of hidradenitis suppurativa in the trials was nearly 12 years. It also noted that the supportive care arm of the model, which is based on the placebo arm of the clinical trials, may not be reflective of clinical practice because the PIONEER trials did permit any supportive care interventions, such as tobacco cessation or weight control counselling (see company response to clarification question A12).

Company's base-case results and sensitivity analysis

5.19 The company's base case deterministic cost-effectiveness analysis showed that adalimumab was more costly and more effective than supportive care, resulting in an incremental cost-effectiveness ratio (ICER) of £15,182 per QALY gained when the discount in the confidential patient access scheme was applied to the price of adalimumab (Table 10). The results of the company's probabilistic sensitivity analysis were very similar, producing an ICER for adalimumab of £16,162 per QALY compared with supportive care. Results from the probabilistic sensitivity analysis indicated that the probability of adalimumab being cost-effective compared with supportive care was 58% and 80% at willingness to pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Table 10 The company's base-case incremental cost-effectiveness analysis results (using adalimumab PAS price, including set up and operational costs of the PAS)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Deterministic analysis					
Supportive care	£128,541	11.61			
Adalimumab	£143,683	12.61	£15,142	1.00	£15,182
Probabilistic analysis					
Supportive care	£128,784	11.61			
Adalimumab	£145,256	12.63	£16,471	1.02	£16,162
Abbreviations: ICER, incremental cost effectiveness ratio; Inc., incremental; PAS, patient access scheme; QALY, quality adjusted life year **Source:** company PAS submission page 20 and ERG addendum					

5.20 The company performed one-way deterministic sensitivity analyses to assess the uncertainty around the parameters and structural assumptions in the model (see pages 190–193 of the company submission). The company performed tests around the 95% confidence interval values of key model parameters, including transition probabilities, discontinuation rates for adalimumab, resource use, unit costs of resource use, adverse event rates and costs, and utilities. The results indicated that the ICER was sensitive to the assumptions about:

- long-term transition probabilities (after week 36)
- number and cost of hospitalisations, specifically the surgery-related hospitalisations, especially in the non-response health state
- utility values for partial and non-response health states (see figure 28 on page 193 of the company submission).

The company stated that the ICER was relatively robust to any other changes in model inputs.

Company scenarios

5.21 The company presented a number of alternative scenario analyses, which are summarised in Table 11. Across all but one of the company scenarios, the ICER for adalimumab compared with supportive care remained below £30,000 per QALY gained and in most scenarios the ICER was below £20,000 per QALY gained (using the patient access scheme price for adalimumab). The ICER for adalimumab was greater than £20,000 per QALY gained, compared with supportive care, in the following scenarios:

- time horizon shortened to 20 or 30 years
- data from PIONEER I excluded (model used only PIONEER II)
- different imputation rule for missing data.

The ICER for adalimumab was greater than £30,000 per QALY gained, compared with supportive care, in the scenario in which people whose disease was not responding to treatment after week 36 did not continue treatment for 12 weeks – an annual discontinuation rate was applied based on the open-label extension study.

Table 11 Company scenario analyses, and results for adalimumab compared with supportive care using adalimumab PAS price and including set up and operational costs of the PAS (source: company PAS submission pages 24–5)

Parameters	Base-case	Scenario analysis	Scenario ICER (£/QALY)
Time horizon	Lifetime	20 years	£25,956
		30 years	£20,108
Annual discount rate	3.5%	0%	£3353
		5%	£19,630
Clinical trial source	Weeks 0–12: PIONEER I & II Weeks 12–36: PIONEER I & II for ADA, PIONEER II for supportive care	PIONEER II	£22,929
TP extrapolation method	Modelled TP extrapolation: generalised logit model	LSCF extrapolation	£25,411
		Mean TP extrapolation	£12,567
Long-term TPs for ADA (week 36+)	Based on OLE	Based on PIONEER I & II	£1862
Missing value imputation	NRI	LOCF	£10,345
Discontinuation rates			
Weeks 12–36	Same rate for all health states	Response-specific rates	£14,765
Week 36+	OLE response-specific rates	PIONEER I & II response-specific rates	£12,164
Week 36+, non-responders	Non-responders continue until week 48 before stopping (expert opinion)	Annual rate after week 36 from OLE	£30,254
Compliance (week 12+)	Based on PIONEER (97.4%)	Assume 100%	£15,916

Abbreviations: ADA, adalimumab; LOCF, Last observation carried forward; LSCF, last health state carried forward; NRI, Non-Responder Imputation; OLE, open-label extension; PAS, patient access scheme; TP, transition probabilities

ERG exploratory analyses

5.22 Based on the issues identified in its critical appraisal of the company's model (see sections 5.3 and 5.10–5.14), the ERG performed 8 sets of additional analyses using the discounted price for adalimumab agreed in the confidential patient access scheme. The ERG incorporated the one-off set up costs and ongoing operational costs associated with the patient access scheme, applied in the same way as the company (refer to the company PAS submission for the derivation of these costs). Analyses 1–3 reflect the ERG's preferred base case; analyses 5–8 used the assumptions in the ERG's preferred base case and examined outstanding uncertainties (Table 12).

Table 12 Summary of the ERG's exploratory analyses

	Description	**ERG critique of company methods (PMB section number)**
1	Correction of minor model errors	5.17
2	Incorporation of tunnel states (model 'memory'), for people whose disease does not respond to adalimumab after 36 weeks (see pages 117–9 of the ERG report for methods) *Includes correction of minor model errors (analysis 1)*	5.11
3	ERG preferred base case: Use of alternative assumptions about the costs of surgery inpatient admissions *Includes assumptions in analysis 1 and analysis 2*	5.15
4	Includes only PIONEER II data *Includes assumptions in analyses 1–3*	5.13
5	Alternative assumptions about transition probabilities beyond week 36: • Generalised logit model to extrapolate open-label extension study data, but without LOCF imputation • Extrapolation of mean transition probabilities from weeks 12–36 of the PIONEER studies *Includes assumptions in analyses 1–3*	5.14
6	People with partial response or no response at 12 weeks discontinue treatment *Includes assumptions in analyses 1–3*	5.10

	Description	ERG critique of company methods (PMB section number)
7	Assumed no differences in costs or health benefits according to depth of response *Includes assumptions in analyses 1–3*	5.3
8	Combination of scenarios 6 and 7 *Includes assumptions in analyses 1–3*	5.3 and 5.10
Abbreviations: LOCF, last observation carried forward		

5.23 For ERG exploratory analysis 3 (alternative costs of surgery-related admissions), the ERG made assumptions based on clinical advice:

- the company's modelled estimate of total lifetime surgeries for people receiving supportive care (33.87 procedures) was reasonable, and the length of stay associated with a wide excision (5.1 days) was appropriate, but not all procedures would involve wide excisions or inpatient stays
- [redacted] of all surgeries are intermediate procedures undertaken in an outpatient setting (based on the company's retrospective study using Hospital Episode Statistics data, page 30 of the company submission)
- of the remaining [redacted] of surgeries, people have an average of 2 wide excisions over their lifetime
- all other remaining surgeries are comprised of an equal mix of planned and unplanned intermediate procedures with an average stay of 2 days
- a wide excision costs £5488, an outpatient intermediate procedure costs £943, and an inpatient intermediate procedure costs £2103.

The ERG's alternative assumptions resulted in an estimated cost of approximately £1526 per surgical procedure.

5.24 In ERG scenario 7 the utility values, resource use estimates and discontinuation rates for the complete response and response states, and for the partial response and no response states, were assumed to be the same. These estimates were based on the alternative model submitted by the company during clarification (see table 49 on page 104 of the ERG

report). In this ERG analysis, people with a partial response after 12 weeks were assumed to continue adalimumab treatment but derived no more benefit than people whose disease has not responded to treatment, as in the company base case. The ERG tested the impact of stopping treatment for people with only a partial response at week 12 in its sixth scenario analysis, and combined the assumptions from scenarios 6 and 7 in its eighth scenario. The ERG noted that, in scenarios 6 and 8, it was only able to apply the discontinuation rule for partial response up to week 36; beyond week 36 the assumptions about people with a partial response reflected the company base case (that is, they continued treatment). Therefore, the ERG was unable to comment on the true impact of applying the discontinuation rules to people with a partial response in both the induction and maintenance phases of the model. The ERG stated that this is an important uncertainty which cannot be fully addressed with the available evidence.

5.25 The results of the ERG's exploratory analyses are presented in Table 13. In its preferred base case, adalimumab produced a deterministic ICER of £28,555 and a probabilistic ICER of £29,725 per QALY compared with supportive care.

Table 13 Results of the ERG exploratory analyses (using adalimumab PAS price, including set up and operational costs of the PAS)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
Company's base case	£143,683	12.61	£15,142	1.00	£15,182
ERG scenario 1	£144,369	12.64	£15,939	1.00	£15,941
ERG scenario 2	£149,430	12.72	£21,000	1.07	£19,551
ERG scenario 3 (preferred base case)	**£94,689**	**12.72**	**£30,671**	**1.07**	**£28,555**
ERG scenario 4	£99,913	12.63	£35,906	0.99	£36,372
ERG scenario 5					
GLM	£93,354	12.68	£29,335	1.04	£28,110
Mean TPs	£95,678	12.58	£30,027	1.17	£25,610
ERG scenario 6	£86,809	12.62	£22,791	0.98	£23,341
ERG scenario 7	£87,334	13.20	£30,278	0.74	£40,923
ERG scenario 8	£80,039	13.13	£22,974	0.67	£34,152

Abbreviations: GLM, Generalised logit model; ICER, incremental cost effectiveness ratio; Inc., incremental; PAS, patient access scheme; QALY, Quality adjusted life year; TP, transition probability
Source: company PAS submission page 20 and ERG addendum

Innovation

5.26 The company provided justifications for considering adalimumab to be innovative:

- There is no standard of care for hidradenitis suppurativa and no approved medical treatments.
- People receive treatment according to clinical experience, rather than evidence-based guidelines.
- Current treatment strategies do not offer reliable disease control and treatment success is rare:
  - in a UK-based study, 24% of people with hidradenitis suppurativa had failed to find anything at all to help their condition, despite an average treatment duration of almost 19 years.
  - people have active disease for almost one-half of the month.
- Surgical and laser therapies can be associated with significant post-procedure morbidity and uncertain long-term disease control; wounds take a long time to heal; and hidradenitis suppurativa can recur, meaning people may require multiple surgeries.

- Adalimumab offers people with hidradenitis suppurativa the potential to significantly reduce disease activity, reduce pain and improve quality of life.

5.27 Patient experts also considered adalimumab to be an innovative therapy for hidradenitis suppurativa, because it has a less burdensome dosing regimen. They suggested that taking adalimumab as an injection saves time compared with adhering to a schedule of other treatments that often have to align with meal times. They preferred the convenience of taking the treatment at home rather than at hospital.

6 Equality issues

6.1 In one of the submissions it was noted that hidradenitis suppurativa is more common in people of African family origin, and that many people with the condition have other disabilities. It was also suggested that hidradenitis suppurativa affects genders differently and that difficulties with personal appearance and mental health are more likely to be dismissed if the person is male. It was also noted that it may be difficult for people with a phobia of needles to take adalimumab.

7 Authors

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with input from the Lead Team (Ian Davidson, Murray Smith and Tracey Cole).

Appendix A: Clinical efficacy section of the draft European public assessment report

European Public Assessment Report (EPAR):

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000481/WC500195564.pdf

The Summary of Product Characteristics (SmPC) for adalimumab recommends "continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period." The EPAR discusses the background to this and appears to define "no improvement" as people with a reduction in AN count less than 25%:

Page 88 EPAR: "In the post-hoc analyses of the sub-group of AN25 responders (partial responders), it was found that among the group of HiSCR non-responders, this sub-group was able to reach HiSCR, in particular with adalimumab 40 mg ew/ew. Based on this, the MAH considers the statement in the SmPC section 4.2. that "Continued therapy beyond 12 weeks is recommended except in those patients without any improvement for whom continued therapy should be reconsidered" to be supported. This wording was revised in the final SmPC and was found acceptable to the CHMP."

Page 121 EPAR: "In the post-hoc analyses of the sub-group of AN25 responders (partial responders), it was found that among the group of HiSCR non-responders, this sub-group was able to reach HiSCR, in particular with adalimumab 40 mg ew/ew. Based on this, continued therapy beyond 12 weeks is recommended except in those patients without any improvement for whom continued therapy should be reconsidered."

Page 76 EPAR: "Post-hoc analyses revealed that subjects who achieved a partial responses (≥ 25% reduction in AN count relative to baseline in the ITT_B_NR Population) and HiSCR responders (in the ITT_B_R Population) had greater potential to achieve or maintain HiSCR with longer treatment of 40 mg ew until Week 36. In this population, HiSCR at Week 36 was achieved by a higher proportion of

subjects in the ew/ew group compared to the ew/eow or ew/pbo groups (refer to table and figure below)."

Page 80 EPAR: "Among subjects who achieved at least AN25 response (partial responders or HiSCR responders) at Week 12, the HiSCR rate was above 60% from Week 8 through Week 72."

Summary of Product Characteristics (SmPC):

https://www.medicines.org.uk/emc/medicine/21201

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Adalimumab for treating moderate to severe hidradenitis suppurativa

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of adalimumab within its marketing authorisation for treating moderate to severe hidradenitis suppurativa.

Background

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil's disease, is a chronic inflammatory skin disorder. HS is caused by blocked hair follicles which are connected to apocrine sweat glands. This stops sweat from escaping onto the skin and leads to the formation of pus-filled abscesses which can become infected. These are painful and can cause itching, redness, burning, excessive sweating, and eventually scarring. In severe cases the pus tunnels deep under the surface of the skin and forms widespread networks of interconnected channels that can break out on the surface and leak pus. Symptoms begin around puberty and most commonly appear in the second or third decade of life. The disease affects areas with apocrine sweat glands such as the groin and genitals, buttocks and inner thighs, armpits and below the breasts (in women). The cause of HS is unclear but may be hormonal or the result of an underlying autoimmune disorder.

There are approximately 90,000 people with HS in England. The disease is more common in women than in men and people of African family origin have a higher incidence than people of European family origin.

There is no standard treatment pathway for this condition. Current clinical management includes antibiotics (including combination treatment with clindamycin plus rifampicine), retinoids (such as acitretin), ciclosporin, dapsone, and tumour necrosis factor (TNF)-inhibitors (such as infliximab plus methotrexate). None of these treatments have a marketing authorisation in the UK for HS. Surgery may be considered for people with chronic HS to remove the sweat glands in the affected areas of skin although the disease can reoccur after surgery.

The technology

Adalimumab (Humira, AbbVie) is a fully human recombinant monoclonal IgG1 antibody specific for TNF-alpha. It blocks interaction with cell-surface receptors, thereby limiting the promotion of inflammatory pathways. It is administered by subcutaneous injection.

Adalimumab has a marketing authorisation in the UK for treating active moderate to severe hidradenitis suppurativa in adults whose disease has not responded to conventional systemic hidradenitis suppurativa therapy.

Intervention(s)	Adalimumab
Population(s)	Adults with active moderate to severe hidradenitis suppurativa which has not responded to conventional therapy
Comparators	Established clinical management without adalimumab
Outcomes	The outcome measures to be considered include: • Disease severity • Clinical response • Inflammation and fibrosis • Discomfort and pain • Adverse effects of treatment • Health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England: A12/S/a 2013/14 NHS Standard Contract For Specialised Dermatology Services (all ages) (2013)

	Department of Health: Department of Health (2014) NHS Outcomes Framework 2015-2016

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • AbbVie (adalimumab) Patient/carer groups • Action on Pain • African Health Policy Network • Black Health Agency • British Skin Foundation • Changing Faces • Hidradenitis Suppurativa Trust • Muslim Council of Britain • Pain Concern • Pain Relief Foundation • Pain UK • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • British Association of Dermatologists • British Dermatological Nursing Group • British Geriatrics Society • British Society for Cutaneous Allergy • Primary Care Dermatology Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of PathologistsRoyal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association Others	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Allergan UK(retinoids, dapsone) • AstraZeneca (metformin) • Auden Mckenzie (dapsone) • Boehringer Ingelheim (metformin) • Crawford Healthcare (clindamycin) • Genus Pharmaceuticals (retinoids, metformin) • GlaxoSmithKline (isotretinoin) • Hospira UK (infliximab biosimilar, Inflectra) • Janssen-Cilag (metformin) • Merck Sharp & Dohme Ltd (infliximab, metformin) • Napp Pharmaceuticals (infliximab

Consultees	**Commentators (no right to submit or appeal)**
• Department of Health • NHS England • NHS Medway CCG • NHS Wokingham CCG • Welsh Government	biosimilar, Remsima) • Novartis (metformin) • Pfizer (clindamycin) • Rosemont Pharmaceutical (metformin) • Sanofi (rifampicine) • Takeda (metformin) • TEVA (erythromycin) • Wockhardt (metformin) • Zentiva (metformin) <u>Relevant research groups</u> • British Epidermo-Epidermiology Society • Centre of Evidence-based Dermatology, University of Nottingham • Cochrane Skin Group • MRC Clinical Trials Unit • National Institute for Health Research • Skin Research Centre • Skin Treatment & Research Trust <u>Evidence Review Group</u> • Kleijnen Systematic Reviews Ltd • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Clinical Guidelines Centre <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Adalimumab for treating moderate to severe hidradenitis suppurativa

ID812

Company evidence submission

October 2015

File name	Version	Contains confidential information	Date
		Yes	

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables 5
Figures 7
Abbreviations 8
1 Executive summary 11
1.1 Statement of decision problem 14
1.2 Description of the technology being appraised 16
1.3 Summary of the clinical effectiveness analysis 18
1.4 Summary of the cost-effectiveness analysis 22
2 The technology 26
2.1 Description of the technology 26
2.2 Marketing authorisation/CE marking and health technology assessment 26
2.3 Administration and costs of the technology 27
2.4 Changes in service provision and management 29
2.5 Innovation 30
3 Health condition and position of the technology in the treatment pathway 33
3.3 Equity and equality 43
4 Clinical effectiveness 44
4.1 Identification and selection of relevant studies 46
4.1.1. Eligibility criteria 46
4.1.1.1. Population 46
4.1.1.2. Interventions 46
4.1.1.3. Comparators 46
4.1.1.4. Outcomes 47
4.1.1.5. Study design 47
4.1.2. Literature search 47
4.1.3. Study selection 47
4.1.4. Quality and risk of bias appraisal 48
4.1.5. Evidence base 48
4.1.6. Study characteristics 49
4.1.7. Risk of bias and methodological quality results 51
4.2 List of relevant randomised controlled trials 54
4.3 Summary of methodology of the relevant randomised controlled trials 57
4.3.1 M10-467 57
4.3.2 PIONEER I and PIONEER II 60
4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials 68
4.5 Participant flow in the relevant randomised controlled trials 70
4.5.1 Participant flow in M10-467 70
4.5.2 Participant flow in PIONEER I 71
4.5.3 Participant flow in PIONEER II 72
4.5.3 Patient characteristics 72
4.6 Quality assessment of the relevant randomised controlled trials 76
4.7 Clinical effectiveness results of the relevant randomised controlled trials 76
4.7.1 M10-467 76
4.7.1.1 Primary end-point: improvement in HS-PGA at week 16 76
4.7.1.2 Secondary end-points at week 16 77
4.7.1.3 End-points at week 52 79

4.7.2 PIONEER I and PIONEER II 79
4.7.2.1 Primary end-point: improvement in HiSCR at week 12 79
4.7.2.2 Secondary end-points at week 12 81
4.7.2.3 PRO outcomes 85
4.7.2.4 Outcomes at week 36 89
4.8 Subgroup analysis 93
4.8.1 Details of the subgroup analyses 93
4.8.2 Results of the subgroup analyses 95
4.9 Meta-analysis 100
4.10 Indirect and mixed treatment comparisons 100
4.11 Non-randomised and non-controlled evidence 100
4.11.1 Summary of methodology 101
4.12 Adverse reactions 108
4.12.1 M10-467 108
4.12.2 PIONEER I and PIONEER II 111
4.12.2.1 Period A 111
4.12.2.2 Period B 113
4.12.3 OLE 115
4.12.4 Overview of safety in relation to the decision problem 116
4.13 Interpretation of clinical effectiveness and safety evidence 117
4.13.1 Clinical benefits and harms 117
4.13.2 Strengths and limitations 120
4.13.3 Life expectancy and number of patients suitable for treatment 124
4.14 Ongoing studies 126
5 Cost effectiveness 127
5.1 Published cost-effectiveness studies 128
5.2 De novo analysis 134
5.2.1 Introduction 134
5.2.2 Patient population 134
5.2.3 Model structure 134
5.3 Intervention technology and comparators 137
5.3.1 Clinical parameters and variables 137
5.5 Cost and healthcare resource use identification, measurement and valuation 169
5.5.1.1 Cost and resource use studies 169
5.6 Summary of base-case de novo analysis inputs and assumptions 178
5.7 Base-case results 186
5.8 Sensitivity analyses 189
5.9 Subgroup analysis 195
5.10 Validation 195
5.11 Interpretation and conclusions of economic evidence 196
6 Assessment of factors relevant to the NHS and other parties 199
State the estimated annual budget impact on the NHS in England 200
References 202
Appendices 210

Tables

Table 1: The decision problem 14
Table 2: Technology being appraised 16
Table 3: Incremental cost-effectiveness results 22
Table 4: Costs of the technology being appraised 28
Table 5: Hurley severity for HS[7] 35
Table 6: Characteristics of included studies 52
Table 7: Randomised controlled trials of ADA 40 mg in moderate to severe HS. 56
Table 8: HS-PGA scale 59
Table 9: Comparative summary of trial methodology for M10-467, PIONEER I and PIONEER II 65
Table 10: Summary of statistical analyses in M10-467, PIONEER I and PIONEER II 69
Table 11: Patient characteristics at baseline in M10-467, PIONEER I and PIONEER II[29-31 82 83 85] 74
Table 12: Summary of study quality according to the NICE checklist 76
Table 13: M10-467 – secondary efficacy end-points at week 16: protocol-specified analysis (LOCF)[31] 78
Table 14: PIONEER I and PIONEER II – % of patients achieving HiSCR at week 12 (ITT population)[29 30 82 83 85 93] 80
Table 15: PIONEER I and PIONEER II – % of patients who achieved AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline and all patients[29 30 82 83 85] 82
Table 16: PIONEER II – mean change from baseline in EQ-5D at week 12 (LOCF)[30 86] 85
Table 17: PIONEER I and PIONEER II – mean change from baseline in DLQI and HSQOL at week 12 (LOCF)[29 30 86]{Armstrong, 2014 #97} 87
Table 18: PIONEER I and PIONEER II – mean change from baseline in Patient's Global Assessment of Skin Pain at worst among patients with baseline ≥3 at worst at week 12 (LOCF)[29 30]{Armstrong, 2014 #97} 88
Table 19: PIONEER I and PIONEER II – mean change from baseline in activity impairment in the WPAI scale at week 12 (LOCF)[30] 88
Table 20: Proportion of patients in PIONEER I and II (amalgamated data) achieving HiSCR during period B 91
Table 21: PIONEER I and PIONEER II – secondary end-points at week 36 (ITT_B_R)[29 30] 92
Table 22: Subgroups for analysis of the primary end-point in MI0-467, PIONEER I and PIONEER II[29-31] 94
Table 23: M10-467 – clinical response at week 16 (proportion of patients achieving HS PGA of clear minimal or mild with at least a 2-grade improvement relative to baseline at week 16[31] 96
Table 24: List of relevant non-randomised and non-controlled evidence 101
Table 25: Patient disposition in OLE[32] 105
Table 26: Patient characteristics at baseline in OLE[32] 105
Table 27: Quallity assessment of OLE 106
Table 28: Proportion of patients achieving HiSCR over time from the first dose of ADA (LOCF)[32] 107
Table 29: AE in study M10-467[31] 109

Table 30: AE occurring in >5% of patients in study M10-467[31] 110
Table 31: AE in PIONEER I and PIONEER II during period A (first 12 weeks)[29 30 33 82 83 85]. 112
Table 32: AE occurring in >5% of patients PIONEER I and PIONEER II during period A (first 12 weeks)[29 30 83{Jemec GBE, 2015 #67 85] 112
Table 33: AE in PIONEER I and PIONEER II during period B[29 30] 114
Table 34: AE occurring in >5% of patients PIONEER I and PIONEER II during period B[29 30] 114
Table 35: AE in OLE in the all ADA population and in the EW/EW/EW population[32] 116
Table 36: AE occurring in >5% of in patients in OLE in the all ADA population and in the EW/EW/EW population[32] 116
Table 37: Baseline demographics from PIONEER I and II and a UK patient cohort. 123
Table 38: Key differences between PIONEER I and PIONEER II study designs. 124
Table 39: Estimated number of patients eligible for HS ADA treatment in England and Wales 125
Table 40: Inclusion/exclusion criteria (cost-effectiveness studies) 130
Table 41: Inclusion/exclusion criteria (cost and resource use studies) 132
Table 42: Features of the de novo analysis 137
Table 43: Discontinuation rates for ADA during the maintenance period 139
Table 44: Inclusion/exclusion criteria (HRQL studies) 147
Table 45: Characteristics of the included HRQOL and utility studies 150
Table 46: Relevant outcomes reported in HRQOL and utility studies 154
Table 47: Summary of utility values for cost-effectiveness analysis 169
Table 48: Characteristics of studies included for resource use data 170
Table 49: Resource use outcomes reported in the identified studies 171
Table 50: Unit price and compliance rate of ADA 175
Table 51: Resource use rates by health states 175
Table 52: Unit cost of resource use 176
Table 53: Annual AE rates for patients receiving ADA or SC 177
Table 54: Unit cost of resource use associated with AE 177
Table 55: Summary of variables applied in the economic model 179
Table 56: Main model assumptions used in base case analysis 184
Table 57: Base-case results 186
Table 58: Base-case results validation against phase III pivotal clinical trials during Week 0 to Week 36 186
Table 59: Summary of QALY gain by health state 188
Table 60: Summary of costs by health state 189
Table 61: Summary of predicted resource use by category of cost 189
Table 62: Scenario analyses – ADA vs SC 193
Table 63: Scenario analyses results – ADA vs SC 195
Table 64: ADA projected eligible patient population for years 1 to 5 199
Table 65: Number of patients receiving ADA based on anticipated market share 199
Table 66: Cost per patient per year as estimated in the cost effectiveness analysis 200
Table 67: Total annual treatment costs with ADA introduction 201
Table 68: Total annual treatment costs without ADA introduction 201
Table 69: Incremental budget impact of ADA introduction 201

Figures

Figure 1: Typical clinical presentation of active HS (a) Moderate Hurley grade II (b) severe Hurley grade II (c) Hurley grade III[7] 35
Figure 2: Mean HS DLQI score compared to other skin diseases[69] 37
Figure 3: Disease burden of HS[7] 39
Figure 4: Study flowchart 49
Figure 5: Study design for M10-467[31] 58
Figure 6: Study design for PIONEER I and PIONEER II 61
Figure 7: Participant flow in M10-467[31] 70
Figure 8: Participant flow in PIONEER I[29] 71
Figure 9: Participant flow in PIONEER II[30] 72
Figure 10: Study M10-467 –% of patients achieving HS-PGA at week 16[31] 77
Figure 11: PIONEER I and PIONEER II – % of patients achieving HiSCR at week 12 (ITT population), *p<0.05, **p<0.01 ***p<0.001[29 30 82 83 85] 80
Figure 12: PIONEER I and PIONEER II – % of patients achieving HiSCR by visit in period A (ITT population) *p<0.05, **p<0.01 ***p<0.001[29 30 82 83 85] 81
Figure 13: PIONEER I and PIONEER II – % of patients achieving NRS30 by visit (ITT population). *p<0.05, p<0.01, ***p<0.001[29 30 85] 84
Figure 14: PIONEER I and PIONEER II – mean improvement from baseline in MSS, LOCF (ITT population). *p<0.05,**p<0.01, ***p<0.001[29 30 82] 85
Figure 15: PIONEER I– change in the physical components in the SF-36 from baseline to week 12, *p<0.05,**p<0.01, ***p<0.001[29] 86
Figure 16: Change in TSQM domain scores from baseline to week 12, ***p<0.001[35] 89
Figure 17: PIONEER I and PIONEER II – % of patients achieving HiSCR during period B (ITT population)[29 30] 90
Figure 18: HiSCR rate with continuous ADA 40 mg EW dosing integrated across PIONEER I, II and OLE[33] 92
Figure 19: PIONEER I – proportion of patients achieving HISCR at week 12 (NRI) by subgroup.[29] 98
Figure 20: PIONEER II – proportion of patients achieving HISCR at week 12 (NRI) by subgroup.[30] 99
Figure 21: Flow of studies (PRISMA flowchart) 133
Figure 22: Model structure 135
Figure 23: Flow of studies (PRISMA flowchart) 148
Figure 24: Base-case ADA Markov trace of health states over time 187
Figure 25: Base-case SC Markov trace of health states over time 188
Figure 26: Cost-effectiveness plane of incremental cost and QALYs of ADA vs. SC 190
Figure 27: CEAC of ADA vs. SC at a WTP of £30,000 191
Figure 28: DSA results – Tornado diagram 194

Abbreviations

A&E	Accident and Emergency
AAD	American Academy of Dermatology
ACMD	Advances in Cosmetic and Medical Dermatology
ADA	Adalimumab
AE	Adverse Event
AN	Abscess and Inflammatory Nodule
AS	Ankylosing Spondylitis
AWMSG	All Wales Medicines Strategy Group
BMI	Body Mass Index
CEA	Cost-effectiveness Analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRP	C-reactive protien
CSRs	Clinical Study Reports
CUA	Cost Utility Analysis
DLQI	Dermatology Life Quality Index
DMARDs	Disease Modifying Anti-Rheumatic Drugs
EMA	European Medicines Agency
EOW	Every Other Week
EQ-5D	EuroQol
ESDR	European Society for Dermatological Research
EW	Every Week
HADS	Hospital Anxiety and Depression Scale
HES	Hospital Episode Statistics
HiSCR	HS Clinical Response
HRQOL	Health Related Quality of Life

HS	Hidradenitis Suppurativa
HS-LASI	HS-Lesion, Activity and Severity
HS-PGA	HS Physician's Global Assessment
HSQOL	HS Quality of Life
HSSI	HS Severity Index
HTA	Health Technology Appraisal
ICER	Incremental Cost-Effectiveness Ratio
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
LOR	Loss of Response
LYG	Life Years Gained
MCID	Minimum Clinically Important Difference
MDI	Major Depression Inventory
MSS	Modified Sartorius Score
NICE	National Institute for Health and Care Excellence
NRI	Non Responder Imputation
NRS-30	Patient's Global Assessment of Skin Pain
NSAIDs	Non steroidal anti-inflammatory drugs
OLE	Open Label Extension Study
PASI	Psoriasis Area Severity Index
PHQ-9	Patient Health Questionnaire-9
PRO	Patient Reported Outcomes
PSS	Personal Social Services
QALYs	Quality-Adjusted Life Years
QOL	Quality of Life

RCT	Randomised controlled trial
SAE	Serious Adverse Events
SC	Supportive care
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form-36 Health Status Survey
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SSG	Split Skin Draft
STA	Single Technology Appraisal
TB	Tuberculosis
TDAP	Thoracodorsal Artery Perforator
TNF-α	Tumour Necrosis Factor Alpha
TP	Transition probabilities
TSQM	Treatment Satisfaction Questionnaire for Medication
TWPI	Total Work Productivity Impairment
VAS	Visual Analogue Scale
WCD	World Congress of Dermatology
WOAI	Worsening or Absence of Improvement
WPAI-SHP	Work Productivity and Activity Impairment-Specific Health Problem

1 Executive summary

People with hidradenitis suppurativa (HS):

- Have poor quality of life (QOL); the impact on patients' QOL is greater than that seen in severe psoriasis.
- Find that their disease has a significant impact on their ability to work and contribute to society.
- Experience significant delays in diagnosis (up to 12 years) during which they incur healthcare costs and undergo unnecessary treatments.
- Had no licensed or approved treatments available until the license for adalimumab (ADA) was granted.

HS is a common, chronic, relapsing inflammatory skin condition, characterised by recurrent deep-seated painful boils and inflammatory nodules affecting the skin around the apocrine (sweat) glands, most commonly the axillary (armpits), inguinal (crease between the torso and the thigh) and anogenital regions[7]. The inflammatory nodules and abscesses may rupture and discharge purulent drainage and progress to form fistulas and scarring in some patients[1 2].

The exact prevalence of HS is unknown, however, the 1-year prevalence of symptomatic HS, including mild to severe disease, has been estimated at 0.97% in France[3] and 1.0% in Copenhagen, Denmark[4]. Two recent studies of the prevalence of HS in large, US-based patient groups suggest that the diagnosed prevalence of HS in the US is approximately 0.05%[5 6].

HS is a long-term, underdiagnosed condition[7-11], and has a substantial burden of disease, particularly in patients with more severe manifestations. Mean Dermatology Life Quality Index (DLQI) scores of 5.77, 13.1, and 20.4 have been reported for Hurley stage I (mild), II (moderate) and III (severe) classifications, respectively (for comparison, reported mean DLQI scores for clinical trial patients with moderate to severe psoriasis are 11.3)[12 13]. HS patients also have higher mean DLQI scores compared with other dermatological conditions[11-13]. HS is an extremely painful condition, and patients report that pain is the most significant factor contributing to

impaired health related quality of life (HRQOL). Pain scores are high at between 4 and 10 on a 0-10 pain scale[11 14].

HS causes significant physical and psychosocial distress with a peak onset in the early 20s, a formative period of adulthood[15], and can have a devastating impact on patients' lives: in forming relationships, choices in life, such as education or career, ability to work and everyday activities[7]. HS inflicts a considerable impact on activities of daily living, work/school attendance, physical activities and emotional states[16]. Although the skin lesions can be hidden by clothing, active disease is associated with a foul smelling discharge which is embarrassing and results in social stigma, low self-worth and poor interpersonal relationships[7]. HS patients exhibit higher sexual dysfunction and sexual distress[17] and depression is relatively common, occurring in 20% to 40% of patients[12 18]. Patients with HS have higher depression scores compared with patients with other common disabling skin conditions[19].

Lack of awareness amongst the general public and in primary care delays presentation and diagnosis. Therefore, HS is often diagnosed after a long delay and is often misdiagnosed as a simple infection. A study shows the median time to diagnosis was 12 years (range 1 month to 23 years)[20]. Misdiagnoses and convoluted time to diagnosis mean that patients are often at 'crisis point' by the time they receive a diagnosis[21].

Current treatment aims to control disease and reduce the number of outbreaks. Current HS treatments are used on an off-label basis and do not offer reliable disease control. Treatment success is rare, in a UK-based study published in 2000, 24% of patients had failed to find anything at all to help their condition, despite an average treatment duration of almost 19 years[22]. In practice, the UK treatment pathway is highly complex with no clear referral pathway[10]. As a result of the lack of disease awareness, an unclear treatment pathway and limited treatment guidelines[11], many patients do not receive appropriate treatment[9 23] and remain in considerable pain and distress over many years, leading to a life of despair and isolation[21].

The cost to the NHS of a delay in treatment is likely to be sizable both in terms of additional appointments and use of inappropriate treatment. Research shows that in

the average Clinical Commissioning Group, the cost per patient of treating HS patients is higher than other skin diseases[10]. Furthermore, Accident & Emergency admissions in HS patients represent a significant impact on hospital resources[24]. In-patient costs are also considerable for HS, since HS surgery is often carried out as a non-elective intervention[24]. Other costs may be significant but are not necessarily reflected in healthcare budgets[10 25]

The economic burden of HS to the patient is substantial since onset and peak disease activity occurs during the patient's productive years[7], especially those with moderate to severe active disease, who often have poor work productivity[25]. Many patients, especially women, report an increased number of absences from work due to their HS[7 26], while patients with inadequately controlled disease are often unable to work or rendered unemployed[27].

Until recently, licensed treatments have not been available for HS patients and such treatments have little or no evidence. ADA (Humira) is the only product with a license to treat moderate to severe HS[28].

1.1 Statement of decision problem

Table 1: The decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	Adults with active moderate to severe HS which has not responded to conventional therapy	Adults with active moderate to severe HS which has not responded to conventional therapy	As specified in the scope
Intervention	ADA (Humira)	ADA (Humira)	As specified in the scope
Comparator (s)	Established clinical management without ADA	Where the data allows AbbVie has performed comparisons in line with the licence	As per scope where data allows
Outcomes	The outcome measures to be considered include: • Disease severity • Clinical response • Inflammation and fibrosis • Discomfort and pain • Adverse effects (AE) of treatment • Health-related quality of life (HRQOL)	The outcome measures to be considered include: • Disease severity • Clinical response • Inflammation and fibrosis • Discomfort and pain • AE of treatment • HRQOL	As specified in the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.	• Cost-effectiveness will be presented as incremental cost per QALY. • The time horizon for the modelling is a lifetime. • Costs will be considered from an NHS and PSS perspective.	As specified in the scope

Subgroups to be considered	None stated	None stated	As specified in the scope
Special considerations including issues related to equity or equality	None stated	None stated	As specified in the scope

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Adalimumab (ADA) (Humira)
Marketing authorisation/CE mark status	Humira is indicated for the treatment of active moderate to severe HS (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy
Indications and any restriction(s) as described in the summary of product characteristics	Indications as follows[28] *Rheumatoid arthritis* ADA in combination with methotrexate, is indicated for: the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDS) including methotrexate has been inadequate and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. ADA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. ADA has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate. *Juvenile idiopathic arthritis* *Polyarticular juvenile idiopathic arthritis* ADA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more DMARDs. ADA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. ADA has not been studied in patients aged less than 2 years. *Enthesitis-related arthritis* ADA is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. *Axial spondyloarthritis* *Ankylosing spondylitis (AS)* ADA is indicated for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy. *Axial spondyloarthritis without radiographic evidence of AS* ADA is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated c reactive protein and/or magnetic resonance imaging, who have had an inadequate response to, or are intolerant to non steroidal anti-inflammatory drugs (NSAIDs). *Psoriatic arthritis* ADA is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response

	to previous disease-modifying anti-rheumatic drug therapy has been inadequate. ADA has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function. *Psoriasis* ADA is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen combined with ultraviolet A. *Paediatric plaque psoriasis* ADA is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. *Crohn's disease* ADA is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. *Paediatric Crohn's disease* ADA is indicated for the treatment of severe active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies. *Ulcerative colitis* ADA is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies
Method of administration and dosage	The recommended ADA dose regimen for adult patients with HS is 160 mg initially at day 1 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later at day 15 (given as two 40 mg injections in 1 day). Two weeks later (day 29) continue with a dose of 40 mg every week (EW). Antibiotics may be continued during treatment with ADA if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with ADA. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period[28].

1.3 Summary of the clinical effectiveness analysis

1.3.1 Clinical effectiveness

Three placebo-controlled studies – a dose finding study (M10-467) and two large randomised controlled studies (PIONEER I and PIONEER II) demonstrate that ADA 40 mg EW significantly improves HS clinical response and severity of HS compared with placebo[29-31]. An open label extension (OLE) study, M12-555, to the PIONEER studies provides additional long-term data on efficacy and safety of ADA 40 mg each week (EW)[32].

In the dose finding study (M10-467) significantly more patients in the ADA 40 mg EW group achieved a clinical response (defined as achieving a HS Physician's Global Assessment [HS-PGA] score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16) than patients receiving placebo, 17.6% versus 3.9%, $p<0.025$[31]. Significant improvements were also seen at week 16 in individual symptoms, overall disease severity and pain scores with ADA 40 mg EW. Clinically relevant pain reduction was seen as early as week 2 in 40% of patients receiving ADA 40 mg EW.

In PIONEER I and II significantly more patients in the ADA 40 mg EW group achieved a clinical response (defined as achieving HS Clinical Response [HiSCR] of at least a 50% reduction in the total abscess and inflammatory nodule [AN] count with no increase in abscess count and no increase in draining fistula count relative to baseline at week 12) than patients receiving placebo, 41.8% versus 26.0%, $p=0.003$ in PIONEER I and 58.9% versus 27.6%, $p<0.001$ in PIONEER II. This difference was maintained regardless of disease severity as assessed by Hurley status (PIONEER I and II) and antibiotic use (PIONEER II only). Response was seen early in treatment with a significant difference as early as 2 weeks, response was particularly marked in PIONEER II[29 30].

Significant improvements were also seen in disease severity, inflammation, fibrosis and pain. The NICE scope specifies inflammation and fibrosis as outcomes and this information is captured within the Modified Sartorius Score (MSS) (fibrosis) and improvement in AN count (inflammation). All outcomes were significant in PIONEER

II, however, in PIONEER I some of the outcomes with ADA 40 mg EW were numerically but not significantly higher than placebo.

Subgroup analyses revealed that patients achieved benefit with ADA 40 mg EW regardless of their baseline characteristics. It should be noted, that some of the subgroups contained few people which makes the results difficult to interpret[29 30].

HRQOL is an important consideration for patients with HS. Patient reported outcomes (PRO) were consistently improved in patients receiving ADA 40 mg EW in all three studies[29-31]. In PIONEER I and II, ADA 40 mg EW significantly improved HRQOL as measured by EuroQol (EQ-5D), the physical components of Short Form-36 Health Status Survey (SF-36), DLQI and the HS Quality of Life (HSQOL) compared with placebo. Significant improvements in work activity were seen with ADA 40 mg EW versus placebo[29 30].

Improvements were maintained for the duration of the studies up to 36 weeks in the PIONEER studies. Re-randomisation during the second part (period B) of the PIONEER studies and protocol-driven discontinuation during period B for patients with loss of response (LOR) or worsening or absence of improvement (WOAI) means that patient numbers are low in the group receiving EW for the total study duration (21 in PIONEER I and 20 in PIONEER II). There was a loss of effect for patients re-randomised to placebo or ADA 40 mg EOW[29 30].

Outcomes were maintained in patients who went on to enter the OLE[32].

Amalgamated data from the PIONEER studies and OLE study presented at WCD 2015 demonstrates that patients with a partial response (defined as HiSCR non-responders with ≥25% reduction in AN count relative to baseline) or a complete response to treatment (HiSCR responders) at week 12 continue to benefit from treatment[33]. Patients who are non-responders at week 12 are unlikely to respond if treatment is continued, and continued therapy beyond 12 weeks in non-responders should be carefully reconsidered which has clear benefits in terms of drug expenditure.

1.3.2 Adverse events

ADA 40 mg EW was well tolerated in the dose finding study (M10-467) and in both of the PIONEER studies. The proportion of patients experiencing serious AEs (SAEs) or discontinuing treatment due to AEs was low and similar in both ADA and placebo arms[29-31]. In an integrated study of PIONEER I and II (n=633), six patients receiving placebo (1.9%) and three receiving ADA 40 mg EW (0.9%) gave AE as their primary reason for discontinuation during period A[34].

The AEs for patients treated with ADA 40 mg EW were comparable to placebo and consistent with the known ADA safety profile. The majority of AE were mild to moderate in severity. In a treatment satisfaction assessment carried out in PIONEER II there was no difference in patient perceived side effects in patients receiving ADA 40 mg EW or placebo[35].

The most common AE were exacerbation of HS, nasopharyngitis and headache. Rates of infectious AEs were similar for both patients receiving ADA and those receiving placebo. There were no reported tuberlucosis (TB) infections.

The OLE study[32] did not identify any new safety risks for ADA.

1.3.3 Strengths and limitations

All three placebo-controlled studies have robust internal validity, as demonstrated by strong critical appraisal scores.

A number of factors influence external validity, and are listed below.

- All outcomes detailed in the NICE scope were considered as end-points in the clinical trials (disease severity, clinical response, inflammation and fibrosis, discomfort and pain, AE of treatment and HRQOL).
- The HiSCR score was developed for use in the PIONEER studies and is not currently used in clinical practice. However, it has been validated against other measures of response in HS (Hurley stage, MSS and HS-PGA) and has been shown to be a valid and meaningful end-point for assessment of HS treatment effectiveness[36]. Expert clinical opinion from a UK advisory board held by Abbvie

in 2015, revealed that UK advisors generally welcomed HiSCR and thought that it allowed appropriate assessment of response to therapy[37].

- The NICE scope specifies 'established clinical management without ADA' as the comparison treatment. However, there is a lack of consensus around treatment for HS, indeed guidelines for the management of HS have only just been published this year[38],and patients are managed according to individual clinician experience. Patients receive numerous different medicines; in a 5-year retrospective survey of 142 patients from 10 UK hospitals; patients took an average of 10 medications within the 5-year retrospective period (range 1-43)[39]. Therefore, placebo was chosen as the comparator rather than an active treatment, this reflects a pragmatic approach, and reflects clinical opinion in England, based on feedback from clinical experts[40-42].
- Patients in the clinical study programme reflect patients in routine clinical practice. Although patients were not recruited from the UK, patients were recruited from North America, elsewhere in Europe and Australia), all of which have similar demographics to the UK. A study funded by Abbvie Ltd compared the PIONEER populations with a UK patient dataset and found that demographics were similar[39], which was confirmed by expert opinion from English clinicians[40-42].

The main study limitation is that there is a paucity of data for the licensed dose beyond 12 or 16 weeks due to re-randomisation at 12 or 16 weeks and protocol-driven discontinuation during period B for patients with LOR or WOAI in the PIONEER studies. However, the OLE study will provide further data out to 60 weeks to fill this data gap and an interim data cut provides information on patients for a median of 348 days (range 5-883 days)[32]. Data is available for 84 patients who received continuous ADA 40 mg EW, with a mean exposure of 444.7 days (median, 430; range, 154 to 883 days).

1.4 Summary of the cost-effectiveness analysis

Table 3: Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)
SC	£128,541	22.73	11.61				
ADA	[redacted]	22.73	12.61				
ADA vs. SC	-	-	-	[redacted]	0.000	1.00	[redacted]

The economic model demonstrates that ADA is a cost-effective treatment option for patients with active moderate to severe HS in the UK with an ICER of [redacted]

In this submission, the cost-effectiveness analysis (CEA) compares ADA to supportive care (SC). This reflects the placebo arms in the PIONEER clinical trials[29] [30]. SC is a suitable comparator due to the lack of evidence available for most therapies currently used to treat HS[43] and is consistent with the feedback received from the UK clinical experts who advised that biologics are used after all other options have been exhausted[37] . ADA is the only licensed treatment for moderate to severe HS.

The target population consists of adult patients with active moderate to severe HS (acne inversa) who have had an inadequate response to conventional systemic therapy. This population is in line with the patient population in the PIONEER trials and reflects the population defined in the scope and decision problem for this NICE technology appraisal.

In the model, patients start treatment with either ADA or SC in the non-response health state and then transition across four mutually exclusive health states based on patients' response status (high response, response, partial response or non-response) and one absorbing state (death), based on their responses to treatment and natural mortality rate. These health states were considered due to the outcomes of preliminary analyses of the EuroQol (EQ-5D) data collected in the PIONEER II trial[30] indicating a statistically significant difference in the utility values between the high response and response health states, and between the values of the partial response and non-response health states.

As per the marketing authorisation, in the model all patients treated with ADA have a 12-week induction period and receive the following dosing: 160 mg at week 0, 80 mg at week 2, and 40 mg of ADA EW starting at week 4. At week 12, patients with non-response to ADA discontinue treatment, and the remaining patients continue receiving ADA at a dose of 40 mg EW. After week 12, patients in the non-response state are discontinued from ADA treatment based on a specified discontinuation rate observed in the clinical trials. Subsequent discontinuation rates implemented in the model reflect the discontinuation rates observed in the clinical trials as well as the opinion of clinical experts[40-42 44]. In the maintenance period responders and non-responders were discontinued with the rates observed in the PIONEER trials. At the end of this period, all patients in the non-responder state discontinue after an additional 12 weeks, following clinical experts' advice suggesting that patients who do not respond to ADA treatment will be assessed and discontinued if no improvement is observed. Patients who are discontinued in the model are moved to the SC arm and will follow transition probabilities (TPs) from the SC.

Patients incur treatment costs (i.e. costs of ADA or SC), costs associated with treatment-related AEs and other medical costs. Medical costs consist of surgery-related costs and non-surgery related costs and are assigned to each health state, independent of the treatment received. Surgery is not considered an appropriate comparator, as surgery and ADA are not alternative or exclusive treatment choices. Indeed, patients receiving ADA in the PIONEER trials were allowed surgery for symptom control.

The frequency of surgical interventions depends on health states and the differing level of local HS manifestations, reflecting the fact that surgery provides only temporary relief to local HS manifestations. The frequency of non-surgery-related resource use associated with out-patient and Accident and Emergency (A&E) visits is also evaluated by health states. Health state specific utilities, based on EQ-5D information from the PIONEER II study, are used in the model to estimate Quality Adjusted Life Years (QALYs).

The model simulates the lifetime disease progression of people with HS, and predicts that patients with active moderate to severe HS treated with ADA will

experience improvements in terms of QALYs relative to those treated with SC resulting in an incremental cost-effectiveness ratio (ICER) of [redacted] for ADA compared to SC (Table 3). Therefore, ADA is both a clinically and cost-effective treatment option for patients with active moderate to severe HS in the UK.

The main strength of this model is that the core analysis comparing ADA to SC was based on direct evidence from the randomised PIONEER I and PIONEER II clinical trials, which evaluated ADA and SC among adults with active moderate to severe HS with an inadequate response to or who were intolerant to conventional systemic antibiotic HS therapy[29 30]. This patient population is considered representative of the patients who will be receiving ADA in clinical practice in the UK (as confirmed by the clinical experts consulted)[40-42 44]. Evidence from direct head-to-head randomised controlled clinical trials is considered the "gold standard" because it eliminates the impact of unobserved confounders (such trials have high internal validity)[45 46]. In addition, the model used all available data to inform relevant inputs, i.e., data from both the phase III PIONEER clinical trials were pooled for analyses where feasible and data from the OLE trials was used to model long term efficacy.

Furthermore, the EQ-5D, the NICE-preferred instrument for HRQOL measurements to be used in CEA modelling[47 48], was administered in the PIONEER II clinical trial (but not in the PIONEER I clinical trial) and these data were directly used to inform the utility values for each health state. The EQ-5D is an appropriate HRQOL measurement instrument in patients with skin conditions[49 50]. There was no need for alternative or indirect measures of determining HRQOL outside the trial setting.

Moreover, extensive sensitivity analyses – related to both model settings and model inputs – were conducted to test the robustness of the model. Overall, the model results were robust to all studied inputs, except for the methods used for extrapolation beyond the trial period which is not surprising given the significant assumptions required in such long-term extrapolations.

However, as it is the case with most economic models there were some limitations with the analysis presented. Firstly, due to the lack of long-term efficacy data for ADA and SC, extrapolation beyond the trial period was required. Modelled TP

extrapolation was applied in the base-case. Sensitivity analyses were also conducted using the mean TP extrapolation where the TPs were estimated based on the mean of the TP matrices from week 12-36. The estimates on the long term extrapolation would most likely improve when the final results from the OLE trial become available in the future.

Secondly, there is a lack of real-world data related to resource use by health states among HS patients. Frequencies of resource use were obtained from a physician survey conducted among UK physicians who were actively treating HS patients[39]. The results from the physician survey was further evaluated and validated by a focus group discussion with UK physicians who are treating HS patients[37]. However, these results need to be validated against the real-world resource use incurred by HS patients. The model also tested uncertainties in the sensitivity analyses. In the future, resource use data from real-world studies could be used to improve the robustness of the model.

No disutilities of AEs were considered in this economic evaluation. However, this is likely to have a minimal impact on the results as the AEs rates were similar between patients who received ADA and patients who received placebo in the phase III PIONEER clinical trials[29 30]. In addition, the utility of each health state used in the model was estimated based on all patients with the indicated health state from the clinical trials, which could include patients who were experiencing AEs.

In addition, the model used the compliance rate of ADA observed in the phase III PIONEER clinical trials[29 30]. However, in the real-world, patient compliance is likely to be lower than that observed in the clinical trials.

2 The technology

2.1 Description of the technology

Adalimumab (ADA) (Humira) is a cytokine modulator or TNF-inhibitor; it inhibits the activity of the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α).

TNF-α is produced primarily by activated monocytes/macrophages and plays a key role in inflammation. TNF-α acts via its receptors –TNF receptor 1, the major mediator of TNF-α action initiates inflammatory responses and mediates apoptosis, and T NF receptor 2 which facilitates antiviral immune responses via cytotoxic T-lymphocytes[51].

ADA is a humanised bivalent mouse IgG1 monoclonal antibody, which binds specifically to TNF-α and blocks its interaction with both TNF receptor 1 and TNF receptor 2[51].

ADA is licensed for the treatment of inflammatory conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, axial spondyloarthritis, ankylosing spondylitis (AS), psoriatic arthritis, psoriasis, paediatric plaque psoriasis, Crohn's disease, paediatric Crohn's disease and ulcerative colitis, see Table 2[28].

It has been demonstrated that secretion of cytokines is significantly elevated in HS. A small study (n=9) revealed that ADA treatment was associated with decreased production of cytokines in HS skin and significantly reduced the number of inflammatory cells[52].

2.2 Marketing authorisation/CE marking and health technology assessment

The European Medicines Agency (EMA) has confirmed that the Committee for Medicinal Products for Human Use (CHMP) adopted a Positive Opinion on 25th June 2015 for Humira variation EMEA/H/C/481/II/137 regarding the use of ADA in HS[53].

The agreed indication is as follows:

Humira is indicated for the treatment of active moderate to severe HS (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

Marketing authorisation was given on 28 July 2015, the launch date is expected to be January 2016.

Appendix 1 contains the Summary of Product Characteristics and the European Public Assessment Report.

2.3 Administration and costs of the technology

The recommended ADA dose regimen for adult patients with HS is 160 mg initially at day 1 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days), followed by 80 mg 2 weeks later at day 15 (given as two 40 mg injections in 1 day). Two weeks later (day 29) continue with a dose of 40 mg every week (EW). Antibiotics may be continued during treatment with ADA if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with ADA. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

There are no administration costs. ADA will be provided via AbbVie Care (home care) and administered in the patient's home.

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Subcutaneous (SC) injection	Summary of Product Characteristics[28]
Acquisition cost (excluding VAT) *	£352.14	List price (both auto injection pen and pre-filled syringe) from British National Formulary[54]
Method of administration	Subcutaneous (SC) injection	Summary of Product Characteristics[28]
Doses	ADA is available in the following two presentations: • Provided as a 40 mg solution for injection in a single-use pre-filled syringe (type I glass) for patient use: packs of two pre-filled syringes (0.8 ml sterile solution), each with one alcohol pad. • Provided as a single-use, disposable, automatic injection delivery system (HUMIRA PEN) with needleguard that delivers 40 mg ADA by pushbutton, designed for administration in hospital, home, or elsewhere, by caregiver or patient; which is available as a 40 mg solution for injection in a single-use pre-filled syringe (type I glass) with needleguard: packs of: two pre-filled syringes with needleguard (0.8 ml sterile solution) each with one alcohol pad.	Summary of Product Characteristics[28]
Dosing frequency	ADA 160 mg at week 0, 80 mg at week 2 and 40 mg EW from week 4.	PIONEER I & II trials [29 30]
Average length of a course of treatment	1 year's ADA treatment EW consists of 54 injections	Summary of Product Characteristics[28]
Average cost of a course of treatment	Average cost year 1 is £19,015 Average cost year 2 £18,311	British National Formulary[54]
Anticipated average interval between courses of treatments	Not applicable.	
Anticipated number of repeat courses of treatments	Not applicable.	
Dose adjustments	Dose adjustments are not recommended.	
Anticipated care setting	Secondary care/ Homecare	
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.		

2.4 Changes in service provision and management

Market research carried out by Abbvie which consisted of an online survey of 60 respondents (30 dermatologists, 15 general surgeons and15 plastic surgeons), two extended screening questionnaires with GPs and hospital clinicians and 15 qualitative interviews with GPs and hospital clinicians suggests that use of biologics is relatively rare in patients with HS, of the dermatologists surveyed only 17% (5/30) had started a patient on biologics in the previous 12 months[55]. Qualitative interviews carried out with dermatologists reveal difficulty in obtaining funding for biologics and considerable variation in the duration of funding, in some Clinical Commissioning Groups funding is for a maximum of only 3 months[55]. This is confirmed by an online survey of members of the UK Dermatology Trials Network and British Association of Dermatologists (n=134) who noted that access to biologic agents was restricted by funding issues[56].

Data from the market research suggests that around 4% of diagnosed moderate to severe patients with HS are currently treated with a biologic (n=700). Most biologic use is within the NHS and is mainly infliximab (45%), ADA (36%) or a mixture of both agents. It is anticipated that all patients will receive ADA given that infliximab remains unlicensed.

The market research suggests that biologics are exclusively prescribed within secondary care (dermatology). At present, around 15% of patients with moderate to severe diagnosed HS do not seek medical attention and around one-half of patients who present to their GP with moderate to severe HS remain in primary care. Therefore, it is expected that referrals to secondary care may increase as more patients seek biologic treatment. However, it should be noted that the patient pool is relatively small – only around 37% of patients with diagnosed moderate to severe HS are suitable for biologic treatment[55].

At present HS is a considerable drain on healthcare resources, a 5-year retrospective review of patients with HS seen in 10 UK hospitals revealed that 30% of patients had at least one inpatient visit with a mean length of stay of 6.68 days

(median 3.5 days) and 14% of patients attended at A&E (typically once or twice a year)[39].

Further work from a retrospective cohort study using HES data confirms the burden of HS in patients using hospital services. Patients with a primary diagnosis code for HS [redacted] during an inpatient admission [redacted] between 1st April 2007 and 31st December 2013 were identified. Data for all inpatient, outpatient and A&E episodes during the study period were extracted[57]. Most admissions were due to skin related surgery [redacted] – and [redacted] were day case, although [redacted] of patients attended A&E (mean [redacted] per patient per year) and [redacted] were admitted to hospital the same day as their A&E visit. There were a mean of [redacted] outpatient appointments per year [redacted] over the study period), most of which were for dermatology [redacted] or plastic surgery [redacted].

Length of stay was higher than that seen in the study above (mean of 8.04 days for elective and 11.87 days for non elective). Patients were mainly women (69.9%) and young (mean age of male patients was 39 [13.08] years and female patients 36 [11.66].

It is anticipated that the use of ADA in patients with HS will not require additional infrastructure to be put in place. ADA is administered as a SC injection and patients are able to self-inject at home using ADA delivered by homecare services. As such, ADA is expected to not to add any additional burden to hospital services.

Training by a nurse at the beginning of treatment to educate patients on the appropriate administration of the drug is usually required (three 1 hour sessions). AbbVie provides this nurse led programme in the community (ie. AbbVie care) and no additional costs are incurred by the NHS.

2.5 Innovation

Abbvie considers ADA for the treatment of HS to be innovative, offering a step change in the way that HS patients are treated.

HS is a common, chronic, relapsing inflammatory skin condition, characterised by recurrent painful boils and nodules affecting the skin around the apocrine (sweat)

glands[7]. Disease flares are characterised by increased pain and suppuration with a foul smelling discharge, which stains clothing[1 7 15].

At present there is no standard of care for HS and no approved medical treatments. Patients receive treatment according to clinical experience, rather than evidence-based guidelines.

Current treatment options, both medical and surgical, aim to control disease and reduce the number of outbreaks. However, current treatment strategies do not offer reliable disease control and treatment success is rare. In a UK-based study published in 2000, 24% of patients had failed to find anything at all to help their condition, despite an average treatment duration of almost 19 years[22].

The same UK-based survey revealed that patients with HS reported a median of two new boils per month, each with an average duration of 6.9 days, which is equivalent to almost one-half of the month with active disease. In addition, around two-thirds of patients reported at least one permanent painful boil which failed to subside[22].

HS causes significant physical and psychosocial distress to both men and women with a peak onset in the early 20s, a formative period of adulthood[15].

HS has a clear and substantial impact on quality of life (QOL) and surgical and laser therapies can be associated with significant post-procedure morbidity and uncertain long-term disease control. In its advanced stage the skin parts affected by HS can be removed in extensive skin surgery and the wounds are left to a lengthy secondary healing. HS can re-appear at the border of the surgery or other areas of the body, so patients may require multiple surgeries over time. Indeed, an observational cross-sectional study funded by Abbvie retrospectively reviewed patient notes for 101 patients from 10 UK hospitals for the 5 years prior to July 2014-April 2015[39]. Of those patients, 41% had surgery (86 surgeries over 5 years). Of the 86 surgeries 13.9% (n=12) had surgical complications, and 34.1% (n=14) had recurrent surgery most of which was at the same site (78.6%, n=11). The median time to next surgery was 5 months and the median time to recurrence of disease was 10.2 months (range 0.2 - 66 months).

It is clear that there is significant medical unmet need in this patient group, ADA offers patients the potential to significantly reduce HS activity, reduce pain and improve QOL.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease burden

HS is a common, chronic, relapsing inflammatory skin condition, characterised by recurrent painful boils and inflammatory nodules affecting the skin around the apocrine (sweat) glands, most commonly the axillary (armpits), inguinal (crease between the torso and the thigh) and anogenital regions[7 58]. It causes significant physical and psychosocial distress to both men and women with a peak onset in the early 20s, a formative period of adulthood[15].

HS has a point prevalence of between 1% and 4%, although poor rates of diagnosis and diagnosis late in the course of the disease suggest that the true prevalence is probably higher[1]. In the two most frequently cited references for prevalence rates, the 1-year prevalence of symptomatic HS, including mild to severe disease, was estimated to be 0.97% in France[3] and 1.0% in Copenhagen County, Denmark[4]. Two recent studies of the prevalence of HS in large, US-based patient groups suggest that the diagnosed prevalence of HS in the US is approximately 0.05%[5 6].

Market research carried out by Abbvie which consisted of an online survey of 60 respondents (30 dermatologists, 15 general surgeons and15 plastic surgeons), two extended screening questionnaires with GPs and hospital clinicians and 15 qualitative interviews with GPs and hospital clinicians has estimated the UK prevalence at 977,900 adults or 1.94% of the UK population[55]. The UK HS population appears to be largely undiagnosed, indeed just over one-quarter of patients (27.2%) are under medical care, which suggests that around three-quarters of patients with HS remain undiagnosed.

HS is 2 to 5-times more common in women than in men and around one-third of patients have a family history of the disease. Other risk factors for HS include obesity and cigarette smoking[9 59].

HS is associated with a number of inflammatory diseases, including inflammatory bowel disease, spondyloarthropathies and pyoderma gangrenosum. Squamous cell

carcinoma rates are also higher in patients with HS than the general population[1 7]. Patients with HS also have an increased risk of metabolic syndrome, depression and suicide compared with the general population[60-62].

In patients with HS, hair follicles in the apocrine gland-bearing regions (axilla, genital area, groin, infra-mammary region, peri-anal region and buttocks) become blocked and inflamed resulting in painful recurrent deep-seated nodules or boils. In most patients disease flares occur at varying intervals, often occurring pre-menstrually in women. Disease flares are characterised by increased pain and suppuration with a foul smelling discharge, which stains clothing[1 7 15].

A UK-based survey revealed that patients reported a median of two new boils per month, each with an average duration of 6.9 days, which is equivalent to almost one-half of the month with active disease. In addition, around two-thirds of patients reported at least one permanent painful boil which failed to subside[22]. Eventually, boils and nodules may progress to abscesses, sinus tracts and scarring[1 7 15].

The excessive scarring and fibrosis produced by HS lesions can lead to contractures and limitations in limb mobility, especially in the axilla. In addition, inflammation and scarring in the genitofemoral region may predispose to anal, urethral and rectal strictures[60 63]. Patients with anogenital HS may also have disease in the anal canal (30 of 132 patients in one study). HS in the anal canal lies superficial to the internal sphincter and begins in the lower two-thirds of the canal. This corresponds with the distribution of apocrine glands and hair follicles in the anal canal. If lesions are seen proximal to this area, disorders such as Crohn's disease should be considered since up to 17% of patients with Crohn's disease may have co-morbid HS[64].

Fatigue is relatively common, occurring in around 40% of patients, and may prevent suffers from performing everyday tasks[12].

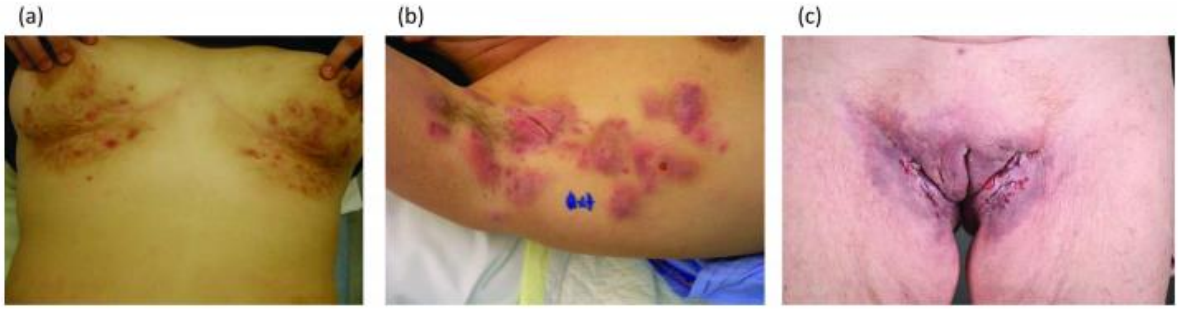
Abnormal immunity plays a role in the pathogenesis of HS. Studies of immunological markers of inflammation in HS lesions show that levels of several inflammatory and anti-inflammatory cytokines are elevated[15].

The Hurley staging score is used in clinical practice to grade severity of disease from I (mild) to III (severe), see Table 5 and Figure 1[7]. Most patients have grade I or II disease, estimates suggest that between 1% and 22% of patients have severe grade III disease[1 7]. Severe disease is associated with higher body mass index (BMI), atypical location of lesions, a history of severe acne and absence of a family history of HS and male gender[7].

Table 5: Hurley severity for HS[7]

Degree of involvement	Definition
I	Abscess formation, single or multiple, without sinus tracts and cicatrisation (scarring and fibrosis)
II	Recurrent abscesses with sinus tracts and cicatrisation; single or multiple widely separated lesions
III	Diffuse or almost diffuse involvement, or multiple interconnected tracts and abscess across entire area

Figure 1: Typical clinical presentation of active HS (a) Moderate Hurley grade II (b) severe Hurley grade II (c) Hurley grade III[7]



Retrospective studies suggest that HS may be a progressive disease in some patients, with some patients reporting a progression in Hurley stage from Hurley stage I to II to III over time; the risk factors that predispose patients to progression include smoking and obesity[65 66].

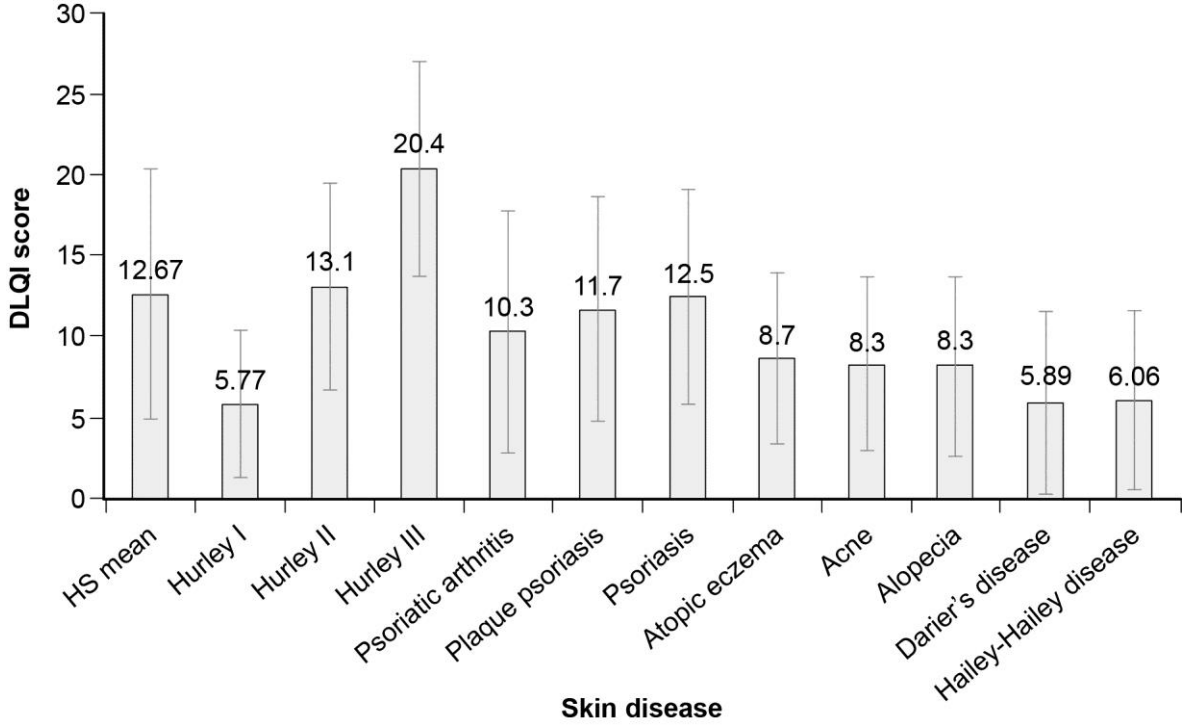
The modified Sartorius score (MSS) is used in clinical trials, and was used in the two phase III studies for ADA in HS. The MSS scores each region separately (seven regions), 3 points are awarded for each region affected. For each region the number and severity of lesions (1 point for each nodule and 3 for each fistulae), longest distance between two relevant lesions (1 point for <5 cm, 3 points for 5-10 cm and 9 points for >1 cm) and whether the lesions are clearly separated by normal skin (0 points for yes and 9 points for no) is scored independently and then totaled. The higher the score, the more severe the disease[67].

HS is often diagnosed after a long delay, since the disease is often misdiagnosed as a simple infection. In one study, the median time to diagnosis was 12 years (range 1 month to 23 years)[20]. Data from an observational cross-sectional study funded by Abbvie, which retrospectively reviewed patient notes for 142 patients from 10 UK hospitals for the 5 years prior to July 2014-April 2015[39], found that the onset of symptoms to diagnosis was a mean of 8.8 years (range 0-41 years), median 5.2 years. This is confirmed by data from the UK market research commissioned by Abbvie suggests that of those patients who present to a GP, patients experience a median of 3 years of symptoms prior to presentation, patients then wait a median of a further year before the diagnosis is made, giving a median of 4 years prior to diagnosis[55]. Given that only around one-quarter of UK patients with HS seek medical attention; there is a large pool of HS undiagnosed patients who remain untreated and in considerable pain and distress.

The DLQI is used to score QOL in patients with skin disorders, the scale consists of 10 questions about the impact of skin disorders on patients' lives, it is scored from 0 (no impact) to 30 (maximum impact on QOL).

A number of studies have demonstrated that QOL and general health in patients with HS is poorer than that seen in patients with disabling other skin conditions, for example psoriasis, alopecia, acne, atopic dermatitis[11 19 68] and with other serious medical conditions such as cancer, chronic lung disease and cardiovascular disease[12]. Figure 2 illustrates the impact of HS, particularly severe HS (Hurley stage III) on QOL as measured by the DLQI[69].

Figure 2: Mean HS DLQI score compared to other skin diseases[69]



The DLQI score in 251 Swedish patients with HS was 10 (range 0-30); patients scored soreness and pain, clothing and embarrassment/self-consciousness as the most problematic features of HS[67]. Mean DLQI scores of 5.77, 13.1, and 20.4 have been reported for Hurley stage I, II and III classifications, respectively (for comparison, reported mean DLQI scores for clinical trial patients with moderate to severe psoriasis are 11.3)[12 13]. Patients with advanced disease (Hurley stage III, multiple lesions), anogenital lesions or visible lesions on uncovered skin, particularly the face, have the poorest QOL of all[12 70].

UK data from patients receiving treatment at 10 UK hospitals (n=130) reported a mean DLQI score of 14.2 (range 0-30)[39]. Two-thirds of patients (87/130) said that HS had a very large or large impact on QOL (DLQI score of 11 or more).

HS patients exhibit higher sexual dysfunction and sexual distress compared with healthy matched controls[17].

HS is an extremely painful condition, and patients report that pain is the most significant factor contributing to impaired QOL. Pain has been reported as hot, burning, pressure, stretching, cutting, sharp, taut, splitting, gnawing, pressing sore,

throbbing and aching. Pain scores are high at between 4 and 10 on a 0-10 pain scale[11 14].

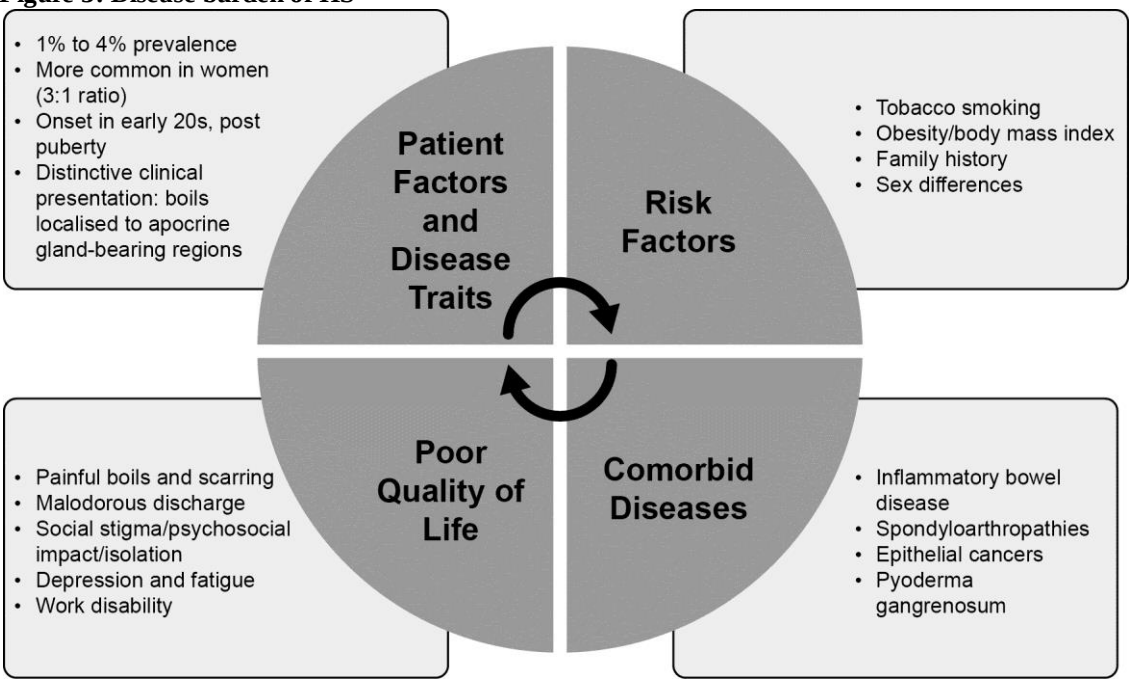
Although the skin lesions can be hidden by clothing, active disease is associated with a foul smelling discharge which is embarrassing and results in social stigma, low self-worth and poor interpersonal relationships[7]. Patients often have low self-worth and depression is relatively common, occurring in 20% to 40% of patients[12 18]. Furthermore, patients with HS have higher depression scores compared with patients with other common disabling other skin conditions[19].

Given that the peak onset of HS is during the early 20s, it can have a devastating impact on patients' lives: in forming relationships, ability to work and everyday activities[7]. UK data from patients receiving treatment at 10 UK hospitals revealed that one-third of patients were not in a relationship and of those patients 77% attributed this to their HS[39].

Active disease makes going to work difficult, due to pain, discharge and unpleasant smell associated with active HS. Given that active disease may be present for half of each month[22] this is likely to have a considerable impact on productivity. In one study, 58% of patients reported missing work due to their HS; sick days lasted for 4-96 days and occurred 1-10 times per year[25].

Work carried out in the UK using HES data and patient records[39 57] reveals that the mean length of stay for patients receiving inpatient treatment is between [redacted] and [redacted] days, patients who attend hospital had a mean of [redacted] outpatient appointments per year. Given that patients were in their mid-thirties to early forties and of working age, hospital appointments and admissions will have a considerable impact on their ability to work and attendance at work.

Figure 3: Disease burden of HS[7]



3.2 Pathway of care and current management

There is no standard pathway of care for HS and until recently there was a lack of published guidelines to assist with treatment choices. The European guidelines were published in 2015 and recommend that the disease should be treated based on its individual subjective impact and objective severity[38]. The guidelines recommend medical treatment either as monotherapy or in combination with radical surgery for widely spread lesions and surgery/laser for locally recurring lesions. Medical therapy includes antibiotics (clindamycin plus rifampicine, tetracyclines), acitretin and biologics (ADA, infliximab). Adjuvant management, such as pain management, treatment of superinfections, weight loss and tobacco abstinence should also be considered.

The guidelines recommend that stage I (localised) disease is managed with topical antibiotic therapy (clindamycin), whereas systemic antibiotic therapy (tetracycline, clindamycin-rifampicin) is recommended for more widespread or severe disease[38].

Second-line options include dapsone in mild to moderate disease, systemic retinoids e.g. acitretin and anti-androgens (female patients only). Systemic retinoids should be

used with caution given their serious adverse events (SAE) and tetragenic effects. Ciclosporin is recommended as a fourth line treatment. Steroids are recommended for the management of acute flare or recalcitrant nodules and sinus tracts (intralesional steroids). Biologics such as ADA, infliximab, enteracept and ustekinumab are recommended as potential treatment options in moderate to severe disease, although only ADA is licenced for HS[38].

Laser treatment is a potential treatment option early in the course of the disease. Surgery to remove unresponsive lesions is an option, local excision early in the disease and wide surgical excision later in the treatment pathway. The guidelines point out that it is very difficult to compare surgical treatment modalities for HS because of the complex nature of the disease, the numerous complicated surgical interventions widely used for treatment and the variable results reported in the literature[38].

Wide surgical excision is generally used in patients with advanced disease, the skin areas affected by HS are removed in extensive skin surgery and the wounds are left to secondary healing, which can take up to 3 months. HS can re-appear at the border of the surgery or other areas of the body, so patients may require multiple surgeries over time. There is a substantial humanistic burden associated with surgery, and treatments with the potential to delay surgery would be of great value.

Indeed, an observational cross-sectional study funded by Abbvie retrospectively reviewed patient notes for 101 patients from 10 UK hospitals for the 5 years prior to July 2014-April 2015[39]. Of those patients, 41% had surgery (86 surgeries over 5 years). Of the 86 surgeries 13.9% (n=12) had surgical complications, and 34.1% (n=14) had recurrent surgery most of which was at the same site (78.6%, n=11). The median time to next surgery was 5 months and the median time to recurrence of disease was 10.2 months (range 0.2 -66 months).

A systematic review published in 2012 revealed that a clindamycin-rifampin combination regimen, a course of infliximab, monthly Nd:YAG laser sessions and surgical excision and primary closure with a gentamicin sulfate-collagen sponge were all effective treatments for HS. However, most therapies used to treat HS were supported by limited or weak scientific evidence[71]. A Cochrane review published in

October 2015[72], confirmed that there is a lack of good evidence for treatments for HS, the review found 12 studies each with a median of 27 patients between 1983 and 2015 and did not include the two pivotal studies for ADA 40 mg EW. They concluded that many knowledge gaps exist in RCT evidence for HS.

Current UK management of HS was investigated in online survey of members of the UK Dermatology Trials Network and British Association of Dermatologists, carried between 1 November and 5 December 2014. Of the 134 respondents, 37% saw three or more HS patients each month and 68% had at least six HS patients under current follow-up[56]. The results of the survey broadly mirror the European guidance, which was issued after the survey was carried out.

Topical therapy was commonly used, 88% of respondents routinely used antiseptics and 67% prescribed topical antibiotics. Respondents were given a list of 30 potential treatments for moderate to severe HS and asked to rank them from first to tenth choice. Oral antibiotics were the most common treatment choice, oral tetracyclines (ranked number 1 by 75% of respondents) as first-line treatment and clindamycin and rifampicin as second-line choice. Acitretin, isotretinoin, dapsone and ciclosporin were ranked third, fourth, fifth and sixth choice interventions respectively. Many respondents noted that use of biologic agents was restricted by funding issues but 46% included infliximab in their top 10 treatments, 27% included ADA and 9% included ustekinumab. Oral prednisolone (26%), intralesional triamcinolone injections (24%) and the oral contraceptive pill (21%) were also included in the top ten treatments.

The two surgical treatment options listed in the survey were ‘Narrow margin excision of most active lesion(s)’ and ‘Wide local excision of most active region’. The limited excision option was offered to 32% of patients and extensive excision to 41%. Surgery was generally used later in the treatment pathway (mode of seventh choice).

Laser, light, phototherapy and photodynamic therapies were infrequently used.

The management of acute flare was also included within the survey, the most common response was incision and drainage (43%), a week long course of

antibiotics was the treatment of choice in 29% of respondents. Analgesia (opiate and non-opiate and intra-lesional triamcinolone were also used during an acute flare.

Expert clinical opinion from a UK advisory board held by Abbvie in 2015, echoes the findings of the UK survey and suggests that there is an urgent need for a UK-based consensus/guidelines for the management of HS. At present, medical treatment is often given in a stepwise fashion, starting with systemic antibiotics, then dapsone (antibiotic), retinoids, followed by immunomodulators (cyclosporin) and biologics. Each therapy is given as a 3- to 6-month course; treatment is escalated if patients fail to respond within 6 months. Corticosteroids are frequently prescribed during flares and intravenous (IV) antibiotics are rarely used. The consensus from the meeting was that treatment should be given as early as possible for optimal outcomes[37].

Patients receive numerous different medicines, in a 5-year retrospective survey of 142 patients from 10 UK hospitals; patients took an average of 10 medications within the 5-year retrospective period (range 1-43)[39].

However, treatment success is rare, in a UK-based study published in 2000, 24% of patients had failed to find anything at all to help their condition, despite an average treatment duration of almost 19 years[22].

Expert clinical opinion from a UK advisory board held by Abbvie in 2015, suggests that ADA and other biologics will be used after failure of antibiotic therapy and before other therapies such as dapsone (antibiotic), retinoids and immunomodulators (cyclosporin) or surgery[37]. This is confirmed by data from patient records (n=15) of patients currently receiving an unlicensed biologic, which reveal that 20% received a biologic as second-line treatment, 20% as third-line, 20% fourth-line and 40% as fifth-line or beyond[55].

As revealed in the UK survey, TNF-inhibitors, such as infliximab (and its biosimilars) and ADA, are already being used in the treatment of HS[56]. Data suggests that around 4% of diagnosed moderate to severe patients with HS are currently treated with a biologic (n=700). Most biologic use is within the NHS and is mainly infliximab (45%), ADA (36%) or a mixture of both agents. However, it should be noted that

ADA is the only TNF-inhibitor which is licensed for HS and undergoing NICE Single Technology Appraisal (STA) for HS, therefore it is anticipated that all patients will receive ADA in the future[55].

A prospective double blind study of infliximab (n=15) versus placebo (n=23) with an active treatment phase of 8 weeks followed by a 22-week open label phase with infliximab failed to meet the primary end-point of a 50% or greater decrease from baseline in HS severity index score at week 8, 5.6% versus 26.9% (figures taken from a graph), p=0.092[73]. An earlier paper which reviewed a case series of seven consecutive patients receiving infliximab found a short-term response which was associated with significant toxicity[74]. An open label study of etanercept in 15 patients had a poor response rate (20%) and two patients discontinued the study as a result of skin infections at the site of HS lesions[75].

3.3 Equity and equality

Currently, there are no therapies approved for the treatment of HS in England and a broad range of therapeutic options are used off-label in clinical practice. The limited published research in this area has resulted in little scientific evidence as a basis for treatment. The use of unlicensed non-NICE recommended treatments in HS not only exposes patients to potential safety risks but also results in variations in clinical practice and inequities with respect to access to effective treatments.

4 Clinical effectiveness

Four studies provide evidence for ADA 40 mg EW in moderate to severe HS. Three placebo-controlled studies, M10-467, PIONEER I and PIONEER II, demonstrate that ADA 40 mg EW significantly improves HS clinical response and severity of HS versus placebo[29-31] and one OLE study demonstrate that the benefit is sustained over the longer-term[32].

In a dose finding study (M10-467) significantly more patients in the ADA 40 mg EW group achieved a clinical response (defined as achieving a HS-PGA score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16) than patients receiving placebo, 17.6% versus 3.9%, $p<0.025$[31]. Significant improvements were also seen at week 16 in individual symptoms, overall disease severity and pain scores with ADA 40 mg EW. Clinically relevant pain reduction was seen as early as week 2 in 40% of patients receiving ADA 40 mg EW.

In PIONEER I and II significantly more patients in the ADA 40 mg EW group achieved a clinical response (defined as achieving HiSCR [at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline] at week 12) than patients receiving placebo, 41.8% versus 26.0%, $p=0.003$ in PIONEER I and 58.9% versus 27.6%, $p<0.001$ in PIONEER II. This difference was maintained regardless of disease severity as assessed by Hurley status (PIONEER I and II) and antibiotic use (PIONEER II only). Significant improvements were also seen in disease severity, inflammation, fibrosis and pain. Response was seen early in treatment with a significant difference as early as 2 weeks, response was particularly marked in PIONEER II[29 30].

Subgroup analyses of PIONEER I and PIONEER II revealed that patients achieved benefit with ADA 40 mg EW regardless of their baseline characteristics.[29 30].

PRO were consistently improved in patients receiving ADA 40 mg EW in all three studies[29-31]. In PIONEER I and II, ADA 40 mg EW significantly improved QOL as measured by EQ-5D, the physical components of SF-36, DLQI and HSQOL

compared with placebo. Significant improvements in work activity were seen with ADA 40 mg EW versus placebo[29 30].

Improvements were maintained for the duration of the studies up to 36 weeks in the PIONEER studies[29 30].

Outcomes were maintained in patients who went on to enter the OLE[32].

Amalgamated data from the PIONEER studies and OLE study presented at WCD 2015 demonstrates that patients with a partial response (defined as HiSCR non-responders with ≥25% reduction in AN count relative to baseline) or a complete response to treatment (HiSCR responders) at week 12 continue to benefit from treatment[33]. Patients who are non-responders at week 12 are unlikely to respond if treatment is continued which clinicians to stop treatment in patients who have not responded to ADA 40 mg EW which has clear benefits in terms of drug expenditure.

ADA 40 mg EW was well tolerated in the dose finding study (M10-467) and in both of the PIONEER studies. The proportion of patients experiencing SAEs or discontinuing treatment due to AEs was low and similar in both ADA and placebo arms[29-31]. In an integrated study of PIONEER I and II (n=633), six patients receiving placebo (1.9%) and three receiving ADA 40 mg EW (0.9%) gave AE as their primary reason for discontinuation during period A[34].

The AEs for patients treated with ADA 40 mg EW were comparable to placebo and consistent with the known ADA safety profile. The majority of AE were mild to moderate in severity. In a treatment satisfaction assessment carried out in PIONEER II there was no difference in patient perceived side effects in patients receiving ADA 40 mg EW or placebo[35].

The most common AE were exacerbation of HS, nasopharyngitis and headache. Rates of infectious AEs were similar for both patients receiving ADA and those receiving placebo. There were no reported TB infections.

The OLE study[32] did not identify any new safety risks for ADA.

4.1 Identification and selection of relevant studies

A systematic literature review was performed to gather evidence on the comparative efficacy and safety of interventions in HS.

4.1.1. Eligibility criteria

Relevant English language studies were selected based on the pre-specified PICOS (population, interventions, comparisons, outcomes, and study design) criteria, described in the sections below.

4.1.1.1. Population

Adult patients with moderate to severe HS were included. The inclusion criteria were not limited by the definition of HS severity, and hence, severity, as defined by HS severity index (HSSI), HS-PGA or Hurley score were included.

4.1.1.2. Interventions

Interventions or procedures that are employed to treat patients with moderate to severe HS were included in the systematic review. No restrictions were placed on the line of therapy; the list included biologics, antibiotics, corticosteroids and surgery:

- Biologics: ADA, etanercept and infliximab
- Antibiotics: erythromycin, metronidazole, minocycline, clindamycin, cephalosporins, penicillins, long-term antibiotics (erythromycin, tetracycline etc.)
- Steroids: high-dose oral steroids, prednisolone, intralesional corticosteroid injection, oestrogens and dapsone
- Retinoids (acitretin)
- Surgery: laser

4.1.1.3. Comparators

The comparators of interest included placebo, any of the interventions of interest mentioned above or standard of care. The choice of comparators matches the commonly used comparators in the trials of HS.

4.1.1.4. Outcomes

Efficacy outcomes that are regularly measured and reported in the literature for measuring the effectiveness of HS treatment were included. At least one of the following efficacy measures should be reported in the relevant studies identified:

- Clinical response as assessed by HiSCR, HS-Physician's global assessment (HS-PGA) or HS severity index (HSSI)
- Hurley score
- HS-Lesion, activity and severity (HS-LASI) score
- Patient skin pain assessment
- MSS
- DLQI
- Major Depression Inventory (MDI)

Safety outcomes of interest included discontinuations due to AEs and SAEs.

4.1.1.5. Study design

The study selection was restricted to RCTs conducted in more than 10 patients. Data reported at the end of the first period of randomised crossover studies were considered.

4.1.2. Literature search

A comprehensive search algorithm was developed and employed within the major medical databases (MEDLINE, Cochrane Central Register and EMBASE) to identify relevant publications. Databases were searched from inception to July 20, 2015. The search strategies are presented in Appendix 2. Additionally, clinicaltrials.gov, was searched to identify potentially eligible trials that had produced final results but were not yet published in a peer-reviewed publication.

4.1.3. Study selection

Titles and abstracts of citations retrieved from the database searches and secondary sources were screened for inclusion by two independent reviewers based on the pre-specified eligibility criteria. The same two reviewers independently assessed the eligible full-texts for inclusion. Conflicts between the two reviewers were resolved by consensus for all levels of screening, and involving a third reviewer if necessary.

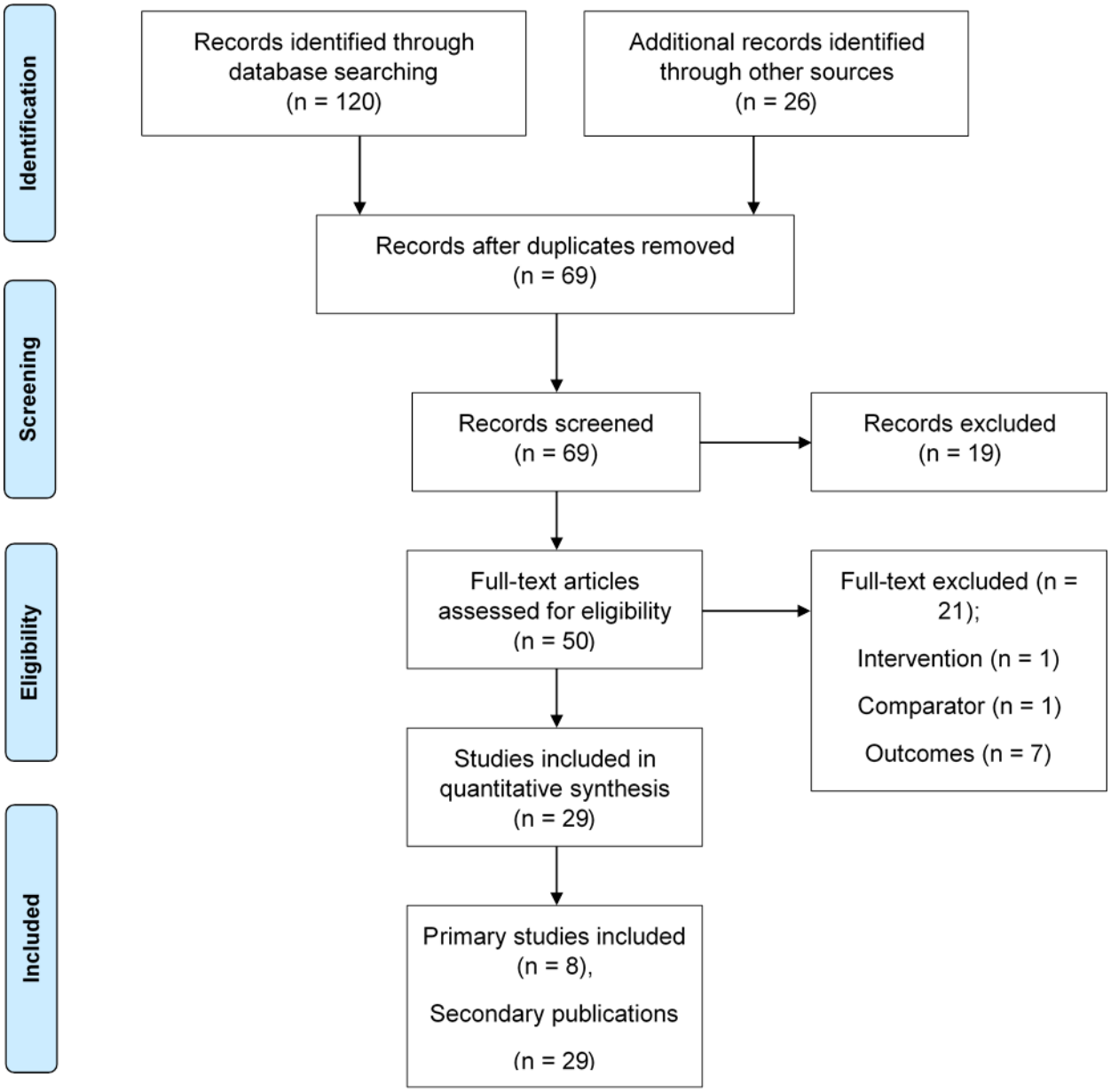
4.1.4. Quality and risk of bias appraisal

Two independent reviewers appraised the quality and risk of bias by using the Cochrane risk of bias tool for RCTs[76]. This instrument is used to evaluate seven key domains: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. If any discrepancies occurred between the two investigators, a third reviewer provided arbitration.

4.1.5. Evidence base

The search identified 120 records. Additionally, two clinical study reports in ADA (PIONEER I and PIONEER II) were also included. Full-text assessment of 50 records resulted in the inclusion of eight eligible studies (29 reports). The study flowchart is shown in Figure 4. A complete reference list for excluded studies is provided in Appendix 3.

Figure 4: Study flowchart



4.1.6. Study characteristics

The study design characteristics of included studies are provided in Table 6. Among the eight included studies, the comparisons were as follows:

- ADA EW vs. placebo: (PIONEER I[29], PIONEER II[30] and Kimball 2012[31]),
- ADA EW vs. ADA 40 mg every other week (EOW) (dose finding study [MI0-467], Kimball 2012)[31]
- ADA EOW vs. placebo: (dose finding study [MI0-467] Kimball 2012[31] and Miller 2011[77])

- Etanercept vs. placebo (Adams 2010)[78]
- Infliximab vs. placebo (Grant 2010)[73]
- Topical antibiotics (clindamycin 1% phosphate) vs. systemic antibiotics (tetracycline 1 g daily) (Jemec 1998)[79]
- Nd:Yg Laser + topical antibiotics (1% clindamycin lotion or gel and benzoyl peroxide wash) vs. topical antibiotics (Tierney 2009)[80]

All studies employed a randomised, active or placebo-controlled, double-blind study design, except for Tierney 2009 which was a single blind study[80]. Studies in etanercept (Adams 2010)[78], infliximab (Grant 2010)[73], and ADA (Kimball 2012)[31] had an initial double-blind, randomised, placebo-controlled phase, followed by an open-label placebo cross-over phase, in which the patients in the placebo arm received the active treatment. For the purpose of this review, results from the randomised period before the placebo cross-over have been considered.

In PIONEER I and PIONEER II studies, patients were randomised to ADA 40 mg EW or placebo for 12 weeks in Period A, followed by a subsequent re-randomisation of patients in ADA 40 mg EW arm to ADA 40 mg EW/EOW/placebo for 24 weeks in Period B. Again, only results from the 12-week randomised period have been considered[29 30].

Tierney 2009, comparing laser therapy to topical antibiotics, was a randomised, right-left, within-patient controlled trial in which the patients received laser and topical antibiotics on the treated half of the body and topical antibiotics only on the control side of the body[80].

All trials in ADA were multicentre studies. PIONEER I and PIONEER II were two large multicentre phase III RCTs in ADA conducted across the US, Europe and Australia in more than 300 patients[29 30]. Another phase II, multicentre study in ADA included 154 patients[31]; sample size was less than 50 patients in all other studies[73 78-80]. The study duration ranged from 16 to 52 weeks across the studies.

The eligibility criteria specified the inclusion of studies with moderate to severe HS patients. However, due to limited evidence base, a study in stage I or II comparing

topical antibiotics (clindamycin 1% phosphate) vs. systemic antibiotics (tetracycline 1 g daily) HS was also included[79].

4.1.7. Risk of bias and methodological quality results

The risk of bias results for the seven domains specified in Cochrane risk of bias assessment tool is presented in Appendix 4. Risk of bias for random sequence generation and allocation concealment was low except for Adams 2010, Miller 2011 and Tierney 2009 studies[77 78 80], for which the risk was unclear. There was a high risk of attrition bias in Grant 2010[73] and Jemec 1998 studies[79].

Table 6: Characteristics of included studies

Study name	Interventions	Study duration	Study design	Location	Inclusion criteria	Exclusion criteria
Biologics						
Adams 2010	Etanercept vs. Placebo	24 weeks	12 week double blind randomised controlled phase followed by a 12 week open label phase in which all patients received Etanercept.	USA (single centre)	Men or women ≥ 18 years of age, chronic HS for > 6 months, active disease, not pregnant, history of surgical sterility, women were postmenopausal for ≥ 5 years, using contraception	Concurrent active infections, hypersensitivity to etanercept, currently enrolled or enrolled in another trial for treatment of HS, concurrent therapy or therapy 30 days prior to study entry with systemic corticosteroids, systemic immunosuppressants, systemic retinoids or anti-TNF agents
Grant 2010	Infliximab vs. Placebo	52 weeks	8 week double blind randomised controlled phase followed by an open label phase from week 8 through week 22 in which all patients received infliximab; week 22 through week 52 was observation phase	USA (single center)	Men or women ≥ 18 years with moderate to severe HS as defined by a HS severity index score >8; and at least one of the following: HS duration>1 year; intralesional steroid injections of more than 5/year (none within 2 weeks of entry); failed systemic retinoid treatment (not within 3 months of entry); failed at least one prior course of antibiotic therapy, (not within 2 weeks of entry, excluding the recommended antibiotic regimen); or history of reconstructive surgery (not within 3 months of entry)	History of chronic or opportunistic infections within 6 months before screening; a history of active or latent tuberculosis; lymphoproliferative disease or active malignancies, malignancy within the previous 5 years; any exposure to monoclonal antibody treatment or human/murine recombinant products, or any use of systemic antiinflammatory medications except nonsteroidal antiinflammatory drugs, low-dose systemic steroids, or both
PIONEER II	ADA 40 mg EW vs. Placebo	36 weeks	12 week double blind randomised controlled phase (Period A) followed by a 24 week double-blind phase (Period B) in which patients treated with ADA EW in period A were re-randomised to ADA EW or EOW or placebo. Patients who were on placebo in period A continued on placebo in period B	North America, Europe and Australia	Men or women ≥ 18 years; HS diagnosis >1 year, HS lesions in at least two distinct anatomical areas, one of which must be at least Hurley Stage II or Hurley Stage III, stable HS for at least 60 days prior to screening visit, inadequate response to at least a 90 day treatment of oral antibiotics for treatment of HS, and a count of ≥3 at baseline	Previously treated with ADA or another anti-TNF therapy (e.g., infliximab or etanercept); not on a stable dose of antibiotic for at least 28 days prior to the baseline visit; received oral concomitant analgesics (including opioids) for HS-related pain, on opioid analgesics, not on a stable dose of non-opioid oral analgesics, within 14 days prior to Baseline visit
PIONEER I	ADA 40 mg EW vs. Placebo	36 weeks	12 week double blind randomised controlled phase (Period A) followed by a 24 week double-blind phase (Period B) in which patients treated with ADA EW in period A	North America, Europe and Australia	Men or women ≥ 18 years; HS diagnosis >1 year, HS lesions in at least two distinct anatomical areas, one of which must be at least Hurley Stage II or Hurley Stage III, stable HS for at least 60 days prior to screening visit, inadequate response to at least a 90 day treatment of oral antibiotics for	Previously treated with ADA or another anti-TNF therapy (e.g., infliximab or etanercept); not on a stable dose of antibiotic (for at least 28 days prior to entry; received oral concomitant analgesics (including opioids) for HS-related pain, on opioid analgesics, not on a stable dose of non-opioid oral analgesics, within 14 days prior to entry

			were re-randomised to ADA EW or EOW or placebo. Patients who were on placebo in period A were assigned (using re-randomisation numbers) to receive ADA 40 mg ew		treatment of HS, and a count of ≥3 at baseline	
Kimball 2012	ADA 40 mg EW vs. ADA 40 mg EOW vs. Placebo	52 weeks	16 week double blind randomised controlled phase followed by a 36 week open label phase in which all patients received ADA	USA and Europe	≥18 years, moderate to severe HS (HS-PGA score of moderate or worse) in at least 2 distinct anatomical areas and were unresponsive or intolerant to oral antibiotics as assessed by the investigator were eligible for enrollment.	Prior treatment with ADA or any other TNF antagonist therapy (e.g., infliximab or etanercept) or had received any systemic nonbiologic therapy within 4 weeks of baseline. Patients were allowed stable doses of oral (tetracycline, doxycycline, or minocycline) or topical (clindamycin) antibiotic treatment for HS
Miller 2011	ADA 40 mg EOW vs. Placebo	24 weeks	12 week double blind randomised controlled treatment period was followed by an observational period of 12 weeks	Denmark (multicenter)	≥18 years and a clinical diagnosis of moderate to severe HS defined as Hurley stage II or III for at least 6 months. Wash-out periods were a minimum of 4 weeks prior to baseline assessment	Current conventional treatment of HS 4 weeks prior to baseline and throughout the trial, prior exposure to biologics within the previous 6 months, chronic or recurrent infections, allergy to ADA or its constituents, untreated or latent tuberculosis, poorly controlled medical conditions, history of neurological disease
Non-biologics (antibiotics only)						
Jemec 1998	Tetracycline-Systemic vs. Clindamycin-Topical	16 weeks	Double blind randomised study	Denmark (single center)	Early-stage (Hurley stage 1 or 2: single abscesses without sinus tracts, or recurrent but widely separated lesions with sinus tracts and scarring) hidradenitis suppurativa) were included	Acne conglobata; staphylococcal infection; staphylococcosis; had systemic or topical antibiotic within the past 7 days; hypersensitivity to tetracycline, lincosamides; systemic infection; history of impaired renal or liver function; known severe underlying disease; treatment with steroids within the past 7 days; treatment with depo-steroids within the past 6 weeks; chronic bowel diseases or diarrhea; treatment with cyproterone acetate within the past 6 months; and more than 10 lesions from all sites together or Hurley stage 3
Surgery						
Tierney 2009	Laser + topical antibiotics (benzoyl peroxide wash 10%, clindamycin 1% gel or 1% lotion) vs. Topical antibiotics	24 weeks	Patients were randomised for treatment with topical antibiotics on the control half of the body and with Nd:YAG laser and topical antibiotics on the treated half of the body	USA (single center)	≥18 years; HS Hurley Stage II to III with bilateral and symmetric disease with one or more anatomic sites of involvement.	Concomitant use of systemic treatments for HS. Patients had to discontinue all forms of oral therapy such as systemic antibiotics and retinoids for 2 weeks before the start of the laser treatment

4.2 List of relevant randomised controlled trials

Four placebo-controlled trials provide evidence for ADA in moderate to severe HS[29-31 77].

This submission excludes the study by Miller et al[77] since it only included 21 patients (14 receiving ADA and 5 receiving placebo). In addition, the only ADA dose explored in this study was the ADA 40 mg EOW dose which is not the licensed dose for ADA 40 mg in HS.

This submission includes three placebo controlled studies, see Table 7:

- A placebo-controlled dose-finding study comparing ADA 40 mg EW from week 4 after initial doses of ADA 160 mg at week 0 and ADA 80 mg at week 2; with ADA 40 mg EOW from week 1 after an initial dose of ADA 80 mg at week 0 for 16 weeks, followed by a 36 week open period. This study has been published[31] and the published paper has been used wherever possible, some additional information is taken from the clinical study report (CSR)[81].
- Two randomised controlled trials (RCT), PIONEER I and PIONEER II, which compared placebo and ADA 40 mg EW for 12 weeks, starting at week 4 after ADA 160 mg at week 0 and ADA 80 mg at week 2 (period A). This was followed by a 24 week phase (period B) in which patients on ADA 40 mg EW remained on treatment or switched to either ADA 40 mg EOW or placebo, patients on placebo were switched to ADA 40 mg EW in PIONEER I and remained on placebo in PIONEER II. PIONEER I and PIONEER II have not been published, although data has been presented at scientific meetings. The CSRs have been used to inform this submission, together with information from the posters below
    - PIONEER I, period A data: presented at the 44th Annual European Society for Dermatological Research (ESDR) meeting, Copenhagen, Denmark, 10-13 September 2014[82] and at Advances in Cosmetic and Medical Dermatology (ACMD) conference, Maui Hawaii, 26-30 January 2015[83]. Data has also been published in abstract form in *J Invest Dermatol*[84]
    - PIONEER II, period A data: presented at the ACMD conference in 2015[85] and at the American Academy of Dermatology (AAD) in San Franciso, 20-24

March 2015[86]. Data has also been published in abstract form in *J Am Acad Dermatol*[87]

- Period B data for HiSCR with continuous ADA weekly dosing: integrated across PIONEER I, II and the open label extension (OLE) was presented at the 23rd World Congress of Dermatology (WCD), Vancouver, Canada, 8-13 June 2015[33].
- Joint demographic data for PIONEER I and II were presented at WCD in 2015[88].

Table 7: Randomised controlled trials of ADA 40 mg in moderate to severe HS.

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
M10-467	Moderate to severe HS	Period 1 (16 weeks) ADA 40 mg EW (from week 4 after ADA 160 mg at week 0 and ADA 80 mg at week 2) ADA 40 mg EOW (from week 1 after ADA 80 mg at week 0) Period 2: open label (36 weeks) ADA 40 mg EOW	Period 1 (16 weeks) Placebo Period 2: open label (36 weeks) ADA 40 mg EOW	[31]
M11-313 PIONEER I	Moderate to severe HS	Period A (12 weeks) ADA 40 mg EW (from week 4 after ADA 160 mg at week 0 and ADA 80 mg at week 2) Period B (24 weeks) ADA 40 mg EW ADA 40 mg EOW	Period A (12 weeks) Placebo Period B (24 weeks) Placebo	[29 82 83]
M11-810 PIONEER II	Moderate to severe HS	Period A (12 weeks) ADA 40 mg EW (from week 4 after ADA 160 mg at week 0 and ADA 80 mg at week 2) Period B (24 weeks) ADA 40 mg EW ADA 40 mg EOW	Period A (12 weeks) Placebo Period B (24 weeks) Placebo	[30 85]

Given that there is no standard of care for moderate to severe HS, placebo is an appropriate comparator for ADA 40 mg.

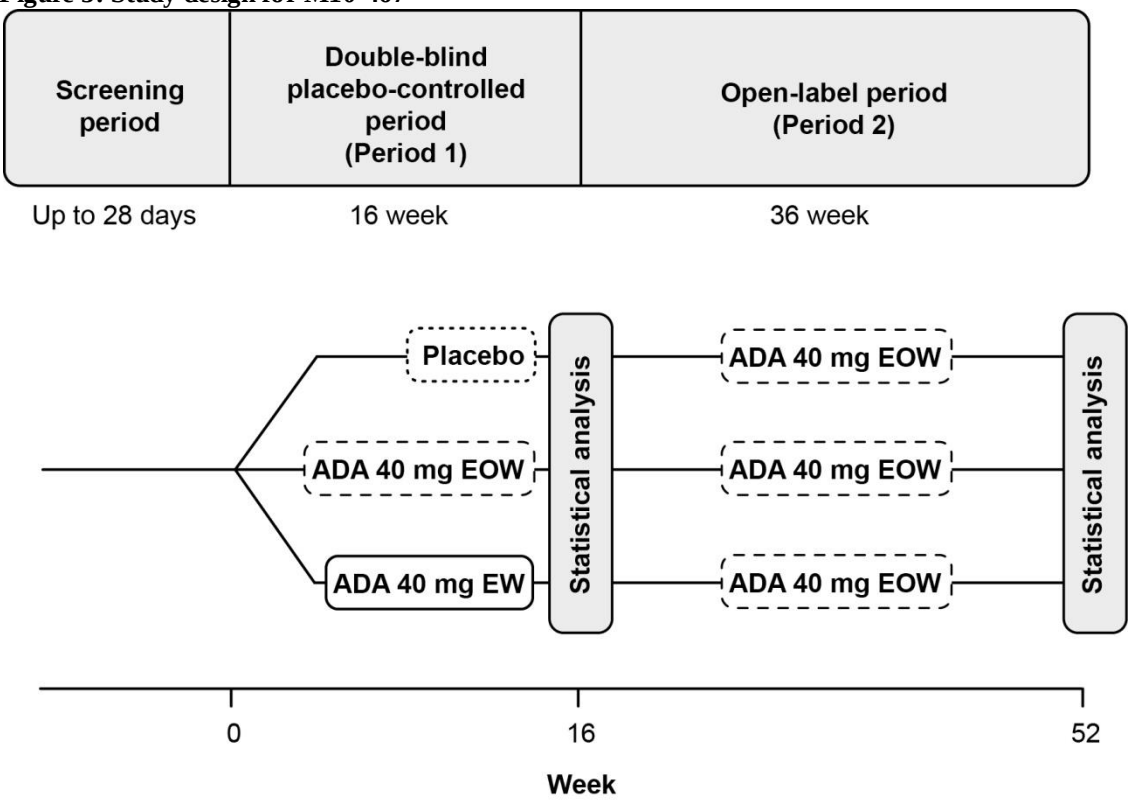
4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 M10-467

M10-467 was a phase II parallel randomised placebo-controlled two part dose-finding trial. The first part of the study was blinded for 16 weeks and the second part was an open label 36-week study, see Figure 5. All study personnel, investigators and patients remained blinded throughout the study period. To maintain blinding, placebo and ADA were packaged in identical syringes, and all patients received an equal number of injections for each dosing session. Patients were enrolled by investigators and centrally randomly assigned via an interactive voice-response system and interactive Web-response system.

In period 1 patients were randomised to placebo, ADA 40 mg EW (week 4 through week 15, after initial doses of ADA 160 mg at week 0 and ADA 80 mg at week 2) or ADA 40 mg EOW (week 1 through week 15, after an initial dose of 80 mg at week 0). In period 2, all patients who completed period 1 started with ADA 40 mg EOW. Patients who had received placebo in period 1 received initial blinded ADA 80 mg at week 16, and patients who had received active therapy in period 1 received blinded placebo at week 16. At weeks 28 or 31, any patient with an HS-PGA score of moderate or worse (score >3) was eligible to escalate to ADA 40 mg EW for the rest of the study.

Figure 5: Study design for M10-467[31]



Patients aged 18 years or older with moderate to severe HS (HS Physician's Global Assessment [HS-PGA] score of moderate or worse, see .

Table 8) in at least two distinct anatomical areas and were unresponsive or intolerant to oral antibiotics as assessed by the investigator were eligible for enrolment.

Patients were ineligible if they had previously received treatment with ADA or any other anti-TNF or had received any systemic non-biologic therapy within 4 weeks of baseline.

Patients were allowed oral (tetracycline, doxycycline, or minocycline) or topical (clindamycin) antibiotic treatment for HS if they had received a stable dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study.

M10-467 was carried out in 26 academic and private practice centres in the US and Europe (Germany, Denmark, The Netherlands).

At screening and study visits, physicians assessed counts of nodules (inflammatory and non-inflammatory), abscesses and fistulas (draining and non-draining) and

assigned patients to one of six categories (clear, minimal, mild, moderate, severe, or very severe) of the HS-PGA scale (see Table 8).

Table 8: HS-PGA scale

Rating	Description
Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules and 0 non-inflammatory nodules
Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules and presence of non-inflammatory nodules
Mild	0 abscesses, 0 draining fistulas, and 1–4 inflammatory nodules or 1 abscess or draining fistula and 0 inflammatory nodules
Moderate	0 abscesses, 0 draining fistulas, and ≥ 5 inflammatory nodules or 1 abscess or draining fistula and ≥ 1 inflammatory nodule or 2–5 abscesses or draining fistulas and <10 inflammatory nodules
Severe	2–5 abscesses or draining fistulas and ≥10 inflammatory nodules
Very severe	>5 abscesses or draining fistulas

The MSS[67], a clinical scoring system that assesses the number of involved anatomical regions, the number and type of lesions, the extent of involvement and the Hurley stage, was used to assess disease activity. Pain was assessed by using a questionnaire with a VAS ranging from 0 mm (no pain) to 100 mm (maximum pain).

Patients completed all questionnaires before clinical assessment or interaction with site personnel to avoid biasing the responses.

The primary outcome measure was the proportion of patients achieving a HS-PGA score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16.

Pre-specified secondary outcome measures included:

- Mean percentage of improvement in abscesses, draining fistulas, or inflammatory nodules from baseline to week 16.
- Mean change in the MSS score from baseline to week 16.
- Mean change in patient reported outcomes (PRO) from baseline to week 16.
    - DLQI questionnaire (which measures dermatology specific health-related QOL and ranges from 0 to 30, with 0 being no impairment)

  - Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) questionnaire (which ranges from 0 to 100, with 0 being no impairment)
  - Patient Health Questionnaire-9 (PHQ-9) (self-assessment for depression ranging from 0 to 27, with 0 being no depressive symptoms) were included to assess patient-reported outcomes.
- Proportion of patients achieving clinical response at weeks 2, 4, 8, and 12 and all study visits during period 2.

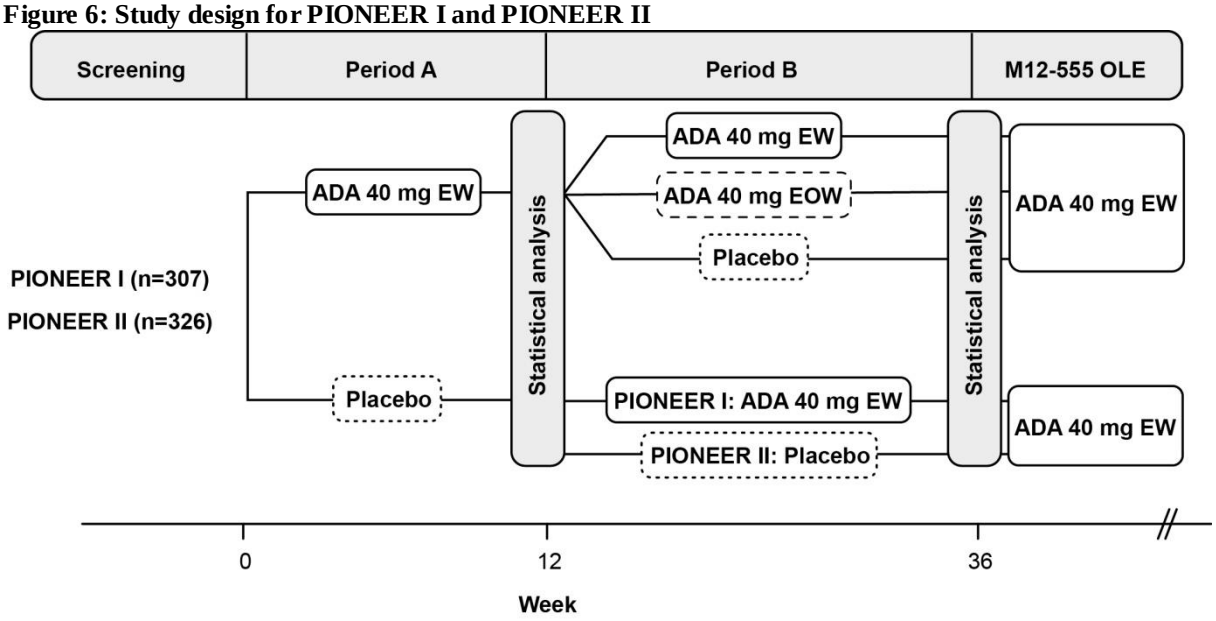
4.3.2 PIONEER I and PIONEER II

PIONEER I and PIONEER II were very similar in design, see Figure 6.

Both studies were double-blind, placebo-controlled phase III studies and each included a 30 day screening period and two study periods:

- Period A to assess the efficacy and safety of ADA 40 mg EW compared to placebo for the first 12 weeks of treatment
- Period B to explore the safety and efficacy of different maintenance regimens over 24 weeks. Patients who were randomised to ADA 40 mg EW in period A were re-randomised to one of ADA 40 mg EW, ADA 40 mg EOW or placebo in period B.
- PIONEER OLE (M12-555/NCT01635764) – an OLE trial to PIONEER I and PIONEER II to evaluate long-term safety, tolerability and efficacy of ADA in moderate-severe HS. Interim data is available for OLE and is discussed later in this submission.

Figure 6: Study design for PIONEER I and PIONEER II



Blinding for both studies was as per M10-467. Patients were stratified by Hurley status (PIONEER I and II) and antibiotic use (PIONEER II only).

In both studies patients were randomised to placebo or ADA 40 mg EW (week 4 through week 15, after initial doses of ADA 160 mg at week 0 and ADA 80 mg at week 2) during period A. Patients randomised to ADA 40 mg EW in period A were re-randomised to either placebo or ADA 40 mg EOW or remained on ADA 40 mg EW. In PIONEER I, patients in the placebo arm were re-randomised to ADA mg EW, whereas in PIONEER II patients in the placebo arm remained on placebo.

Continuation in both the PIONEER studies was determined by clinical response.

- Patients who achieved a clinical response (HiSCR) at week 12 patients were enrolled in period B to the end of week 36. If there was loss of response (LOR) then patients were excluded from the study and given the option of enrolling in the OLE study (M12-555).
- Patients who did not achieve HiSCR at week 12 were enrolled in period B to week 16 and up to week 36. If a patient had worsening or absence of improvement (WOAI) at week 16 or after week 16 they were excluded from the study and given the option of enrolling in the OLE study (M12-555).

Eligible patients were aged 18 years or older with a diagnosis of HS for at least 1 year. HS lesions had to be present in at least two distinct anatomical areas, one of which had to be Hurley stage II or III. Patients had to have a total abscess and inflammatory nodule (AN) count of >3 at the baseline visit. Patients unresponsive or intolerant to oral antibiotics were eligible for enrolment.

An inadequate response to antibiotics was defined as follows. If, after at least 90 days of oral antibiotic therapy, any of the following had occurred, the patient was deemed to have experienced an inadequate response, or LOR to oral antibiotics:

- Progression of Hurley Stage (i.e., the Hurley Stage of at least one affected anatomic region has progressed from I→II, II→III, or I→III).
- Requirement for at least 1 intervention (e.g., incision and drainage or intra-lesional injection of corticosteroid).
- Pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or paracetamol).
- Pain requiring opioids, including tramadol.
- Drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily)
- An increase in the number of anatomic regions affected by HS.
- At least one new abscess or one new draining fistula.

Patients were ineligible if they had previously received treatment with ADA or any other anti-TNF, oral concomitant analgesics for HS-related pain within 14 days of baseline, were likely to require opioid analgesia for any reason or had >20 draining fistulae at baseline.

In PIONEER I, patients were excluded if they had received oral antibiotics for HS within 28 days before the baseline visit. Rescue therapy with doxycycline or minocycline was allowed starting at week 4 or week 8.

In PIONEER II, patients were allowed oral (doxycycline or minocycline) antibiotic treatment for HS if they had received a stable dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study.

Study visits occurred at baseline, week 2, week 4, week 8, week 12, week 14, week 16, week 20, week 24, week 28, week 32, week 36, and at the premature discontinuation visit if the subject discontinued prior to week 36.

Both studies were multi-centre studies, PIONEER I was carried out in Australia, Canada, Denmark, France, Greece, The Netherlands, Sweden, Switzerland, Turkey and the US. PIONEER II was carried out in Australia, Canada, Czech Republic, Germany, Hungary and the US.

The primary outcome measure was the proportion of patients achieving HiSCR at week 12. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline. HiSCR was developed in consultation with regulatory health authorities and has been validated against other measures of response in HS (Hurley stage, MSS and HS-PGA) in 138 patients with three or more AN enrolled in the dose finding study (M10-467) for ADA in HS and has been shown to be a valid and meaningful end-point for assessment of HS treatment effectiveness[36]. HiSCR is more responsive to change and better able to discriminate improvement in ADA-treated patients, compared to HS-PGA[89], as validated in a post-hoc population of 132 patients with three or more AN and draining fistula count of ≤20 enrolled in the dose finding study (M10-467) for ADA in HS. It is therefore anticipated that HiSCR would be expected to provide a more dynamic assessment than HS-PGA, and better able to capture changes over the course of the phase III trials[90]. HiSCR was also expected to more accurately predict the non-worsening of key inflammations that would eventually require surgery[90]. Finally, HiSCR is a simple measure to conduct, since it only requires counting of the inflammatory nodules, abscesses and draining fistulas before and after an intervention[91].

Key secondary end-points in period A were

- Proportion of patients who achieved AN count of 0, 1, or 2 at week 12, among patients with Hurley Stage II at baseline.
- Proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at week 12 among patients with baseline NRS ≥ 3.

- Change in MSS score from baseline to week 12.

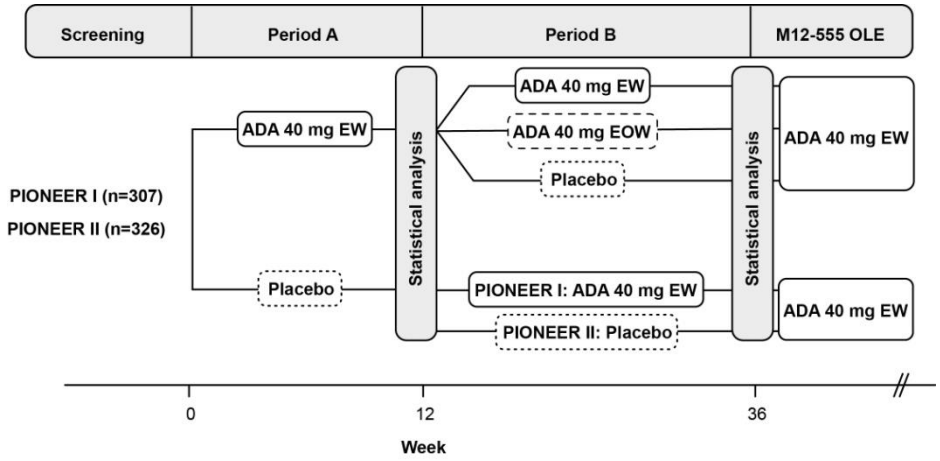
Secondary end-points in period B were

- The key secondary efficacy end-points listed in period A were summarised for each sub-population in the intention to treat (ITT) population in Period B. Treatment comparisons were performed in patients randomised to ADA 40 mg EW in period A and were week12 HiSCR responders.
- Time to LOR in patients randomised to ADA 40 mg EW in period A who were week12 HiSCR responders and re-randomised to placebo.
- Time to WOAI, defined as the second incidence of the two-consecutive visits with AN count higher than the baseline AN count in patients randomised to ADA 40 mg EW in period A who were week12 HiSCR non-responders.

PRO outcomes were also assessed in PIONEER I and PIONEER II – the tools used were slightly different in each study:

- DLQI
- HS quality of life (HSQOL)
- Short Form-36 Health Status Survey (SF-36) (PIONEER I only)
- EuroQol (EQ-5D) (PIONEER II only)
- WPAI:SHP
- Patient Global Assessment of Skin Pain (Numeric Rating Scale 0-10)
- Hospital Anxiety and Depression Scale (HADS) (PIONEER I only).

Table 9: Comparative summary of trial methodology for M10-467, PIONEER I and PIONEER II

	M10-467	PIONEER I	PIONEER II
Location	US, Germany, Denmark, The Netherlands	Australia, Canada, Denmark, France, Greece, The Netherlands, Sweden, Switzerland, Turkey and US	Australia, Canada, Czech Republic, Germany, Hungary and US
Trial design	Phase II parallel randomised placebo-controlled two part trial. The first part of the study was blinded for 16 weeks and the second part was an open label 36-week study	Double-blind, placebo-controlled Phase III studies, with 30 day screening period and two study periods 	
Eligibility criteria	Patients aged 18 years or older with moderate to severe HS (HS-PGA score of moderate or worse) in at least two distinct anatomical areas and unresponsive or intolerant to oral antibiotics	Eligible patients were aged 18 years or older with a diagnosis of HS for at least 1 year. HS lesions had to be present in at least two distinct anatomical areas, one of which had to be Hurley stage II or III. Patients had to have an AN count of >3 at the baseline visit. Patients unresponsive or intolerant to oral antibiotics were eligible for enrolment.	
Trial drugs	In period 1 patients were randomised to placebo, ADA 40 mg EW (week 4 through week 15, after initial doses of ADA 160 mg at week 0 and ADA 80 mg at week 2) or ADA 40 mg EOW (week 1 through week 15, after an initial dose of 80 mg at week 0). In period 2, all patients who completed period 1 started with ADA 40 mg EOW. At weeks 28 or 31, any patient with an HS-PGA score of moderate or worse (score >3) was eligible to	In period A patients were randomised to placebo or ADA 40 mg EW (week 4 through week 15, after initial doses of ADA 160 mg at week 0 and ADA 80 mg at week 2). In period B patients randomised to ADA 40 mg EW in period A were re-randomised to either placebo or ADA 40 mg EOW or remained on ADA 40 mg EW.	In period A patients were randomised to placebo or ADA 40 mg EW (week 4 through week 15, after initial doses of ADA 160 mg at week 0 and ADA 80 mg at week 2). In period B patients randomised to ADA 40 mg EW in period A were re-randomised to either placebo or ADA 40 mg EOW or remained on ADA 40 mg EW

	escalate to ADA 40 mg EW for the rest of the study. Patients were allowed oral (tetracycline, doxycycline or minocycline) or topical (clindamycin) antibiotic treatment for HS if they had received a stable dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study.	In period B patients randomised to placebo in period A were re-randomised to ADA 40 mg EW. Patients were excluded if they had received oral antibiotics for HS within 28 days before the baseline visit. Rescue therapy with doxycycline or minocycline was allowed starting at week 4 or week 8.	In period B patients randomised to placebo in period A remained on placebo Patients were allowed oral (doxycycline or minocycline) antibiotic treatment for HS if they had received a stable dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study.
Study continuation		Continuation in both the PIONEER studies was determined by clinical response. Patients who achieved a clinical response (HiSCR) at week 12 patients were enrolled in period B to the end of week 36. If there was loss of response then patients were excluded from the study and given the option of enrolling in the OLE study (M12-555). Patients who did not achieve HiSCR at week 12 were enrolled in period B to week 16 and up to week 36. If a patient had WOAI at week 16 or after week 16 they were excluded from the study and given the option of enrolling in the OLE study (M12-555).	
Primary outcome	Proportion of patients achieving a HS-PGA score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16	Proportion of patients achieving HiSCR at week 12. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline	
Secondary outcomes	Proportion of patients achieving clinical response at weeks 2, 4, 8, and 12 and all study visits during period 2. Proportion of patients achieving an HS-PGA score of clear, minimal, or mild at week 16. Mean change in the MSS score from baseline to week 16 Mean percentage of improvement in abscesses, draining fistulas, or inflammatory nodules from baseline to week 16. Mean change in C-reactive protein levels from baseline to week 16.	Proportion of patients who achieved AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline. Proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at week 12 among patients with baseline NRS ≥ 3. Change in MSS from baseline to week 12. Secondary end-points in period B were The key secondary efficacy end-points listed in period A were summarised for each subpopulation in the Intent-to-Treat (ITT) population in Period B. Treatment comparisons were performed in patients randomised to ADA in period A and were week12 HiSCR responders. Time to LOR in patients randomised to ADA in period A who were week12 HiSCR responders and re-randomised to placebo. Time to WOAI in patients randomised to ADA in period A who were week12	

		HiSCR non-responders.	
PRO outcomes	DLQI WPAI:SHP PHQ-9	DLQI HSQOL WPAI:SHP Patient Global Assessment of Skin Pain SF-36 HADS	DLQI HSQOL WPAI:SHP Patient Global Assessment of Skin Pain EQ-5D

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Table 10 details the statistical analysis and definition of study groups for M10-467 and the PIONEER studies. In all studies the efficacy analyses were carried out on the ITT population, which was defined as all patients randomised to treatment at week 0. All three studies used the Cochran-Mantel-Haenszel test adjusted for baseline strata and all statistical tests were 2-sided and had a significance level of 5%.

Study M10-467 was designed to enrol 150 patients, to provide 80% power to detect a clinically relevant treatment difference at week 16 with a 2-sided type I error level of 5%, assuming clinical response rates of 10% for patients receiving placebo and 35% for patients receiving ADA. The response rate in M10-467 informed the sample size calculation for the PIONEER studies; a sample size of 150 per arm provided more than 90% power to detect the treatment difference with 0.05 two-sided Type I error.

In all three studies, any patient with a missing evaluation, including those missing because of discontinuation, was classified as a non-responder. In the PIONEER studies non responder imputation (NRI) was used as the primary approach for missing values.

Table 10: Summary of statistical analyses in M10-467, PIONEER I and PIONEER II

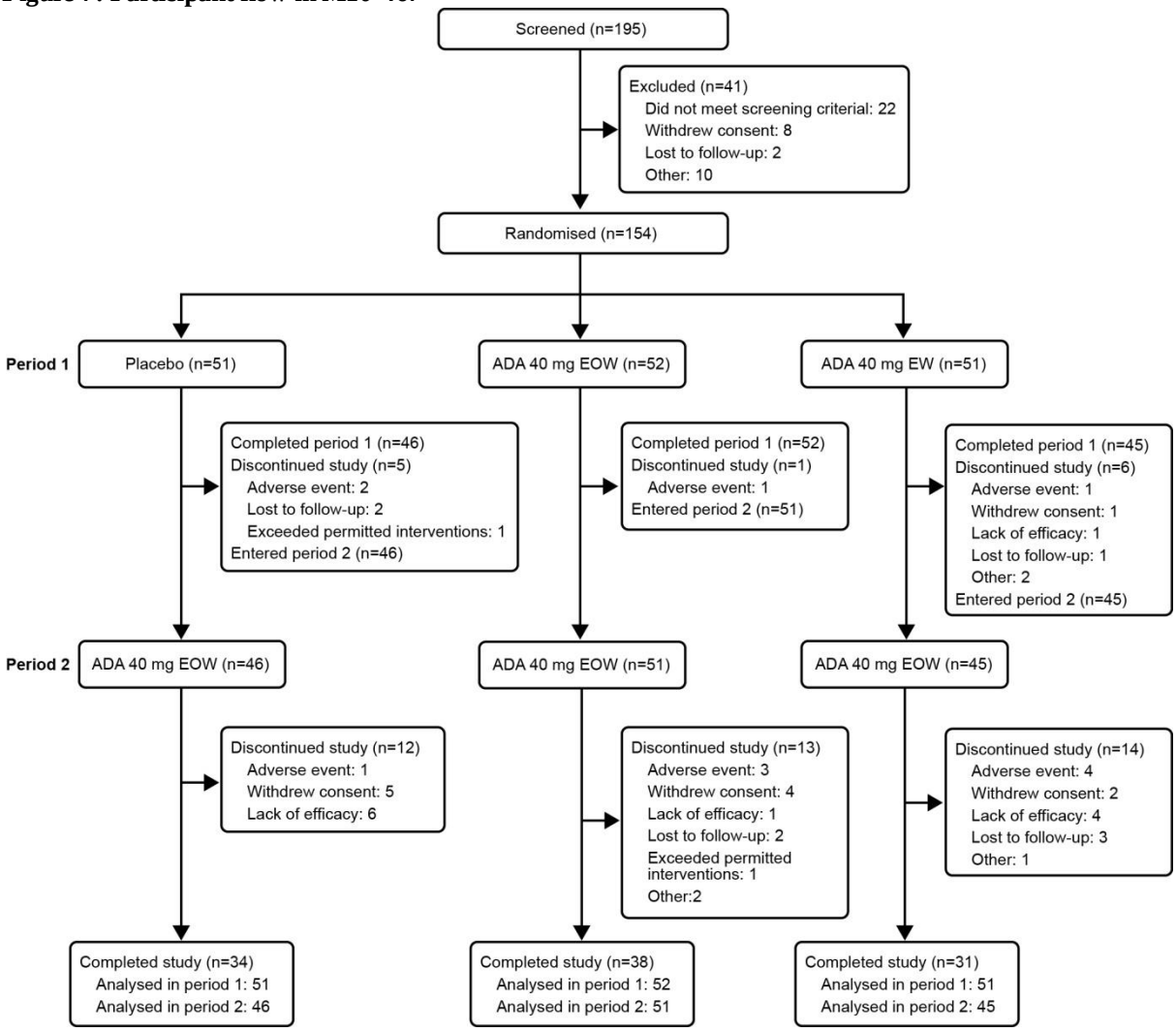
Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
M10-467	That ADA would improve clinical response as measured by HS-PGA more than placebo at week 16.	Efficacy analyses were carried out on the ITT populations. For period 1, the ITT population consisted of all patients randomly assigned at week 0. The primary efficacy analysis was carried out using the Cochran-Mantel-Haenszel test adjusted for baseline strata (Hurley stage I or II vs. stage III). All statistical tests were 2-sided and had a significance level of 5%	Study was designed to enrol 150 patients, to provide 80% power to detect a clinically relevant treatment difference at week 16 with a 2-sided type I error level of 5%, assuming clinical response rates of 10% for patients receiving placebo and 35% for patients receiving ADA	Any patient with a missing evaluation, including those missing because of discontinuation, was classified as a non-responder.
PIONEER I **PIONEER II**	That ADA would improve clinical response as measured by HiSCR more than placebo at week 12.	Efficacy analyses were carried out on the ITT populations. For period A, the ITT population consisted of all patients randomly assigned at week 0. The primary efficacy analysis was carried out using the Cochran-Mantel-Haenszel test adjusted for baseline strata (Hurley stage I or II vs. stage III) and concomitant use of oral antibiotics (Y/N) in PIONEER II only All statistical tests were 2-sided and had a significance level of 5%	The response rates M10-467 for HiSCR at Week 12 were 61% for ADA 40 mg EW and 16% for placebo. A sample size of 150 per arm provided more than 90% power to detect the treatment difference with 0.05 two -sided Type I error.	Any patient with a missing evaluation, including those missing because of discontinuation, was classified as a non-responder. NRI was used as the primary approach for missing values.

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Participant flow in M10-467

The participant flow in M10-467 is shown in Figure 7.

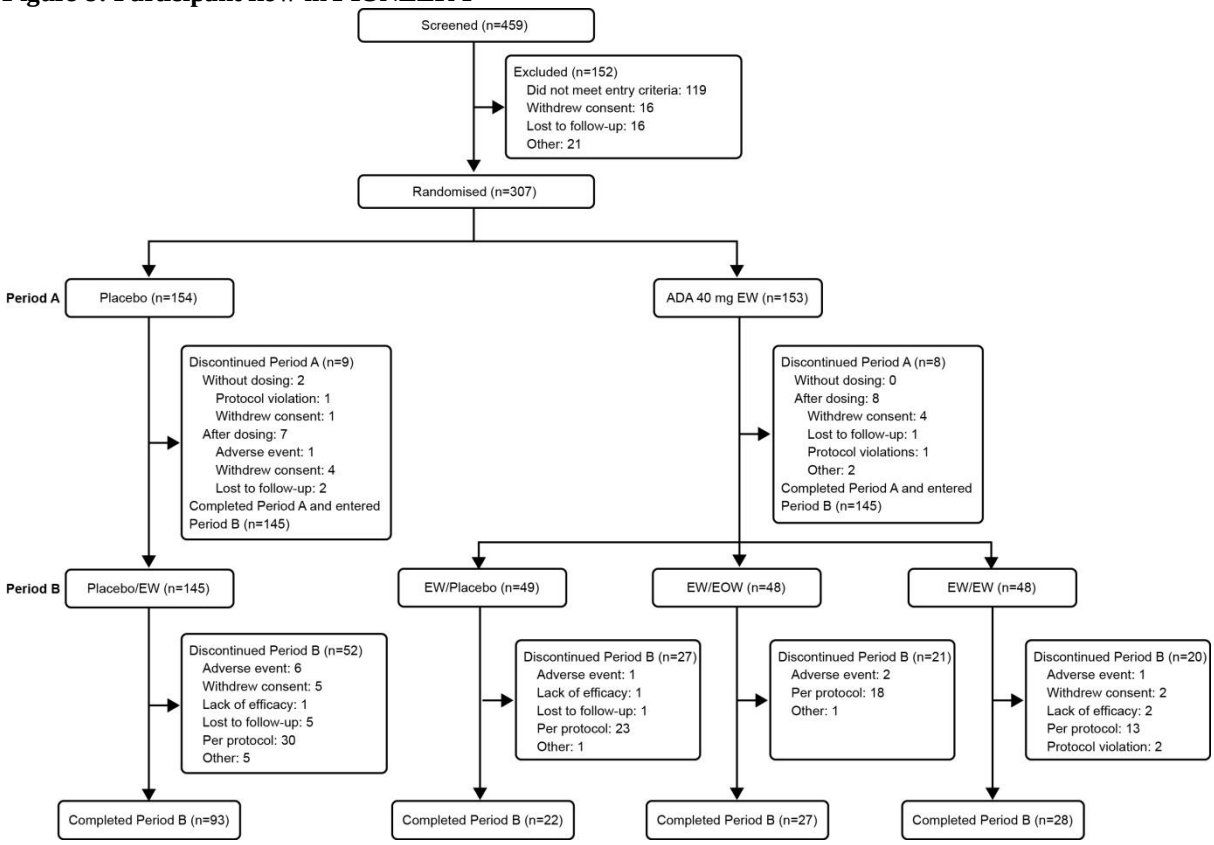
Figure 7: Participant flow in M10-467[31]



4.5.2 Participant flow in PIONEER I

A total of 307 patients were randomised in period A; however, two of the 307 randomised patients did not receive study drug. Of the 307 patients, 290 (94.5%) completed period A and continued on to period B. Of the patients randomised and dosed in period B, 170 (58.6%) patients completed Period B, see Figure 8. It should be noted that 84 (29%) were discontinued primarily due to lack of response per protocol, the majority of whom were in the ADA 40 mg EW group switched to placebo.

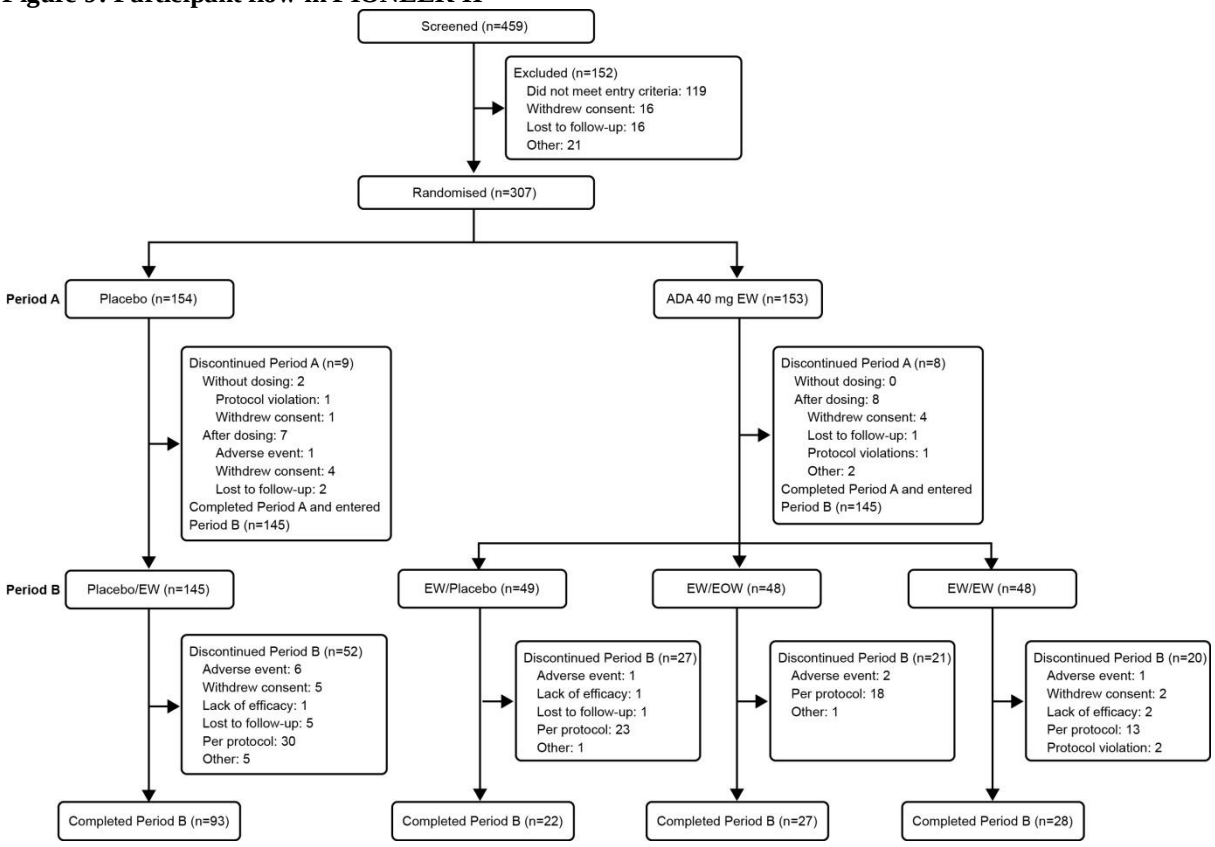
Figure 8: Participant flow in PIONEER I[29]



4.5.3 Participant flow in PIONEER II

A total of 326 patients were randomised in period A, of the 326 patients, 306 (93.8%) completed period A and continued on to period B. Of the patients randomised and dosed in period B, 116 (37.9%) patients completed Period B, see Figure 9. It should be noted that 151 (49%) were discontinued primarily due to lack of response per protocol, the majority of whom were in the ADA 40 mg EW group switched to placebo.

Figure 9: Participant flow in PIONEER II[30]



4.5.3 Patient characteristics

Patient characteristics in M10-467, PIONEER I and II were well balanced across treatment groups and represented the known presentation of the disease.

The average duration of HS ranged from 10.9 years in the ADA 40 mg EOW arm to 13.4 years in the placebo arm of M10-467. Patients were predominantly women (71.4%) aged in their mid to late thirties. In M10-467, 18.8% of patients were African American.

The average duration of HS was 11.5 years in PIONEER I and 11.6 years in PIONEER II. Patients were predominantly women (63.8% in PIONEER I and 67.8% in PIONEER II) aged in their mid to late thirties. In PIONEER I, 20.2% of patients were African American compared to only 8.8% in PIONEER II. Patients in PIONEER I had more severe disease than in PIONEER II; as demonstrated by higher mean MSS score, 149.1 versus 115, higher AN count 14.3 versus 11.3 and higher worst pain score 5.0 versus 4.5.

The patient characteristics at baseline are shown in Table 11.

Table 11: Patient characteristics at baseline in M10-467, PIONEER I and PIONEER II[29-31 82 83 85]

	M10-467			PIONEER I			PIONEER II		
	Placebo (n=51)	ADA EW (n=51)	ADA EOW (n=52)	Placebo (n=154)	ADA EW (n=153)	Total (n=307)	Placebo (n=163)	ADA EW (n=163)	Total (n=326)
Female, n (%)	36 (70.6)	36 (70.6)	38 (73.1)	105 (68.2)	91 (59.5)	196 (63.8)	113 (69.3)	108 (66.3)	221 (67.8)
White, n (%)	37 (72.5)	37 (72.5)	36 (69.2)	118 (76.6)	116 (75.8)	234 (76.2)	130 (79.8)	143 (87.7)	273 (83.7)
Black, n (%)	8 (15.7)	9 (17.6)	12 (23.1)	29 (18.8)	33 (21.6)	62 (20.2)	20 (12.3)	9 (5.5)	29 (8.9)
Other	6 (11.7)	5 (9.8)	4 (7.6)	7 (4.5)	4 (2.6)	11 (3.6)	13 (7.9)	11 (6.7)	24 (7.3)
Age, years; mean [SD]	37.8 [12.1]	35.1 [10.7]	36.1 [12.5]	37.8 [11.33]	36.2 [10.83]	37.0 [11.10]	36.1 [12.18]	34.9 [9.96]	35.5 [11.13]
Hurley stage I, n (%)	36 (70.6)	36 (70.6)	37 (71.2)		-				
Hurley stage II, n (%)				81 (52.6)	80 (52.3)	161 (52.4)	89 (54.6)	86 (52.8)	175 (53.7)
Hurley stage III, n (%)	15 (29.4)	15 (29.4)	15 (28.8)	73 (47.4)	73 (47.7)	146 (46.6)	74 (45.5)	77 (47.2)	151 (46.3)
Disease duration, years; mean [SD]	13.4 [10.4]	11.3 [9.1]	10.9 [9.0]	11.6 [8.86]	11.3 [9.00]	11.5 [8.92]	11.8 [9.41]	11.3 [8.66]	11.5 [9.03]
AN count; mean [SD]				14.4 [14.80]	14.3 [11.92]	14.3 [13.42]	11.9 [11.02]	10.7 [8.10]	11.3 [9.68]
MSS; mean [SD]				147.3 [97.16]	151.0 [131.17]	149.1 [115.19]	122.6 [88.00]	107.5 [80.03]	115 [84.32]
NRS skin pain at worst; mean [SD]				(n=146) 4.8 [2.68]	(n=151) 5.1 [2.51]	(n=297) 5.0 [2.60]	(n=155) 4.8 [2.73]	(n=159) 4.3 [2.62]	(n=314) 4.5 [2.69]
BMI, kg/m^2; mean [SD]				(n=154) 34.5 [7.94]	(n=152) 33.0 [7.62]	(n=306) 33.8 [7.80]	32.9 [7.94]	31.3 [7.41]	32.1 [7.71]

Body weight, kg, mean [SD]	96.5 [24.8]	95.4 [22.9]	99.8 [26.8]						
Prior surgery for HS, n (%)				13 (8.4)	21 (13.7)	34 (11.1)	18 (11)	27 (16.6)	45 (13.8)
HS-CRP (C-reactive protein), mg/L; mean [SD]	13.3 [15.0]	21.5 [33.1]	17.8 [2.9]	17.4 [20.2]	20.3 [25]	18.9 [22.75]	18.3 [30.72]	13.3 [17.96]	15.8 [25.25]
Current smokers, n (%)	29 (56.9)	30.0 (58.8)	26 (50.0)	92 (59.7)	81 (52.9)	173 (56.4)	109 (67.3)	105 (64.4)	214 (65.8)

4.6 Quality assessment of the relevant randomised controlled trials

A summary of study quality assessment as per the NICE checklist is given in Table 12. The results for PIONEER I and PIONEER II are published only as two abstracts. Therefore, most of the details required for quality assessment are not reported for these two studies. Kimball et al. (2012)[31] was assigned low risk of bias against all items of the NICE checklist.

Table 12: Summary of study quality according to the NICE checklist

	M10-467[31]	**PIONEER I[84]**	**PIONEER II[87]**
Was randomisation carried out appropriately	Low risk	Intermediate risk	Intermediate risk
Was the concealment of treatment allocation adequate	Low risk	Intermediate risk	Intermediate risk
Were the groups similar at the outset of the study in terms of prognostic factors?;	Low risk	Low risk	Low risk
Were the care providers, participants and outcome assessors blind to treatment allocation	Low risk	Intermediate risk	Intermediate risk
Were there any unexpected imbalances in drop-outs between groups?;	Low risk	Intermediate risk	Intermediate risk
Is there any evidence to suggest that the authors measured more outcomes than they reported	Low risk	Intermediate risk	Intermediate risk
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk	Intermediate risk	Intermediate risk

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 M10-467

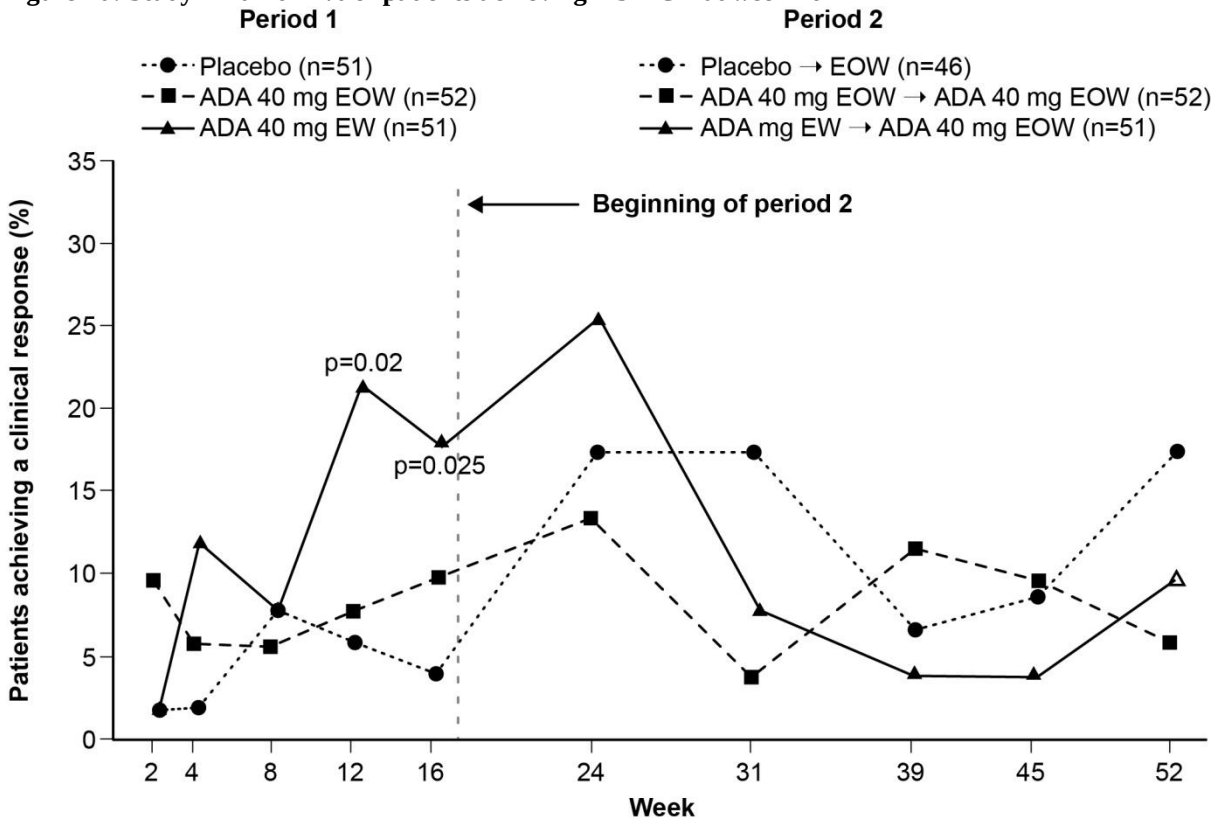
4.7.1.1 Primary end-point: improvement in HS-PGA at week 16

The primary end-point in M10-467 was the proportion of patients achieving a HS-PGA score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16.

Significantly more patients in the ADA 40 mg EW group and numerically more in the ADA 40 mg EOW achieved the primary end-point compared with patients in the placebo group (3.9% in the placebo group, 9.6% in the EOW group, and 17.6% in the EW group; EOW versus placebo difference, 5.6% [95% CI 4.0% to 15.3%];

p<0.25; EW versus placebo difference, 13.7% [95% CI 1.7% to 25.7%]; p<0.025), see Figure 10.

Figure 10: Study M10-467 –% of patients achieving HS-PGA at week 16[31]



4.7.1.2 Secondary end-points at week 16

The key secondary end-points are shown in Table 13.

Patients receiving ADA 40 mg EW demonstrated a significant improvement in individual symptoms (inflammatory nodules and draining fistulae) and in overall disease severity as measured by the MSS. PRO including QOL, work productivity and activity and depression all improved significantly with treatment. The improvement in symptoms was seen early in treatment; at least half of the lesion count improvement seen at week 16 was seen by week 4: mean improvement at week 4 was 25.2% for inflammatory nodule count, 68.8% for abscess count and 50.0% for draining fistula count.

There were numerical improvements with ADA 40 mg EOW but they were not clinically or statistically significant.

Table 13: M10-467 – secondary efficacy end-points at week 16: protocol-specified analysis (LOCF)[31]

Variable	Placebo	ADA EOW	ADA EW	Difference (95% CI)		p value (EW vs. placebo)
				EOW versus placebo	EW versus placebo	
Mean percentage of improvement from baseline (±SE)						
Inflammatory nodules	13.7 + 11.5	30.4 + 11.5	50.7 + 11.4	16.8 (-14.2,47.7)	37.0 (6.2 , 67.8)	0.019
Abscesses	25.0 + 13.9	46.2 + 14.1	51.8 + 16.3	21.3 (-17.5, 60.0)	26.8 (-16.0, 69.5)	0.22
Draining fistulae	-7.5 + 13.0	-7.7 + 13.9	44.4 + 13.3	0.26 (-37.2, 37.7)	36.9 (0.1, 73.7)	0.050
Change from baseline						
Median MSS score (SD)	-7.5 (47.3)	-16.0 (82.5)	-30.0 (52.7)	-9.0 (21.0, 6.0)	-18.0 (-33.0, -2.0)	0.014
Mean DLQI score (+ SE)	-1.9 + 0.9	-2.8 + 0.9	-6.0 + 0.9	-0.9 (-3.3 to 1.4)	-4.2 (-6.6, 1.8)	<0.001
Mean TWPI score (+ SE)	2.9 + 4.2	-0.9 + 4.0	-17.4 + 4.6	-3.9 (-14.6, 6.8)	-20.3 (-31.9, -8.8)	<0.001
Mean PHQ-9 score (+ SE)	-1.2 + 0.9	-1.4 + 0.8	-3.8 + 0.9	-0.2 (-2.4, 2.1)	-2.6 (-5.0, -0.3)	0.025

Most patients were in considerable pain at baseline (94.1% of placebo, 90.4% of EOW and 94.1% of EW patients had VAS pain scores of >10 mm at baseline). In these patients treatment with ADA 40 mg EW resulted in a clinically relevant reduction in pain (at least 30% reduction and 10 mm reduction) at week 16 versus placebo (47.9% versus 27.1%, p<0.037). Clinically relevant pain reduction was seen as early as week 2 in 40% of patients receiving the weekly dose.

Post-hoc analyses of patients enrolled in M10-467 have been carried out to retrospectively assess the efficacy of ADA using HiSCR score in a patient sub-population with baseline AN count ≥3 and draining fistula count ≤20[89 92] and have demonstrated that HiSCR is a valid and meaningful end-point for assessment of HS treatment effectiveness[36] and is more responsive to change and better able to discriminate improvement in ADA-treated patients, compared to HS-PGA[89]. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline

At 12 weeks, the proportion of patients achieving HiSCR in the placebo, EOW and EW groups were 16.3%, 35.6%, and 59.1% respectively (EW versus placebo,

p<0.001). At 16 weeks, the proportion of patients achieving HiSCR were 25.6%, 33.3%, and 54.5% (EW versus placebo, p<0.007)[92].

4.7.1.3 End-points at week 52

The proportion of patients with a clinical response fell after the change from EW dosing in period 1 to EOW dosing in period 2 (see Figure 10). Of the 142 patients who entered period 2, 89 (63%) had a sub-optimal response at weeks 28 or 31 and were dose-escalated to EW dosing of these, 13 (15%) had a clinical response at week 52

4.7.2 PIONEER I and PIONEER II

4.7.2.1 Primary end-point: improvement in HiSCR at week 12

The primary outcome measure was the proportion of patients achieving HiSCR at week 12. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline.

Significantly more patients in the ADA 40 mg EW group achieved the primary end-point compared with patients in the placebo group, Table 14 and Figure 11. This difference was maintained regardless of Hurley status (PIONEER I and II) and antibiotic use (PIONEER II only).

Response was seen early in treatment with a significant difference as early as 2 weeks, response was particularly marked in PIONEER II, see Figure 12.

Table 14: PIONEER I and PIONEER II – % of patients achieving HiSCR at week 12 (ITT population)[29] [30] [82] [83] [85] [93]

	Placebo	ADA EW	Difference (95% CI)	p value
PIONEER I	**40/154 (26.0%)**	**64/153 (41.8%)**	**15.9 (5,3, 26.5)**	**0.003**
Hurley stage II	25/84 (29.8%)	37/83 (44.6%)	14.8 (0.3, 29.3)	0.048
Hurley stage III	15/70 (21.4%)	27/70 (38.6%)	17.1 (22, 32.1)	0.027
PIONEER II	**45/163 (27.6%)**	**96/163 (58.9%)**	**31.5 (20.7, 42.2)**	**<0.001**
Antibiotic use	7/32 (21.9%)	20/31 (64.5%)	42.6 (17.8, 67.5)	<0.001
No antibiotic use	38/131 (29.0%)	76/132 (57.6%)	28.6 (16.9, 40.6)	<0.001
Hurley stage II	32/87 (36.8%)	53/85 (62.4%)	25.5 (10.5, 40.5)	< 0.001
Antibiotic use	3/12 (25.0%)	7/11 (63.6%)	38.6 (1.1, 76.2)	0.004
No antibiotic use	29/75 (38.7%)	46/74 (62.2%)	23.5 (7.9, 39.1)	<0.001
Hurley stage III	13/76 (17.1%)	43/78 (55.1%)	38.1 (22.8, 53.3)	<0.001
Antibiotic use	4/20 (20.0%)	13/20 (65.0%)	45.0 (17.7, 72.3)	0.004
No antibiotic use	9/56 (16.1%)	30/58 (51.7%)	35.7 (19.6, 51.7)	<0.001
Combined data	85/317 (26.8%)	160/316 (50.6%)		<0.001

Figure 11: PIONEER I and PIONEER II – % of patients achieving HiSCR at week 12 (ITT population), *p<0.05, **p<0.01 ***p<0.001[29] [30] [82] [83] [85]

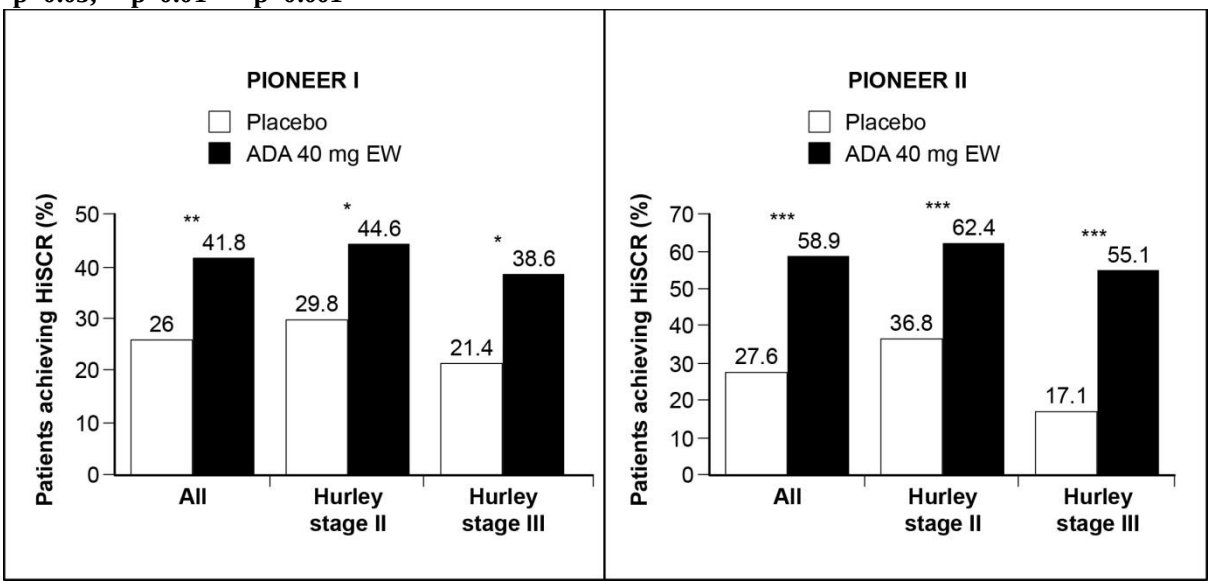
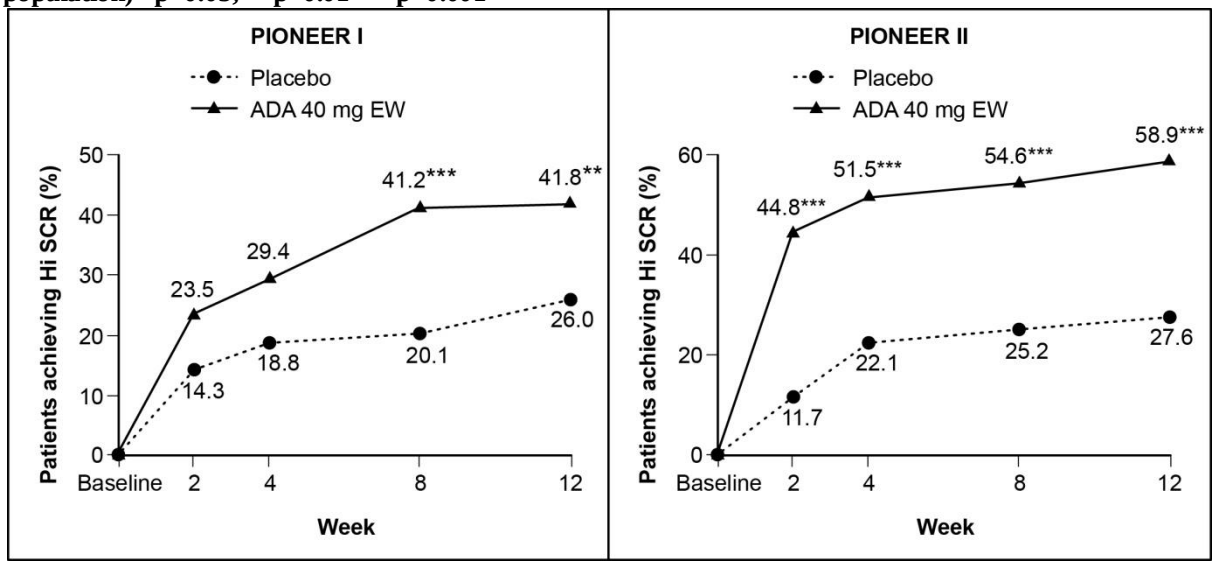


Figure 12: PIONEER I and PIONEER II – % of patients achieving HiSCR by visit in period A (ITT population) *p<0.05, **p<0.01 ***p<0.001[29 30 82 83 85]



Treatment with ADA EW also prevented worsening of disease, as measured by reduced frequency and duration of flares. The proportion of patients who experienced disease flare, defined as at least a 25% increase in AN count with a minimum increase of two relative to baseline, was lower in both studies during period A for patients randomised to ADA 40 mg EW than for patients randomised to placebo. At least one occurrence of flare was experienced by 13.7% of patients in the ADA 40 mg EW group and 35.7% of patients in the placebo group (p<0.001) in PIONEER I and 11% of patients in the ADA 40 mg EW group and 35% of subjects in the placebo group (p<0.001) in PIONEER II.

Furthermore, of the patients who experienced disease flare in period A, the mean number of days on flare was significantly shorter for those in the ADA 40 mg EW group than those in the placebo group (32.0 versus 19.1 days; p=0.018). The risk of worsening of disease was based on all occurrences (i.e. not excluding any cases after a patient used rescue medication).

4.7.2.2 Secondary end-points at week 12

Proportion of patients who achieved AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline

In PIONEER I, the proportion of patients achieving AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline, was similar in both groups. When

the total population was considered, numerically more patients in the ADA 40 mg EW group achieved an AN count of 0, 1, or 2 at week 12 than placebo patients, [redacted], see Table 15.

In PIONEER II, the proportion of patients achieving AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline, was significantly higher in the ADA 40 mg EW group versus the placebo group, p=0.01. When the total population was considered, significantly more patients in the ADA 40 mg EW group achieved an AN count of 0, 1, or 2 at week 12 than placebo patients, p<0.001 at all time-points, see Table 15.

Table 15: PIONEER I and PIONEER II – % of patients who achieved AN count of 0, 1, or 2 at week 12, among patients with Hurley stage II at baseline and all patients[29 30 82 83 85]

Visit	Placebo	ADA EW	Difference (95% CI)	p value
PIONEER I (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II (week 12)	**28/87 (32.2%)**	**44/85 (51.8%)**	**19.6 (4.7, 34.2)**	**0.01**
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]

Proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at week 12 among patients with baseline NRS ≥ 3

Figure 13 shows the proportion of patients achieving NRS30 in each study.

In PIONEER I, the proportion of patients in the ADA 40 mg EW group achieving NRS30 was significantly higher than that in the placebo group (p<0.05) at weeks 2, 4 and 8, and numerically higher at week 12.

In PIONEER II, the proportion of patients in the ADA 40 mg EW group achieving NRS30 was significantly higher than that in the placebo group ($p<0.001$) at weeks 2, 4, 8 and 12[85].

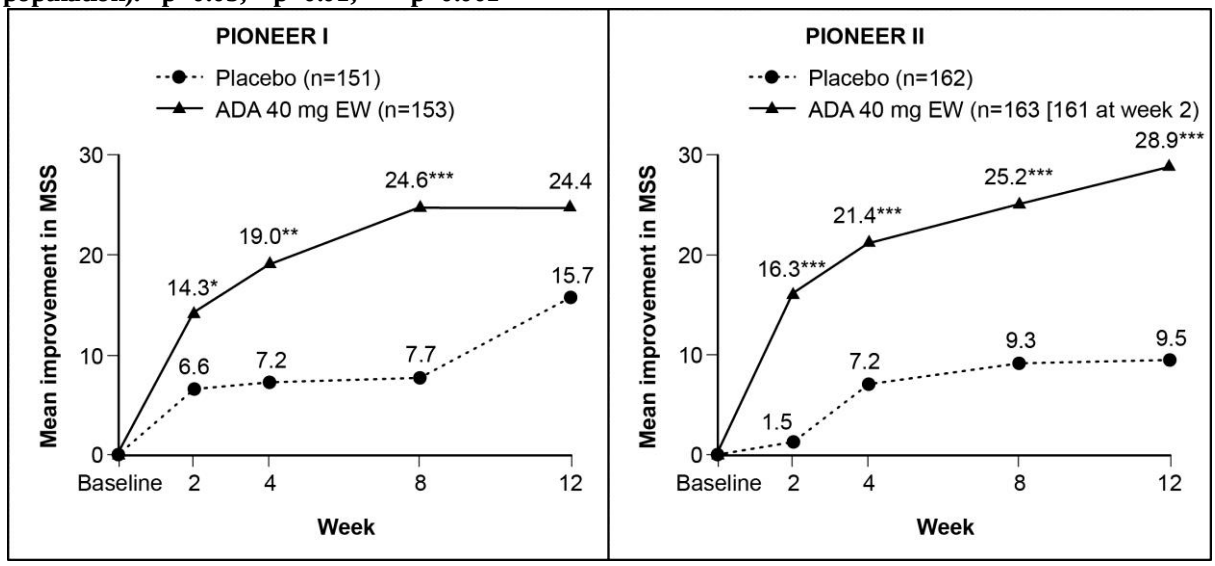
Figure 13: PIONEER I and PIONEER II – % of patients achieving NRS30 by visit (ITT population). *p<0.05, p<0.01, ***p<0.001[29 30 85]

Change in MSS from baseline to week 12

In PIONEER I, the mean MSS improved from baseline to a greater extent in patients in the ADA 40 mg EW group compared with placebo[82]. The score was significantly higher than that in the placebo group ($p<0.05$) at weeks 2, 4 and 8, and numerically higher at week 12, see Figure 14.

In PIONEER II, the mean MSS improved from baseline to a greater extent in patients in the ADA 40 mg EW group compared with placebo, the difference was also larger than that seen in PIONEER I. The score was significantly higher than that in the placebo group ($p<0.001$) at each time-point, see Figure 14.

Figure 14: PIONEER I and PIONEER II – mean improvement from baseline in MSS, LOCF (ITT population). *p<0.05,p<0.01, ***p<0.001[29 30 82]**



4.7.2.3 PRO outcomes

All the PRO outcomes discussed in this section were for period A, the first 12 weeks of the studies.

Quality of life: DLQI, SF-36 and EQ-5D

ADA 40 mg EW significantly improved QOL as measured by EQ-5D, SF-36, DLQI and HSQOL compared with placebo.

PIONEER II assessed overall QOL using the EQ-5D (health state and VAS), and demonstrated a significant benefit in QOL with ADA 40 mg EW compared to placebo, p<0.001 for both[86], see Table 16.

Mean (SD) baseline EQ-5D were 0.5 (0.36) in the placebo arm and 0.6 (0.33) in the ADA 40 mg EW arm for health state and 58.3 (23.07) and 59.2 (23.50) for VAS respectively[86].

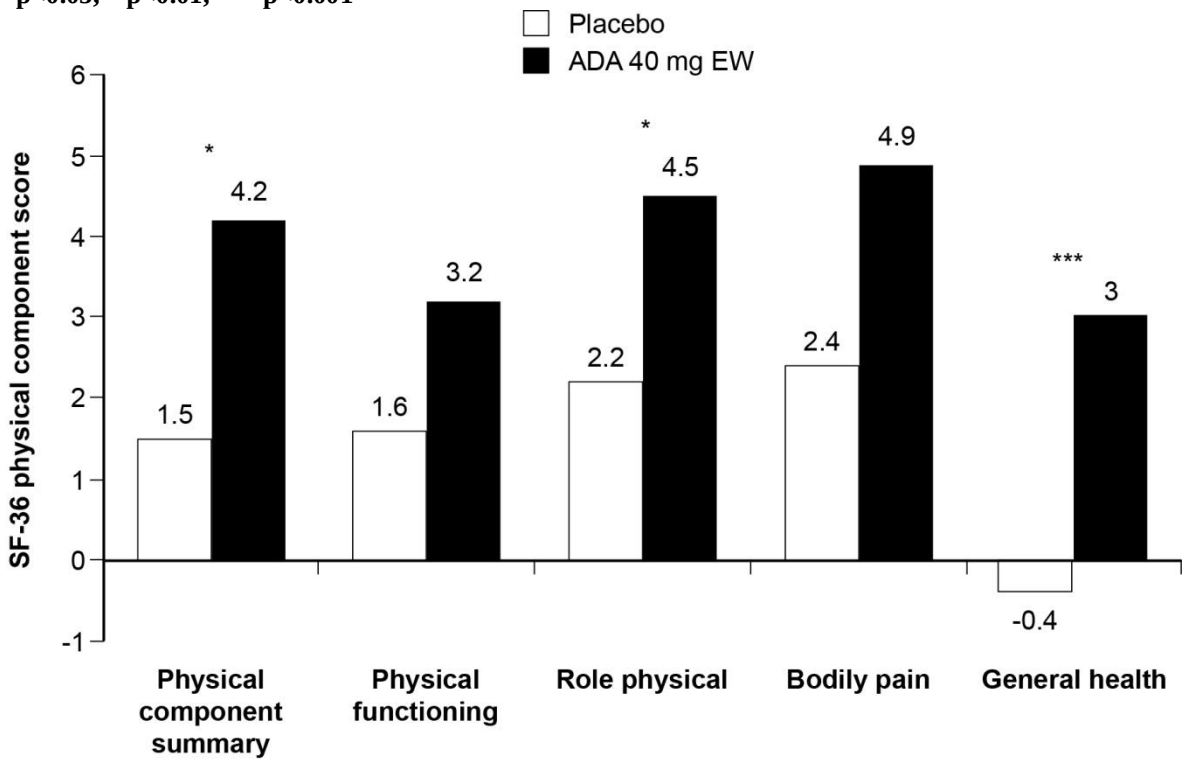
Table 16: PIONEER II – mean change from baseline in EQ-5D at week 12 (LOCF)[30 86]

	Within group change (LS mean ± SE)		Between group change	p value
	Placebo	ADA EW	LS mean difference (95% CI)	
Health state	0 ± 0.02	0.1 ± 0.02	[redacted]	<0.001
VAS	0.5 ± 1.87	9.2 ± 1.88	[redacted]	<0.001

PIONEER I assessed overall QOL using the SF-36, and demonstrated a significant benefit in the physical component of the SF-36 with ADA 40 mg EW compared to placebo, p<0.05 for all, see Figure 15. The differences in the mental component of the SF-36 were not significantly different between the two groups (data not shown).

The baseline SF-36 values (mean [SD]) for placebo and ADA 40 mg EW arms respectively were 39.5 (9.51) and 39.7 (9.35) for physical component summary, 40.9 (10.76) and 42.2 (11.04) for physical functioning, 39.2 (11.06) and 39.7 (11.87) for role physical, 36.5 (10.2) and 36.1 (9.01) for bodily pain and 40.1 (9.89) and 40.7 (10.95) for general health.

Figure 15: PIONEER I– change in the physical components in the SF-36 from baseline to week 12, *p<0.05,p<0.01, ***p<0.001[29]**



In SF-36, the minimum clinically important difference (MCID) is an increase in physical components of ≥ 2.5; an increase in mental components of ≥ 2.5; an increase in bodily pain of ≥5. In PIONEER I, significantly more patients receiving ADA 40 mg EW achieved a MCID in SF-36 than patients receiving placebo, [redacted]

DLQI scores range from 0 to 30, with higher scores indicating a more impaired QOL. Mean (SD) baseline DLQI scores in PIONEER I were 16.0 (7.11) in the placebo arm and 16.3 (6.64) in the ADA 40 mg EW arm, baseline scores in PIONEER II[86] were 14.9 (7.33) and 14.1 (7.65) respectively.

In PIONEER I and PIONEER II, patients receiving ADA 40 mg EW had significantly improved DLQI scores compared with placebo patients, p<0.001, see Table 17. In both studies, the mean change from baseline in DLQI at week 12 for patients in the ADA 40 mg EW group exceeded the MCID of 5. In PIONEER I, the percentage of patients with a meaningful change in DLQI at week 12 was [redacted] with ADA 40 mg EW versus [redacted] with placebo [redacted] corresponding figures for PIONEER II[86] were 49% versus 34% (p=0.011).

The HSQOL was used to assess QOL with HS, and is a HS-specific QOL questionnaire. Ratings range from 0 (worst possible) to 10 (best possible). In PIONEER I and PIONEER II, patients receiving ADA 40 mg EW had significantly improved HSQOL scores compared with placebo patients, [redacted] see Table 17 .In HSQOL MCID is defined as an increase in HSQOL 50% or greater than the standard deviation of HSQOL for all patients at baseline. In PIONEER I, numerically more patients in the ADA 40 mg EW arm achieved MCID, [redacted] However, in PIONEER II the difference was significant [redacted]

Table 17: PIONEER I and PIONEER II – mean change from baseline in DLQI and HSQOL at week 12 (LOCF)[29 30 84 86]

	Within group change (LS mean ± SE)		Between group change	p value
	Placebo	**ADA EW**	**LS mean difference (95% CI)**	
DLQI				
PIONEER I	-2.9 ± 0.5	-5.4 ± 0.5	-2.5 (-3.0,-1.8)	<0.001
PIONEER II	-2.3 ± 0.53	-5.1 ± 0.53	-2.8 (-4.1,-1.5)	<0.001
HSQOL				
PIONEER I	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II	[redacted]	[redacted]	[redacted]	[redacted]

Skin pain

Skin pain was assessed by the patient using Patient's Global Assessment of Skin Pain. Patient's Global Assessment of Skin Pain is a numerical rating scale ranging

from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). It was used in the PIONEER studies to assess the worst skin pain and the average skin pain due to HS. Patients entered their skin pain scores in a daily diary.

Table 18 shows the [redacted] reduction in pain with ADA 40 mg EW versus placebo in patients with baseline pain ≥3.

Table 18: PIONEER I and PIONEER II – mean change from baseline in Patient's Global Assessment of Skin Pain at worst among patients with baseline ≥3 at worst at week 12 (LOCF)[29 30 84]

	Within group change (LS mean ± SE)		Between group change	p value
	Placebo (n=104)	ADA EW (n=115)	LS mean difference (95% CI)	
PIONEER I	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo (n=109)	ADA EW (n=105)		
PIONEER II	[redacted]	[redacted]	[redacted]	[redacted]

Work: WPAI:SHP

The WPAI score is subdivided into absenteeism, presenteeism, overall work impairment and activity impairment. [redacted]

see Table 19

Table 19: PIONEER I and PIONEER II – mean change from baseline in activity impairment in the WPAI scale at week 12 (LOCF)[30]

	Within group change (LS mean ± SE)		Between group change	p value
	Placebo	ADA EW	LS mean difference (95% CI)	
PIONEER I	[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II	[redacted]	[redacted]	[redacted]	[redacted]

Anxiety and depression: HADS

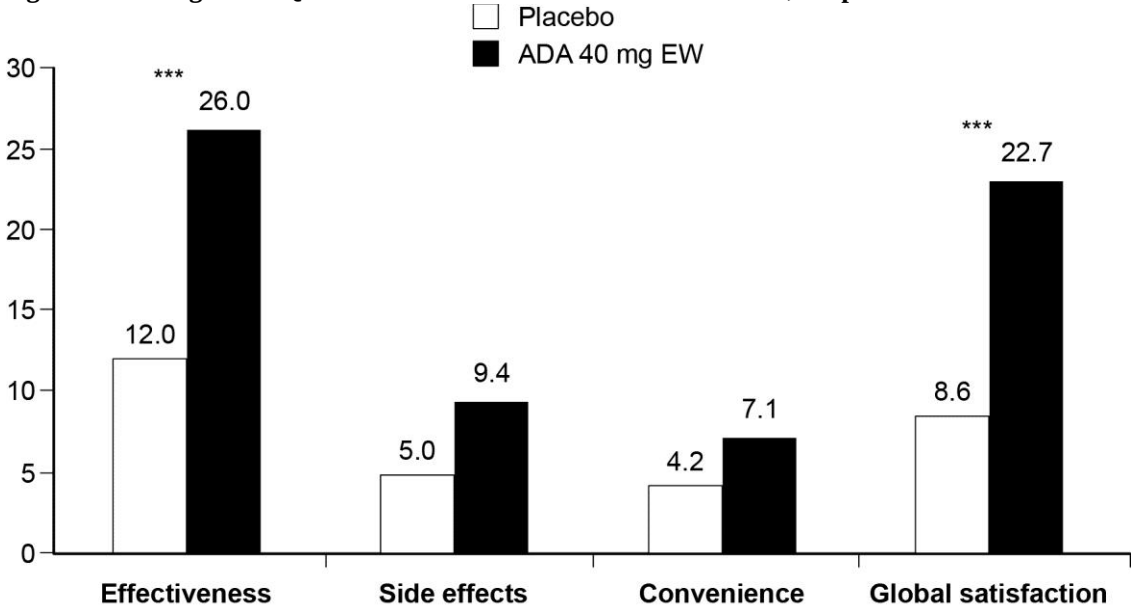
HADS was used to assess the impact of ADA 40 EW and placebo on anxiety and depression from baseline to week 12 in PIONEER I. [redacted]

Treatment satisfaction

Treatment satisfaction was assessed in PIONEER II using the Treatment Satisfaction Questionnaire for Medication (TSQM) which consists of14 items across four domains: effectiveness, side effects, convenience, and global satisfaction. Each domain is rated on a 100-point scale with higher scores indicating greater satisfaction. Baseline TSQM was scored based on the patient's most recent treatment for HS.

Results were presented at the 73rd Annual Meeting of the AAD, held in San Francisco, California in March 2015[35] and demonstrated that patients were more satisfied overall with ADA 40 mg EW than with placebo at 12 weeks, due to the significant improvement in effectiveness. There was no difference in patient perceived side effects or convenience between the two groups, see Figure 16 below.

Figure 16: Change in TSQM domain scores from baseline to week 12, ***p<0.001[35]



4.7.2.4 Outcomes at week 36

Data for period B clinical response have not yet been published and the following data are taken from the CSRs[29 30] and from a poster presented at WCD, 2015[33]

Treatment comparisons were performed in patients randomised to ADA 40 mg EW in period A and who were week12 HiSCR responders (ITT_B_R). These patients were re-randomised to EW, EOW or placebo, abbreviated to EW/EW, EW/EOW and EW/placebo in this document. It should be noted that patient numbers are small in

each subgroup; in PIONEER I: EW/placebo [redacted], EW/EOW [redacted] and EW/EW [redacted] and PIONEER II: EW/placebo [redacted] EW/EOW [redacted] and EW/EW [redacted] This is due to re-randomisation during the second part (period B) of the studies and protocol-driven discontinuation during period B for patients with LOR or WOAI.

Time to WOAI defined as the second incidence of the two-consecutive visits with AN count higher than the baseline AN count in patients randomised to ADA in period A who were week12 HiSCR non-responders (ITT_B_R) was also a pre-specified end-point. It should be noted that patient numbers are also small in each subgroup; in PIONEER I: EW/placebo [redacted] EW/EOW [redacted] and EW/EW [redacted] and PIONEER II: EW/placebo [redacted] EW/EOW [redacted] and EW/EW [redacted]

Improvement in HiSCR

[redacted] Figure 17.

Figure 17: PIONEER I and PIONEER II – % of patients achieving HiSCR during period B (ITT population)[29 30]

[redacted]

Data from the poster presented at WCD 2015 illustrates the proportion of patients in both studies (amalgamated data) achieving HiSCR during period B[33]. In the patients who were week 12 responders or partial responders (HiSCR non-responders with ≥25% reduction in AN count relative to baseline), HiSCR was achieved by week 36 in a greater proportion of patients re-randomised to ADA 40 mg EW than to placebo or ADA 40 mg EOW, see Table 20.

Table 20: Proportion of patients in PIONEER I and II (amalgamated data) achieving HiSCR during period B

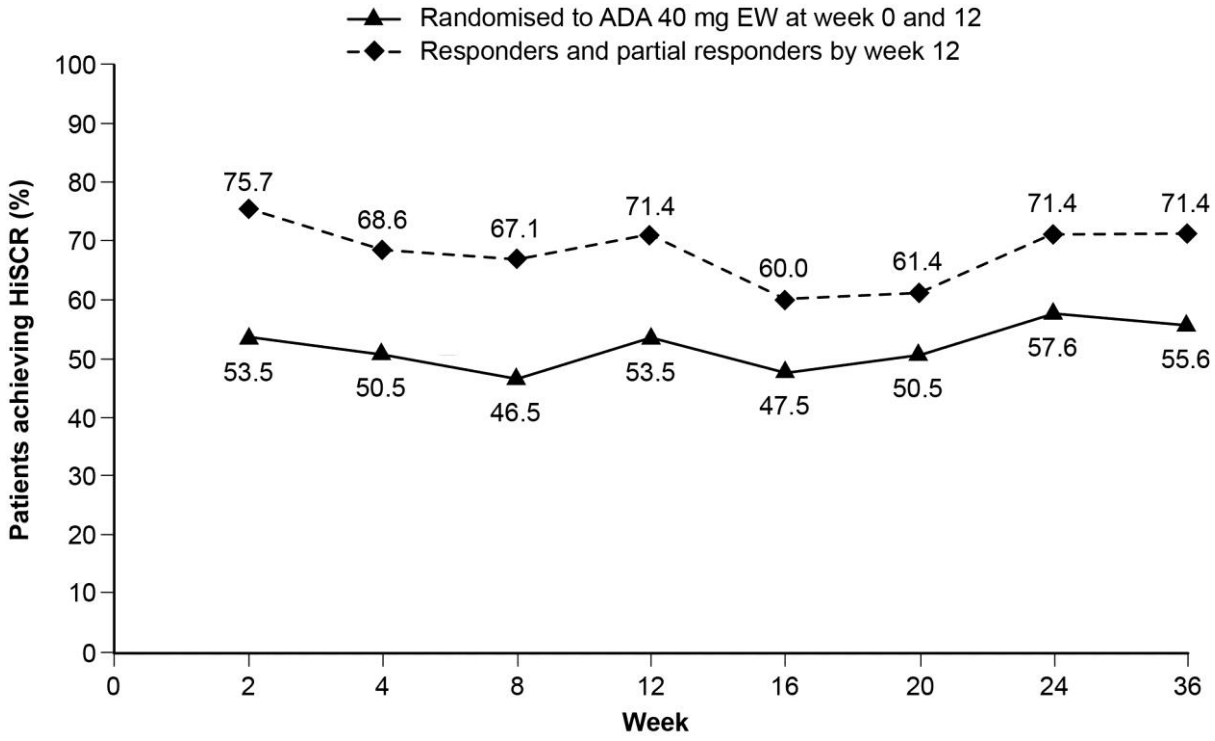
	Period B dose	N	HiSCR rate at week 12 n (%)	HiSCR rate at week 24 n (%)	HiSCR rate at week 36 n (%)
All patients	Placebo	100	53 (53%)	30 (30%)	28 (28%)
	ADA 40 mg EOW	101	52 (51.5%)	37 (36.6%)	31 (30.7%)
	ADA 40 mg EW	99	53 (53.5%)	44 (44.4%)	43 (43.4%)
Week 12 responders and partial responders	Placebo	73	53 (72.6%)	24 (32.9%)	22 (30.1%)
	ADA 40 mg EOW	70	52 (74.3%)	36 (51.4%)	28 (40%)
	ADA 40 mg EW	70	53 (75.7%)	40 (57.1%)	39 (55.7%)

The apparent reduction in HiSCR rate over time in period B is likely to be due to the study design, any patient who experienced protocol-defined LOR during period B (which may have been due to temporary exacerbation of disease) was discontinued from the study and imputed as a non-responder for this period, although could reach HiSCR in a subsequent visit in the OLE study (M12-555).

Therefore, to adjust for protocol-driven discontinuation during period B, maintenance of response was analysed for patients who had the opportunity to receive continuous ADA 40 mg EW dosing during period B and within the OLE study.

For week-12 HiSCR responders and partial responders HiSCR was generally maintained through week 36, see Figure 18.

Figure 18: HiSCR rate with continuous ADA 40 mg EW dosing integrated across PIONEER I, II and OLE[33]



Secondary end-points at week 36

The key secondary end-points are shown in Table 21, outcomes are improved in patients receiving EW/EOW or EW/EW, with the greatest improvement seen in patients receiving EW/EW.

Table 21: PIONEER I and PIONEER II – secondary end-points at week 36 (ITT_B_R)[29 30]

	PIONEER I			PIONEER II		
	EW/placebo (n=22)	**EW/EOW (n=20)**	**EW/EW (n=21)**	**EW/placebo (n=20)**	**EW/EOW (n=21)**	**EW/EW (n=20)**
AN count of 0/1/2	5 (22.7%)	6 (30%)	9 (42.9%)	9 (29%)	13 (40.6%)	10 (32.3%)
NRS30*	(n=15) 1 (6.7%)	(n=18) 4 (22.2%)	(n=16) 5 (31.3%)	(n=20) 1 (5%)	(n=11) 2 (11.8%)	(n=19) 3 (15.8%)
MSS (LS change from baseline ± SE)	-41.9 ± 9.76	-41.4 ± 10.27	-47.7 ± 9.99	-33.8 ± 13.19	-42.4 ± 12.59	-37.1 ± 11.8

* Proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at week 12 among patients with baseline NRS ≥ 3

Time to loss of response

[redacted]

Time to WOAI

[redacted]

4.8 Subgroup analysis

4.8.1 Details of the subgroup analyses

Pre-planned analyses in the three studies are shown in Table 22, the variables were chosen to assess the consistency of the primary efficacy end-point by demographic and baseline characteristics.

In the dose-finding study (M10-467), a post hoc analysis was also carried out to compare the clinical response for patients in the ADA 40 mg EW group versus those in the placebo group.

Table 22: Subgroups for analysis of the primary end-point in MI0-467, PIONEER I and PIONEER II[29-31]

	M10-467	PIONEER I	PIONEER II
Baseline concomitant use of oral antibiotics (yes/no)	✓		✓
Age group (< 40; 40-64; ≥ 65, if less than 10% of patients were in the ≥ 65 group, that group was combined with the 40-64 group)		✓	✓
Sex (male, female)		✓	✓
Race (white, non-white)		✓	✓
Duration of HS (by median)		✓	✓
Weight (by median)		✓	✓
BMI category: normal (< 25), overweight (25 – < 30), obese (30 – < 40), morbid obesity(≥ 40)		✓	✓
BMI (by median)	✓		
Current smoking status (Y/N)	✓	✓	✓
Baseline hs-CRP level (by median)		✓	✓
Baseline AN count (≤ 5, 6-10, 11+)	✓	✓	✓
Baseline AN count (< median, ≥ median)		✓	✓
Hurley stage (I or II, III)	✓		
Prior HS surgery history (yes, no)		✓	✓
Smoking habit change (increase, decrease)*.		✓	✓
Time from prior HS surgery to the first dose of study drug (by median)		✓	✓

*Increase in smoking habit was defined as an at least 25% increase from baseline in both the urine cotinine and the urine nicotine level. Decrease in smoking habit was defined as patients with at least 25% decrease from baseline in both the urine cotinine and the urine nicotine level. A change from ND (not detectable) to detectable (< 2 ng/ml or any value ≥ 2 mg/ml) was considered as an increase in smoking habit; and a change from detectable to not detectable was considered as a decrease in smoking habit.

Patients within each subgroup were well matched, with the exception of baseline AN count (≤ 5, 6-10, 11+) which was significantly different in PIONEER I between ADA 40 mg EW and placebo arms; more patients were in the<5 and >11 bands in the placebo group than in the ADA 40 mg EW group, p=0.018. However, there was no significant difference in AN count by median.

In the PIONEER studies, 95% CI for adjusted difference was calculated according to the extended Mantel-Haenszel statistic for the comparison of two treatment groups and the p value to compare ADA versus placebo was based on the Chi-square test (or Fisher's exact test if ≥25%of the cells had expected counts <5. Each variable was also assessed by strata (Hurley stage in both studies and antibiotic use in PIONEER II). Within each stratum the 95% CI for difference was calculated based on normal approximation to the binomial distribution. The data was analysed twice, using NRI and LOCF to account for missing data.

The interaction between treatment and subgroup on the proportion of patients achieving HISCR at week 12 (NRI and LOCF) was also assessed. The p value was calculated using logistic regression with HISCR at week 12 as the response variable and treatment, subgroup, Hurley stage strata and treatment subgroup interaction as factors.

4.8.2 Results of the subgroup analyses

Patients achieved benefit with ADA 40 mg EW regardless of their baseline characteristics.

In the dose-finding study (M10-467), post-hoc analysis showed a clinical response for patients in the ADA 40 mg EW group versus those in the placebo group showed a larger treatment effect versus the respective corresponding subgroup for patients with Hurley stage I or II disease, those who were current smokers and those with a BMI greater than or equal to the median, see Table 23. It should be noted, that some of the subgroups contained few people.

Table 23: M10-467 – clinical response at week 16 (proportion of patients achieving HS PGA of clear minimal or mild with at least a 2-grade improvement relative to baseline at week 16[31]

Variable	Placebo (n=51)	ADA EOW (n=52)	ADA EW (n=51)	Difference (95% CI)	
				EOW vs. placebo	EW vs. placebo
Hurley stage					
I or II, n/N (%)	2/36 (5.6%)	5/37 (13.5%)	8/36 (22.2%)	8.0 (-5.4, 21.3)	16.7 (1.2, 32.2)
III, n/N (%)	0/15 (0)	0/15 (0)	1/15 (6.7%)	NA	6.7 (-6.0,19.3)
Current smokers					
Yes, n/N (%)	1/29 (3.4%)	3/26 (11.5%)	7/30 (23.3%)	7.0 (-6.9, 20.8)	18.4 (0.7, 36.1)
No, n/N (%)	1/22 (4.5%)	2/26 (7.7%)	2/21 (9.5%)	4.3 (-9.9, 18.5)	7.2 (-8.8, 23.1)
Received concomitant oral antibiotics for HS					
Yes, n/N (%)	0/4 (0)	0/6 (0)	4/9 (44.4%)	NA	39.4 (-2.2, 81.0)
No, n/N (%)	2/47 (4.3%)	5/46 (10.9%)	5/42 (11.9%)	6.5 (-4.2,17.1)	8.0 (-3.1, 19.1)
BMI					
>median, n/N (%)	0/25 (0)	3/30 (10.0%)	5/22 (22.7%)	10.5 (-1.7, 22.7)	26.2 (8.5, 44.0)
<median, n/N (%)	2/26 (7.7%)	2/22 (9.1)	4/29 (13.8%)	0.5 (-15.2,16.3)	5.4 (-11.5, 22.4)
CRP level					
>median, n/N (%)	1/21 (4.8%)	1/20 (5.0%)	3/18 (16.7%)	0.8 (-12.4, 14.1)	13.1 (-5.6, 31.8)
<median, n/N (%)	1/18 (5.6%)	4/20 (20.0%)	4/20 (20.0%)	14.3 (-7.4,35.9)	14.3 (-8.0, 36.6)

[redacted]

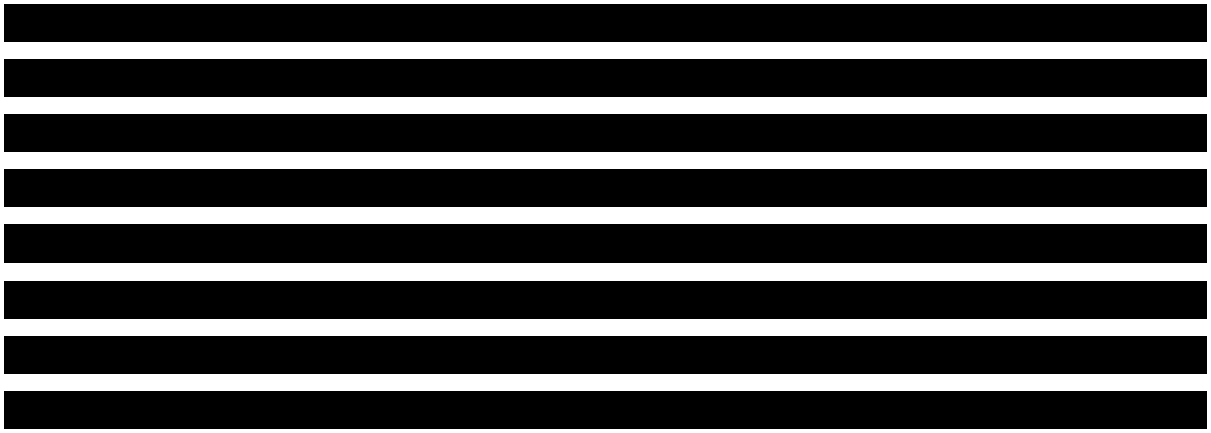


Figure 19: PIONEER I – proportion of patients achieving HISCR at week 12 (NRI) by subgroup.[29]

Figure 20: PIONEER II – proportion of patients achieving HISCR at week 12 (NRI) by subgroup.[30]

4.9 Meta-analysis

Not applicable.

4.10 Indirect and mixed treatment comparisons

To determine the appropriateness of conducting a network meta-analysis (NMA) on the eligible set of clinical trials identified in the SLR (section 4.1), a feasibility assessment was carried out. In order to gauge the appropriateness of proceeding with a NMA, the feasibility assessment study included:

1. An assessment of whether the RCT evidence for the interventions of interest form one evidence network for each outcome of interest; and
2. An assessment of the distribution of study and patient characteristics that may affect treatment effects across direct comparisons of the evidence networks

Overall, the networks of evidence for all outcomes of interest were small (<4 nodes). In addition to this, baseline characteristics, though sparsely populated, had some variations between the comparisons of interest.

Trials were consistent with respect to baseline BMI, body weight and duration of HS. However, there was some variation in age, gender, race and ethnicity and proportion of nicotine users at baseline. Across the comparisons in CRP levels and disease severity at baseline, there was substantial heterogeneity between the ADA and infliximab studies which potentially biases the NMA results for these outcomes. Due to the lack of available trials and reporting of baseline characteristics, accounting for this bias using sensitivity analysis and/or meta-regression would not be feasible. Combined with the fact that few networks were formed, a NMA was not considered feasible (Please see Appendix 5 for more detailed information regarding the feasibility assessment for a NMA).

4.11 Non-randomised and non-controlled evidence

One non-randomised open study provides additional long-term data for ADA 40 mg in patients with moderate to severe HS. The OLE is a continuation study for patients enrolled in PIONEER I and PIONEER II. The information in this section is drawn from an interim analysis of the study published in a CSR[32].

Table 24: List of relevant non-randomised and non-controlled evidence

Study number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
PIONEER OLE M12-555	Long-term safety, tolerability and efficacy of ADA 40 mg EW	Moderate to severe HS patients who had been enrolled in PIONEER I or II	ADA 40 mg EW	None	CSR [32]	Provides long-term data

4.11.1 Summary of methodology

The OLE is an extension to PIONEER I and PIONEER II in which all subjects receive ADA 40 mg EW to determine the long-term safety, tolerability and efficacy of ADA in subjects with moderate to severe HS, Figure 6: Study design for PIONEER I and PIONEER II

Approximately 600 patients from PIONEER I and PIONEER II were eligible to enrol in the OLE. Patients were evaluated for entry into the OLE at the final study visit of the prior phase III study in which they participated.

The study duration was at least 60 weeks, or until marketing authorization or permanent withdrawal of the marketing application in the patient's country of residence.

This was an open study so blinding and randomisation is not relevant.

The inclusion criteria were as follows:

- Patients who participated in PIONEER I or PIONEER II and completed the study; or
- Achieved HiSCR at the start of period B then experienced LOR (defined as AN count > than the average AN counts at baseline and week 12 of the earlier PIONEER study); or
- Did not achieve HiSCR at the start of period B then experienced WOAI on or after week 16 of the earlier PIONEER study (defined as an AN count of ≥ baseline AN count at two consecutive visits, excluding week 12, occurring ≥ 14 days apart)
- Women were required to avoid conception

The exclusion criteria were as follows:

- Prior treatment with any other anti-TNF or participation in an ADA study other than the PIONEER studies.
- Any active skin disease which could interfere with the assessment of HS.
- Use of oral antibiotics for HS within 28 days of baseline (except those used in prior PIONEER studies), use of prescription topical therapies for HS within 14 days of baseline, use of systemic non-biologic therapies for HS <28 days before baseline, use of oral concomitant analgesia (including opioids) for HS-related pain within 14 days of baseline or received any other investigational drug for HS within 30 days or five half-lives of baseline.
- Co-morbid conditions: infection requiring IV anti-infective treatment, history of moderate to severe heart failure, history of demyelinating disease, history of invasive infection, chronic recurring infections or active TB.
- Evidence of dysplasia or history of malignancy.
- Pregnant or breast-feeding women.
- Clinically significant drug or alcohol use.

Starting at baseline, all patients received open-label ADA 40 mg EW regardless of treatment assignment in the PIONEER studies. The dose could be reduced to ADA 40 mg EOW at any time on or after week 24 of the OLE if patients achieved HiSCR during the OLE relative to the baseline visit of the prior phase III study and achieved an AN count of 0 or 1 on at least two consecutive study visits and the clinician and patient decided that the risk/benefit of reducing the dose of ADA was favourable. The dose could be increased back up to ADA 40 mg EW if required by the clinician or patient, although the dose could only be increased once.

The following concomitant drugs were not allowed: use of oral antibiotics for HS within 28 days of baseline (except those used in prior PIONEER studies), use of prescription topical therapies for HS within 14 days of baseline, use of systemic non-biologic therapies for HS <28 days before baseline, use of oral concomitant analgesia (including opioids) for HS-related pain within 14 days of baseline or received any other investigational drug for HS within 30 days or five half-lives of baseline.

Study visits occurred at baseline, week 4, week 8, week 12, week 18, week 24, week 36 and every12 weeks thereafter, at least through week 60. Patients who prematurely discontinued from the trial, or who completed the trial and did not initiate ADA therapy outside the context of the clinical trial, had study visits 4 and 8 weeks after the last administration of study drug to collect blood samples for the measurement of serum ADA concentrations and anti-ADA antibody.

If after week 24, there was no clinically relevant response, then the clinician and the patient explored the risk/benefit of remaining on treatment.

The primary outcome was the proportion of subjects achieving HiSCR, defined as at least a 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to baseline.

4.11.2 Statistical analysis

Patients must have received at least one dose of ADA in the OLE to be included in any of the following populations.

- EW/EW/EW: patients who received ADA 40 mg EW in the previous PIONEER studies
- EW/EOW/EW: patients who received ADA 40 mg EW in period A and ADA 40 mg EOW in period B in the previous PIONEER studies
- EW/PBO/EW: patients who received ADA 40 mg EW in period A and placebo in period B in the previous PIONEER studies
- PBO/EW/EW: patients who received placebo in period A and ADA 40 mg EW in period B in PIONEER I
- PBO/PBO/EW: patients who received placebo in period A and in period B in PIONEER II

Missing data were imputed using NRI, LOCF and as observed.

The OLE study was open in nature therefore descriptive statistics were used.

4.11.3 Participant flow in the studies

These results are an interim data cut, as of 29 April 2014, 497 patients received at least one dose of study drug. A total of 368 (74.0%) subjects remained ongoing at the data cut, see Table 25.

Patients were similar across the analysis populations and reflect the known presentation of the disease, see Table 26. Approximately two-thirds of the study population were women. Most were white and under 40 years of age (median, 36 years), patients were obese and most were smokers.

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Table 25: Patient disposition in OLE[32]

Subject disposition	EW/EW/EW n (%)	EW/EOW/EW n (%)	EW/PBO/EW n (%)	PBO/EW/EW n (%)	PBO/PBO/EW n (%)	Continuous EW n (%)	All ADA n (%)
Treated	84	90	91	115	117	316	497
Ongoing	62 (73.8%)	68 (75.6%)	66 (72.5%)	85 (73.9%)	87 (74.4%)	234 (74.1%)	368 (74.0)
Discontinued	22 (26.2%)	22 (24.4%)	25 (27.5%)	30 (26.1%)	30 (25.6%)	82 (25.9%)	129 (26.0)
Primary reason:							
AE	4 (4.8%)	5 (5.6%)	3 (3.3%)	5 (4.3%)	5 (4.3%)	14 (4.4%)	22 (4.4)
Lack of efficacy	9 (10.7%)	5 (5.6%)	10 (11.0%)	5 (4.3%)	7 (6.0%)	21 (6.6%)	36 (7.2)
Exceeded protocol-specified no of interventions	0	0	1 (1.1%)	0	0	0	1 (0.2)
Protocol deviation	0	0	0	0	0	0	0
Withdrew consent	5 (6.0%)	5 (5.6%)	8 (8.8%)	10 (8.7%)	6 (5.1%)	21 (6.6%)	34 (6.8)
Lost to follow-up	1 (1.2%)	5 (5.6%)	2 (2.2%)	9 (7.8%)	7 (6.0%)	17 (5.4%)	24 (4.8)
Other	3 (3.6%)	2 (2.2%)	1 (1.1%)	0	4 (3.4%)	7 (2.2%)	10 (2.0)
Missing	0	0	0	1 (0.9%)	1 (0.9%)	2 (0.6%)	2 (0.4)

Table 26: Patient characteristics at baseline in OLE[32]

Demographic variable	EW/EW/EW n=84	EW/EOW/EW n=90	EW/PBO/EW n=91	PBO/EW/EW n=115	PBO/PBO/EW n=117	Continuous EW n=316	All ADA n=497
Female, n (%)	53 (63.1)	60 (66.7)	49 (53.8)	79 (68.7)	81 (69.2)	213 (67.4)	322 (64.8)
White, n (%)	78 (92.9)	70 (77.8)	75 (82.4)	92 (80.0)	98 (83.8)	268 (84.8)	413 (83.1)
Black, n (%)	4 (4.8)	16 (17.8)	11 (12.1)	17 (14.8)	12 (10.3)	33 (10.4)	60 (12.1)
Age (years) Mean ± SD	35.4 ± 10.48	36.1 ± 10.50	36.3 ±10.97	38.5 ± 11.92	37.2 ± 12.44	37.2 ± 11.78	36.8 ± 11.40
BMI (kg/m^2) Mean ± SD	32.1 ± 7.32	31.8 ± 7.51	32.3 ± 7.94	34.4 ± 8.31	32.1 ± 7.74	33.0 ± 7.90	32.6 ± 7.84
Smoker, n (%)	49 (58.3)	55 (61.1)	48 (52.7)	68 (59.1)	81 (69.8)	198 (62.9)	301 (60.7)
Hurley Stage, n (%)							
II	41 (48.8)	47 (52.2)	51 (56.0)	59 (51.3)	63 (53.8)	163 (51.6)	261 (52.5)
III	43 (51.2)	43 (47.8)	40 (44.0)	56 (48.7)	54 (46.2)	153 (48.4)	236 (47.5)
AN count, Mean ± SD	12.3 ± 10.55	12.2 ± 10.52	12.4 ± 8.95	14.6 ± 16.44	10.7 ± 9.98	12.5 ± 12.91	12.4 ± 11.85
Abscess count, Mean ± SD	2.0 ± 2.60	2.6 ± 3.13	2.6 ± 3.27	2.7 ± 3.96	2.1 ± 3.12	2.3 ± 3.34	2.4 ± 3.28
Draining fistula count, Mean ± SD	3.5 ± 4.05	3.4 ± 4.62	4.2 ± 5.00	4.1 ± 4.57	3.7 ± 5.33	3.8 ± 4.73	3.8 ± 4.76
Inflammatory nodule count, Mean ± SD	10.3 ± 9.82	9.6 ± 9.62	9.8 ± 7.30	11.9 ± 15.42	8.6 ± 8.63	10.2 ± 11.87	10.0 ± 10.76

4.11.4 Quality assessment

The quality assessment is shown below in Table 27. Given that this study is not published the CSR[32] was used as the basis for the quality assessment. The OLE is of a good standard as shown below.

Table 27: Quallity assessment of OLE

Criterion	Assessment	
Bias in results?	Was there significant potential for bias? List the reasons that have led to this conclusion.	No Clear inclusion and exclusion criteria
Study question	Does the study clearly address a specific question? Has the study question been specifically stated?	Yes Yes
Methodology	Were the methods clearly described, with enough detail that you could repeat the study exactly? Were appropriate methods used to answer the specified research question? Were the outcome measures used appropriate? Are the methods sufficiently flawed as to make the results unreliable?	Yes Yes Yes No
Population and data collection	Was the population under study described adequately? Were the inclusion/exclusion criteria sufficiently described? Was the population under study selected/ recruited in an appropriate way? Was the collection of data complete enough (in terms of size of population and follow-up period)?	Yes Yes Yes, OLE Interim results only
Results and confounding factors	Were the results presented in a clear and useful manner? Were the tables/graphs clearly labeled, easily interpretable, and discussed sufficiently to enable understanding of the meaning of the results? Could the results be due to chance or bias (as highlighted by the authors and/or by your own judgment)? Have the authors identified possible confounding factors that may have influenced the results (such as age, gender, ethnicity, socioeconomic status, occupation, etc.)? Have these factors been incorporated into the analysis (i.e. have the results been presented as crude and adjusted ratios)?	Yes Yes No Not relevant Not relevant No
Statistical methods	Were the statistical methods clearly described? Was any rationale given for the methodology of analysis used? Were the factors used to adjust a model (if any) detailed clearly, with reasoning given for their selection? Were any unusual methods used?	Yes Yes Not relevant No
Conclusions	Do the authors provide a clear discussion of the results that leads to a single, specified conclusion in answer to the specified study question? Do the authors relate their results to any previous literature in the field? Is there consistency between the conclusions and the results presented?	Yes, but interim results Yes Yes

4.11.5 Clinical effectiveness results

[redacted]

It should be noted that patient numbers are small beyond week 36 since as of the data cut-off date not all ongoing patients had visits beyond week 26. The number of patients with observations at week 48, 60 and 72 were [redacted] and [redacted], respectively for EW/EW/EW; [redacted] and xxx respectively, for EW/EOW/EW; and [redacted] and [redacted] respectively, for EW/PBO/EW.

Among EW/EW/EW subjects who achieved at least a partial response (AN25) at the end of Period A in the prior study, the proportion of subjects achieving HiSCR was [redacted] at week 36 and [redacted] at weeks 48, 60, and 72.

Table 28: Proportion of patients achieving HiSCR over time from the first dose of ADA (LOCF)[32]

Weeks of ADA treatment (relative to the first dose in the PIONEER studies)	EW/EW/EW (n=84)			EW/EOW/EW (n=90)			EW/PBO/EW (n=91)		
2		[redacted]			[redacted]			[redacted]	
4									
8									
12									
16									
20									
24									
36									
48									
60									
72									

Given that this is an interim analysis we have not provided details of the secondary outcomes, however, the HiSCR results shown in Table 28 are supported by other efficacy end-points, including MSS and skin pain as measured by the Patient's Global Assessment of Skin Pain (NRS30).

4.12 Adverse reactions

4.12.1 M10-467

During the initial 16 week period, rates of AE were higher in the ADA arms than in the placebo arm (63.5% in the ADA 40 mg EOW arm, 70.6% in the ADA 40 mg EW arm versus 58.8% in the placebo arm), most of the excess AE in the ADA arms were due to headache, typically described as mild or moderate in severity. The majority of AE were grade 1 or 2 and similar across all treatment groups. AE were consistent with those seen with ADA in previous studies in other indications.

The rates of discontinuation due to AE were low in all arms (3.8%, 3.9% versus 0%) as were serious AE (SAE) (5.8%, 7.8% versus 3.9%).

Rates of infectious AE were comparable across all three groups (42.3%, 33.3% versus 35.3%) and there was one infectious SAE in each of the ADA arms (2%).

Over the entire study period, a greater proportion of patients re-randomised to EOW from EW experienced AE compared to those in the placebo to EOW, EOW to EOW and dose escalation groups. Patients who had dose escalation in period 2 had AE rates similar to those of patients who received EOW.

Fifteen patients had one or more SAE during exposure to ADA, with the most common events being HS worsening or infectious complications of HS (n=8) and anaemia (n=2, one with a history of intermittent gastro-intestinal bleeding from ulcerative colitis and one with a low haemoglobin concentration at screening).

There were no deaths or cancer diagnoses during the study.For full details please see Table 29.

Table 30 shows the most common AE were headache, HS and nasopharyngitis. AE which occurred in >5% of patients

Table 29: AE in study M10-467[31]

AE, n(%)	Period 1				Periods 1 and 2		
	Placebo (n=51)	ADA EOW (n=52)	ADA EW (n=51)	Difference EW versus placebo Relative risk (95% CI)	Placebo-to-EOW Plus EOW-to-EOW (n=98)	EW to-EOW (n=51)	Dose escalation (n=89)
Death	0	0	0		0	0	0
Any AE leading to discontinuation of study drug	0	2 (3.8%)	2 (3.9%)		4 (4.1%)	5 (9.8%)	5 (5.6%)
Any AE	30 (58.8%)	33 (63.5%)	36 (70.6%)	1.2 (0.9, 1.6)	60 (61.2%)	44 (86.3%)	51 (57.3%)
SAE	2 (3.9%)	3 (5.8%)	4 (7.8%)	2 (0.38. 10.44)	5 (5.1%)	6 (11.8%)	5 (5.6%)
Any infectious AE	18 (35.3%)	22 (42.3%)	17 (33.3%)	0.94 (0.55, 1.62)	41 (41.8%)	30 (58.8%)	25 (28.1%)
Infectious SAE	0	1 (1.9%)	1 (2.0%)		1 (1.0%)	3 (5.9%)	3 (3.4%)
Cancer	0	0	0		0	0	0

Table 30: AE occurring in >5% of patients in study M10-467[31]

AE	Period 1				Periods 1 and 2		
	Placebo (n=51)	ADA EOW (n=52)	ADA EW (n=51)	Difference EW versus placebo Relative risk (95% CI)	Placebo-to-EOW Plus EOW-to-EOW (n=98)	EW to-EOW (n=51)	Dose escalation (n=89)
Arthralgia	1 (2.0%)	0	3 (5.9%)	3 (0.2, 27.89)	5 (5.1%)	4 (7.8%)	0 (0%)
Back pain	1 (2.0%)	1 (1.9%)	1 (2.0%)	1 (0.06, 15.56)	2 (2.0%)	3 (5.9%)	1 (1.1%)
Cellulitis	1 (2.0%)	0	0		0	3 (5.9%)	0
Cough	0	1 (1.9%)	3 (5.9%)		1 (1.0%)	4 (7.8%)	1 (1.1%)
Diarrhoea	2 (3.9%)	2 (3.8%)	0		5 (5.1%)	3 (5.9%)	0
Exacerbation of HS	6 (11.8%)	7 (13.5%)	4 (7.8%)	0.67 (0.2, 2.22.)	18 (18.4%)	11 (21.6%)	6 (6.7%)
Fatigue	2 (3.9%)	2 (3.8%)	2 (3.9%)	1 (0.15, 6.83)	5 (5.1%)	4 (7.8%)	2 (2.2%)
Folliculitis	3 (5.9%)	0	0		2 (2.0%)	1 (2.0%)	0
Gastroenteritis	0	1 (1.9%)	0		1 (1.0%)	3 (5.9%)	0
Gastroesophageal reflux disease	0	0	3 (5.9%)		1 (1.0%)	3 (5.9%)	0
Headache	2 (3.9%)	7 (13.5%)	8 (15.7%)	4 (0.89, 17.93)	9 (9.2%)	10 (19.6%)	5 (5.6%)
Influenza	0	1 (1.9%)	2 (3.9%)		2 (2.0%)	4 (7.8%)	1 (1.1%)
Nausea	1 (2.0%)	2 (3.8%)	4 (7.8%)	4 (0.46, 35.57)	2 (2.0%)	6 (11.8%)	1 (1.1%)
Nasopharyngitis	6 (11.8%)	7 (13.5%)	6 (11.8%)	1 (0.35, 2.89)	13 (13.3%)	9 (17.6%)	6 (6.7%)
Oropharyngeal pain	1 (2.0%)	3 (5.8%)	1 (2.0%)	1 (0.06, 15.56)	4 (4.1%)	1 (2.0%)	2 (2.2%)
Pruritus	0	3 (5.8%)	1 (2.0%)		3 (3.1%)	2 (3.9%)	0
Sinusitis	1 (2.0%)	0	2 (3.9%)	2 (0.19, 21.37)	3 (3.1%)	3 (5.9%)	1 (1.1%)
Upper respiratory tract infection	2 (3.9%)	4 (7.7%)	4 (7.8%)	2 (0.38,10.44)	7 (7.1%)	6 (11.8%)	0 (0)
Vomiting	3 (5.9%)	2 (3.8%)	1 (2.0%)	0.33 (0.04, 3.10)	2 (2.0%)	3 (5.9%)	3 (3.4%)

4.12.2 PIONEER I and PIONEER II

4.12.2.1 Period A

ADA 40 mg EW was well tolerated in both of the PIONEER studies and the proportion of patients experiencing SAEs or discontinuing treatment due to AEs was low. The rates of SAEs and discontinuation due to AE were low in all arms, and numerically higher in the placebo arms in both studies[82 83 85].

The pattern of AEs was consistent throughout both PIONEER studies and similar tolerability was reported for both trials. The AEs for the groups treated with ADA 40 mg EW were comparable to placebo and consistent with the known ADA safety profile.

During period A (12 weeks) in both trials, AE rates were lower with ADA 40 mg EW than with placebo (PIONEER I: 52.9% ADA 40 mg EW, 61.8% placebo; PIONEER II: 57.7% ADA 40 mg EW, 66.9% placebo)[82 83 85].

Rates of infectious AEs were similar for both patients receiving ADA and those receiving placebo[82 83 85]. There were no reported TB infections. There were no deaths during period A[33].

For full details please see Table 31.

The most common AE were exacerbation of HS, nasopharyngitis and headache. AE which occurred in >5% of patients are shown in Table 32.

Table 31: AE in PIONEER I and PIONEER II during period A (first 12 weeks)[29 30 33 82 83 85].

	PIONEER I			PIONEER II		
	Placebo (n=152)	ADA EW (n=153)	Difference EW versus placebo Relative risk (95% CI)	Placebo (n=163)	ADA EW (n=163)	Difference EW versus placebo Relative risk (95% CI)
Death	0	0		0	0	
Any AE leading to discontinuation of study drug	3 (2%)	1 (0.7%)	0.33 (0.03, 3.15)	7 (4.3%)	4 (2.5%)	0.57 (0.17, 1.91)
Any AE	94 (61.8%)	81 (52.9%)	0.86 (0.7, 1.04)	109 (66.9%)	94 (57.7%)	0.86 (0.73, 1.02)
SAE	5 (3.3%)	3 (2%)	0.6 (0.14, 2.45)	6 (3.7%)	3 (1.8%)	0.5 (0.13, 1.97)
Any infectious AE	43 (28.3%)	38 (24.8%)	0.88 (0.6, 1.28)	53 (32.5%)	41 (25.2%)	0.77 (0.55, 1.09)
Infectious SAE	0	1 (0.7%)		2 (1.2%)	1 (0.6%)	0.5 (0.005, 5.46)
Cancer	1 (0.7%)	0		0	0	

Table 32: AE occurring in >5% of patients PIONEER I and PIONEER II during period A (first 12 weeks)[29 30 83{Jemec GBE, 2015 #67 85

	PIONEER I			PIONEER II		
	Placebo (n=152)	ADA EW (n=153)	Difference EW versus placebo Relative risk (95% CI)	Placebo (n=163)	ADA EW (n=163)	Difference EW versus placebo Relative risk (95% CI)
Exacerbation of HS	20 (13.2%)	14 (9.2%)	0.7 (0.36, 1.33)	21 (12.9%)	7 (4.3%)	0.33 (0.15, 0.76)
Nasopharyngitis	16 (10.5%)	9 (5.9%)	0.56 (0.25, 1.23)	10 (6.1%)	9 (5.5%)	0.9 (0.38, 2.16)
Headache	15 (9.9%)	14 (9.2%)	0.93 (0.46, 1.86)	21 (12.9%)	21 (12.9%)	1 (0.57, 1.76)
Upper respiratory tract infection				9 (5.5%)	8 (4.9%)	0.89 (0.35, 2.25)
Diarrhoea				4 (2.5%)	9 (5.5%)	2.25 (0.71, 7.16)

4.12.2.2 Period B

AE were similar in period B to those seen in period A, see Table 33 and Table 34. [redacted]

[redacted]

There were no clinically meaningful changes in laboratory parameters or vital signs in either PIONEER study.

Table 33: AE in PIONEER I and PIONEER II during period B[29 30]

	PIONEER I				PIONEER II			
	Placebo/EW (n=145)	EW/placebo (n=49)	EW/EOW (n=48)	EW/EW (n=48)	Placebo/placebo (n=151)	EW/placebo (n=51)	EW/EOW (n=53)	EW/EW (n=51)
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any infectious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious infectious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: AE occurring in >5% of patients PIONEER I and PIONEER II during period B[29 30]

	PIONEER I				PIONEER II			
	Placebo/EW (n=145)	EW/placebo (n=49)	EW/EOW (n=48)	EW/EW (n=48)	Placebo/placebo (n=151)	EW/placebo (n=51)	EW/EOW (n=53)	EW/EW (n=51)
Exacerbation of HS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contact dermatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.12.3 OLE

The OLE study[32] did not identify any new safety risks for ADA; the safety profile of ADA treatment observed in the OLE is expected given the population of moderate to severe HS.

[redacted]

In the All ADA population (defined as patients who received at least one dose of ADA 40 mg EW during the OLE), [redacted] had serious AEs during open label treatment which were considered possibly or probably related to ADA.

AE leading to discontinuation were experienced by [redacted] of patients during the OLE, [redacted] patients due to HS and [redacted] due to psoriasis.

No new opportunistic infections were reported, [redacted]

[redacted]

[redacted]

Among the populations used for the safety analyses, the longest mean exposure to ADA 40 mg EW is represented by the EW/EW/EW population (n=84), which had a mean exposure of [redacted] days (median, [redacted]; range, [redacted] to [redacted] days). All patients received 40 mg EW upon entering the OLE. As permitted by protocol after week 24, [redacted] patients subjects reduced their dose from EW to EOW dosing as of the cut-off date.

We have presented the AE for the EW/EW/EW population since they reflect patients with continuous ADA 40 mg EW use as per the proposed use of ADA 40 mg in clinical practice, together with the all ADA population.

Table 35: AE in OLE in the all ADA population and in the EW/EW/EW population[32]

	All ADA (n=497)	EW/EW/EW (n=84)
Death	[redacted]	[redacted]
Any AE leading to discontinuation of study drug	[redacted]	[redacted]
Any AE	[redacted]	[redacted]
SAE	[redacted]	[redacted]
Any infectious AE	[redacted]	[redacted]
Serious infectious AE	[redacted]	[redacted]
Cancer	[redacted]	[redacted]

Table 36: AE occurring in >5% of in patients in OLE in the all ADA population and in the EW/EW/EW population[32]

	All ADA (n=497)	EW/EW/EW (n=84)
Skin and subcutaneous tissue disorders		
Exacerbation of HS	[redacted]	[redacted]
Infection and infestations		
Nasopharyngitis	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders		
Arthralgia	[redacted]	[redacted]
Backache	[redacted]	[redacted]
Nervous system disorders		
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Gastro-intestinal disorders		
Diarrhoea	[redacted]	[redacted]

4.12.4 Overview of safety in relation to the decision problem

ADA 40 mg EW was well tolerated in study M10-467 and in both of the PIONEER studies. The proportion of patients experiencing SAEs or discontinuing treatment due to AEs was low. In an integrated study of PIONEER I and II (n=633), six patients receiving placebo (1.9%) and three receiving ADA 40 mg EW (0.9%) gave AE as their primary reason for discontinuation during period A[34].

The AEs for patients treated with ADA 40 mg EW were comparable to placebo and consistent with the known ADA safety profile. The majority of AE were mild to moderate in severity.

The most common AE were exacerbation of HS, nasopharyngitis and headache.

Rates of infectious AEs were similar for both patients receiving ADA and those receiving placebo. There were no reported TB infections.

In study M10-467 there were four infectious SAE, no deaths and no malignancies over the 52 week study. In both PIONEER studies there were three infectious SAE, one death and one malignancy in 480 patients receiving ADA over the 36 week study period.

The OLE study[32] did not identify any new safety risks for ADA.

There were no clinically meaningful changes in laboratory parameters or vital signs in any of the clinical trials.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Clinical benefits and harms

Three placebo-controlled studies – a dose finding study (M10-467) and two large randomised controlled studies (PIONEER I and PIONEER II) demonstrate that ADA 40 mg EW significantly improves HS clinical response and severity of HS compared with placebo[29-31]. An OLE study, M12-555, to the PIONEER studies provides additional long-term data on efficacy and safety of ADA 40 mg EW[32].

In the dose finding study (M10-467) significantly more patients in the ADA 40 mg EW group achieved a clinical response (defined as achieving a HS-PGA score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16) than patients receiving placebo, 17.6% versus 3.9%, $p<0.025$[31]. Significant improvements were also seen at week 16 in individual symptoms, overall disease severity and pain scores with ADA 40 mg EW. Clinically relevant pain reduction was seen as early as week 2 in 40% of patients receiving ADA 40 mg EW.

In PIONEER I and II significantly more patients in the ADA 40 mg EW group achieved a clinical response (defined as achieving HiSCR [at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline] at week 12) than patients receiving placebo, 41.8% versus 26.0%, p=0.003 in PIONEER I and 58.9% versus 27.6%, p<0.001 in PIONEER II. This difference was maintained regardless of Hurley status (PIONEER I and II) and antibiotic use (PIONEER II only). Response was seen early in treatment with a significant difference as early as 2 weeks, response was particularly marked in PIONEER II[29 30].

Significant improvements were also seen in disease severity, inflammation, fibrosis and pain. The NICE scope specifies inflammation and fibrosis as outcomes and this information is captured within MSS (fibrosis) and improvement in AN count (inflammation). All outcomes were significant in PIONEER II, however, in PIONEER I some of the outcomes with ADA 40 mg EW were numerically but not significantly higher than placebo.

Subgroup analyses revealed that patients achieved benefit with ADA 40 mg EW regardless of their baseline characteristics. It should be noted, that some of the subgroups contained few people which makes the results difficult to interpret[29 30].

QOL is an important issue for patients with HS. PRO were consistently improved in patients receiving ADA 40 mg EW in all three studies[29-31]. In PIONEER I and II, ADA 40 mg EW significantly improved QOL as measured by EQ-5D, the physical components of SF-36, and DLQI compared with placebo. Significant improvements in work activity were seen with ADA 40 mg EW versus placebo[29 30].

Treatment satisfaction was assessed in PIONEER II and demonstrated that patients were more satisfied overall with ADA 40 mg EW than with placebo at 12 weeks, due to the significant improvement in effectiveness. There was no difference in patient perceived side effects or convenience between the two groups[35].

Improvements were maintained for the duration of the studies up to 36 weeks in the PIONEER studies. Re-randomisation during the second part (period B) of the PIONEER studies and protocol-driven discontinuation during period B for patients

with LOR or WOAI means that patient numbers are low in the group receiving EW for the total study duration (21 in PIONEER I and 20 in PIONEER II). There was a loss of effect for patients re-randomised to placebo or ADA 40 mg EOW[29 30].

Outcomes were maintained in patients who went on to enter the OLE[32].

Amalgamated data from the PIONEER studies and OLE study presented at WCD 2015 demonstrates that patients with a partial response (defined as HiSCR non-responders with ≥25% reduction in AN count relative to baseline) or a complete response to treatment (HiSCR responders) at week 12 continue to benefit from treatment[33]. Patients who are non-responders at week 12 are unlikely to respond if treatment is continued which clinicians to stop treatment in patients who have not responded to ADA 40 mg EW which has clear benefits in terms of drug expenditure.

As discussed earlier, wide surgical excision is generally used in patients with advanced disease, the skin areas affected by HS are removed in extensive skin surgery and the wounds are left to secondary healing, which can take up to 3 months. HS can re-appear at the border of the surgery or other areas of the body, so patients may require multiple surgeries over time. Treatment with ADA 40 mg EW has the potential to prevent or delay the progression of HS and thus avoid or delay surgery.

Overall, patients receiving ADA 40 mg EW in the PIONEER II study had better outcomes than those in PIONEER I, this is probably due to different patient demographics across the two studies. Patients in PIONEER I had more difficult to treat disease: higher mean MSS score, 149.1 versus 115, higher AN count 14.3 versus 11.3 and higher worst pain score 5.0 versus 4.5)[29 30]. Further data analysis is ongoing, with an aim to fully understand these differences.

Patients in PIONEER II were allowed to use concomitant antibiotics from the start of treatment and a slightly higher treatment effect (HiSCR at week 12) was observed in patients treated with concomitant antibiotics (difference in HiSCR at week 12 between placebo and ADA 40 mg EW of 42.6 (95% CI 20.7, 42.2) in patients receiving antibiotics and difference of 28.6 (95% CI 16.9, 40.6) in patients not receiving antibiotics. However, the magnitude of this difference and the small

number of patients treated with antibiotics in the trial (63/326 [19.3%]) does not account for the difference in treatment effect observed between the trials.

ADA 40 mg EW was well tolerated in the dose finding study (M10-467) and in both of the PIONEER studies. The proportion of patients experiencing SAEs or discontinuing treatment due to AEs was low and similar in both ADA and placebo arms[29-31].. In an integrated study of PIONEER I and II (n=633), six patients receiving placebo (1.9%) and three receiving ADA 40 mg EW (0.9%) gave AE as their primary reason for discontinuation during period A[34].

The AEs for patients treated with ADA 40 mg EW were comparable to placebo and consistent with the known ADA safety profile. The majority of AE were mild to moderate in severity. In the treatment satisfaction assessment carried out in PIONEER II there was no difference in patient perceived side effects in patients receiving ADA 40 mg EW or placebo[35].

The most common AE were exacerbation of HS, nasopharyngitis and headache. Rates of infectious AEs were similar for both patients receiving ADA and those receiving placebo. There were no reported TB infections.

No harms were seen in any of the patients enrolled in the dose finding study (M10-467), PIONEER I or PIONEER II.

The OLE study[32] did not identify any new safety risks for ADA.

4.13.2 Strengths and limitations

Three placebo-controlled studies provide evidence for the efficacy and safety of ADA 40 mg EW (n=367) in patients with moderate to severe HS who have failed to respond to, or intolerant of, antibiotic treatment[29-31]. An OLE study, M12-555, to the PIONEER studies provides additional long-term data on efficacy and safety of ADA 40 mg EW[32].

All three placebo-controlled studies have robust internal validity, as demonstrated by strong critical appraisal scores.

A number of factors influence external validity, and are listed below.

- All outcomes detailed in the NICE scope were considered as end-points in the clinical trials (disease severity, clinical response, inflammation and fibrosis, discomfort and pain, AE of treatment and health-related QOL).
- The HiSCR score was developed for use in the PIONEER studies and is not currently used in clinical practice. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline. HiSCR was developed in consultation with regulatory health authorities and has been validated against other measures of response in HS (Hurley stage, MSS and HS-PGA) in 138 patients with three or more AN enrolled in the dose finding study (M10-467) for ADA in HS and has been shown to be a valid and meaningful end-point for assessment of HS treatment effectiveness[36]. HiSCR is more responsive to change and better able to discriminate improvement in ADA-treated patients, compared to HS-PGA[89], as validated in a post-hoc population of 132 patients with three or more AN and draining fistula count of ≤20 enrolled in the dose finding study (M10-467) for ADA in HS. It is therefore anticipated that HiSCR would be expected to provide a more dynamic assessment than HS-PGA, and better able to capture changes over the course of the phase III trials[90]. HiSCR was also expected to more accurately predict the non-worsening of key inflammations that would eventually require surgery[90]. Finally, HiSCR is a simple measure to conduct, since it only requires counting of the inflammatory nodules, abscesses and draining fistulas before and after an intervention. Expert clinical opinion from a UK advisory board held by Abbvie in 2015, revealed that UK advisors generally welcomed HiSCR and thought that it allowed appropriate assessment of response to therapy[37].
- The NICE scope specifies ‘established clinical management without ADA’ as the comparison treatment. However, there is lack of consensus around treatment for HS, indeed , indeed guidelines for the management of HS have only just been published this year[38], and patients are managed according to individual clinician experience. Patients receive numerous different medicines, in a 5-year retrospective survey of 142 patients from 10 UK hospitals; patients took an average of 10 medications within the 5-year retrospective period (range 1-43)[39]. Therefore, placebo was chosen as the comparator rather than an active

treatment, this reflects a pragmatic approach and reflects clinical opinion in England, based on feedback from clinical experts[40-42].

- Patients in the clinical study programme reflect patients in routine clinical practice. as confirmed by clinical experts[40-42]. Patients were not recruited from the UK (patients were recruited from North America, elsewhere in Europe and Australia), all countries with similar demographics to the UK. A study funded by Abbvie Ltd set out to determine the demographics of patients from the UK[39]. In the study, 142 patients were enrolled between the dates of July 2014-April 2015 from 10 UK hospitals. Retrospective data over the previous 5 years was obtained from patient notes. Table 37 shows the differences between the study populations in PIONEER I and II and a UK population. Patients from the UK were slightly older (41 years versus 36.2 years in the overall PIONEER population), there were fewer smokers (45% versus 62%), patients had shorter disease duration (9 years versus 11.5 years) and more patients had prior surgery (41% versus 12.5%). The higher levels of prior surgery in the UK are a reflection of the patient cohort, which were patients who have been seen in secondary care. In the UK, most secondary care admissions are due to skin-related surgery. Interestingly, there was a paucity of data on Hurley score, demonstrating that the Hurley score is not generally used in UK clinical practice. It should be noted that the UK data does not provide information on whether patients are intolerant or resistant to antibiotics, as per the PIONEER population. This work gives an insight into the UK population, however, it should be remembered that the sample size is small and the study only considered patients who had been referred to hospital.

Table 37: Baseline demographics from PIONEER I and II and a UK patient cohort.

	PIONEER I (n=307)	**PIONEER II (n=326)**	**UK patient cohort (n=142)**	
Female, n (%)	196 (63.8)	221 (67.8)	93 (65%)	
Age, years; mean [SD]	37.0 [11.10]	35.5 [11.13]	41 [11.2]	
Hurley stage I, n (%)				
Hurley stage II, n (%)	161 (52.4)	175 (53.7)	(n=13) 6 (46%)	
Hurley stage III, n (%)	146 (46.6)	151 (46.3)	(n=13) 7 (54%)	
Disease duration, years; mean [SD]	11.5 [8.92]	11.5 [9.03]	8.8	
BMI, kg/m^2; mean [SD]	(n=306) 33.8 [7.80]	 32.1 [7.71]	Female 34.2 [6.7]	Male 29.5 [6.6]
Prior surgery for HS, n (%)	34 (11.1)	45 (13.8)	(n=101) 41 (41%)	
Current smokers, n (%)	173 (56.4)	214 (65.8)	63 (45%)	

There are a number of study limitations; the main limitation is the paucity of data for the licensed dose beyond 12 or 16 weeks due to re-randomisation at 12 or 16 weeks and protocol-driven discontinuation during period B for patients with LOR or WOAI in the PIONEER studies. However, the OLE study will provide further data out to 60 weeks to fill this data gap and an interim data cut provides information on patients for a median of 348 days (range 5-883 days)[32]. Data is available for 84 patients who received continuous ADA 40 mg EW, with a mean exposure of 444.7 days (median, 430; range, 154 to 883 days).

Other limitations include a higher than expected response rate in the placebo arms in the PIONEER trials[37]. HS is a chronic disease characterized by relapses and flares. The within patient variation in disease severity have not been completely elucidated[7]. Indeed, HS has never been prospectively followed and therefore fluctuations in disease severity are unknown. The placebo response observed in the PIONEER trials cannot be compared to other dermatological conditions since placebo rates are a reflection of nature of the disease.

There are also differences in study design between PIONEER I and PIONEER II, as shown in Table 38 below, which means that the results of PIONEER I and PIONEER II are not directly comparable.

Table 38: Key differences between PIONEER I and PIONEER II study designs.

	PIONEER I	PIONEER II
Study sites	US, Canada, Australia, Czech Republic, Germany and Hungary	Australia, Canada, Denmark, Greece, Netherlands, Sweden, Switzerland, Turkey and US
Concomitant oral antibiotics	Not allowed at study entry; rescue therapy with minocycline or doxycycline allowed starting week 4 or week 8	Doxycycline or minocycline allowed if dose is stable >28 days at baseline visit
Stratification factors	Randomisation stratified by baseline Hurley stage (II vs III)	Randomisation stratified by baseline Hurley stage (II versus III) and concomitant oral antibiotic use (Yes versus No)
Period B dosing	Subjects randomised to placebo in period A receive blinded ADA in period B	Subjects randomised to placebo in period A continue on blinded placebo in period B
PRO outcomes	SF-36, HADS	EQ-5D

4.13.3 Life expectancy and number of patients suitable for treatment

There is currently no evidence to suggest that HS has any impact on life expectancy, however in severe patients requiring surgical treatment for HS, major complications might occur (ie. infections, bleeding), which could result in premature mortality.

The patient population in which ADA is licensed and considered in this submission is for adults with active moderate to severe HS who have had an inadequate response to or are intolerant to conventional systemic HS therapy.

In order to estimate the total patient number eligible for treatment with ADA the prevalence of the condition among patients aged 18 and over in England and Wales is first calculated (457,624). Market research conducted by Abbvie[55] suggests that only a small proportion of patients with HS are diagnosed (19%) and not all (82%) are treated for HS. Since ADA is a biologic treatment it will only be prescribed by a dermatologist and based on market research only 45% of HS patients are currently seen by a dermatologist in the UK. ADA is only licensed for moderate to severe HS patients and as such it was also necessary to estimate how many patients would fulfil these criteria (53.2%). Finally as ADA will not be prescribed in all patients the proportion of moderate to severe dermatology treated patients who would be prescribed a biologic was also estimated (2.4%-8%).

The total number of patients that would be eligible to receive treatment with ADA in any given year in England and Wales was estimated to range between 410 and 1,417. Please refer to Table 39 for an outline of how the total population of patients eligible for ADA in England and Wales was calculated.

Table 39: Estimated number of patients eligible for HS ADA treatment in England and Wales

	Population Estimates 2016	Source
Population estimate for England and Wales (2016)	58,139,219	ONS[94]
Proportion of all aged 18 & over in England and Wales (78.7%)	45,762,384	ONS[95]
Number of patients with the condition (Prevalence 1%)	457,624	Revuz, 2008[3]
Proportion of patients diagnosed with HS (19%)	86,949	AbbVie Market research[55]
Proportion of patients treated for HS (82%)	71,298	AbbVie Market research[55]
Proportion of patients treated by a dermatologist (45%)	32,084	AbbVie Market research[55]
Proportion of patients moderate to severe (53.2%)	17,069	AbbVie Market research[55]
Proportion of moderate to severe dermatology patients treated with a biologic (range 2.4%-8%)	410 to 1,417	AbbVie estimate

4.14 Ongoing studies

Study M12-555 is an OLE to the PIONEER studies and is currently underway (NCT 01635764)[96]. The study started recruitment in April 2012 and aimed to recruit 540 patients. An interim data cut, as of 29 April 2014 provides information on 497 patients for a median of 348 days (range 5-883 days)[32] and is discussed in this submission. Final data from OLE M12-555 is expected in 2016.

5 Cost effectiveness

A de novo health economic model was developed using a Markov type analysis. The model structure was similar to previous ones used in dermatology.

The model assessed the cost-effectiveness of ADA (Humira ®) vs SC as represented by the placebo arm in the PIONEER I & II trials, for the treatment of adult patients with active moderate to severe HS who have had an inadequate response to conventional systemic therapy.

The model considered four mutually exclusive health states based on patients' response status (high response, response, partial response or non-response) and one absorbing state (death). The model health states were defined based on the primary efficacy measures used in the PIONEER phase III clinical trials.

The evaluation took an NHS/PSS perspective and evaluated costs and health outcomes (in terms of QALYs) over a life time horizon, both discounted at 3.5%.

Data from the PIONEER clinical trials was used to define the efficacy of ADA and SC in the economic model for the first 36 weeks. TPs during the first 36 weeks were directly derived based on the observed cross-tabulations of patient distributions among the four health states evaluated at subsequent visits in the PIONEER phase III clinical trials.

Extrapolation beyond the trial period was based on a modelled approach. For patients on ADA TPs were estimated using a generalised logit model using week 0-24 data from the OLE trial (corresponding to weeks 36-60). TPs for ADA discontinuers and patients on SC were estimated using a generalised logit model using week 12-36 data from the PIONEER phase III clinical trials.

AEs selected for inclusion in the model were the most frequently reported (≥ 5%) treatment emergent AEs observed in the PIONEER I and II clinical trials during the entire induction and maintenance period.

Health utilities were assumed to depend only on health states, independent of treatments received. The results of the EQ-5D evaluation from the PIONEER II study

were used to estimate the health utility associated with each health state. Patients' utility values for each health state were estimated using week 12-36 data.

Resource use was assumed to depend only on health states, independent of treatments received. The model considered surgery-related resource use and non-surgery related resource use. Resource use by health states was estimated based on inputs from a survey of physicians (n=40) who actively treat moderate to severe HS patients in the UK.

In the base case analysis ADA was found to be more costly [redacted] vs. £128,541) but also more effective (12.61 QALY vs. 11.61 QALY) compared to SC resulting in an incremental cost-effectiveness ratio (ICER) per QALY of [redacted]

Uncertainty in the model assumptions and inputs was explored through sensitivity analysis:

The results of the PSA based on 5,000 iterations of the model estimated an ICER per QALY of [redacted]. The probability of ADA being cost effective at a WTP threshold of £30,000 was [redacted]

The results of the DSA showed little variations in the incremental cost per QALY. The model was most sensitive to assumptions around the TPs used in the extrapolation period (after week 36), the utility values, the number and cost of hospitalisations for surgery and the discontinuation rates of ADA.

5.1 Published cost-effectiveness studies

A Cochrane review was published in October 2015[72] after this SLR was completed and is not included in the results below. The review did not identify any additional studies not indentified by the SLR.

A SLR was conducted to identify healthcare resource use, costs, cost drivers, previous economic evaluations and health technology assessment (HTA) economic models of treatments for patients with moderate to severe HS.

The cost-effectiveness and cost and resource use searches were run together in order to avoid potential duplicates caused by the presence of common search terms in these study design facets.

The searches were limited to the last 15 years to focus on the most recent cost, resource use and cost-effectiveness data. Only studies published in English were included. Searches were conducted up to 3 July 2015 (Please see Appendix 6 for full details of the search strategy and dates).

The following electronic databases were searched:

- MEDLINE and EMBASE (using EMBASE.com)
- MEDLINE In-Process
- EconLit (using EBSCO.com)
- The Cochrane Library, including the following:
    - The Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effectiveness
    - Cochrane Central Register of Controlled Trials
    - Health Technology Assessment Database

Additionally, key HTA websites (NICE, the Scottish Medicines Consortium [SMC] and the All Wales Medicines Strategy Group [AWMSG]) were searched for relevant HTA evaluations/models. Conference searches were also performed to identify potentially relevant conference posters or abstracts of interest. These searches were restricted to the last two years and covered the following conferences:

- AAD
- ESDR
- WCD
- International Society For Pharmacoeconomics and Outcomes Research (ISPOR)

The inclusion and exclusion criteria used to identify potentially relevant economic articles in the review are summarised in Table 40.

Table 40: Inclusion/exclusion criteria (cost-effectiveness studies)

Inclusion criteria	Exclusion criteria
Population • Studies with adult patients with moderate to severe HS. The disease is also known as acne inversa, pyoderma fistulans significa, Verneuil's disease or smoker's boils ***Interventions*** Any treatment for HS, including but not limited to the following: • Antibiotics – Oral tetracyclines such as lymecycline and doxycycline – Combination of clindamycin and rifampicin • Retinoids such as acitretin and isotretinoin • Dapsone • Ciclosporin • Biologics (such as ADA, infliximab, ustekinumab and other anti-TNF agents) • Surgical options (narrow margin excision of most active lesion(s) and wide local excision of most active region) • Oral prednisolone • Intralesional triamcinolone injections • Oral contraceptive pills • Incision, drainage and analgesia (for painful acute HS) ***Outcomes*** • Studies with a comparison of costs between the intervention and comparator arms • Results reported in terms of cost per disease-specific clinical event, cost per quality-adjusted life year (QALY) gained, cost per life year gained, or just cost if accompanied by a cost-minimisation argument ***Study design***	***Population*** • Healthy volunteers • Studies with children only • Patients with any skin diseases other than HS ***Interventions*** • No exclusion on the basis of interventions ***Outcomes*** • Cost-only outcomes without a cost-minimisation argument (e.g. burden of illness studies) ***Study design*** • Reviews (systematic or otherwise), letters and comment articles • Burden of illness studies ***Other criteria*** • Studies that failed to present sufficient methodological detail • Studies that failed to present extractable results

Inclusion criteria	Exclusion criteria
• Full economic evaluations, comparing at least two interventions in terms of: – Cost–consequence – Cost-minimisation – Cost-effectiveness – Cost–utility – Cost–benefit ***Other criteria*** • Studies which presented sufficient detail regarding the methodology used • Studies which provided extractable results	
Key: HS, hidradenitis suppurativa; QALY, quality-adjusted life-years; TNF, tumour necrosis factor.	

The inclusion and exclusion criteria used to identify potentially relevant cost and resource use articles are summarised in Table 41.

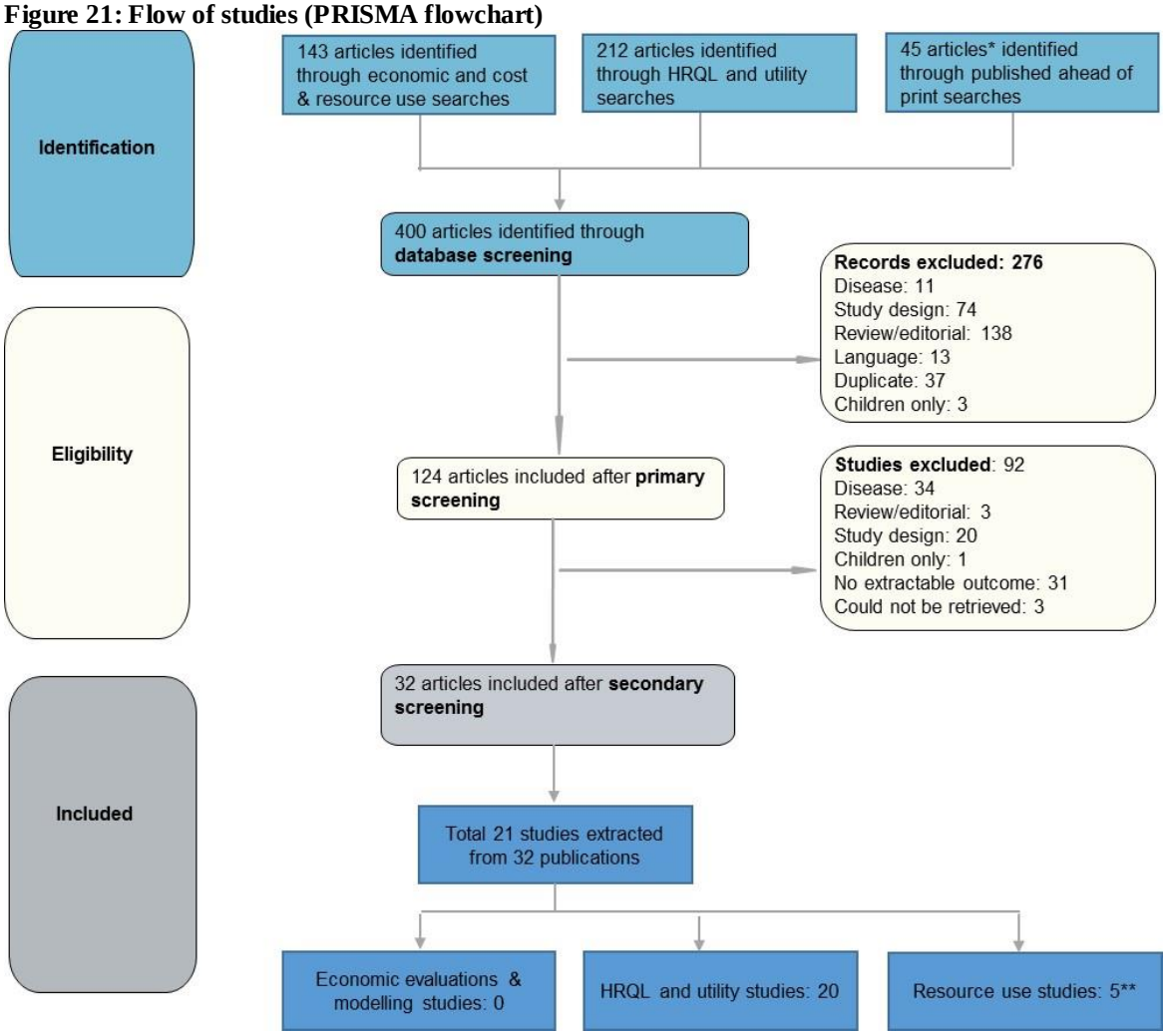
Figure 21 presents the flow of studies for this systematic review using a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram (Moher et al., 2009).

Table 41: Inclusion/exclusion criteria (cost and resource use studies)

Inclusion criteria	Exclusion criteria
Population • Treated and/or untreated adult patients with moderate to severe HS. The disease is also known as acne inversa, pyoderma fistulans significa, Verneuil's disease or smoker's boils ***Interventions*** Any treatment for HS, including but not limited to: • Antibiotics – Oral tetracyclines such as lymecycline and doxycycline – Combination of clindamycin and rifampicin • Retinoids such as acitretin and isotretinoin • Dapsone • Ciclosporin • Biologics (such as ADA, infliximab, ustekinumab and other anti-TNF agents) • Surgical options (narrow margin excision of most active lesion(s) and wide local excision of most active region) • Oral prednisolone • Intralesional triamcinolone injections • Oral contraceptive pills • Incision, drainage and analgesia ***Outcomes*** • Any study quantifying the costs or resource use requirements of HS and its management • Any study quantifying the costs or resource use associated with disease- or treatment-related AEs ***Study design*** • Cost studies • Resource use studies	***Population*** • Patients with any other skin disease than HS • Healthy volunteers • Studies with children only ***Interventions*** • No exclusion on the basis of interventions ***Outcomes*** • Studies that do not report either cost or resource use information ***Study design*** • Reviews (systematic or otherwise), letters and comment articles ***Other criteria*** • Studies that fail to present sufficient methodological detail • Studies that fail to present extractable results

Inclusion criteria	Exclusion criteria
• Economic evaluations reporting costs or resource use ***Other criteria*** • Studies must present sufficient detail regarding the methodology used • Studies must provide extractable results • Studies must present cost and resource use data (preferably for UK but studies reporting data for other countries will also be included)	
Key: HS, hidradenitis suppurativa; TNF, tumour necrosis factor; UK, United Kingdom.	

Figure 21: Flow of studies (PRISMA flowchart)



Key: HRQOL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Note: *These studies were identified using search terms for disease only. Thus, they may include both cost-effectiveness and HRQOL and utility studies; **Four studies also reported HRQOL outcomes.

The systematic review identified 143 economic and cost of resource studies and 45 published ahead of print studies were identified from PubMed (these included both cost-effectiveness and utility and HRQOL studies as study design filter was not run for these searches). The screening of all identified articles was done together in this systematic review to increase efficiency and avoid retrieval of duplicates. After preliminary screening of all abstracts and titles and following secondary screening, relevant data were extracted from 21 studies (reported in 32 publications). Of these five (including four which also reported HRQL and utility outcomes) reported resource use data for patients with moderate to severe HS. No relevant HTAs were identified on the NICE, SMC or AWMSG websites and no economic evaluations or modelling studies were identified for HS patients.

5.2 De novo analysis

5.2.1 Introduction

The SLR did not identify any existing economic models for HS as such a de novo analysis was conducted to assess the cost-effectiveness of ADA (Humira ®), for the treatment of adult patients with active moderate to severe HS who have had an inadequate response to conventional systemic therapy.

5.2.2 Patient population

The target population consists of adult patients with active moderate to severe HS (acne inversa) who have had an inadequate response to conventional systemic therapy, see Section 3.2. This is consistent with the licensed population in the EU, and is in line with the patient population evaluated in the two phase III clinical trials of ADA in HS, PIONEER II and PIONEER I[29 30]. This population also reflects the patient population defined in the scope and decision problem for this NICE technology appraisal.

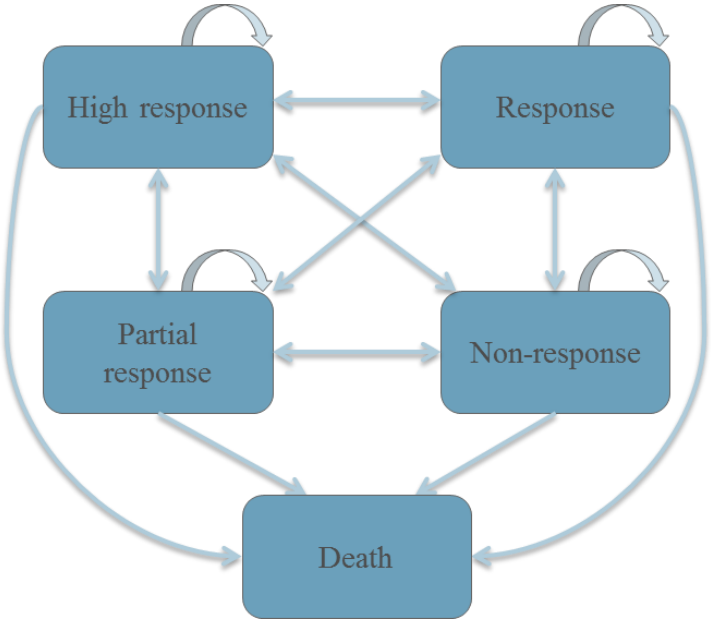
5.2.3 Model structure

A Markov model was developed to compare the cost-effectiveness of ADA versus Supportive Care (SC). The Markov modelling approach was adopted for this analysis as it permitted the transparent modelling of transitions between health states and

also provided a flexible structure for the exploration of treatment efficacy beyond the pivotal clinical trial period (i.e. after 36 months).

A 4 week cycle length was selected, with the exception of the first two cycles which were 2 weeks long. The cycle lengths were selected after taking into consideration the dosing schedule of ADA and the schedules of efficacy as measured in the PIONEER I and PIONEER II trials. A half cycle correction was applied to estimate costs and QALY with the exception of ADA treatment costs since these costs were incurred at the beginning of the model cycle as discrete events, not gradually over the model cycle. The model structure is shown in Figure 22.

Figure 22: Model structure



The model health states were defined based on the primary efficacy measures used in the PIONEER I and II trials. In addition, the model also included a death state. The following four health states and an absorbing state were considered in the model (Figure 22):

- High response: defined as at least 75% total abscess and inflammatory nodule (AN) count reduction, with no increase in abscesses or draining fistulas from baseline
- Response: defined as at least 50% but less than 75% AN reduction, with no increase in abscesses or draining fistulas from baseline

- Partial response: defined as at least 25% but less than 50% AN reduction, with no increase in abscesses or draining fistulas from baseline; or at least 25% AN reductions, with an increase in abscesses and/or draining fistulas
- Non-response: defined as less than 25% AN reduction
- Death: absorbing state

The high response and response health states together constitute the HiSCR, the primary efficacy end-point measured in the PIONEER trials[29 30] trials. Patients with partial response or non-response to treatment were considered HiSCR non-achievers in the PIONEER trials. Preliminary analyses of the EuroQol (EQ-5D) data collected in the PIONEER II trial[30] indicated that there was a statistically significant difference in the utility values between the high response and response health states, and between the values of the partial response and non-response health states. Therefore, to better evaluate the impact of treatment on HRQOL, the analysis considered four separate response health states. Patients in each response state could transition to death at any time in the model – based on natural mortality statistics for the general population in England and Wales[97]. The definition of health states based on relative changes from baseline was consistent with prior cost-effectiveness analyse (CEAs) for biologic treatments. For example, in the appraisal submission of ADA in psoriasis[98], health states were defined by percentage reductions from baseline in the Psoriasis Area Severity Index (PASI) scores, which represent the affected area and severity of skin lesions.

In the model patients start treatment with either ADA or SC and then transition across the four health states and the absorbing state, based on their responses to treatment and their natural mortality rate. Patients incur treatment costs (i.e. costs of ADA or SC), costs associated with treatment-related AEs, and other medical costs. Medical costs consist of surgery-related costs and non-surgery related costs and are assigned to each health state, independent of treatment received. The frequency of surgical interventions depends on health states and the differing level of local HS manifestations, reflecting the fact that surgery can only be a temporary relief to local HS manifestations. The frequency of non-surgery-related resource use associated

with A&E visits is also evaluated by health states. Health state specific utilities, based on EQ-5D information are used in the model to estimate QALYs.

Key features of the analysis are shown in Table 42.

Table 42: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Life time horizon (66 years; 859 model cycles)	HS is a chronic condition that adversely affects patients' HRQOL over a long period of time. Likewise, treatment with ADA is expected to impact on the costs and outcomes associated with the disease over the long term. To best represent those real-life scenarios, the model adopts a lifetime horizon.
Were health effects measured in QALYs; if not, what was used?	QALYs	HS has been demonstrated to have a significant impact on patients' HRQOL and as such health effects in this measured in QALYs
Discount of 3.5% for utilities and costs	Costs and efficacy were discounted at 3.5%	To reflect positive time preference
Perspective (NHS/PSS)	(NHS/PSS)	As per NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years		

5.3 *Intervention technology and comparators*

5.3.1 Clinical parameters and variables

5.3.1.1 Intervention

The intervention assessed in the cost-effectiveness model is ADA, a fully human recombinant monoclonal Immunoglobulin G1 (IgG1) antibody with high specificity for TNF-α. ADA is indicated for the treatment of active moderate to severe HS (acne inversa) in adults who have had an inadequate response to or are intolerant to conventional systemic HS therapy.

Efficacy data for ADA in HS were drawn from the intervention arms in the phase III PIONEER I and II clinical trials[29 30], both of which used HiSCR as the primary efficacy endpoint. Both trials evaluated ADA vs. placebo, and included both an induction period, during which patients were randomised to receive either ADA or placebo, and a maintenance period in which ADA patients were re-randomised to

receive either ADA or placebo, and placebo patients continued to receive placebo in PIONEER II and were crossed-over to ADA in PIONEER I.

The intervention was implemented in the model as per the treatment's marketing authorisation with respect to the target population and dosing regimens. Specifically, all patients treated with ADA had a 12-week induction period and received the following dosing: 160 mg at week 0, 80 mg at week 2, and 40 mg ADA EW starting at week 4. At week 12, patients with non-response to ADA discontinue treatment, and the remaining patients continue receiving ADA at a dose of 40 mg EW. After week 12, patients could discontinue ADA based on a specified discontinuation rate (see below).

Treatment continuation rule with ADA

Induction period (0-12 weeks): At the end of the induction period (week 12), patients starting ADA discontinue if they are in the non-response state. This is consistent with the Summary of Product Characteristics agreed with the EMA, which states that "*continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period*"[28].

Maintenance period (12-36 weeks): ADA initial responders (i.e., patients who are not in the non-response state at week 12) discontinue ADA based on a constant discontinuation rate. The discontinuation rate for week 12-36 was estimated using the clinical trial data from the PIONEER studies[29 30] based on the observed discontinuation rates among ADA initial responders (other than thosing enroling into the OLE clinical trial in order to further continue ADA treatment). Using the constant hazard assumption, the observed discontinuation rates were used to estimate 4-week discontinuation rates, which were then used in the model for weeks 12-36. The discontinuation rate was applied to all ADA-treated patients regardless of response state.

Long term discontinuation (over 36 weeks): Response-specific discontinuation rates for responders (including high responders, responders and partial responders) and non-responders were considered in the extrapolation period. To estimate the rates of discontinuation of ADA after week 36, the OLE clinical trial was used[32].

Response-specific discontinuation rates were estimated using the person-year

approach. In particular, the length of time that patients spent in a specific response state was calculated using the available OLE clinical trial data. Patients were assumed to remain in their prior health states until a change in the health state was observed, and patients' health states at the time of discontinuation were used to categorize response-specific discontinuation events. The analysis used all ADA-treated patients who were week 12 responders, who received ADA during the maintenance periods of the phase III PIONEER trials and who were later enrolled into the OLE clinical trial.

For patients non-responding to ADA at week 36 the discontinuation rate from the OLE clinical trial[32] was only applied up to week 48 in the base case. This was based on input from clinical experts suggesting that patients who do not respond to ADA treatment will be discontinued in clinical practice after a re-assessment period and 12 additional weeks of treatment[40-42 44]. Furthermore the ADA drug label indicates that "*the benefit and risk of continued treatment should be periodically evaluated after week 12*"[28]. As such in the model base case all patients who were in the non-response health state at week 36 discontinued ADA treatment at week 48. Patients who discontinue ADA treatment, transition to SC and follow TPs from SC.

Table 43: Discontinuation rates for ADA during the maintenance period

ADA discontinuation rates	Annual rate	4-week rate	Data source
Maintenance period (week 12-36)			
All states	20.48 %	1.75 %	PIONEER I and PIONEER II[29 30]
Maintenance period (after week 36)			
High response, response or partial response	7.47 %	0.60 %	OLE[32]
Non-response	44.99 %	4.49 %	

5.3.1.1 Comparators

Currently, there are no therapies licensed for the treatment of HS in the UK and a number of different pharmacological treatments are currently used off-label in clinical practice to manage HS including antiseptics, antibiotics, NSAIDs, immunosuppressants, corticosteroids, anti-androgens, retinoids and TNF-α inhibitors. However, as demonstrated by the systematic review of efficacy in HS

conducted by AbbVie[43], there is a lack of robust clinical evidence demonstrating efficacy of any of these treatments in HS.

Furthermore, there is no standard pathway of care for HS in the UK and until recently there was a lack of published guidelines to assist with treatment choices. Recent guidelines for the treatment of HS were published in 2015 by a panel of European clinicians (see Section 3)[38]

Expert clinical opinion from a UK advisory board held by AbbVie in 2015 suggested that at present, medical treatment for HS is off-label and often given in a stepwise fashion, starting with systemic antibiotics, then dapsone (antibiotic), retinoids, followed by immunomodulators (ciclosporin) and ultimately biologics. Each therapy is given as a 3- to 6-month course; treatment is escalated if patients fail to respond within 6 months. Corticosteroids are frequently prescribed during flares and IV antibiotics are rarely used[37]. This stepwise approach was further confirmed by the UK clinical experts consulted for this submission[40-42 44].

During the course of the disease, patients may undergo different surgical interventions. However, surgery was not considered an appropriate comparator in this analysis, given that surgery and ADA are not alternative or exclusive treatment choices. Patients receiving ADA in the clinical trials were allowed surgery for symptom control. Furthermore, an online survey of members of the UK Dermatology Trials Network and British Association of Dermatologists the UK survey revealed that extensive surgery was generally used later in the treatment pathway (mode of seventh choice)[91], see Section 3

Antibiotics were also not considered a relevant comparator in this analysis as they tend to be used throughout the treatment pathway and may be used concomitantly with ADA. In the PIONEER II clinical trial[30], concomitant use of oral antibiotics was allowed in both the ADA and placebo arms. In the PIONEER I trial[29], patients who received any oral antibiotic treatments within 28 days prior to baseline were excluded; although, rescue therapy with antibiotics was permitted throughout the trial, see Section 4.3.2.

A comparison versus dapsone, retinoids and immunomodulators (ciclosporin) was also not performed since the UK clinical experts consulted for this submission suggested that these therapies would currently be prescribed before ADA in the UK[40-42 44]. Furthermore, as identified by the SLR, there is currently a lack of efficacy evidence for these therapies in HS.

Results from AbbVie's global multi-country market research targeting 422 dermatologists (60 from the UK) treating HS patients shows that both biologics (ADA and infliximab) are used[99]. However, clinician input from a UK Advisory Board suggests higher clinician satisfaction with ADA treatment and that infliximab is used in very specific patient subgroups, for example in very overweight patients[37]. Comparison of ADA versus other biologics currently used in clinical practice, such as infliximab, was not possible, as the identified studies in the SLR differed in the proportion of mild/moderate/severe HS patients as well as baseline CRP levels (the mean CRP levels spanned through 15-18 mg/L in ADA comparisons to 32 mg/L in infliximab vs. placebo comparison, at baseline). Few studies were identified; only one reported on infliximab versus placebo[73], which prevents meta-analyses with sufficient power to draw definitive conclusions on relevant outcomes. In addition, results from the feasibility assessment suggested that NMA would not be feasible owing to limited evidence base and heterogeneity among the ADA and infliximab comparisons with respect to baseline CRP levels and disease severity

Based on the feedback received from the UK clinical experts (ie. biologics prescribed after all other options have been exhausted)[37] and due to the lack of evidence available for most therapies currently used to treat HS[43] the main comparator in this analysis is SC, as represented by the placebo arms in the PIONEER clinical trials[29 30].

5.3.1.3 Efficacy

Data from the PIONEER clinical trials is used to define the efficacy of ADA and SC in the economic model[29 30].

Both the PIONEER trials were double-blinded and placebo-controlled during the induction period, in which patients were randomised to receive either ADA or

placebo. In the maintenance period in both trials, patients who had been randomised to ADA in the induction period were re-randomised to receive either ADA or placebo. Patients who had been randomised to placebo in the induction period were continued on placebo during the maintenance period in the PIONEER II trial, however they were all crossed-over to ADA in the PIONEER I trial (see Section 4.3.2.).

As a result, the PIONEER II trial included patients receiving ADA in both the induction and maintenance periods, patients receiving ADA in the induction period and switching to placebo in the maintenance period, and patients receiving placebo in both periods. The PIONEER I trial only included patients receiving ADA in both periods (induction and maintenance) and patients receiving ADA in the induction period and switching to placebo in the maintenance period; it did not include patients receiving placebo in both the induction and maintenance periods. Therefore in order to utilise all available data to estimate the TPs for the economic analysis the following trial sources were utilised:

- Induction period: Pooled data from the PIONEER I and PIONEER II trials for both the ADA and SC arms
- Maintenance period: Pooled data from the PIONEER I and PIONEER II for the ADA arm, and PIONEER II data for the SC arm

Transition probability trial period (0-36 weeks)

Patients' distributions across the four health states of high response, response, partial response and non-response in the PIONEER clinical trials were used to inform the TPs of the ADA and SC arms in the model. Missing values were imputed using the NRI method to be consistent with the primary efficacy analysis imputation method specified in the clinical trial protocol (an alternative imputation method, using LOCF, was considered in sensitivity analyses). TPs during the first 36 weeks were directly derived based on the observed cross-tabulations of patient distributions among the four health states evaluated at subsequent visits in the PIONEER phase III clinical trials[29 30]. In particular, at each assessment week all patients were classified into health states based on their current status (i.e., high response, response, partial response or non-response). At baseline, all patients were classified

as being in the non-response health state. After this classification, the distribution of patients' health states at the next assessment visit was tabulated and the corresponding proportions were used as estimates of the transition probabilities (TPs). This calculation was performed separately for the ADA and SC arms. For each arm, the TPs were estimated separately for each cycle, i.e., for weeks 0-2, 2-4, 4-8, 8-12, 12-16, 16-20, 20-24, 24-28, 28-32, 32-36.

For the initial 12 weeks, the TPs during ADA treatment were based on all patients randomised to ADA observed during the induction period. As the model discontinued ADA among non-responders at week 12, the TPs of ADA during weeks 12-36 were based on ADA-treated patients who were week 12 responders. Only ADA-treated patients who received EW dosing regimens during the maintenance period were considered to be consistent with the dosing regimen evaluated in the model. The TPs for ADA discontinuers during weeks 12-36 were generated based on patients who received ADA in the induction period and who then switched to placebo in the maintenance period. The TPs for the SC arm were estimated using all patients who received placebo in both induction and maintenance periods of the clinical trials.

Transition probabilities beyond the trial period (after week 36)

Since the two PIONEER pivotal clinical trials had a duration of 36 weeks[29 30], extrapolation beyond the trial period was required to evaluate long-term outcomes. Beyond the trial period, extrapolation was based on modelled TPs.

For patients on ADA TPs were estimated using a generalised logit model using week 0-24 data from the OLE trial, which corresponds to week 36-60 if counting from the initiation of the PIONEER phase III trials; LOCF was used when conducting the analysis since less than half of the patients had follow-up up to 24 weeks at the time of the interim data cut. The dependent variable was the current health state, and the independent variables were the previous health state.

Patients who received ADA in the induction period and switched to placebo in the maintenance period in the trials were used to estimate TPs for ADA discontinuers. Patients who received placebo in both the induction period and maintenance period in the trials were used to estimate TPs for patients on SC. To estimate the TPs of

ADA discontinuers and patients on SC, the dependent variable was the current health state, and the independent variable was the previous health state.

The model also evaluated a last health state carried forward (LSCF) extrapolation method and a mean TP extrapolation in the sensitivity analyses. The LSCF extrapolation method assumed that the proportions of patients in each health state would remain the same for the remaining model period for ADA-treated patients and SC-treated patients. In the mean extrapolation method TPs after week 36 were estimated based on the means of TPs from week 12-36 for patients on ADA, ADA discontinuers and patients on SC, respectively from the PIONEER phase III clinical trials.

5.3.1.4 Use of clinical experts

Clinical experts [redacted] experienced in the treatment of HS in the NHS in England were consulted to discuss modelling assumptions and findings[40-42]. In particular, the following issues were discussed: model time horizon, treatment pathway and comparators, treatment continuation rule with ADA, extrapolation of efficacy beyond the trial period, resource use and compliance. Communication took place through a teleconference, followed-up with email correspondence when necessary.

An advisory board was also held in June 2015 and helped to inform the modelling assumptions and findings[37]. Other experts (dermatologists, surgeons) were also consulted on an ad hoc basis.

5.4 Measurement and valuation of health effects

5.4.1 HRQOL data from clinical trials

The PIONEER II clinical trial collected EQ-5D information as a measurement of HRQOL, while the PIONEER I trial did not collect EQ-5D data[29 30].

In PIONEER II, EQ-5D instruments were administered at baseline, week 12 and at week 36 visits, and patients' responses to treatments were evaluated at week 12 and week 36.

5.4.2 HRQOL studies

A systematic literature review was conducted to identify utility and health-related quality of life (HRQOL) studies for patients with moderate to severe HS.

The searches were limited to the last 15 years and only studies published in English were included. Searches were conducted up to 3 July 2015 (Please see Appendix 6 for full details of the search strategy and dates).

The following electronic databases were searched:

- MEDLINE and EMBASE (using EMBASE.com)
- MEDLINE In-Process
- EconLit (using EBSCO.com)
- The Cochrane Library, including the following:
  - The Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effectiveness
  - Cochrane Central Register of Controlled Trials
  - Health Technology Assessment Database

Additionally, key HTA websites (NICE, the Scottish Medicines Consortium [SMC] and the All Wales Medicines Strategy Group [AWMSG]) were searched for relevant HTA evaluations/models. Conference searches were also performed to identify potentially relevant conference posters or abstracts of interest. These searches were restricted to the last 2 years and covered the following conferences:

- AAD
- ESDR
- WCD
- ISPOR

The inclusion and exclusion criteria used to identify potentially relevant HRQL articles in the review are summarised in Table 44.

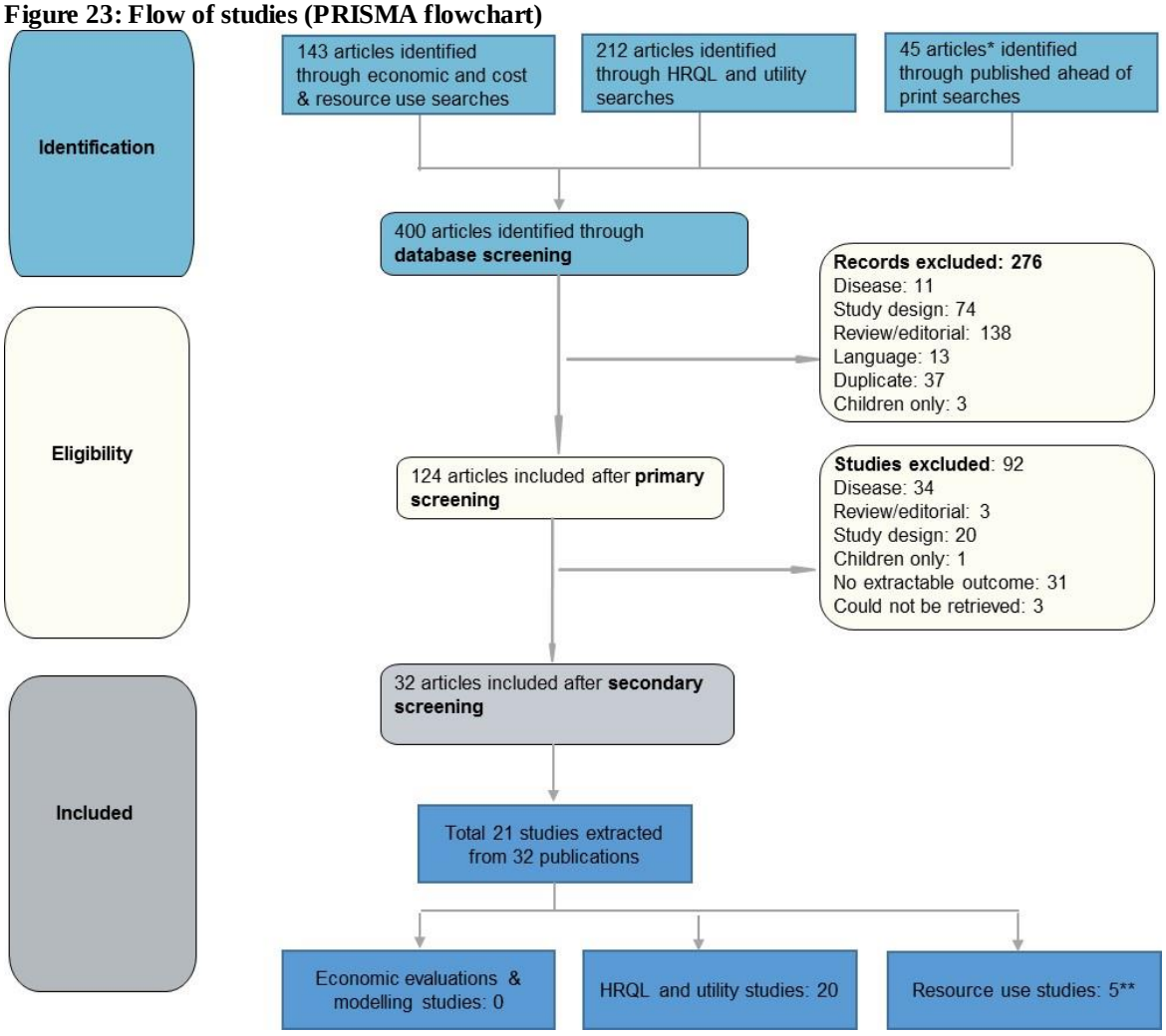
Figure 23 presents the flow of studies for the systematic review using a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram[100].

Table 44: Inclusion/exclusion criteria (HRQL studies)

Inclusion criteria	Exclusion criteria
Population • Treated and/or untreated adult patients with moderate to severe HS. The disease is also known as acne inversa, pyoderma fistulans significa, Verneuil's disease or smoker's boils ***Interventions*** Any treatment for HS, including but not limited to: • Antibiotics – Oral tetracyclines such as lymecycline and doxycycline – Combination of clindamycin and rifampicin • Retinoids such as acitretin and isotretinoin • Dapsone • Ciclosporin • Biologics (such as ADA, infliximab, ustekinumab and other anti-TNF agents) • Surgical options (narrow margin excision of most active lesion(s) and wide local excision of most active region) • Oral prednisolone • Intralesional triamcinolone injections • Oral contraceptive pills • Incision, drainage and analgesia ***Outcomes*** • Utility values produced using generic, preference-based measures of patient utility, disease-specific measures or vignettes ***Study design*** • QoL studies • Economic evaluations reporting patient utility values • Observational studies reporting QoL/utility data	***Population*** • Healthy volunteers • Studies with children only • Patients with any other skin diseases than HS ***Interventions*** • No exclusion on the basis of interventions ***Outcomes*** • Disease specific and non-preference-based measures not converted to utilities ***Study design*** • Reviews (systematic or otherwise), letters and comment articles ***Other criteria*** • Studies that failed to present sufficient methodological detail • Studies that failed to present extractable results

Inclusion criteria	Exclusion criteria
Other criteria • Studies must present sufficient detail regarding the methodology used • Studies must provide extractable results	
Key: HRQL, health-related quality of life; HS, hidradenitis suppurativa; QoL, quality of life; TNF, tumour necrosis factor.	

Figure 23: Flow of studies (PRISMA flowchart)



Key: HRQOL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Note: *These studies were identified using search terms for disease only. Thus, they may include both cost-effectiveness and HRQOL and utility studies; **Four studies also reported HRQOL outcomes.

The systematic review identified 212 utility and HRQOL studies, and 45 published ahead of print studies were identified from PubMed (these included both cost-effectiveness and utility and HRQOL studies as study design filter was not run for these searches). The screening of all identified articles was done together in this systematic review to increase efficiency and avoid retrieval of duplicates. After preliminary screening of all abstracts and titles and following secondary screening, relevant data were extracted from 21 studies (reported in 32 publications). Of these 20 reported HRQOL and utility data.

Study characteristics

Details of study design, objectives and setting of included studies are presented in Table 45. The outcomes presented in Table 46 were extracted from each study identified for the HRQOL and utility review

Most of the studies were observational in nature (11 studies in total: Blanco et al., 2009[101] Blok et al., 2015[102]; Cusack and Buckley, 2006[103]; Delage et al., 2011[104]; Fardet et al., 2007[74]; Martin-Ezquerra et al., 2015[105]; Matusiak et al., 2010[25]; Mekkes and Bos, 2008[106]; Van Rappard et al., 2012[107]; Wollina et al., 2012[108]; Wormald et al., 2014[109]). Three studies were prospective, interventional, single-arm trials (Amano et al., 2010[110]; Lee et al., 2009[75]; Lesage et al., 2012[111]). Alavi et al. (2015)[70] was a prospective case-series. A few of the included studies were multicentre RCTs, which evaluated the efficacy and safety of different treatments and their impact on HRQOL in patients with HS (Armstrong et al., 2015[87]; Armstrong et al., 2014[84]; Grant et al., 2010[73]; Kimball et al., 2012[31]; Miller et al., 2011[77]). All studies were conducted during the last 15 years.

Table 45: Characteristics of the included HRQOL and utility studies

Study name	Setting/country	Objective	Study design	Duration/period
Alavi *et al.* 2015	Multicentre/Canada	To identify QOL impairment in HS patients and the aspects that are most affected, and to assess the correlation between disease severity and QOL impairment	Prospective case series of 55 patients	
Amano *et al*. (2010) (NCT00827996)	Single-centre/United States	To evaluate the safety and efficacy of ADA for the management of HS	Prospective, open-label, phase II, interventional study	February to November 2007; 12-week study; patients followed up to 13 weeks
Armstrong *et al.* (2014) (PIONEER I)	Multicentre International/ United Sates, Australia, Canada, Czech Republic, Germany, Hungary	To evaluate the safety and efficacy of ADA versus placebo in patients with moderate to severe HS	12-week, double-blind, randomised, placebo-controlled phase followed by a 24-week double-blind treatment phase	36 weeks
Armstrong *et al.* (2015) (PIONEER II)	Multicentre International/ United States, Canada, Australia, Denmark, France, Greece, Netherlands, Puerto Rico, Sweden, Switzerland, Turkey	To assess whether ADA improves HRQOL and TS-M in patients with moderate to severe HS	Multicentre, randomised, double-blind, placebo-controlled trial	12 weeks
Blanco *et al.* (2009)	Single-centre/Spain	To evaluate the long term efficacy and safety of ADA therapy in six patients with refractory HS	Findings from six patients treated with ADA for refractory HS were reviewed	Mean (SD) follow-up: 21.5 (7.1) months; but was longer than 2 years in 3 patients
Blok *et al.* (2015)	Single-centre/The Netherlands	To investigate characteristics, surgical outcomes and patient satisfaction of HS patients who underwent deroofing or STEEP under general anaesthesia	Clinical records-based retrospective analysis conducted for all patients who had surgery under general anaesthesia between 1999 and 2013	From May 1999 and January 2013
Cusack and Buckley (2006)	Single-centre/Ireland	To determine the efficacy of subcutaneous ETA, a competitive	Cohort study which included 6 patients with severe,	9 months from November 2003

		inhibitor of TNF-α in the control of HS symptoms	treatment-resistant HS	
Delage *et al.* (2011)	Single-centre/France	To evaluate the efficacy and safety of INF in seven patients with moderate to severe HS resistant to local and systemic treatments	Retrospective open study of all consecutive patients treated with INF for moderate to severe HS at a dermatology department in France	Between 2006 and 2009; mean follow up: 72 weeks
Fardet *et al.* (2007)	Single-centre/France	To evaluate the safety and efficacy of INF in a series of patients with severe HS	Files of all patients with severe HS, treated with INF in a department in France between October 2004 and December 2005 were reviewed	Between October 2004 and December 2005
Grant *et al.* (2010)	United States	To assess the efficacy and safety of INF for the treatment of moderate to severe HS	Prospective double-blind treatment phase of 8 weeks (patients received INF or placebo), followed by an open label phase where placebo patients were given the opportunity to cross over to INF, and an observational phase	
Kimball *et al.* (2012) (NCT00918255)	Multicentre International/ United States, Denmark, the Netherlands and Germany	To evaluate the efficacy and safety of ADA, an anti–TNF-antibody, in patients with moderate to severe HS	Parallel-group, randomised, placebo controlled trial consisting of a 16-week double-blind and a 36-week open label period	Between April 2009 and November 2010
Lee *et al.* (2009) (NCT00107991)	Single-centre/United States	To evaluate the safety and efficacy of ETA for patients with severe HS	Prospective, Phase II, single-arm, single-dose, non-controlled, open label, modified	18 weeks

			Simon's two stage clinical trial	
Lesage *et al.* (2012)	Single-centre/France	To prospectively evaluate the efficacy and tolerance of prolonged infliximab treatment of moderate to severe HS	Prospective, monocentric, open, interventional study	April 2009 to August 2011
Martin-Ezquerra *et al.* (2015)	Multicentre/Spain	To review the recent use of biologics in patients with HS	Retrospective chart review of HS patients treated with biologics	November 2011 to December 2012
Matusiak *et al.* (2010)	Poland	To determine the influence of HS on a broad spectrum of psychophysical factors	Assessed the influence of HS on psychological factors using several questionnaires	-
Mekkes and Bos (2008)	Single-centre/Netherlands	To evaluate the long-term efficacy of a single course of INF in patients with severe HS	Observational study assessing the long-term efficacy of a single-course of INF in 10 severe HS patients who were followed for at least 1 year	Between 2004 and 2005
Miller *et al.* (2011)	Multicentre/Denmark	To evaluate the efficacy of ADA in HS	Prospective, randomised, double-blind, placebo-controlled two-centre clinical trial	2007–July 2010; 12-week treatment period followed by 12-week observational period
Van Rappard *et al.* (2012)	Single-centre/Netherlands	To compare the efficacy and safety of INF and ADA in the treatment of HS	Retrospective study comparing two cohorts (one treated with INF and other with ADA) of 10 patients suffering from severe, recalcitrant HS	Between 2005 and 2009
Wollina *et al.* (2012)	Single-centre/Germany	To evaluate the role of surgery in the treatment of severe anogenital HS	Retrospective analysis of patients with anogenital HS treated in an academic teaching hospital	Between 2000 and 2010; mean (SD) follow-up: 56.9 (41.3) months

Wormald *et al.* (2014)	Single-centre/UK	To compare the split skin graft (SSG) and Thoracodorsal Artery Perforator (TDAP) techniques for the management of extensive axillary HS in terms of operative and psychosocial outcomes	Prospective observational study of 27 patients with Hurley's stage III HS of the axilla who underwent surgical excision with reconstruction using either SSG or TDAP flap	September 2008 to September 2012
Key: ADA, Adalimumab; ETA, etanercept; HRQOL, health-related quality of life; HS, hidradenitis suppurativa; INF, infliximab;; QOL, quality of life; SD, standard deviation; SSG, split-skin graft; STEEP, skin-tissue-saving excision with electrosurgical peeling; TDAP, thoracodorsal artery perforator; TNF, tumour necrosis factor; TS-M, treatment satisfaction with medication; UK, United Kingdom.				

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Table 46: Relevant outcomes reported in HRQOL and utility studies

Study name	Population (sample size)	Baseline/population values	Treatment arms	HRQOL data	Utility data
Alavi *et al.* 2015	HS patients with Hurley stage I (n=10), II (n=29), and III (n=16)	Mean age: 39 years (range 21–69)	-	**DLQI score** Hurley stage II[a] =8.3 (7.9) Hurley stage III[b]=17.6 (8.0) **SF-36v2 health domains** **PCS:** Hurley stage II[a]: 47 (11.3); Hurley stage III[b]: 40[c] (9.4) **MCS:** Hurley stage II[a]: 49 (9.8); Hurley stage III[b]: 41[c] (12.0) **PF:** Hurley stage II[a]: 48 (11.3); Hurley stage III[b]: 42[c] (12.5) **RP:** Hurley stage II[a]: 48 (12.4)**;** Hurley stage III[b]: 39[c] (12.9) **BP:** Hurley stage II[a]: 47 (10.8)**;** Hurley stage III[b]: 37[c] (12.3) **GH:** Hurley stage II[a]: 48 (12.5)**;** Hurley stage III[b]: 40[c] (10.1) **VT:** Hurley stage II[a]: 49 (12.7)**;** Hurley stage III[b]: 44[c] (9.5) **SF:** Hurley stage II[a]: 44[c] (12.9); Hurley stage III[b]: 36[c] (14.4) **RE:** Hurley stage II[a]: 48 (11.5); Hurley stage III[b]: 39[c] (16.9) **MH:** Hurley stage II[a]: 51 (7.9); Hurley stage III[b]: 43[c] (10.9)	-
Amano *et al*. (2010) (NCT00827996)	Patients with moderate to severe HS as defined by HSSI ≥8; N=10	Age range: 18-52 years Median HSSI score: 17.0 Median VAS score: 60.0 Median DLQI score: 13.0	ADA SC (160mg at Week 0, 80mg at Week 1 and 40mg EOW thereafter until Week 12)	**Median VAS scores for pain:** At Week 2: 20.0 (p=0.17); At Week 4: 20.0 (p=0.42); At Week 8: 30.0 (p=0.29); At Week 12: 57.5 (p=0.55) **Median DLQI score** At Week 2: 7.0 (p=0.03); At Week 4: 12.0 (p=0.57); At Week 8: 7.0 (p=0.37); At Week 12: 12.0 (p=0.65)	

Armstrong *et al.* (2014) (PIONEER I)	Patients with moderate to severe HS	At BL, patients had a diagnosis of HS for 1 year, a total abscess and inflammatory nodule count 3, HS lesions in 2 body areas, Hurley stage II or III, and were anti-TNF–naïve. At BL the disease burden of HS had a large impact on the HRQOL scores (mean DLQI >15, and all SF-36 domains under 44)	ADA (160mg at Week 0, 80 mg at Week 2; 40 mg EW from Week 4) Placebo	**<u>At the end of 12 weeks:</u>** **ADA:** Mean improvement in DLQI=5.4 HS related skin pain reduced by=19.6% Mean improvement in PCS on SF-36=4.2 Mean improvement in Role physical on SF-36=4.5 Mean improvement in Body pain on SF-36=4.9 Mean improvement in General health on SF-36=3.0 TSQM-global satisfaction=56.5 TSQM-effectiveness=51.3 TSQM-side effects=91.9 Improvement from BL in TSQM-effectiveness=19.8 Improvement from BL in TSQM-GS=17 **Placebo:** Mean improvement in DLQI=2.9 (p<0.001) HS related skin pain reduced by=6.5% (p=0.016) Mean improvement in PCS on SF-36=1.5 (p=0.005) Mean improvement in role physical on SF-36=2.2 (p=0.039) Mean improvement in body pain on SF-36=2.4 (p=0.018) Mean improvement in general health on SF-36=-0.4 (p<0.002) TSQM-global satisfaction=46.9 (p=0.004) TSQM-effectiveness=39.7 (p<0.001) TSQM-side effects=93.3 (p=0.55) Improvement from BL in TSQM-effectiveness=8.5 (p=0.001) Improvement from BL in TSQM-GS=8.4 (p=0.009)	

Armstrong *et al.* (2015) (PIONEER II)	Moderate to severe HS patients; N=not reported	Mean (SD) EQ-5D index score: 0.5 (0.35) Mean (SD) DLQI: 14.5 (7.49) Mean (SD) VAS: 58.7 (23.25)	ADA (160mg at Week 0; 80 mg at Week 2; 40 mg at Week 4; 40 mg EW thereafter) Placebo	**ADA** **Mean (SD) improvements at Week 12 in:** DLQI: 5.1 (0.53) VAS: 9.2 (1.88) TSQM-effectiveness: 26.0 TSQM-global satisfaction: 22.7 **TSQM-global satisfaction scores at Week 12:** 61.5 **TSQM-satisfaction of effectiveness scores at Week 12:** 56.8 **TSQM-satisfaction in side effects scores at Week 12:** 95.1 **Placebo** **Mean (SD) improvements at Week 12 in:** DLQI: 2.3 (0.53); p<0.001 VAS: 0.5 (1.87); p<0.001 TSQM-effectiveness: 12.0; p<0.001 TSQM-global satisfaction: 8.6; p<0.001 **TSQM-global satisfaction scores at Week 12:** 47.5; p<0.001 **TSQM-satisfaction of effectiveness scores at Week 12:** 43.1; p<0.001 **TSQM-satisfaction in side effects scores at Week 12:** 90.6; p=0.065	**ADA** Mean (SD) improvements at Week 12 in EQ-5D^m index score: 0.1 (0.02) **Placebo** Mean (SD) improvements at Week 12 in EQ-5D^m index score: 0 (0.02); p<0.001
Blanco *et al.* (2009)	Patients with severe HS; N=6	Men, n=2; Women, n=4 Mean (SD) [range] age: 39.3 (12.9) [22-56] years Mean (SD) [range] disease duration, 22.5 (11.7) [22-56] years Mean (SD) DLQI	ADA (40 mg SC); initially 40 mg EOW, in case of relapse or inadequately controlled disease: 40 mg/week	Compared with baseline DLQI decreased at 1 month and 1 year (p=0.03 for both)	

		score: 23.7 (5.9)			
Blok *et al.* (2015)	HS patients who underwent deroofing or the STEEP procedure under general anaesthesia; N=113	Men, n=36; women, n=77 Hurley stage I: 11.5% Hurley stage II: 77.9% Hurley stage III: 10.6%	Surgery	**Median satisfaction scores for medical effects of surgery[k]:** 8.0 of 10 **Median satisfaction scores for cosmetic effects of surgery[k]:** 6.0 of 10 **Complication of pain for >4 weeks:** occurred in 5 (1%) cases of all operations **Complication of nerve irritation:** occurred in 5 (1%) cases of all operations 76% responder patients[k] rated surgery under general anaesthesia as the best treatment for HS	
Cusack and Buckley (2006)	Patients with severe (Hurley stage ≥2) chronic HS unresponsive to ≥2 conventional treatments; N=6	Women, n=6 Mean age: 32.3 (range 16–42) years Mean disease duration: 5.7 (range 4–11) years	ETA initiated at 25 mg SC twice-daily	**Mean % decrease in self-reported DLQI:** 64% (range: 44-73%) **Mean DLQI reduction (n=5):** 11.6	
Delage *et al.* (2011)	Patients with moderate to severe HS (Hurley stage II-III); N=7	Men: n=3; Women: n=4 Mean age: 37 years Mean disease duration: 12 years Hurley stage II: n=6 Hurley stage III: n=1 Before INF treatment median (range) DLQI score: 18 (10–19)	INF (patients received a median (range) of 6 (3–19) perfusions of INF 5mg/kg, at Weeks 0, 2, and 6 and then every 8 weeks)	**After INF treatment:** Median (range) DLQI score: 8 (0–18) Improvement in DLQI (n/N): 6/7 Global improvement without aggravation (n/N): 6/7 Median change for global improvement: 70% Median change for pain: 70% Median change for seepage: 70%	
Fardet *et al.* (2007)	Patients with severe HS who were	**Mean (SD) Sartorius score**: 82 (30)	INF (5mg/kg); patients	**Mean (SD) Skindex-29[i] Score**: **At Week 6** (evaluable n=7)	

	resistant to usual medical therapies and reluctant to undergo surgery; N=7	**Mean (SD) Skindex-29[i] Score**: Emotion: 25 (9) Symptoms: 13 (5) Function: 28 (12)	received at least 3 infusions (Weeks 0, 2, and 6). Five received a 4th infusion in Week 10	Emotion: 21 (13) Symptoms: 10 (5) Function: 19 (13) **At Week 10** (evaluable n=5) Emotion: 22 (8) Symptoms: 12 (8) Function: 22 (12)	
Grant *et al.* (2010)	Patients with moderate to severe HS as defined by a HSSI score of > 8; N=38	**INF** Age, mean (SD): 34.0 (13.44) years n (%) male: 3 (20.0) HSSI, mean (SD): 16 (2.07) DLQI, mean (SD): 17.2 (8.06) VAS, mean (SD): 53.3 (25.96) **Placebo** Age, mean (SD): 33.2 (11.42) years n (%) male: 9 (39.1) HSSI, mean (SD): 14.8 (2.43) DLQ, mean (SD): 16.5 (7.07) VAS, mean (SD): 48.8 (29.53)	INF (5mg/kg) on Weeks 0, 2 and 6 (n=15) Placebo on Weeks 0, 2 and 6 (n=23)	At Week 8: **INF:** Mean DLQI change from BL: 10.0 Mean VAS (pain) change from BL: 39.8 **Placebo:** Mean DLQI change from BL: 1.6; p=0.003 Mean VAS (pain) change from BL: 0.6; p<0.001	
Kimball *et al.* (2012) (NCT00918255)	Moderate to severe HS based on HS-PGA score of moderate or worse in at least 2 distinct anatomical areas and	**Hurley stage I/II, n (%):** Placebo: 36 (70.6) ADA EOW: 37 (71.2) ADA EW: 36 (70.6)	Placebo (n=51) ADA 40mg/EOW* (n=52) ADA	**Mean reduction (improvement) from baseline at Week 16 in** DLQI Placebo: 2.3 ADA EOW: 3.2	

	were unresponsive/intolerant to oral antibiotics; N=154	**Hurley stage 3, n (%)**: Placebo: 15 (29.4) ADA EOW: 15 (28.8) ADA EW: 15 (29.4) **HS-PGA score of moderate, n (%):** Placebo: 33 (64.7) ADA EOW: 35 (67.3) ADA EW: 35 (68.6) **HS-PGA score of severe/very severe, n (%):** Placebo: 17 (33.3) ADA EOW: 16 (30.8) ADA EW: 16 (31.4) **Mean (SD) DLQI score:** Placebo: 15.4 (7.7) ADA EOW: 13.5 (7.7) ADA EW: 16.4 (7.5) **Mean (SD) PHQ-9 score:** Placebo: 9.1 (6.8) ADA EOW: 8.1 (6.1) ADA EW: 11.1 (7.0) **Patients with VAS pain score of ≥10 mm**[d] Placebo: 94.1% ADA EOW: 90.4% ADA EW: 94.1%	40mg/week (n=51)	ADA EW: 6.3 (p value versus placebo=0.001) PHQ-9 depression measure Placebo: 0.9 ADA EOW: 1.3 ADA EW: 3.7 (p-value versus placebo=0.015) **Patients with at least 30% and 10mm reduction in VAS pain score at Week 16** Placebo: 27.1%; p=0.037 ADA EW: 47.9%	
Lee *et al.*	Patients with severe	Men, 2; women 13	ETA 50mg SC	**At 12 weeks of treatment:**	

(2009) (NCT00107991)	HS (Hurley stage II or III disease); N=15	Mean (median) age: 42 (45) Mean (median) duration of disease: 15.46 (12) Mean (median) patients' self- reported pain scores on 10cm VAS: 6.19 (6.4) Mean (median) DLQI: 20.4 (19)	once a week for 12 weeks	Median patients' self-reported pain scores on 10cm VAS: 4.1 (p=0.08) Median DLQI: 15 (p=0.02)	
Lesage *et al.* (2012)	Patients with progressive, moderate to severe HS (with Hurley stage≥2) ineligible for surgery, or who relapsed after surgery; N=10	Men, n=5; Women, n=5 Median (range) age: 24-34 years Hurley stage II, n=6; Hurley stage III, n=4 Mean (range) initial DLQI: 20/30 (9-30)	INF infusions (5mg/kg) at weeks 0, 2 and 6, and then every 4 weeks as maintenance	**Mean (range) DLQI** after 12 months of INF therapy: 6/30 (1-13) (p<0.001)	
Martin-Ezquerra *et al.* (2015)	Patients diagnosed of HS treated with at least one biologic; (N=19) [Hurley stage II, n=8 and stage III, n=11]	Male, n=10; Women, n=9 Hurley stage II, n=8; stage III, n=11 Average (SD) age at diagnosis: 24 (8.8) years	Pre-treatment with first-line biologics (ADA, INF, ustekinumab and ETA) Post-treatment with first-line biologics (ADA, INF, ustekinumab and ETA)	**Prior to biologics treatment (N=19):** Average VAS pain score=7.3 points **Post first-line biologics treatment (N=15):** Average (SD) reduction in VAS pain score=3.27 (2.76)	
Matusiak *et al.* (2010)	Polish patients with active, but stable, course of HS; N=54	Men, n=26; Women, n=28 Mean (SD) age: 39.94	-	**Mean DLQI** Hurley stage II: 13.10 ± 6.41 Hurley stage III: 20.40 ± 6.67 (p<0.001)	**EQ-5D^n** Hurley stage I: 0.80 ± 0.15

		(11.63) years Mean (SD) disease duration: 10.16 (7.64) [1.5-36] years Hurley stage I, n (%)=13 (24.1) Hurley stage II, n (%)=29 (53.7) Hurley stage III, n (%)=12 (22.2)		**BDI-SF** Hurley stage II: 5.38 ± 3.65 Hurley stage III: 10.90 ± 5.99 (p<0.01) **6-item scale: Lu et al.** Hurley stage II: 4.52 ± 3.68 Hurley stage III: 5.40 ± 3.98 (p<0.01) **EQ-5D VAS** Hurley stage II: 59.93 ± 14.66 Hurley stage III: 40.50 ± 23.03 (p<0.01) **FACIT-F** Hurley stage II: 34.21 ± 9.43 Hurley stage III: 20.30 ± 10.47 (p<0.01) **Q-LES-Q-SF** Hurley stage II: 59.83 ± 12.33 Hurley stage III: 41.50 ± 17.87 (p<0.01)	Hurley stage II: 0.70 ± 0.10 Hurley stage III: 0.35 ± 0.33 (p<0.01)
Mekkes and Bos (2008)	Patients with severe HS, unresponsive to standard Treatment; N=10	Men, n=4; Women, n=6 Mean age: 41 years Mean disease duration: 18.5 years Mean (SD) DLQI before treatment: 18.4 (7.9)	INF (three infusions of 5mg/kg at Weeks 0, 2 and 6)	**Mean DLQI** after 1 year treatment: 9.3 (9.1); p=0.007 **Patients' evaluation scores**[i] for effectiveness of INF: At 1 month: 7.5 After 1 year: 7.9	
Miller *et al.* (2011)	Patients with moderate to severe HS defined as Hurley stage II or III for at least 6 months; N=21	**ADA (n=15)** Women, n=12 Age[h]=38.7 (30.9-46.4) years DLQI[h]=16.07 (12.13–20.00) VAS pain[h]=58.00 (40.63–75.37) Sartorius score[h]=45.20	**ADA** 80mg SC at week 0 followed by 40mg EOW for 12 weeks (n=15) **Placebo** (n=6)	**At Week 24** **ADA** VAS pain[h]= 57.33 (39.63–75.04) DLQI[h]=16.60 (12.50–20.70) Change from BL in DLQI[h]: 0.53 (-4.66–5.73) **Placebo** VAS pain[h]=34.00 (7.63–60.37) [p = 1.0] DLQI[h]=9.00 (3.61–14.39) [p = 0.88]	

		(29.97–60.43) Hurley score[h]=2.33 (2.06–2.60) **Placebo (n=6)** Women, n=5 Age[h]=40.2 (25.8-54.5) years DLQI[h]=8.33 (4.66–12.01) VAS pain[h]=36.17 (5.97–66.37) Sartorius score[h]=32.83 (15.97–49.70) Hurley score[h]=2.33 (1.79–2.88)		Change from BL in DLQI[h]: 0.67 (-2.56–3.90)	
Van Rappard *et al.* (2012)	Severe recalcitrant HS; N=19 (20 patients were enrolled; 10 in each cohort at different time points; one patient was considered as drop-out due to psychological problems in the ADA group)	**INF (n=10; 6 females, 4 males) before treatment** Average age = 41 Average disease duration = 18.5 years Mean (SD) DLQI score = 18.4 (7.9) **ADA (n=9; 1 female, 8 males) before treatment** Average age = 48 Average disease duration = 19 years Mean (SD) DLQI score = 13.3 (7.1)	INF IV (3 infusions of 5mg/kg at Weeks 0, 2, and 6) ADA SC 40mg EOW	**INF (n=10) after 1 year of treatment** Mean (SD) DLQI score= 9.3 (9.1) (p=0.007) Patient judgement of effectiveness[e] = 7.9 (2)[f] **ADA (n=9) after 1 year of treatment** Mean (SD) DLQI score = 11.7 (9.9) (p=0.66) Patient judgement of effectiveness[e] = 5.1 (2.8)[f]	
Wollina *et al.* (2012)	Patients with HS with Hurley stage 3, with diffuse involvement,	Men, n=36; women, n=31	Surgery	VAS pain scores, at Week 10 to 12 after surgery, mean (SD)=0.8 (0.7)	

	multiple strands, and abscesses; N=67	Age, mean (SD), [range] =38.6 (11.7), [20-68] years Disease duration, mean (SD), [range]=5.6 (3.9), [3-12] years VAS-pain scores, mean (SD)=6.3 (1.5)			
Wormald *et al.* (2014)	Patients with Hurley's stage 3 HS of the axilla; N=27	Mean (SD) age of all patients (n=27): 34.7 (6.9) years Men, n=8; Women, n=19 DLQI range for all 27 patients: 21-31 **TDAP Group (n=15)** DLQI pre-op., Mean (SD)= 27.9 (2.9); p=0.87 VAS pre-op., Mean (SD)= 7.7 (1.4); p=0.93 **SSG Group (n=12)** DLQI pre-op., Mean (SD)=27.7 (3.1); p=0.87 VAS pre-op., Mean (SD)=7.7 (1.5); p=0.93	TDAP reconstruction (n=15) SSG reconstruction (n=12)	**TDAP Group (n=15)** DLQI post-op., Mean (SD)= 4.7 (1.9) DLQI reduction., Mean (SD) 23.1 (4.24) VAS post-op., Mean (SD) =2.7 (1.9) VAS reduction., Mean (SD)= 5.0 (2.2) **SSG Group (n=12)** DLQI post-op., Mean (SD)= 8.4 (3.8); p<0.005 DLQI reduction., Mean (SD)=19.3 (3.9); p=0.02 VAS post-op., Mean (SD) =3.8 (1.5); p=0.15 VAS reduction-Mean (SD)= 3.9 (1.6); p=0.17	
Key: ADA, adalimumab; BP, bodily pain; cm, centimetre; DLQI, Dermatology Life Quality Index; EOW, every other week; GH, general health; HRQOL, health-related quality of life; HS, hidradenitis suppurativa; HSSI, hidradenitis suppurativa severity index; IV, intravenous; MCS, mental component summary; mg, milligram; MH, mental health; mm, millimetre; n, number; PCS, physical component summary; PF, physical functioning; PGA, physician global assessment; PHQ-9, patient health questionnaire-9; RE, role emotional; RP, role physical; SC, subcutaneous; SD, standard deviation; SF, social functioning; SF-36v2, Short Form 36 Version 2; SSG, split-skin graft; STEEP, skin-tissue-saving excision with electrosurgical peeling; TDAP, thoracodorsal artery perforator; TSQM, Treatment Satisfaction Questionnaire For Medication; TSQM-GS, Treatment Satisfaction Questionnaire For Medication-Global Satisfaction; VAS,					

visual analogue scale; VT, vitality.

Notes: [a], n = 29; [b], n=16; [c], these scores were significantly lower than normal (p≤0.05); [d], proportion of patients with a clinically relevant improvement in pain (at least 30% reduction and 10-mm reduction) at Week 16 was significantly higher for patients in the EW group (47.9%) than in the placebo group (27.1%) (difference, 20.4% [CI, 1.2% to 39.7%], p=0.037); [e], patients were asked to give an overall judgment of the effectiveness of infliximab after 1 year, on a 10-point scale (1 = no improvement to 10 = excellent result); [f], mean (SD) score for patients' overall judgment of the effectiveness of treatment on a 10-point scale reported; [g], results represent a significant reduction in both groups and correlate with a reduction to 54% of baseline for the INF group and 66% of baseline for the ADA group; [h], mean (95% confidence interval) reported; [I], patients rated the efficacy of infliximab on a 10-point scale; [J], Skindex-29 France;.[k], based on response of 66 of 105 patients to whom the questionnaire was sent; [l], self-evaluation of improvement or aggravation (percentage of improvement globally, in pain and in seeping on a VAS, scores range from 0 to 100 mm); [m], method of elicitation and valuation of EQ-5D scores was not clearly reported; [n], for EQ-5D, a utility score was assigned to each health state using the York A1 tariff. Additionally, it was supplemented by EQ-VAS.

A total of 20 studies reported data for HRQOL outcomes and utilities associated with moderate to severe HS patients and their treatments.

Two of the included studies reported utility values (Armstrong et al., 2015[87] and Matusiak et al., 2010[25]). In Matusiak et al. (2010), health index was assessed as EQ-5D scores, which was supplemented by a VAS (EQ-VAS; 0–100 scale) on which patients' assessment of their overall health status on that day was recorded. Patients with higher disease severity had lower health index (mean [SD] EQ-5D values were 0.70 [0.10] and 0.35 [0.33] for Hurley stage II and III HS patients, respectively) which correlated with the EQ-VAS scores for these patients (mean (SD): 59.93 [14.66] for Stage II and 40.50 [23.03] for Stage III patients). The EQ-5D results observed in this study are very low and are usually observed in cases of very severe diseases such as cancer (Eastern Cooperative Oncology Group, performance status 2 patients), bronchial asthma or chronic obstructive pulmonary disease (the Global Initiative for Chronic Obstructive Lung Disease=3 patients) and cerebral stroke patients[112-114]. In PIONEER II (Armstrong et al., 2015)[87], the mean improvements in EQ-5D index scores at Week 12 were significantly higher with ADA versus placebo ($p<0.001$).

DLQI was the most commonly reported outcome in all studies included for HRQOL and utility review (reported in 17 studies). DLQI was reported for patients with Hurley stage II or III HS in two studies (Alavi et al., 2015[70] and Matusiak et al., 2010[25]) to assess the impact of disease on HRQOL. The mean DLQI scores for patients with Hurley stage III HS was higher than that for patients with Hurley stage II HS suggesting increased impairment in HRQOL in patients with increased disease severity. Other studies reported DLQI scores or change from baseline in DLQI scores for moderate to severe HS patients treated with either TDAP, SSG, ADA, placebo, infliximab or etanercept to evaluate the effect of these interventions on dermatology specific HRQOL. The mean reduction in DLQI was significantly higher with TDAP than SSG (23.1 versus 19.3; $p=0.02$) (Wormald et al., 2014)[109]. Seven studies reported a mean reduction from baseline in DLQI scores or mean DLQI scores for ADA treated moderate to severe HS patients (Amano et al., 2010[110]; Armstrong et al., 2015 [PIONEER II][87]; Armstrong et al., 2014 [PIONEER I][84]; Blanco et al., 2009[101]; Kimball et al., 2012[31]; Miller et al., 2011[77]; Van Rappard et al., 2012[107]). The mean reduction in DLQI scores from baseline was significantly higher

with ADA 40 mg/week than with placebo (p≤0.001) in three studies (Armstrong et al., 2014 [PIONEER I][84]; Armstrong et al., 2015 [PIONEER II][87]; Kimball et al., 2012[31]). However, there was no such significant reduction (improvement) observed with ADA 40 mg EOW regimen (Kimball et al., 2012)[31]. With ADA 40 mg EOW, the mean reduction in DLQI varied between 0.53 and 12.0 among three studies (Amano et al., 2010[110]; Kimball et al., 2012[31]; Miller et al., 2011[77]). A total of five studies reported the same outcome for infliximab treated moderate to severe HS patients (Delage et al., 2011[104]; Grant et al., 2010[73]; Lesage et al., 2012[111]; Mekkes and Bos, 2008[106]; Van Rappard et al., 2012[107]). Three studies (Lesage et al., 2012[111]; Mekkes and Bos, 2008[106]; Van Rappard et al., 2012[107]) reported significantly lower mean DLQI scores after 1 year of infliximab treatment than that before treatment. In Van Rappard et al. (2012)[107], the mean DLQI score after 1 year of treatment also decreased in patients receiving ADA 40 mg EOW treatment but the effect was not significantly different than that before treatment. In this study, patient-rated effectiveness of treatment was higher for infliximab than ADA. Grant et al. (2010)[73] reported mean DLQI change from baseline, which was significantly higher with infliximab than placebo (p=0.003). One study reported mean reduction in self-reported DLQI scores for etanercept treated patients as 11.6 (this was not compared with pre-treatment values and statistical significance was not reported) (Cusack and Buckley, 2006)[103]. Another study (Lee et al., 2009)[75] reported median DLQI score of 15 at 12 weeks after treatment with etanercept.

In Wormald et al. (2014)[109], the DLQI scores, relating to the effect on the patient's life, were classified as follows: 0-1 = disease has no effect, 2-5 = disease has limited effect, 6-10 = disease has a moderate effect, 11-20 = disease has a significant effect, 21-30 = disease has a very significant effect. In the TDAP group, five patients reported improvements to a 'moderate effect on QOL' (6-10) and nine patients reported improvements to a 'small effect on QOL' (2-5). For the SSG group, one patient reported a 'very large effect on QOL' (11-20), ten patients reported a 'moderate effect on QOL' (6-10) and one patient reported a 'small effect on QOL' (2-5).

Pain was assessed on VAS (scores ranging from 0 to 100 mm) in eight studies (Amano et al., 2010[110]; Delage et al., 2011[104]; Grant et al., 2010[73]; Kimball et al.,

2012[31]; Lee et al. 2009[75]; Martin-Ezquerra et al., 2015[105]; Miller et al., 2011[77]; Wollina et al., 2012[108]). In Kimball et al. (2012)[31], the proportion of patients with at least 30% and 10 mm reduction in pain intensity at Week 16 from baseline was significantly higher with ADA (40 mg EW) than placebo (p=0.037). In Lee et al. (2009)[75], the median patients' self-reported pain scores decreased from 6.29 at baseline to 4.1 after 12 weeks of etanercept therapy on a 10 cm VAS. Similar decrease was observed in Martin-Ezquerra et al. (2015)[105] after first-line biologics treatment (ADA, infliximab, ustekinumab and etanercept). In Grant et al. (2010)[73], mean change from baseline in VAS score was significantly higher with infliximab therapy compared to placebo therapy (39.8 versus 0.6; p<0.001). In Wormald et al. (2014)[109], pain and discomfort was assessed on a VAS of 0–10 where 0 indicated no discomfort/pain and 10 indicated worst possible discomfort/pain). The mean reduction in VAS score after surgery was similar between TDAP and SSG group (5.0 versus 3.9; p=0.17). In Matusiak et al. (2010)[25], patient rated their overall health status on a 0–100 VAS scale (0 indicated worst and 100 indicated best imaginable health state). In PIONEER II (Armstrong et al., 2015)[87], VAS (0-100 scale) was used but the parameter, which was rated on VAS, was not clearly reported. In this study, the mean improvement in VAS score at the end of 12-week, double-blind period was significantly greater with ADA 40 mg EW than placebo (9.2 versus 0.5; p<0.001).

Alavi et al. (2015)[70] and PIONEER I (Armstrong et al., 2014)[84] reported summary scores for different health domains of SF-36 version 2 (SF-36v2) for patients with Hurley stage II and III HS. In Kimball et al. (2012)[31], PHQ-9 was used to assess patients' self-reported depression scores between 0 and 27 where 0 indicated no depressive symptoms. The mean decrease from baseline in PHQ-9 scores at Week 16 was significantly higher in ADA 40 mg EW group compared to the placebo group 3.7 versus 0.9; p=0.015. In Van Rappard et al. (2012)[107], the patients' rated effectiveness of treatment was higher for infliximab than ADA 40 mg EOW (7.9 vs 5.1). In Matusiak et al. (2010)[25], Beck Depression Inventory-Short Form (BDI-SF; questionnaire comprised 13 items [score ranges 0-39]), Lu et al. "6-Item Scale" (to assess stigmatisation level [score range 0–18]), Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-F; 13-item questionnaire [score ranges 0-52]) and Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-

LES-Q-SF; 16-item instrument where scores reported as percentage of maximum possible) were used to evaluate a wide spectrum of psychosocial aspects of HS patients. These results highlight the important impact of HS on a wide spectrum of psychophysical aspects and impairment of related QOL among HS patients.

In both PIONEER I (Armstrong et al., 2014)[84] and PIONEER II (Armstrong et al., 2015)[87] the TSQM was used to assess patient satisfaction for treatment. TSQM has 14 items across four domains: effectiveness, side effects, convenience and global satisfaction. The mean scores and mean improvement from baseline at Week 12 for TSQM global satisfaction and effectiveness were significantly higher with ADA 40 mg EW than placebo in both PIONEER I and PIONEER II.

5.4.3 Adverse reactions

Disutility due to AEs was captured intrinsically by the QOL instruments administered during the PIONEER clinical trials. Thus, the model did not separately consider disutilities for AEs. Moreover, the types and rates of AEs for the ADA arm were comparable to those of the SC arm (Section 4).

Similarly, the model did not consider disutilities for surgeries due to lack of data. In addition, real-world surgery rates could potentially be lower for patients who had received ADA than for patients receiving SC, given the demonstrated effectiveness of ADA in reducing signs and symptoms of HS. In this case, the exclusion of disutilities for surgery would be expected to provide a conservative estimate of the benefit of ADA in this model.

5.4.4 HRQOL data used in cost-effectiveness analysis

Health utilities were assumed to depend only on model health states and were independent of treatments received. The results of the EQ-5D evaluation from the PIONEER II were used to estimate the health utility associated with each health state. Patients' utility values for each health state were estimated using the week 12 and week 36 data.

The utility values for high response, response, partial response and non-response were 0.782, 0.718, 0.576, and 0.472, respectively (Table 47). The differences in

utility values between health states were statistically significant. Death was assumed to have a utility value of 0. The health state-specific utility value was assigned to a health state when the patients was in that state for a model cycle, and a patient could transition across health states over the model horizon. Each patient's cumulative QALYs were then estimated based on its time spent in each health state and the corresponding utility value.

Table 47: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
High response	0.782 (0.018)	(0.746, 0.816)	Section 5.4.4	Response specific utility values as measured in the PIONEER II pivotal trial
Response	0.718 (0.025)	(0.667, 0.766)		
Partial response	0.576 (0.032)	(0.512, 0.639)		
Non-response	0.472 (0.036)	(0.402, 0.542)		
Death	0.000	N/A		Assumption

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

5.5.1.1 Cost and resource use studies

The methods and selection of studies for the cost and resource use studies have already been described in Section 5.1 since the cost-effectiveness and cost and resource use searches were run together.

Study characteristics

Details of the study design and a brief description of the study objectives for all five studies that reported resource use data are presented in Table 48. Four identified studies investigated surgical outcomes in patients with moderate to severe HS (Alharbi et al., 2012[115]; Blok et al., 2015[102]; Wollina et al., 2012[108]; Wormald et al., 2014[109]). The fifth study investigated the efficacy and safety of ADA in a randomised controlled setting (Armstrong et al., 2015 [PIONEER II][87]). Two of the included studies (Alharbi et al., 2012[115] and Wollina et al., 2012[108]) were conducted at a

single-centre in Germany, one in Netherlands (Blok et al., 2015)[102] and one in the UK (Wormald et al., 2014)[109]. The fifth study was conducted in multiple countries (Armstrong et al., 2015 [PIONEER II])[87].

Table 48: Characteristics of studies included for resource use data

Study name	Setting/country	Objective	Study design	Duration/period
Alharbi *et al.* (2012)	Single-centre/Germany	The option of surgical treatment involving wide surgical excision and methods of reconstruction were studied and reviewed	Retrospective analysis that reviewed 50 surgical procedures for 32 patients with chronic inflammatory moderate to severe HS in five anatomical sites	From 2003 to 2009; patients were followed for a mean period of 24 months after surgery
Blok *et al.* (2015)	Single-centre/the Netherlands	To investigate characteristics, surgical outcomes and patient satisfaction of HS patients who underwent deroofing or STEEP under general anaesthesia	Clinical records-based retrospective analysis conducted for all patients who had surgery under general anaesthesia between 1999 and 2013 (N=113)	From May 1999 and January 2013
Kimball *et al.* (2012)	Multicentre International/ United States, Denmark, the Netherlands, and Germany	To evaluate the efficacy and safety of ADA, an anti–TNF antibody, in patients with moderate to severe HS	Parallel-group, randomised, placebo controlled trial consisting of a 16-week DB and a 36-week OL period	Between April 2009 and November 2010
Wollina *et al.* (2012)	Single-centre/Germany	To evaluate the role of surgery in the treatment of severe anogenital HS	Retrospective analysis of patients with anogenital HS treated in an academic hospital	Between 2000 and 2010; mean (SD) follow-up: 56.9 (41.3) months
Wormald *et al.* (2014)	Single-centre/United Kingdom	To compare the SSG and TDAP techniques for the management of extensive axillary HS in terms of operative and psychosocial outcomes	Prospective observational study of 27 consecutive patients with Hurley's stage 3 HS of the axilla who underwent surgical excision with reconstruction using either SSG (n=12) or TDAP flap (n=15)	From September 2008 to September 2012. Follow-up evaluation was conducted at 3, 6 and 12 months after surgery

Key: ADA, adalimumab; DB, double-blind; HS, hidradenitis suppurativa; OL, open-label; SD, standard deviation; SSG, split-skin graft; STEEP, skin-tissue-saving excision with electrosurgical peeling; TDAP, thoracodorsal artery perforator; TNF, tumour necrosis factor

Cost and resource use outcomes

The resource use data presented in Table 49 were reported in the studies identified as eligible for cost and resource use review. None of the identified studies reported any cost data.

Table 49: Resource use outcomes reported in the identified studies

Study name	Patient population; Sample size	Baseline characteristics	Resource use
Alharbi *et al.* (2012)	Patients with chronic inflammatory moderate to severe HS (Hurley stage II and III); N=32	Men, n=12; Women, n=20 Age at the time of presentation: 17-51 years	Average length of hospital stay = 5 days Recurrence= 6 (18.75%) patients
Blok *et al.* (2015)	HS patients who underwent deroofing or the STEEP procedure under general anaesthesia; N=113	Men, n=36; women, n=77 Hurley stage I: 11.5% Hurley stage II: 77.9% Hurley stage III: 10.6% Mean (range) number of previously visited doctors[a,b]: 2.35 (0-7)	Number of regions operated in all patients (N=113): 482 (primary operations, 363; re-operations, 119) Number of primary operations in patients with Hurley stage II/III=276 Complications[c] occurred in=75 (15.5%) cases of all operations
Kimball *et al.* (2012)	Moderate to severe HS based on HS-PGA score of moderate or worse in at least 2 distinct anatomical areas and were unresponsive/intolerant to oral antibiotics; N=154	**Hurley stage I/II, n (%):** Placebo: 36 (70.6) ADA EOW: 37 (71.2) ADA EW: 36 (70.6) **Hurley stage III, n (%)**: Placebo: 15 (29.4) ADA EOW: 15 (28.8) ADA EW: 15 (29.4) **Mean (SD) TWPI score:** Placebo: 31.4 (34.7) ADA EOW: 35.1 (29.5)	**Mean reductions (improvements) in TWPI scores from baseline to Week 16:** Placebo: 1.1 (increase) ADA EOW: 4.3 ADA EW: 18.4

		ADA EW: 45.5 (32.8)	
Wollina *et al.* (2012)	Patients Hurley stage 3 HS, with diffuse involvement, multiple strands, and abscesses; N=67	Men, n=36; women, n=31 Age, mean (SD), [range] =38.6 (11.7), [20-68] years Disease duration, mean (SD), [range]=5.6 (3.9), [3-12] years VAS-pain scores, mean (SD)=6.3 (1.5)	Mean [SD] length of hospitalisation after surgery: 12.6 [11.2] days; range: 2–63 days
Wormald *et al.* (2014)	Patients with Hurley stage 3 HS; N=27 (SSG, n=12; TDAP, n=15)	Mean, n=8; Women, n=19 Mean (SD) age for all 27 patients: 34.7 (6.9) Mean (SD) age for TDAP group (n=15): 34.1 (8.6) Mean (SD) age for SSG group (n=12): 35.3 (3.9)	**TDAP** Number of surgical procedures, mean (SD)=1.2 (0.4) (p=0.02) Operating time, mean (SD)=196.3 (41.6) min (range 130-360 min) (p<0.005) Hospital stay, mean (SD)=4.7 (2.9) days (p=0.49) Recovery time, mean (SD)=5.4 (2.7) weeks (p=0.03) Follow-up clinic appointments/n=1.6 (0.6) (p<0.005) Rate of recurrence/n, mean=1 (p=0.36) Revision surgery/n, mean=2 (p=0.19) Rate of complications/n, mean=1 (p<0.005) **SSG** Number of surgical procedures, mean (SD)=2.1 (1.3) (p=0.02) Operating time, mean (SD)=79.6 (23.4) min (range 50-120 min) (p<0.005) Hospital stay, mean (SD)=6.7 (10.9) days (p=0.49) Recovery time, mean (SD)=14.1 (17.6) weeks (p=0.03) Follow-up clinic appointments/n=5.2 (1.3) (p<0.005) Rate of recurrence/n, mean= 0 (p=0.36) Revision surgery/n, mean=0 (p=0.19) Rate of complications/n, mean=9 (p<0.005)

Key: ADA, adalimumab; EOW, every other week; HS, hidradenitis suppurativa; SSG, split-skin graft; STEEP, skin-tissue-saving excision with electrosurgical peeling; TDAP, thoracodorsal artery perforator; TWPI, total work productivity impairment.

Notes: [a], Data were missing for 50 patients; [b], before patients were referred to the study centre; [c], complication included nerve irritation, wound infection, bleeding, stricture, pain for >4 weeks, hyper granulation, hypertrophic scar, hyperpigmentation, and delayed wound healing.

None of the identified studies reported any cost data. Four studies evaluated the outcomes associated with surgery in patients with HS. The average length of hospital stay was reported in three studies (Alharbi et al. 2012[115]; Wollina et al., 2012[108]; Wormald et al. 2014[109]). The average length of hospitalisation was reported as 5 days for 32 moderate to severe HS patients who underwent wide surgical excision followed reconstruction (by different methods) by Alharbi et al. (2012)[115]. In this study, the reconstruction technique performed was based on the site and size of the defects including primary closure, skin grafting, local flaps as random or pedicle pattern, regional flaps and the more invasive free (microvascular) tissue transfer in selected patients. Recurrence of disease was observed in six patients; all of them had Hurley stage III disease. However, primary closure and skin grafting were not performed based on expected complications such as contractures and excessive scarring. In Wormald et al. (2014)[109], the mean length of hospital stay was reported for patients with Hurley stage III HS who underwent surgical excision followed by reconstruction using either TDAP (4.7 days; n=15) or SSG (6.7 days; n=12). Although, the operating time was significantly less for patients in SSG group than TDAP group (79.6 min vs. 196.3 min; p<0.005), the mean recovery time (14.1 days vs. 5.4 days; p=0.03) and rate of complications after surgery (9 per patient vs. 1 per patient; p<0.005) was significantly higher for the SSG group than the TDAP group. Length of hospitalisation after surgery was also reported by Wollina et al. (2012)[108] (mean [SD]: 12.6 [11.2] days; range: 2–63 days), which primarily reported HRQOL outcomes for patients with Hurley stage III HS who underwent surgery (n=67).

A total of 482 regions were operated (363 were primary operations and 119 were re-operations) in 113 HS patients who underwent deroofing or the STEEP procedure under general anaesthesia (Blok et al., 2015)[102]. In Blok et al. (2015)[102], before the patients were referred to the study centre, the mean number of doctors visited was 2.35.

In Kimball et al. (2012)[31], total work productivity impairment (TWPI) was assessed using the Work Productivity and Activity Impairment-Specific Health Problem questionnaire (which ranges from 0 to 100, with 0 being no impairment). Mean reductions (improvements) in TWPI scores from baseline to Week 16 were 4.3 and 18.4 for patients in ADA 40 mg EOW and ADA 40 mg EW groups, respectively,

compared with an increase (worsening) of 1.1 in the placebo group (EW versus placebo, p<0.001). The mean (SD) TWPI scores at baseline were 35.1 (29.5), 45.5 (32.8) and 31.4 (34.7) for patients in ADA EOW, ADA EW and placebo groups, respectively.

5.5.2 Intervention and comparators' costs and resource use

The unit cost of ADA was obtained from the British National Formulary as illustrated in Table 50[54]. Drug costs were estimated based on the dosing schedule and unit cost of ADA. In addition, the model considered the compliance rate of ADA, which was based on the observed compliance rate of patients treated with ADA in the PIONEER clinical trials[29 30], weighted by their respective sample sizes. Separate compliance rates were specified for the induction and maintenance periods. Compliance rate of ADA during the induction period was estimated based on all patients treated with ADA in the induction period. Similarly, the compliance rate of ADA during the maintenance period was estimated based on all ADA-treated patients in the maintenance period.

No drug costs were considered for SC. Patients on SC might receive conventional HS therapies, such as antibiotics, for the control of HS symptoms. Patients on ADA could also receive such therapies, and it would be reasonable to assume that patients on ADA would receive these therapies less frequently, given the proven efficacy of ADA for disease control. Therefore, the costs of these conventional HS therapies were likely to be lower for patients on ADA than for patients on SC. The exclusion of costs for these therapies would provide a conservative estimate against ADA.

Table 50: Unit price and compliance rate of ADA

Description	Unit cost (2015)	Compliance rate	Source
ADA price per 40 mg dose	£352.14	Induction period (week 0-12): 98.8%	BNF[54] PIONEER II[30] PIONEER I[29]
		Maintenance period (week 12+): 97.4%	

5.5.3 Health-state unit costs and resource use

5.5.3.1 Resource use rates

The model considered surgery-related resource use and non-surgery related resource use. In particular, the model considered in-patient stays due to HS surgery, out-patient visits due to HS surgery, visits to wound-care due to HS surgery, in-patient stays that were unrelated to HS surgery, non-surgical outpatient visits, visits to wound care not due to HS surgery, and A&E visits (Table 51).

The model assumed that resource use was only dependent on health state, and independent of treatments received. Resource use by health states was estimated based on inputs from a survey of physicians (n=40) who actively treat moderate to severe HS patients in the UK[39]. Physicians were surveyed regarding the frequency of each type of resource use, stratified by health state. The information was collected for patients with moderate and severe HS, separately, and weighted based on the proportions of patients in each disease severity category, as observed in the PIONEER clinical trials[29 30].

Table 51: Resource use rates by health states

Type of visit	Resource use (Average number of units per year)				Source
	High response	Response	Partial response	Non-response	
Number of hospitalisations for HS surgeries	0.13	0.22	0.54	0.80	UK Physician survey[39]
Outpatient visits due to HS surgery	0.22	0.35	0.67	0.94	
Visits to wound-care due to HS surgery (presumed outpatients)	0.12	0.17	0.40	0.85	
Number of hospitalisation non-surgery related	0.11	0.23	0.29	0.45	

Routine outpatient visits	3.10	3.51	4.44	4.68	
Visits to wound-care NOT due to HS surgery (presumed outpatients)	0.67	0.47	0.64	0.45	
A&E visits	0.12	0.20	0.47	0.57	

5.5.3.2 Resource use costs

The unit costs of each type of resource use were obtained from NHS reference costs 2013-2014[116] using settings, codes, descriptions and service as specified in Table 52. When multiple categories were available for a specific resource use, an average cost was estimated.

Table 52: Unit cost of resource use

Resource	Unit cost (Day/visit) (2015)	Source
Inpatient stay due to HS surgery	£ 5,488.32	NHS Reference Costs 2013-2014. Elective inpatient: JC40Z Major Skin Procedures.
Outpatient visits due to HS surgery	£ 97.63	NHS Reference Costs 2013-2014. Outpatient attendance: 330 Dermatology
Visits to wound-care due to HS surgery	£ 97.63	NHS Reference Costs 2013-2014. Outpatient attendance: 330 Dermatology
Non-surgical inpatient visits	£ 2,202.14	NHS Reference Costs 2013-2014. Elective inpatient: Weighted average of JD07D Skin Disorders with Interventions (CC Score 0-3) and JD07K Skin Disorders without Interventions (CC Score 0-1).
Non-surgical outpatient visits	£ 97.63	NHS Reference Costs 2013-2014. Outpatient attendance: 330 Dermatology
Visits to wound-care NOT due to HS surgery (presumed outpatients)	£ 97.63	NHS Reference Costs 2013-2014. Outpatient attendance: 330 Dermatology
Emergency room visits	£ 123.67	NHS Reference Costs 2013-2014. Total HRGs: A&E Services unit cost.

5.5.3.3 Adverse reaction unit costs and resource use

The model considered the most frequently reported (≥ 5%) treatment-emergent AEs. The rates of AEs for patients receiving ADA and SC were based on rates of treatment-emergent mild, moderate and severe AEs observed in the PIONEER clinical trials during the entire induction and maintenance period, respectively[29 30] (Table 53).

Table 53: Annual AE rates for patients receiving ADA or SC

Event	Induction period Annual AE rate		Maintenance period Annual AE rate			Source
	ADA	SC	ADA	SC	After Discontinuation	
Headache	0.486	0.505	[redacted]	[redacted]	[redacted]	PIONEER I PIONEER II [29 30]
Hidradenitis	0.291	0.575	[redacted]	[redacted]	[redacted]	
Nasopharingitis	0.250	0.365	[redacted]	[redacted]	[redacted]	
Upper Respiratory tract infection	0.180	0.182	[redacted]	[redacted]	[redacted]	
Diarrhoea	0.167	0.084	[redacted]	[redacted]	[redacted]	
Gastroenteritis	0.069	0.056	[redacted]	[redacted]	[redacted]	
Influenza	0.069	0.084	[redacted]	[redacted]	[redacted]	
Toothache	0.028	0.028	[redacted]	[redacted]	[redacted]	
Bronchitis	0.028	0.084	[redacted]	[redacted]	[redacted]	
Viral gastroenteritis	0.000	0.028	[redacted]	[redacted]	[redacted]	

The cost of each type of AE was estimated based on the assumed resource use required for the treatment of the AE. The unit costs of each type of resource use were obtained from NHS reference costs 2013-2014[116] (Table 54).

Table 54: Unit cost of resource use associated with AE

AE	Proportion severe	Cost severe	Cost mild/moderate	Source	
				Severe	Mild/moderate
Headache	3%	£674.21	£0.00	NHS Reference costs 2013-2014[116]	Assumed 0
Hidradenitis	11%	£0.00	£0.00	Assumed 0	Assumed 0
Nasopharingitis	1%	£908.28	£0.00	NHS Reference costs 2013-2014[116]	Assumed 0

Upper respiratory tract infection	0%	-	£147.22	N/A	NHS Reference costs 2013-2014[116]
Diarrhoea	0%	-	£46.00	N/A	PSSRU[117]
Gastroenteritis	6%	£1,468.01	£46.00	NHS Reference costs 2013-2014[116]	PSSRU[117]
Influenza	5%	£908.28	£0.00	NHS Reference costs 2013-2014[116]	Assumed 0
Toothache	0%	-	£0.00	N/A	Assumed 0
Bronchitis	0%	-	£147.22	N/A	NHS Reference costs 2013-2014[116]
Viral gastroenteritis	20%	£1,345.99	£46.00	NHS Reference costs 2013-2014[116]	PSSRU[117]

5.5.3.4 Miscellaneous unit costs and resource use

No miscellaneous unit cost or resources were incorporated. This analysis assumes no administration costs associated with the use of ADA as these are covered by the AbbVie care program.

5.6 Summary of base-case de novo analysis inputs and assumptions

6.6.1 Summary of base-case de novo analysis inputs

Table 55 provides a summary of all the variables included in the de novo economic model

Table 55: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Patient characteristics			
Age	35	Not varied in sensitivity analyses	Section 4.5.3
% Female	65.9%		
Transition Probabilities	Appendix 7-12	Dirichlet	Section 5.3.1.3
Utility			
	High response: 0.782	0.746 to 0.816 (Beta)	Section 5.4.4
	Response: 0.718	0.667 to 0.766 (Beta)	
	Partial response: 0.576	0.512 to 0.639 (Beta)	
	Non-response: 0.472	0.402 to 0.542 (Beta)	
	Death: 0.000	NA	
Discontinuation rates of ADA (Annual)			
Week 12-36	All states: 20.48%	0.12 to 0.31 (Beta)	Section 5.3.1.1
After Week 36	High response, response and partial response: 7.47%	0.03 to 0.13 (Beta)	
	Non-response: 44.99%	0.28 to 0.63 (Beta)	
ADA treatment cost	£352.14 per 40 mg dose	Not varied in sensitivity analyses	Section 5.5.2

Compliance rate of ADA				
	Induction: 98.8%		Not varied in sensitivity analyses	Section 5.5.2
	Maintenance: 97.4%		Not varied in sensitivity analyses	
Resource use (unit costs)				
	Cost of hospitalisation for HS surgery: £5,488.32		£3,137.05 to £84,86.39 (Gamma)	Section 5.5.3.2
	Cost of outpatient visits due to HS surgery: £97.63		£55.80 to £150.96 (Gamma)	
	Cost of visits to wound-care due to HS surgery: £97.63		£55.80 to £150.96 (Gamma)	
	Cost of non-surgical inpatient days: £2,202.14		£1,258.71 to£ 3,405.09 (Gamma)	
	Cost of routine outpatient visits: £97.63		£55.80 to £150.96 (Gamma)	
	Cost of visits to wound-care NOT due to HS surgery: £97.63		£55.80 to £150.96 (Gamma)	
	Cost of emergency room visits: £123.67		£70.69 to £191.23 (Gamma)	
Adverse events (unit costs)				
	Headache : £20.03		£11.45 to £30.97 (Gamma)	Section 5.5.3.3
	Hidradenitis: £0.00		£0.00	
	Nasopharingitis: £12.62		£7.21 to £19.51 (Gamma)	
	Upper Respiratory tract infection: £147.22		£84.15 to £227.64 (Gamma)	
	Diarrhoea: £46.00		£26.29 to £71.13 (Gamma)	
	Gastroenteritis: £125.00		£71.45 to £193.28 (Gamma)	
	Influenza : £43.25		£24.72 to £66.88 (Gamma)	
	Toothache : £0.00		£0.00	
	Bronchitis: £147.22		£84.15 to £227.64 (Gamma)	
	Viral gastroenteritis: £306.00		£174.90 to £473.15 (Gamma)	

Variable	**Value [CI (distribution)]**				**Reference to section in submission**
Resource use (by type of visit and health state)					
	High response	Response	Partial response	Non-response	

Number of hospitalisations for HS surgeries	0.13 [0.07 to 0.20 (Gamma)]	0.22 [0.13 to 0.34 (Gamma)]	0.54 [0.31 to 0.84 (Gamma)]	0.80 [0.46 to 1.23 (Gamma)]	Section 5.5.3.1
Outpatient visits due to HS surgery	0.22 [0.12 to 0.33 (Gamma)]	0.35 [0.20 to 0.54 (Gamma)]	0.67 [0.38 to 1.04 (Gamma)]	0.94 [0.54 to 1.46 (Gamma)]	
Visits to wound-care due to HS surgery	0.12 [0.07 to 0.18 (Gamma)]	0.17 [0.10 to 0.26 (Gamma)]	0.40 [0.23 to 0.62 (Gamma)]	0.85 [0.49 to 1.31 (Gamma)]	
Number of hospitalisation non-surgery related	0.11 [0.06 to 0.17 (Gamma)]	0.23 [0.13 to 0.35 (Gamma)]	0.29 [0.17 to 0.45 (Gamma)]	0.45 [0.26 to 0.70 (Gamma)]	
Routine outpatient visits	3.10 [1.77 to 4.80 (Gamma)]	3.51 [2.00 to 5.42 (Gamma)]	4.44 [2.54 to 6.86 (Gamma)]	4.68 [2.68 to 7.24 (Gamma)]	
Visits to wound-care NOT due to HS surgery	0.67 [0.39 to 1.04 (Gamma)]	0.47 [0.27 to 0.73 (Gamma)]	0.64 [0.37 to 0.99 (Gamma)]	0.45 [0.26 to 0.69 (Gamma)]	
A&E visits	0.12 [0.07 to 0.18 (Gamma)]	0.20 [0.11 to 0.31 (Gamma)]	0.47 [0.27 to 0.73 (Gamma)]	0.57 [0.33 to 0.89 (Gamma)]	

Adverse events (rates per cycle by trial period)						
	Induction period (AE rate per cycle)		Maintenance period (AE rate per cycle)			
	ADA	SC	ADA	SC	After discontinuation	Section 5.5.3.3
Headache	0.037	0.038	[redacted]	[redacted]	[redacted]	

	[0.019 to 0.060 (Beta)]	[0.020 to 0.062 (Beta)]	[redacted]	[redacted]	[redacted]	
Hidradenitis	0.022 [0.009 to 0.041 (Beta)]	0.043 [0.024 to 0.068 (Beta)]	[redacted]	[redacted]	[redacted]	
Nasopharingitis	0.019 [0.007 to 0.037 (Beta)]	0.028 [0.012 to 0.048 (Beta)]	[redacted]	[redacted]	[redacted]	
Upper Respiratory tract infection	0.014 [0.004 to 0.029 (Beta)]	0.014 [0.004 to 0.029 (Beta)]	[redacted]	[redacted]	[redacted]	
Diarrhoea	0.013 [0.003 to 0.028 (Beta)]	0.006 [0.001 to 0.018 (Beta)]	[redacted]	[redacted]	[redacted]	
Gastroenteritis	0.005 [0.000 to 0.016 (Beta)]	0.004 [0.000 to 0.014 (Beta)]	[redacted]	[redacted]	[redacted]	
Influenza	0.005 [0.000 to 0.016 (Beta)]	0.006 [0.001 to 0.018 (Beta)]	[redacted]	[redacted]	[redacted]	
Toothache	0.002 [0.000 to 0.009 (Beta)]	0.002 [0.000 to 0.009 (Beta)]	[redacted]	[redacted]	[redacted]	
Bronchitis	0.002 [0.000 to 0.009	0.006 [0.001 to 0.018	[redacted]	[redacted]	[redacted]	

	(Beta)]	(Beta)]	[redacted]	[redacted]	[redacted]	
Viral gastroenteritis	0.000	0.002 (0.000 to 0.009 (Beta)]	[redacted]	[redacted]	[redacted]	
CI, confidence interval						

6.6.2 Model assumptions

Table 56 provides a list of all assumptions used in the de novo economic model with a justification of each assumption.

Table 56: Main model assumptions used in base case analysis

Parameter	Assumption	Justification
Model health states	HS patients start treatment with either ADA or SC in the non-response health state	Patients enrolled in the PIONEER trials[29 30] were HS patients who had inadequate response or a contra-indication or were intolerant to a prior antibiotic. Thus, it would be a reasonable assumption to place them in the non-response health state at the start of the model.
Treatment duration and dose	Patients remain on ADA treatment as long as they respond to treatment. The recommended dose of ADA is 160 mg in week 0, 80 mg in week 2, and 40 mg EW from week 4.	Evidence from the OLE trial provides evidence that treatment efficacy with ADA is maintained in the long term (60 weeks) in patients who initially respond to treatment[32]. Reflecting dose and dose frequency as measured in the PIONEER phase III pivotal trials for ADA[29 30].
Discontinuation of ADA	At the end of the induction period (week 12), patients on ADA will discontinue treatment if they were in the non-response state	The model assumed that patients who were non-responders at week 12 would all discontinue ADA. This assumption is consistent with the label indication that states that "Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period"[28].
	During week 12-36, patients on ADA discontinue treatment based on constant discontinuation rates derived from the PIONEER trials[29 30]	During weeks 12-36, discontinuation of ADA was allowed in the model, and the discontinuation rate was based on constant discontinuation rates as observed in the phase III PIONEER trials[29 30]. During this period, the same discontinuation was assumed for all ADA patients, regardless of health states, since all patients remaining on ADA during this period were week 12 responders and if a loss of response might occur, an attempt would most likely be made to regain response instead of aggressive discontinuation as suggested by the experts consulted during this submission.
	For the period extending beyond week 36, patients on ADA are projected to discontinue ADA according to response-specific discontinuation rates from the OLE trial[32]. However for non-responders these rates are only applied up to week 48 as the model assumes that all patients non-	Treatment discontinuation of ADA beyond week 36 was allowed in the model, and the discontinuation rate was based on the response-specific discontinuation rates as observed in the OLE trial[32]. The ADA drug label indicates that "the benefit and risk of continued treatment should be periodically evaluated after week 12"[28]. Experts consulted during this submission suggested that patients who do not respond to ADA treatment in the long term will be discontinued after 12 weeks. As such in the

Parameter	Assumption	Justification
	responding at week 36 will continue treatment for 12 additional weeks (re-evaluation period) and discontinue treatment with ADA at week 48.	model all patients who were in the non-response health state at week 36 discontinued ADA treatment at week 48, after 12 additional weeks of re-evaluation period.
Utilities, resource use and costs	Health utilities and resource use were assumed to depend only on health states, independent of treatments received.	Health states in this analysis reflect disease severity and are defined based on relative changes from baseline. This is consistent with the use of utility and resource information in prior CEAs for biologic treatment of psoriasis, including the 2008 HTA submission for ADA in psoriasis[98]. Thus, it would be reasonable to assume that patients would differ in QOL and resource use, based on their health states. Furthermore, AN count is an important indicator of HS disease severity, i.e., a higher AN count at baseline indicates a more severe form of HS. Thus, health states in the current analysis were defined mainly by the percentage reduction in AN count compared to baseline, together with any increases in abscesses or draining fistulas noted relative to baseline observations. It is possible that ADA treatment confers additional benefits for patients beyond AN count reduction from baseline. If this is the case, the current assumption results in a conservative estimate of ADA's benefits.
	The model assumes no administration costs associated with the use of ADA	ADA is self-injected subcutaneously. Training by a nurse at the beginning of treatment to educate patients on the appropriate administration of the drug is usually required (three 1 hour sessions). AbbVie provides this nurse led programme in the community (ie. AbbVie care) and as such no additional costs are incurred by the NHS.
TP beyond trial period – modelled TP extrapolation	The model assumed that the TPs estimated from the OLE trial[32] could be applied for the remaining model time horizon.	No long-term data is available regarding the efficacy of ADA in HS, thus extrapolation using available short-term data was required to estimate the long-term efficacy of ADA. Data from the OLE trial[32] was used to estimate the TPs, based on a modelling approach.
Mortality	Natural mortality statistics for the general population in England and Wales[118]	HS is assumed to have no effect on mortality.
AEs	Most frequently reported (≥ 5%) treatment emergent AEs observed in the PIONEER I & II clinical trials during the entire induction and maintenance period.	Only the most frequently reported (≥ 5%) treatment emergent AEs would be expected to impact on costs and outcomes in HS.

5.7 Base-case results

Table 57 presents the base-case results for ADA vs SC. ADA was found to be more costly [redacted] vs. £128,541) but also more effective (12.61 QALY vs. 11.61 QALY) compared to SC resulting in an incremental cost-effectiveness ratio (ICER) per QALY of [redacted]

5.7.1 Base-case incremental cost effectiveness analysis results

Table 57: Base-case results

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£) Incremental (QALYs)
SC	£128,541	22.73	11.61				
ADA	[redacted]	22.73	12.61				
ADA vs. SC	-			[redacted]	0.000	1.00	[redacted]

5.7.2 Clinical outcomes from the model

The clinical outcomes from the model, as compared with the clinical trial results, are summarised in Table 58.

Table 58: Base-case results validation against phase III pivotal clinical trials during Week 0 to Week 36

Week	Observed from PIONEER I and PIONEER II				Predicted in the CEA			
	High response (%)	Response (%)	Partial response (%)	Non-response (%)	High response (%)	Response (%)	Partial response (%)	Non-Response (%)
0	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	100.0%
12	42.6%	33.8%	23.5%	0.0%	44.2%	30.2%	25.6%	0.0%
36	[redacted]	[redacted]	[redacted]	[redacted]	36.8%	20.6%	5.9%	36.7%

5.7.2.1 Markov traces

Figure 24 and Figure 25 present the proportion of each patient cohort in various modelled health states – the high response, response, partial response, non-response and death states – over time, for both ADA and SC.

As illustrated below, a greater proportion of patients in the ADA arm achieved high response, response and partial response than those in the SC arm, and the proportion of patients in non-response was lower in ADA arm than in the SC arm.

At week 36, the distributions of patients in the ADA arm in high response, response, partial response and non-response were 28.70%, 15.63%, 7.22% and 48.40%, and the corresponding rates for SC were 10.72%, 4.43%, 7.61% and 77.20%, respectively. The trend persisted in analyses with longer time frames, i.e., at year 5 the non-response rate was 57.13% for ADA and 82.71% for SC, and at year 10 the non-response rate was 64.20% for ADA and 82.19% for SC. The proportion of deceased patients would gradually increase with time, and the model projected that all patients would be deceased at the end of a lifetime horizon analysis (i.e., 100 years).

Figure 24: Base-case ADA Markov trace of health states over time

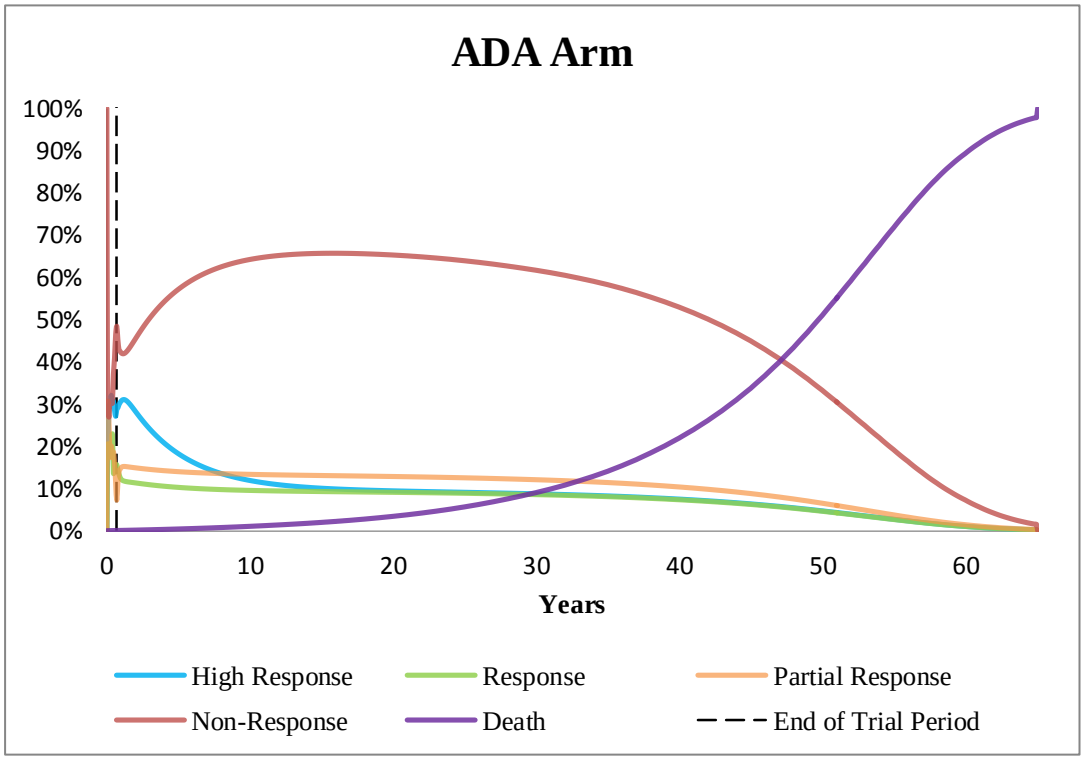
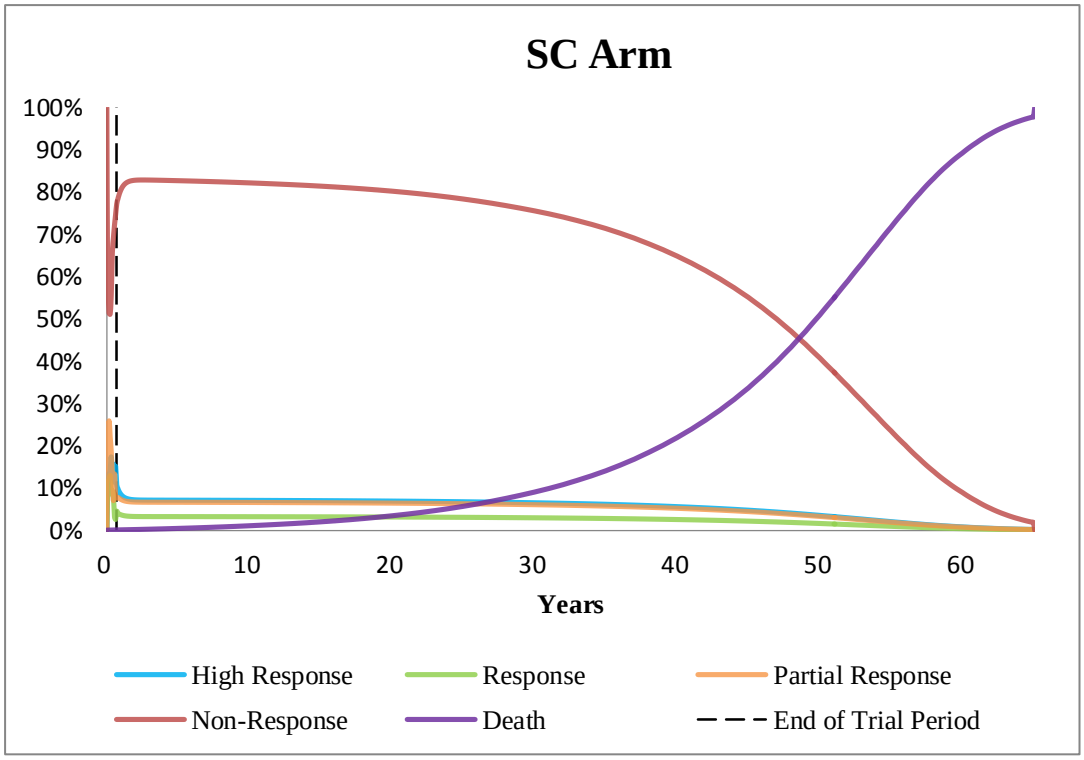


Figure 25: Base-case SC Markov trace of health states over time



5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

Details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost are summarised in Table 59, Table 60 and Table 61 respectively.

Table 59: Summary of QALY gain by health state

Health State	QALY Intervention (ADA)	QALY Comparator (SC)	Increment	Absolute Increment	% Absolute Increment
High response	2.47	1.30	1.16	1.16	21.93%
Response	1.64	0.55	1.09	1.09	20.57%
Partial response	1.80	0.90	0.89	0.89	16.88%
Non-response	6.70	8.85	-2.15	2.15	40.61%
Total	12.61	11.61	1.00	5.30	100.00%

Table 60: Summary of costs by health state

Health State	Cost Intervention (ADA)	Cost Comparator (SC)	Increment	Absolute Increment	% Absolute Increment
High response	[redacted]	£2,438	[redacted]	[redacted]	[redacted]
Response	[redacted]	£1,760	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	£6,932	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	£117,412	[redacted]	[redacted]	[redacted]
Total	[redacted]	£128,541	[redacted]	[redacted]	[redacted]

Table 61: Summary of predicted resource use by category of cost

Cost Category	Cost Intervention (ADA)	Cost Comparator (SC)	Increment	Absolute Increment	% Absolute Increment
Treatment costs	[redacted]	£0	[redacted]	[redacted]	[redacted]
Surgery-related resource use costs	£79,826	£92,847	-£13,021	£13,021	23.56%
Non-surgery related resource use costs	£30,214	£33,207	-£2,993	£2,993	5.42%
AE costs	£2,087	£2,487	-£400	£400	0.72%
Total	[redacted]	£128,541	[redacted]	[redacted]	[redacted]

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) simultaneously varied multiple parameters, based on their distributions, and re-estimated model outputs. Monte Carlo simulation methods were applied in order to make random draws for parameter inputs. The means and CIs of these parameters are presented in Table 55. Dirichlet distributions were considered for TPs given that multiple TPs from the same health state must represent a multinomial distribution. Gamma distributions were used for direct medical costs and AE costs. Beta distributions were used for the utilities and discontinuation rates. Use of the Dirichlet, gamma and beta distributions for PSA is standard practice in cost-effectiveness research.

A Monte Carlo simulation of 5,000 random draws from all parameters with uncertainty was undertaken and the incremental costs, incremental QALYs and the ICER were estimated in each simulation. Parameters were varied independently. Parameters that were not changed in the analysis were held at their base-case values. A scatterplot of cost and QALY values on the cost-effectiveness plane was generated to display the simulation results of this PSA comparing ADA to SC. A cost-effectiveness acceptability curve (CEAC) was generated to illustrate the probability of ADA being cost-effective compared to the SC at varying levels of WTP thresholds.

The results of the PSA based on 5,000 simulations of the model using a scatter plot (Figure 26) and a cost effectiveness acceptability curve (CEAC) (

Figure 27) are presented below. The probability of ADA being cost-effective at a WTP threshold of £30,000 was [redacted]

Figure 26: Cost-effectiveness plane of incremental cost and QALYs of ADA vs. SC

Figure 27: CEAC of ADA vs. SC at a WTP of £30,000

5.8.2 Deterministic sensitivity analysis

To assess the influence of each parameter variation on the results of the model deterministic sensitivity analyses (DSA) were undertaken. The DSA tested parameters related to both model settings (ie. structural assumptions) and model inputs.

The main model inputs were tested by using lower and upper bounds in order to assess the impact these variations produced on the base case ICER using a net monetary benefit (NMB) approach. Among model inputs, the DSA tested parameters related to TPs, discontinuation rates for ADA, resource use, unit costs of resource use, AE rates and costs, and utilities. DSA tested parameters were presented in a tornado plot displaying the 20 most influential parameters sorted by magnitude based on the difference between NMB using the lower bound and upper bound.

Lower and upper bounds of the 95% CI of TPs were estimated using the gamma distribution. The gamma distribution was parameterised by alpha (the number of

observations for a particular transition) and beta (1). For discontinuation rates, cycle rates of AE and utility values, a beta distribution was assumed. The SE for discontinuation rates and cycle rates of AEs was calculated based on the point estimate (mean) and the number of observations (n). The point estimate and SE were then used to estimate the beta curve and to calculate the 95% CI. SEs for utility values were estimated from the patient level data from the PIONEER II study[30]. For resource use and cost parameters a gamma distribution was assumed. The SE was assumed to be 25% of the mean. Using the mean and the SE, the gamma curve was estimated, and 95% CIs were calculated.

5.8.3 Scenario analysis

The structural assumptions of the model were tested in scenario analyses. Model assumptions in terms of time horizon, annual discount rates, source of clinical trial, extrapolation methods for estimating TPs beyond the trial period, missing value imputation methods, ADA discontinuations rates and treatment compliance were tested.

In the base case analysis data from the OLE[32] was included to estimate TP beyond week 36. A DSA was conducted to evaluate the impact of using modelled TP using the week 12-36 data from the PIONEER I and PIONEER II clinical trials[29 30] using generalised logit models. Patients who received ADA in the induction period, who were week 12 responders, and who continued receiving ADA during week 12-36, were used to estimate the TPs of ADA treatment for the period beyond week 36 in the model. The dependent variable was the current health state, and the independent variables were the previous health state and the ADA dosing regimen (EW or EOW). Both patients receiving ADA EW and patients receiving ADA EOW were included in the generalised logit model, in order to increase the sample size and to maximize the utilised data. ADA EW specific TPs were estimated from the generalised logit model and applied to the CEA model.

Different discontinuation rates were also tested since discontinuation rates estimated from the clinical trials (PIONEER I & II and OLE) might not reflect the true discontinuation rate of ADA in clinical practice. Furthermore, the model tested the exclusion of a compliance rate for ADA as most patients would be expected to be

fully compliant with ADA treatment in clinical practice. The detailed list of parameters is presented in Table 62.

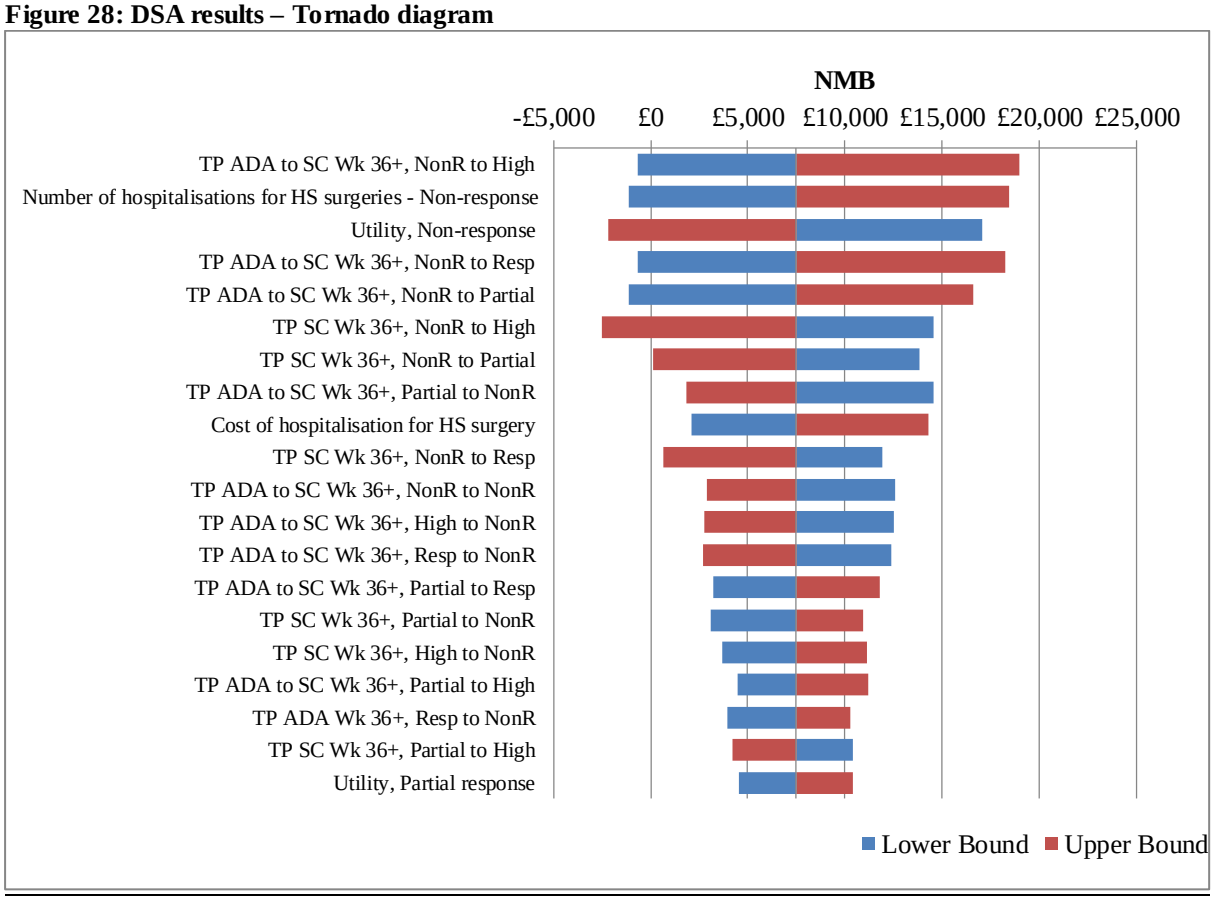
Table 62: Scenario analyses – ADA vs SC

Parameters	Base-case input	DSA Input
Time horizon	Lifetime	20, 30 years
Annual discount rate	3.5%	0%, 5%
Clinical trial source	Induction: PIONEER I & II for both ADA and SC arms; Maintenance: PIONEER I & II for the ADA arm, PIONEER II only for the SC arm	Induction: PIONEER II only for both ADA and SC arms; Maintenance: PIONEER II only for both ADA and SC arms
TP extrapolation method (after week 36)	Modelled TP extrapolation	LSCF extrapolation
		Mean TP extrapolation
TPs for the ADA arm (after week 36)	Estimated based on OLE clinical trial data	Estimated based on PIONEER I & II trial data
Missing value imputation	NRI	LOCF
Discontinuation rates of ADA for week 12-36	Constant discontinuation rate for all states from PIONEER I & II	Response specific discontinuation rates from PIONEER I & II
Discontinuation rates of ADA for week 36+	Response specific discontinuation rates from OLE	Response specific discontinuation rates from PIONEER I & II
Discontinuation rate of ADA non-responders after week 36	All non-responders discontinue ADA treatment at week 48	Annual discontinuation rate of ADA non-responders after week 36 as per OLE trial
Maintenance compliance rate of ADA (week 12+)	Based on PIONEER I & II (97.4%)	Assume 100%

5.8.4 Summary of sensitivity analyses results

The results of the DSA on the main model inputs using lower and upper bounds and the NMB approach showed that the model was sensitive to the assumption around the TPs used in the extrapolation period (after week 36), the number and cost of hospitalisations and the utility values for partial and non-response health states (Figure 28) however the ICER was relatively robust to any other changes in model inputs.

Figure 28: DSA results – Tornado diagram



The scenario analyses results showed that the ICER was robust to most model changes. The parameters that had the highest impact on the ICER were the discount rates chosen and the assumption around the discontinuation rate of ADA non-responders after week 36. When the model time horizons were decreased to 20 and 30 years the ICER increased to [redacted] and [redacted] respectively and when the model used only data from the PIONEER II trial for induction and maintenance inputs for ADA and SC, then the lifetime ICER became [redacted].

By using the mean TP extrapolation of weeks 12-36 for the time period that extended beyond that covered by the trial (rather than the modelled approach), the ICER decreased to [redacted] and when the LSCF extrapolation was used the ICER increased to [redacted] When the LOCF method was used to impute missing values, the ICER also decreased to [redacted] see **Error! Not a valid bookmark self-reference.**.

Table 63: Scenario analyses results – ADA vs SC

Parameters	Base-case input	DSA input	ICER (cost/QALY)
Time horizon	Lifetime	20 years	[redacted]
		30 years	[redacted]
Annual discount rate	3.5%	0%	[redacted]
		5%	[redacted]
Clinical trial source	Induction: PIONEER I & PIONEER II for both ADA and SC arms; Maintenance: PIONEER I & PIONEER II for the ADA arm, PIONEER II only for the SC arm	Induction: PIONEER II only for both ADA and SC arms; Maintenance: PIONEER II only for both ADA and SC arms	[redacted]
TP extrapolation method (after week 36)	Modelled TP extrapolation	LSCF extrapolation	[redacted]
		Mean TP extrapolation	[redacted]
TPs for the ADA arm after week 36	Estimated based on OLE trial data	Estimated based on PIONEER I & II trial data	[redacted]
Missing value imputation	NRI	LOCF	[redacted]
Discontinuation rates of ADA for week 12-36	Constant discontinuation rate for all states from PIONEER I & II	Response specific discontinuation rates from PIONEER I & II	[redacted]
Discontinuation rates of ADA for week 36+	Response specific OLE	Response specific PIONEER I & II	[redacted]
Discontinuation rate of ADA non-responders after week 36	Based on expert opinion (100%)	As per OLE trial (45%)	[redacted]
Maintenance compliance rate of ADA (week 12+)	From PIONEER I & II (97.40%)	Assume full compliance (100%)	[redacted]

5.9 Subgroup analysis

No subgroups were considered for this cost effectiveness analysis.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

Quality-control procedures were performed by two separate modellers who were not involved in model development. The quality-control procedures included program/code validation, varying inputs and comparing them with expected results, and verification of all input data with their original sources. Calculation checks were performed to identify potential errors (e.g. probabilities not summing to 1) and to ensure that symmetry was present, i.e., the same outcomes were analysed for both

treatment arms in all components of the model. In addition, the means of all parameters from the PSA simulations were evaluated against the point estimate in order to ensure accuracy of the analytical model.

5.11 Interpretation and conclusions of economic evidence

The main strength of this model was the fact that the core analysis comparing ADA to SC was based on direct evidence from the randomised PIONEER I and PIONEER II clinical trials, which evaluated ADA and SC among adults with active moderate to severe HS with an inadequate response to or who were intolerant to conventional systemic antibiotic HS therapy[29 30]. This patient population is considered representative of the patients who will be receiving ADA in clinical practice in the UK (as confirmed by the clinical experts consulted)[40-42 44] Evidence from direct head-to-head comparison in randomised controlled clinical trials is considered the "gold standard" because it eliminates the impact of unobserved confounders (such trials have high internal validity)[45 46]. In addition, the model used all available data to inform relevant inputs, i.e., data from both the phase III PIONEER clinical trials were pooled for analyses where feasible and data from the OLE trials was used to model long term efficacy.

Furthermore, the EQ-5D, the NICE-preferred instrument for HRQOL measurements used in CEA modelling[47 48], was administered in the PIONEER II clinical trial (but not in the PIONEER I clinical trial) and these data were directly used to inform the utility values for each health state. EQ-5D is an appropriate HRQOL measurement instrument in patients with skin conditions[49 50]. There was no need for alternative or indirect measures of determining HRQOL outside the trial setting.

Moreover, extensive sensitivity analyses – related to both model settings and model inputs – were conducted to test the robustness of the model. Overall, the model results were robust to all studied inputs, except for the methods used for extrapolation beyond the trial period which is not surprising given the significant assumptions required in such long-term extrapolations.

However, as it is the case with most economic models there were some limitations with the analysis presented.

Firstly, due to the lack of long-term efficacy data for ADA and SC, extrapolation beyond the trial period was required. Modelled TP extrapolation was applied in the base-case. Sensitivity analyses were also conducted using the mean TP extrapolation where the TPs were estimated based on the mean of the TP matrices from week 12-36. The estimates on the long term extrapolation would most likely improve when the final results from the OLE trial become available in the future.

Secondly, there is a lack of real-world data related to resource use by health states among HS patients. Frequencies of resource use were obtained from a physician survey conducted among UK physicians who were actively treating HS patients[39]. The results from the physician survey was further evaluated and validated by a focus group discussion with UK physicians who are treating HS patients[37]. However, these results need to be validated against the real-world resource use incurred by HS patients. The model also tested uncertainties in the sensitivity analysis. In the future, resource use data from real-world studies could be used to improve the robustness of the model.

No disutilities of AEs were considered in this economic evaluation. However, this is likely to have a minimal impact on the results as the AEs rates were similar between patients who received ADA and patients who received placebo in the phase III PIONEER clinical trials[29 30]. In addition, the utility of each health state used in the model was estimated based on all patients with the indicated health state from the clinical trials, which could include patients who were experiencing AEs.

In addition, the model used the compliance rate of ADA observed in the phase III PIONEER clinical trials[29 30]. However, in the real-world, patient compliance is likely to be lower than that observed in the clinical trials.

5.11.1 Conclusion

The economic model was developed, based on clinical trial data and other inputs, for the cost-effectiveness of ADA for the treatment of HS. The model demonstrates that ADA is a cost-effective treatment option for patients with active moderate to severe HS in the UK. When using modelled TPs based on the OLE trial to extrapolate beyond the period studied in clinical trials, the model predicted that ADA had an

ICER of [redacted] per QALY gained when compared to SC over a lifetime horizon. The estimated ICER was robust to most changes in model inputs. The model was most sensitive to the assumption around the TPs used in the extrapolation period (after week 36), the utility values for partial and non-response health states, the number and cost of hospitalisations for surgery and the discontinuation rates of ADA.

6 Assessment of factors relevant to the NHS and other parties

State how many people are eligible for treatment in England. Present results for the full marketing authorisation or CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The total number of patients who would be eligible to receive treatment with ADA in Year 1 would be 410 rising to 1,417 in year 5. Table 64 presents the ADA projected eligible patient population for Years 1 to 5.

Table 64: ADA projected eligible patient population for years 1 to 5

	Year 1	Year 2	Year 3	Year 4	Year 5
Moderate/severe HS patients	17,069	17,353	17,475	17,593	17,710
HS patients treated with a biologic	410	694	935	1,179	1,417

Explain any assumptions that were made about current treatment options and uptake of technologies

Currently there are no licensed treatment options available in England and Wales for HS. As such it is assumed that all patients (100%) would be receiving Supportive Care (SC).

When relevant, explain any assumptions that were made about market share in England

It is anticipated that ADA will achieve a market share of 90% among biologic treated patients and this will be maintained into year 5. The number of patients anticipated to receive ADA in each of the next 5 years is presented in Table 65.

Table 65: Number of patients receiving ADA based on anticipated market share

	Year 1	Year 2	Year 3	Year 4	Year 5
HS patients treated with a biologic	410	694	935	1,179	1,417
ADA market share	90%	90%	90%	90%	90%
Patients receiving ADA	369	625	841	1,061	1,275

In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions)

The costs included in this analysis include all the direct costs to the NHS associated with the management of patients with active moderate to severe HS. These include: drug costs, surgery and non-surgery related management costs and the cost of treating AEs.

State what unit costs were assumed and how they were calculated. If unit costs used in the health economic modelling were not based on national reference costs or payment-by-results tariff, explain how a cost for the activity was calculated.

The costs estimated for the purpose of this section are based on the inputs (and outputs) of the cost-effectiveness analysis as described in Section 5.

Were there any estimates of resource savings? If so, what were they?

There are no estimates of resource savings associated with the introduction of ADA.

State the estimated annual budget impact on the NHS in England

In order to estimate the annual budget impact to the NHS with the introduction of ADA the annual cost per patient of each treatment option (ADA and SC) in Year 1 is multiplied by the total number of patients eligible for each treatment option in each of the years considered in the analysis. The total budget impact for ADA is calculated as the difference between the total costs of treatment if ADA is adopted minus the total cost of treatment if patients continued to receive SC.

Table 66 below reports the cost per patient per year for ADA and SC estimated from the cost effectiveness analysis for years 1 to 5.

Table 66: Cost per patient per year as estimated in the cost effectiveness analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
ADA cost per year, £	£ 17,357	£ 10,963	£ 9,594	£ 8,582	£ 7,797
SC cost per year, £	£ 5,608	£ 5,618	£ 5,637	£ 5,633	£ 5,628

The total annual treatment costs with ADA introduction are presented in Table 67.

Table 67: Total annual treatment costs with ADA introduction

	Year 1	Year 2	Year 3	Year 4	Year 5
HS patients treated with a biologic	410	694	935	1,179	1,417
ADA market share	90%	90%	90%	90%	90%
Patients receiving ADA	369	625	841	1,061	1,275
Total cost of patients receiving ADA	£ 6,399,358	£ 8,485,808	£ 10,105,113	£ 11,804,775	£ 13,276,105

The total annual treatment costs without ADA introduction are presented in Table 68.

Table 68: Total annual treatment costs without ADA introduction

	Year 1	Year 2	Year 3	Year 4	Year 5
ADA market share	0%	0%	0%	0%	0%
Patients receiving SC	369	625	841	1,061	1,275
Total cost of patients receiving SC	£ 2,067,436	£ 3,506,877	£ 4,731,672	£ 5,967,998	£ 7,173,166

The incremental budget impact of ADA introduction is presented in Table 69.

Table 69: Incremental budget impact of ADA introduction

	Year 1	Year 2	Year 3	Year 4	Year 5
Total costs with introduction of ADA	£ 6,399,358	£ 8,485,808	£ 10,105,113	£ 11,804,775	£ 13,276,105
Total costs without introduction of ADA	£ 2,067,436	£ 3,506,877	£ 4,731,672	£ 5,967,998	£ 7,173,166
Incremental overall budget impact	£ 4,331,922	£ 4,978,931	£ 5,373,440	£ 5,836,778	£ 6,102,939

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Appendices

[List the titles of the appendices here. All appendices should be provided as **separate documents to the main submission**.]

[See section 8 of the user guide for examples of appendices that may be used to support the submission.]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Adalimumab (ADA) (Humira) for the treatment of moderate to severe Hidradenitis Suppurativa (HS).

3.2 Please outline the rationale for developing the patient access scheme.

The aim of this scheme is to enable adult patients with a significant unmet need to gain timely access to a licensed treatment with proven efficacy for moderate to severe Hidradenitis Suppurativa, where currently no licensed alternative treatment exists. Adalimumab is currently licensed for multiple therapeutic indications in England and Wales. However, many of these therapeutic indications are already NICE approved, and therefore this Patient Access Scheme is not intended to be extended to these therapeutic indications.

AbbVie conducted three separate Patient Access Scheme consultations for adalimumab with key stakeholders in England and Wales over the last 6 months in order to identify the most appropriate scheme. Key findings from these consultations revealed that the proposed Patient Access Scheme for adult patients with Hidradenitis Suppurativa has the following inherent advantages over all other approaches considered:

1. The concept of the discounted price is simple for customers to understand.

2. The NHS in England and Wales is immediately in receipt of the benefits of managing the scheme, rather than potentially waiting for the benefits with other potential schemes.

3. The benefit of the discount will apply to the patient throughout the duration of their treatment.

4. No rebates will be required (potentially limiting any potential financial governance considerations of managing rebates).

5. No additional clinical intervention is required in administrating the scheme, and no additional testing of patients is required.

In light of the above, the patient access scheme has been designed so that:

1. Additional costs to the NHS in England and Wales are kept to a minimum, avoiding the introduction of additional clinical monitoring;

2. It does not burden the NHS in England and Wales with complex data generation;

3. It is consistent with current NHS financial flows and the current ordering and delivery of adalimumab in England and Wales; and

4. It is simple to communicate and understand.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

This scheme is designed to provide patients with moderate to severe Hidradenitis Suppurativa with adalimumab at a fixed cost, below that of the NHS list price. The scheme will only apply to the Hidradenitis Suppurativa indication and not to any current and future indications.

AbbVie is proposing a discounted price of [redacted] (exclusive of VAT) for each pack of 2x40mg pre-filled syringes or pens of adalimumab for the treatment of moderate to severe adult patients with Hidradenitis Suppurativa with an inadequate response to conventional systemic HS therapies.

Adalimumab is marketed in the United Kingdom (UK) in a pack of 2 x pen/ prefilled syringe with a list price of £704.28. Each 0.8 ml single dose pre-filled syringe or pen contains 40 mg of adalimumab.

Adalimumab is also available as a vial, however this presentation is only available for paediatric therapeutic indications and therefore not subject to the scheme.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

This scheme will apply to the patient population as specified in the license *"treatment of active moderate to severe HS (acne inversa) adult patients with an inadequate response to conventional systemic HS therapy"* (EMEA/H/C/481/II/137). The scheme will not apply to a specific subgroup of patients.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The proposed scheme will apply to all patients as per license (as specified in 3.4). The scheme is a straight discount to the NHS list price and will operate from the date of guidance publication and until NICE reviews the guidance and the reviewed guidance has been published on the NICE website.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The patient population in which adalimumab is licensed is for adults with active moderate to severe HS who have had an inadequate response to or are intolerant to conventional systemic HS therapy.

In order to estimate the total number of patients eligible for treatment with adalimumab, the prevalence of the condition among patients aged 18 and over in England and Wales is first calculated (457,624). Market research conducted by Abbvie[1] suggests that only a small proportion of patients with HS are diagnosed (19%) and not all (82%) are treated for HS. Since adalimumab is a biologic treatment it will only be prescribed by a dermatologist and based on market research only 45% of HS patients are currently seen by a dermatologist in the UK. Adalimumab is only licensed for moderate to severe HS patients and as such it was also necessary to estimate how many patients would fulfil these criteria (53.2%). Finally as adalimumab will not be prescribed to all patients the proportion of moderate to severe dermatology treated patients who would be prescribed a biologic was also estimated (2.4% - 8%).

The total number of patients that would be eligible to receive treatment with adalimumab in any given year in England and Wales was estimated to range between 410 and 1,417. Please refer to **Error! Reference source not found.** for an outline of how the total population of patients eligible for adalimumab in England and Wales was calculated.

Table 1: Estimated number of patients eligible for HS adalimumab treatment in England and Wales

	Population Estimates 2016	Source
Population estimate for England and Wales (2016)	58,139,219	ONS[2]
Proportion of all aged 18 & over in England and Wales (78.7%)	45,762,384	ONS[3]
Number of patients with the condition	457,624	Revuz, 2008[4]

(Prevalence 1%)		
Proportion of patients diagnosed with HS (19%)	86,949	AbbVie Market research[1]
Proportion of patients treated for HS (82%)	71,298	AbbVie Market research[1]
Proportion of patients treated by a dermatologist (45%)	32,084	AbbVie Market research[1]
Proportion of patients moderate to severe (53.2%)	17,069	AbbVie Market research[1]
Proportion of moderate to severe dermatology patients treated with a biologic (range 2.4%-8%)	410 to 1,417	AbbVie estimate

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The discounted price of adalimumab (Humira) (2 x pen/ prefilled syringe) will be fixed at [redacted]. Discounted adalimumab (Humira) will be provided by AbbVie for direct to hospital supplies, and by homecare providers for homecare delivery.

The homecare provider will be charged the full price for supplies ordered; Abbvie will then calculate the rebate owed to the homecare provider. The rebate will be paid within the credit period for which payment for supplies is required, therefore eliminating any related financial burden on homecare providers. The homecare provider will be responsible for invoicing the NHS trust at the proposed reduced price for homecare supply. If ongoing discrepancies occur, Abbvie will assist NHS trusts in resolving these issues. Abbvie will be responsible for invoicing the NHS at the proposed reduced price for direct supply to hospitals.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The scheme requires NHS trusts to first sign an agreement and then complete a scheme-specific, direct-to-hospital supply form with which to register patients and order reduced cost supplies of adalimumab. If an NHS trust chooses to operate the scheme through homecare, then specific homecare forms should be used. An NHS trust must send the direct-to-hospital supply form to Abbvie either by fax or by email to order all supplies through the proposed scheme. Abbvie will provide an electronic tracker as part of the scheme. The scheme recommends that the NHS trust provide a unique patient identifier, which Abbvie proposes is provided by the NHS trust through the use of encryption software. It should not be the patient's NHS number, unless encrypted.

Since data collection is already done by NHS trusts, through the use of a biologics dermatology patient database and pharmacy systems, all the data

needed to operate the proposed scheme are already generally available. However, Abbvie has also proposed the use of its electronic tracker system to assist monitoring (over the secure NHS N3 network), if NHS trusts wish to use it to help administer the proposed scheme. The technology has electronic data interface functionality, and therefore could potentially be utilised to streamline the completion of the schemes Patient Registration & Order form with customer EDI (Electronic Data Interchange) ordering.

All relevant adalimumab orders and registration forms for the condition should specify the indication (ie. Hidradenitis Suppurativa) so that supplies can be correctly ordered and tracked since adalimumab has different dosing schedules for different therapeutic indications. In order to ensure that each patient gets the correct dosage, and to assist information flows and governance within hospitals, Abbvie and the homecare providers have developed specially designed homecare prescription forms and homecare registration forms, which include a field for the indication.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

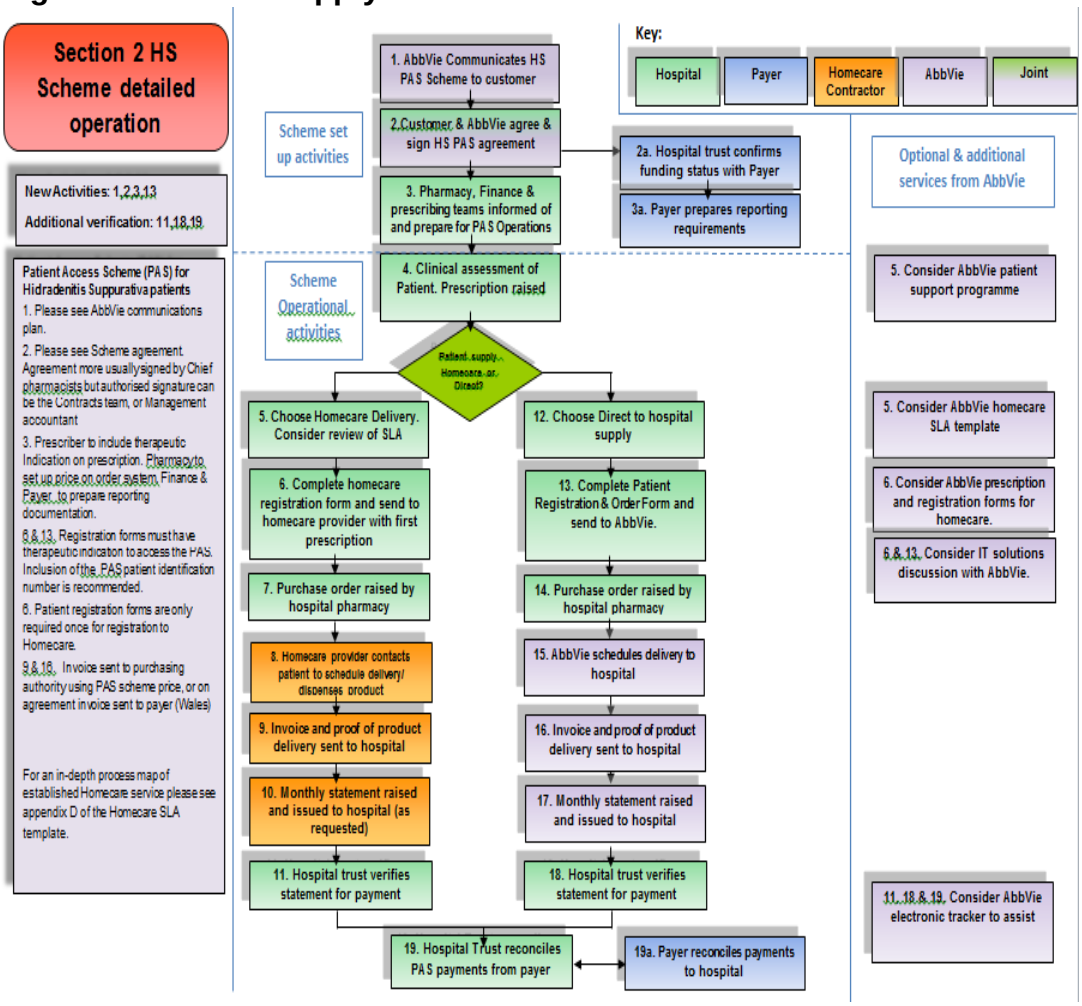
Processes within the NHS in England and Wales for prescribing, ordering, delivery and financial management of adalimumab (Humira) are already well established. Current supply channels are: 1) Homecare delivery and 2) Direct supply to hospitals from AbbVie.

Homecare provision for the NHS and private hospitals is paid for by AbbVie for adalimumab (Humira) patients, and currently accounts for [redacted] of the supply channel for adalimumab (Humira) in England and Wales. From the Patient Access Scheme consultation, evidence suggests that the use of homecare supply of adalimumab (Humira) will continue for adult Hidradenitis Suppurativa patients. Direct supply to hospitals from AbbVie will account for the remaining [redacted].

Figure 1 describes the scheme supply route and financial flows. Additional activities required for the patient access scheme include set up activities (steps 1, 2, and 3), and the completion of the Patient Registration & Order

form for direct to hospital supplies from AbbVie (step 13). Additional verification processes are also required for invoice and payer reconciliation (steps 11, 18, 19).

Figure 1: Scheme supply route and financial flows



The costs to the NHS associated with the implementation of the proposed scheme are described below. AbbVie estimates that to set up the scheme the following NHS resources will be required (Table 2). This is a one-off cost per NHS trust.

Table 2: Costs to each NHS trust associated with the implementation of the proposed scheme

Cost elements	Time taken (minutes)	Role [1,2]	Costs
Working out how to	30	8a pharmacist	£12.92

manage scheme (Scheme Agreement)	30	8b pharmacy procurement	£15.29
Adding new item to system to distinguish different price, and creating a second pharmacy stock line	15	8a pharmacist	£12.92
	10	8a formulary pharmacist	£4.31
	10	5 pharmacy IT	£2.46
Finance flows - adding to high cost drugs reports, informing finance	15	7 service manager	£5.34
	15	8a pharmacist	£12.92
	15	8a finance manager	£12.92
Total			**£79.07**

Sources:

[1] http://www.nhsemployers.org/~/media/Employers/Documents/Pay%20and%20reward/AfC%20pay%20bands%20from%201%20April%202015.pdf
[2] http://www.nhsemployers.org/~/media/Employers/Documents/Pay%20and%20reward/AfC_tc_of_service_handbook_fb.pdf

AbbVie estimates that to operate the proposed scheme the following additional NHS resources will be required (Table 3). These costs will be per order of Adalimumab.

Table 3: Ongoing operational costs - Costs per order

Cost elements	Time taken (minutes)	Role [1,2]	Costs	
			Direct order	Homecare order
Identifying patients and liaising with pharmacy team	15	8b clinical	£6.46	£6.46
Filling out required forms and getting info from other colleagues (eg procurement for an order no)	15	8a pharmacist	£6.46	£0.00
Manual manipulation of finance reports (ie adding additional info required by Payer, indication etc)	10	8a pharmacist	£4.31	£4.31
Finance managing PAS information to Payer (England)	10	8a finance manager	£4.31	£4.31
			£21.53	**£15.07**

Sources:

[1] http://www.nhsemployers.org/~/media/Employers/Documents/Pay%20and%20reward/AfC%20pay%20bands%20from%201%20April%202015.pdf
[2] http://www.nhsemployers.org/~/media/Employers/Documents/Pay%20and%20reward/AfC_tc_of_service_handbook_fb.pdf

3.10 Please provide details of the duration of the scheme.

The proposed scheme will operate from the date of guidance publication and until NICE reviews the guidance and the reviewed guidance has been published on the NICE website.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equalities issues relating to the scheme. Furthermore none were identified by the PASLU review.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

- HS Patient Access Scheme Agreement
- Patient Registration and Order Form
- AbbVie Terms and Conditions
- Example Homecare Registration Form
- Example Homecare Prescription Form

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

N/A

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

N/A

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

N/A

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the economic model a discount of [redacted] is applied to the cost of one adalimumab 40 mg pen/prefilled syringe (£704.28/2 = £352.14*[redacted]

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Data from the PIONEER I and PIONEER II clinical trials is used to define the efficacy of adalimumab and supportive care (SC) in the economic model.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

Please see below a summary of the costs associated with the implementation and operation of the patient access scheme.

Table 4: Costs associated with the implementation and operation of the patient access scheme (PAS)

	Cost
Set-up costs	£79.07 per NHS trust
Staff training	N/A
Stock management	N/A
Operational Costs	
Costs per order - Direct to Hospital	£21.53
Costs per order - Homecare	£15.07

In order to incorporate the set up costs of the scheme in the economic model it was first necessary to translate this cost into a cost per patient for each NHS trust. The estimated number of patients eligible for HS adalimumab treatment in England and Wales (as presented in Table 1) is between 410 and 1,417. AbbVie anticipates that the majority of these patients will be treated in 12 specialist centres in England and Wales (St John's Dermatology Unit; Guy's Hospital, London; University Hospital Wales; Salford Royal, Leeds Teaching Hospitals Trust; University Hospitals Coventry and Warwickshire; Oxford University Hospitals Trust; Portsmouth Hospitals NHS Trust; South Tees

Hospitals NHS Trust; Countess of Chester Hospital; Burton Hospitals; Imperial College Healthcare Trust). If we take the upper bound of this patient estimate (1,417) and then assume that the same proportion of patients is treated in each centre we can estimate the total number of patient treated per centre (1,417/12 =118). This value is then divided by the cost per trust (£79.07) to obtain the cost per patient of setting up the scheme (£0.70).

The existing economic model has an option to include one-off administration costs in the model (currently not included in the base case). The one-off set up cost of the scheme per patient can be incorporated into the analysis by adding this cost (£0.70) to the analysis.

Since the operational costs of the PAS are reported per order, to incorporate this additional cost in the economic model it was first necessary to estimate the frequency of orders per patient per year for the homecare and direct to hospital supply routes (Table 5). These values were then multiplied by the cost per order and then weighted by the order split (% proportion homecare vs hospital orders) to obtain a weighted cost per year [redacted] and then a cost per model cycle ([redacted] £8.21). In order to incorporate the ongoing operational costs into the analysis the order cost per model cycle is added to the cost of the drug in the analysis.

Table 5: Estimate of order cost per model cycle

	Frequency of orders	Deliveries in a year	Costs per order	Total	Order Split
Direct to hospital	Every 4 week	13.0	£21.53	£279.87	[redacted]
Homecare	Every [redacted] weeks [1]	[redacted]	£15.07	[redacted]	[redacted]
Weighted cost per year					[redacted]
Cost per model cycle (4 weeks)					**£8.21**

[1] Homecare delivery schedule, April 2015 ([redacted] every 4 weeks; [redacted] every 8 weeks; [redacted] every 12 weeks)

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the

intervention both with and without the patient access scheme. Please give the reference source of these costs.

There will be no additional treatment-related costs incurred by implementing the patient access scheme.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 6: Base-case cost-effectiveness results

	Adalimumab	Supportive Care
Treatment costs (£)	[redacted]	£0.00
Surgery-related resource use costs	£79,826	£92,847
Non-surgery related resource use costs	£30,214	£33,207
AE costs	£2,087	£2,487
Total costs (£)	[redacted]	£128,541
Difference in total costs (£)	N/A	[redacted]
LYG	22.73	22.73
LYG difference	N/A	0.000
QALYs	11.61	12.61
QALY difference	N/A	1.00
ICER (£)	N/A	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 7: Base-case cost-effectiveness results with the patient access scheme

	Adalimumab	Supportive Care
Treatment costs (£)*	£31,557	£0.00
Surgery-related resource use costs	£79,826	£92,847
Non-surgery related resource use costs	£30,214	£33,207
AE costs	£2,087	£2,487
Total costs (£)	£143,683	£128,541
Difference in total costs (£)	N/A	£15,142
LYG	22.73	22.73
LYG difference	N/A	0.000
QALYs	11.61	12.61
QALY difference	N/A	1.00
ICER (£)	N/A	£15,182

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.* Includes set up costs of the scheme

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 8: Base-case incremental results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)
SC	£128,541	22.73	11.61				
ADA	[redacted]	22.73	12.61				
ADA vs. SC	-	-	-	[redacted]	0.000	1.00	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 9: Base-case incremental results with the patient access scheme

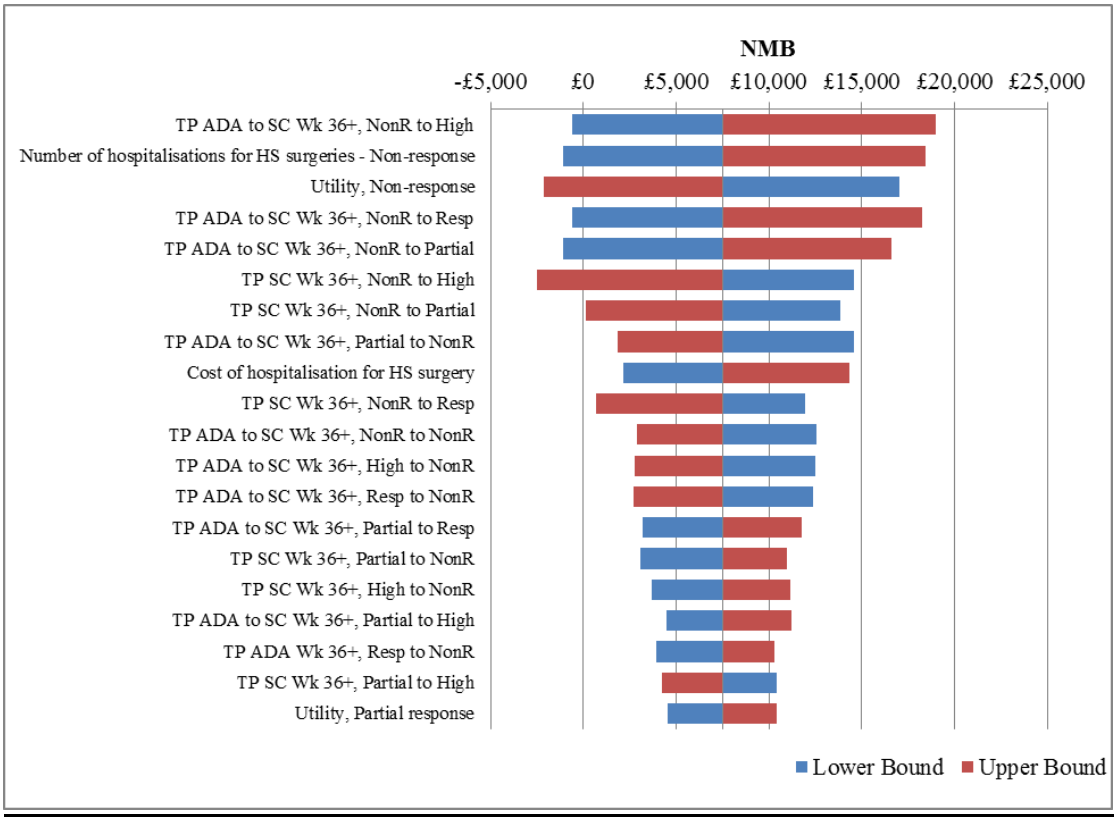
Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)
SC	£128,541	22.73	11.61				
ADA	£143,683	22.73	12.61				
ADA vs. SC	-	-	-	£15,142	0.000	1.00	**£15,182**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 2: DSA results – Tornado diagram



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 3: Cost-effectiveness plane of incremental cost and QALYs of ADA vs. SC

Figure 4: CEAC of ADA vs. SC at a WTP of £30,000

4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Table 10: Scenario analyses results – ADA vs SC

Parameters	Base-case input	DSA input	ICER (cost/QALY)
Time horizon	Lifetime	20 years	[redacted]
		30 years	[redacted]
Annual discount rate	3.5%	0%	[redacted]
		5%	[redacted]
Clinical trial source	Induction: PIONEER I & PIONEER II for both ADA and SC arms; Maintenance: PIONEER I & PIONEER II for the ADA arm, PIONEER II only for the SC arm	Induction: PIONEER II only for both ADA and SC arms; Maintenance: PIONEER II only for both ADA and SC arms	[redacted]
TP extrapolation method (after week 36)	Modelled TP extrapolation	LSCF extrapolation	[redacted]
		Mean TP extrapolation	[redacted]
TPs for the ADA arm after week 36	Estimated based on OLE trial data	Estimated based on PIONEER I & II trial data	[redacted]
Missing value imputation	NRI	LOCF	[redacted]
Discontinuation rates of ADA for week 12-36	Constant discontinuation rate for all states from PIONEER I & II	Response specific discontinuation rates from PIONEER I & II	[redacted]
Discontinuation rates of ADA for week 36+	Response specific OLE	Response specific PIONEER I & II	[redacted]
Discontinuation rate of ADA non-responders after week 36	Based on expert opinion (100%)	As per OLE trial (45%)	[redacted]
Maintenance compliance rate of ADA (week 12+)	From PIONEER I & II (97.40%)	Assume full compliance (100%)	[redacted]

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

N/A

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 11: Results showing the impact of patient access scheme on ICERs

			Without PAS	With PAS
Parameters	**Base-case input**	**DSA input**	**ICER (cost/QALY)**	**ICER (cost/QALY)**
Base Case			[redacted]	**£15,182**
Time horizon	Lifetime	20 years	[redacted]	£25,956
		30 years	[redacted]	£20,108
Annual discount rate	3.5%	0%	[redacted]	£3,353
		5%	[redacted]	£19,630
Clinical trial source	Induction: PIONEER I & PIONEER II for both ADA and SC arms; Maintenance: PIONEER I & PIONEER II for the ADA arm, PIONEER II only for the SC arm	Induction: PIONEER II only for both ADA and SC arms; Maintenance: PIONEER II only for both ADA and SC arms	[redacted]	£22,929

TP extrapolation method (after week 36)	Modelled TP extrapolation	LSCF extrapolation	[redacted]	£25,411
		Mean TP extrapolation	[redacted]	£12,567
TPs for the ADA arm after week 36	Estimated based on OLE trial data	Estimated based on PIONEER I & II trial data	[redacted]	£1,862
Missing value imputation	NRI	LOCF	[redacted]	£10,345
Discontinuation rates of ADA for week 12-36	Constant discontinuation rate for all states from PIONEER I & II	Response specific discontinuation rates from PIONEER I & II	[redacted]	£14,765
Discontinuation rates of ADA for week 36+	Response specific OLE	Response specific PIONEER I & II	[redacted]	£12,164
Discontinuation rate of ADA non-responders after week 36	Based on expert opinion (100%)	As per OLE trial (45%)	[redacted]	£30,254
Maintenance compliance rate of ADA (week 12+)	From PIONEER I & II (97.40%)	Assume full compliance (100%)	[redacted]	£15,916

PAS: patient access scheme.

Appendices

4.14 Appendix A: Additional documents

4.14.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.


22 09 15 HS PAS Scheme agreement w


Abbvie terms & conditions.docx


Patient Registration & Order Form.doc


Example Homecare Prescription form.doc


Example Homecare Registration form.doc

4.15 Appendix B: Details of outcome-based schemes

4.15.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

4.15.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

4.15.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

4.15.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

4.15.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

4.15.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

4.15.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

4.15.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

4.15.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

REFERENCES

1. Abbvie Limited. Data on file (Humira in HS: Patient flow and KOL research) 2015.

2. Office for National Statistics. Subnational Population Projections, 2012-based projections, 2012.

3. Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2014, 2014.

4. Revuz JE, Canoui-Poitrine F, Wolkenstein P, et al. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol 2008;**59**(4):596-601.

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Single Technology Appraisal (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Dear [redacted],

The Evidence Review Group, the University of Sheffield's School of Health and Related Research (ScHARR), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 15 October by AbbVie. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data. Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **24 November 2015**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link:
https://appraisals.nice.org.uk/request/9123

If you have any further queries on the technical issues raised in this letter then please contact Sophie Laurenson, Technical Lead (Sophie.Laurenson@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Systematic literature review

A1. Section 4.1.1, pages 46-47. Please clarify that these inclusion criteria apply to the potential network meta-analysis outlined in Section 4.10 and not to the decision problem or the review that has been conducted and described in Sections 4.2 to 4.9.

A2. Section 4.1, page 48. Please provide a description of the methods of synthesis or meta-analysis of the evidence described and reported in sections 4.2-4.9, and the rationale underpinning these.

A3. Section 4.1, page 48. Please give details of the data extraction process followed by the company. Who conducted the data extraction? What measures were taken to minimise bias in the process? Which data were extracted? Was the data extraction form piloted?

A4. Section 4.1, Figure 4, page 49.

- Please clarify the source of the "additional" 26 citations.
- Please clarify the numbers of full text excluded studies. This is listed as 21, with 1 excluded due to the intervention, 1 the comparator and 7 excluded due to outcomes (total=9/21). Why were the other 12 studies excluded? Please also clarify the details of the outcomes that led to their exclusion (the current tables in the appendices do not report this information).
- Please clarify how "29 included studies" came to be categorised as "8 studies and 29 secondary publications."

A5. Appendices 2 and 6. RCT filters have been used in the clinical effectiveness searches and several filters have been used in the searches for economic studies and utilities, however no sources have been cited in the company submission. Please indicate whether published, validated filters have been used in each of these cases and give details of any alterations made to the filters.

A6. Appendix 2, Tables A1 and A2. Please clarify which platform was used to run the clinical effectiveness searches (some of the syntax resembles that used on Ovid but when the searches were re-run as presented there appeared to be some errors, such as missing brackets).

Network meta-analysis

A7. **PRIORITY QUESTION.** Section 4.9, page 99. Please provide a more complete explanation as to why a meta-analysis is "not applicable." Table 38 (page 123) of the

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company submission indicates that concomitant antibiotic use was the only key study difference for the Week 12 (Period A) data, thereby suggesting that the trials might be directly comparable for outcomes other than quality of life.

A8. Section 4.9, Page 99. Please clarify which patient and/or study characteristics are known or potential prognostic factors or treatment effect modifiers.

Clinical outcomes

A9. **PRIORITY QUESTION.** Section 4.1.1.4, page 47. Please produce a table to clarify exactly which instruments are being used to measure each of the outcomes specified in the decision problem: disease severity, clinical response, inflammation and fibrosis, discomfort and pain. Please give full details of these outcome measures, including any pre-defined and post-hoc thresholds such as clinical response and discontinuation (loss of response [LOR] and worsening of absence of improvement [WOAI]).

A10. **PRIORITY QUESTION.** Section 4.7.2.4, page 89. The hidradenitis suppurativa (HS) Clinical Response (HiSCR) is described in its validation study (reference 38 in the submission) as a "dichotomized clinical response", i.e. response / no response. Please explain and justify the validity of the HiSCR "partial responder" category. This is the first reference to this group other than in summary sections 1.3.1 and 1.4 in the Executive Summary, and the clinical effectiveness chapter summary on page 45. Is this a *post hoc* analysis group?

Adalimumab trial design

A11. **PRIORITY QUESTION.** Section 4.3.2, page 60. For PIONEER I and PIONEER II, please specify exactly who was blinded in these trials (patients and outcome assessors only?).

A12. **PRIORITY QUESTION.** Section 4.3.2 page 60. For PIONEER I and PIONEER II, did patients in either group (apart from placebo or adalimumab 40mg every week) receive any elements of supportive care?

- If so, what were they and were these comparable between groups?
- Apart from oral antibiotics, were there any other concurrent medications or interventions?

A13. **PRIORITY QUESTION.** Section 4.3.2 page 61. Please clarify who determined continuation of treatment by clinical response in PIONEER I and PIONEER II.

A14. **PRIORITY QUESTION.** Section 4.3.2 page 62. Patients in PIONEER I were excluded if they had received oral antibiotics for HS within 28 days before baseline visit whilst

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patients in PIONEER II were permitted to have oral antibiotic treatment. What was the reason for excluding patients receiving oral antibiotics in PIONEER I?

A15. **PRIORITY QUESTION.** Section 4.3.2, page 62. Please explain how participants had to be "*unresponsive or intolerant to oral antibiotics*" to be eligible for enrolment, yet were allowed to take doxycycline or minocycline if they were on a stable dose in PIONEER II, and were permitted "rescue therapy" antibiotics in PIONEER I?

A16. Section 4.1.6, Table 6, page 53 and Table 7 page 56. Please explain why the inclusion criteria for Kimball 2012 (Study M10-467) state that only patients with moderate and severe disease were eligible, whilst Table 11 states that approximately 70% of included patients in this study were diagnosed as Hurley Stage I or II (that is, people with mild and moderate disease).

A17. Section 4.3.2, page 64 and Table 9. Please explain why PIONEER I and II used different instruments to measure quality of life.

A18. Section 4.4, page 68. Please list the pre-specified and *post hoc* subgroup analyses (we acknowledge that some are specified in Sections 4.8.1 and 4.8.2).

A19. Section 4.13.2, page 120. Please explain why the PIONEER trials did not use HS Physician's Global Assessment (HS-PGA) alongside HiSCR? This would have enabled the trials to be pooled more easily in network meta-analysis and would have provided more robust evidence for the validity of HiSCR.

Assessment of bias

A20. **PRIORITY QUESTION.** Section 4.1.7, page 51 and Section 4.6, page 76. Risk of bias assessment.

- Please explain why different judgements of risk of bias are given in Appendix 4 compared with Section 4.6 for the M10-467 trial.
- Please explain why different judgements of risk of bias are given in Appendix 4 compared with 4.6 for the PIONEER trials.

A21. **PRIORITY QUESTION.** Section 4.1.7, page 51 and Section 4.6, page 76.

- Participant flow suggests that the risk of bias might be different between Period A and Period B in all trials (there are possible issues of allocation concealment, blinding and attrition in Period B). Different levels of risk in Period A and Period B of the M10-467 trial are acknowledged in Appendix 4, but only a single level of risk is considered for the PIONEER trials. Please conduct and report a separate risk of bias assessment for both Period A and Period B of the PIONEER trials.

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- Please also specify the source of the information being used to make the risk of bias assessments (abstracts or CSR).

A22. Section 4.1.4, page 48.

- The proposed risk of bias assessment described here relates only to the Cochrane tool for RCT evidence: the findings of this assessment are given in Appendix 4. However, Section 4.6 "Quality assessment of the relevant randomised controlled trials" uses and reports the findings of the "NICE checklist." Please explain and justify the use of two different tools.
- The open-label extension study (M12-555) was not randomised as all eligible participants received the adalimumab every week dose; please describe and justify the choice of risk of bias tool used to assess this study in Section 4.11.4.

A23. Section 4.6, page 76. Please clarify why several aspects of PIONEER I and II are judged to be at an intermediate risk of bias. Please provide a description on the likely direction and magnitude of bias.

Adalimumab trials - Participant flow

A24. **PRIORITY QUESTION.** Section 4.5.3, page 72. Please provide the correct participant flow diagram for PIONEER II (Figure 9 is a reproduction of the PIONEER I flow diagram).

A25. Section 4.3.1, page 57. Please explain the statement for M10-467: "*Patients who had received placebo in period 1 received initial blinded ADA 80 mg at week 16, and patients who had received active therapy in period 1 received blinded placebo at week 16.*" This does not appear to be consistent with the information that precedes it, or in Table 7, or the design described in Figure 5, in which all patients in Period 2 receive adalimumab every other week, irrespective of their initial randomisation.

A26. Section 4.3.2, page 60. For PIONEER I and PIONEER II, please clarify at what point it was determined that patients originally randomised to placebo were allocated in Period B to adalimumab every week or placebo for PIONEER I AND II respectively.

A27. Section 4.3.2, page 61. Please explain the statement: "*In PIONEER I, patients in the placebo arm were re-randomised to ADA mg EW*", as it appears that no randomisation was conducted: these patients were simply switched from placebo to adalimumab every week.

A28. Section 4.5.2, page 71. In Figures 8 and 9, for those who discontinued treatment in Period B, please define what the "other" category encompasses. Likewise, please give details (numbers and categorisation) of the "per protocol" reasons for

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discontinuation. For example, what was the reason for the "per protocol" discontinuation of 30/52 in the placebo/every week Period B group?

A29. Section 4.7.2.4, page 90. Please provide full details of the randomisation process after 12 weeks in PIONEER I and II. Were participants stratified by response in Period A?

Clinical effectiveness results

A30. **PRIORITY QUESTION.** Section 4.7.2.1, page 81-82. Please explain the reason for the placebo response (e.g. Figure 12 and Table 15).

A31. **PRIORITY QUESTION.** Section 4.12, page 107. The clinical study report for PIONEER II discusses the use of surgery during the trial period (page 282) in relation to adverse events, especially surgery relating to HS. Please provide data on pre-planned and unplanned surgery (which was designated an adverse event) in PIONEER I and II.

A32. Sections 4.7.1.1 and 4.7.1.2, pages 76-78 and Section 4.7.2.4, page 89-91. Please explain why the results have been presented for the every other week dose when this is unlicensed and has been described by the cited 2015 Cochrane review as "ineffective"?

A33. Section 4.7.2.1, page 81-82. Please explain why the treatment effect in PIONEER II appears to be greater than that in PIONEER I (e.g. Figure 12 and Table 15).

A34. Section 4.7.2.3, page 86. Please clarify whether these improvements in Dermatology Life Quality Index (DLQI) satisfy the criteria for Minimum Clinically Important Difference (MCID) (a difference of at least 4 points) as defined by Basra *et al* (Dermatology 2015;230: 27–33).

A35. Section 4.7.2.3, page 86-87. Please clarify whether these improvements in skin pain satisfy the criteria for a MCID.

A36. Section 4.11.1, page 101. Please provide discrete outcomes data for patients who did/did not receive the unlicensed adalimumab every other week dose on account of dose reduction if there were any instances other than the 3 patients mentioned in Section 4.12.3 (page 114).

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Section B: Clarification on cost-effectiveness data

Systematic literature review

B1. Appendix 6. Several filters have been used in the searches for economic studies and utilities, however no sources have been cited in the company's submission. Please indicate whether published validated filters have been used in each of these cases and give details of any alterations made.

Model structure: health states

B2. **PRIORITY QUESTION.** Section 5.2.3, pages 133-136. Please provide justification for the structure of the model, in particular, why the HiSCR response health states are segregated into "high response", "response" and "partial response." Why was the model not based on "response" and "no response" as per the PIONEER trials?

- Please also provide a health economic analysis using only the outcomes of response or no response.

B3. **PRIORITY QUESTION.** Section 5.4.4, page 167. The submission states that *"The differences in utility values between health states were statistically significant."* However, in Table 47 of the submission, the 95% confidence intervals for HRQoL for the states of partial response and non-response, and the 95% confidence intervals for HRQoL for the states of high response and response, are overlapping. Please provide further justification for including these as separate states in the model.

B4. Section 5.5.3, page 174. Given that surgery is a key driver of cost in the model, why did the model structure not include surgery as a health state?

Resource use rates

B5. **PRIORITY QUESTION.** Section 5.5.3, page 174. Please provide data on the number of surgical procedures received by patients allocated to adalimumab or placebo within the PIONEER I and II trials.

- Was a reduction in surgery observed in the adalimumab every week groups, compared with the placebo groups?
- Please provide any available data collected from these studies with respect to the number of surgical procedures received in patients achieving "high response", "response", "partial response" and "no response" in each treatment group.
- Is there any other evidence to suggest that patients achieving response undergo fewer surgical procedures?

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B6. **PRIORITY QUESTION.** Section 5.5.3, page 174. Please provide further information on the UK Physician Survey used to inform the resource use assumptions within the model.

- In particular, please explain how estimates were elicited from experts and how these were aggregated across respondents.
- Please provide a copy of the questionnaire document administered to participants in the survey.

B7. **PRIORITY QUESTION.** The executable model appears to predict that patients receiving standard care undergo approximately 34 inpatient surgical admissions over their lifetime (this was derived by setting the cost of inpatient surgical admission to 1, setting all other unit costs to zero, setting the discount rate to zero and calculating the total surgery-related cost). Please provide evidence to support the validity of this prediction.

B8. Section 5.5.3.2, Table 52, page 175. The submission reports the costs of non-surgical inpatient admissions used in the model. Please clarify why patients would require non-surgical inpatient admission. What types of events are these admissions intended to capture?

Costs

B9. **PRIORITY QUESTION.** Section 5.5.2, page 173. Please clarify why the costs of concomitant and rescue medications received by patients in the PIONEER trials were not included in the model. Please summarise the use of concomitant and rescue medications in the PIONEER trials.

- Please provide an analysis in which the costs of these are included in the model.

B10. Section 5.5.3.3, Table 54, pages 176-177. The costs of some severe adverse events appear very high (in particular, nasopharyngitis cost=£908.28 and headache cost=£674.21). Please explain which Reference Costs codes were used for these and justify their use in the model.

B11. Section 5.5.2, pages 173-174. Why is the cost of adalimumab treatment applied only to those patients who are compliant? Would some patients receive the drug but not take it? How does the company expect this to affect the cost effectiveness of adalimumab?

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Utility values

B12. Section 5.4, Table 46, page 155. The table footnote "m" states that the *"method of elicitation and valuation of EQ-5D scores was not clearly reported."* Given that the clinical study report was available to the company, please explain why this information could not be ascertained.

Inputs from trial data

B13. **PRIORITY QUESTION.** Section 5.3.1.1, page 138. The submission states: *"For patients non-responding to ADA at week 36 the discontinuation rate from the OLE clinical trial[32] was only applied up to week 48 in the base case. This was based on input from clinical experts suggesting that patients who do not respond to ADA treatment will be discontinued in clinical practice after a re-assessment period and 12 additional weeks of treatment[40-42 44]."* Please explain the mathematical logic underpinning the implementation of this assumption within the model. Is this assumption of continued adalimumab use assumed to apply only to the 36-48 week time period or is it intended to be applied to all subsequent cycles beyond week 48?

B14. **PRIORITY QUESTION.** Section 4.13, page 122. The submission states *"There are also differences in study design between PIONEER I and PIONEER II, as shown in Table 38 below, which means that the results of PIONEER I and PIONEER II are not directly comparable."*

- Please comment on the appropriateness of pooling these data within the model.
- Please explain how the data were pooled.

B15. Section 5.3.1, page 138. Please provide a justification for breaking the randomisation and combining responses across treatment arms rather than combining treatment effects across studies.

Transition probabilities

B16. **PRIORITY QUESTION.** Section 5.3.1.3, page 142. The submission states *"For patients on ADA TPs were estimated using a generalised logit model using week 0-24 data from the OLE trial, which corresponds to week 36-60 if counting from the initiation of the PIONEER phase III trials; LOCF was used when conducting the analysis since less than half of the patients had follow-up up to 24 weeks at the time of the interim data cut."* Please provide an alternative generalised logit model analysis which does not include any imputation for this population. Please also confirm that imputation was not used in the generalised logit models for the standard care group or the group that discontinued treatment with adalimumab.

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B17. **PRIORITY QUESTION.** Company's model. Please explain the matrix presented in worksheet "Transition probabilities" in cells E124:N134. Why is the transition probability in cell N130 cubed?

B18. Section 5.3.1.3, page 142. The submission states that *"Patients who received ADA in the induction period and switched to placebo in the maintenance period in the trials were used to estimate TPs for ADA discontinuers."* Does this population reflect all adalimumab induction responders who were switched to placebo, or all patients who were initially randomised to adalimumab irrespective of whether they responded at 12 weeks?

B19. Section 5.3.1.3, page 142. The submission states *"The TPs for the SC arm were estimated using all patients who received placebo in both induction and maintenance periods of the clinical trials."* However, elsewhere the submission states that patients could only receive placebo in both the induction and maintenance phase of PIONEER II. Please clarify.

B20. Section 5.3.1.3, pages 140-143. With respect to the extrapolation of transition probabilities, why was the generalised logit model chosen over the ordered logit? What alternative approaches were considered and why were they not selected?

Cost-effectiveness results

B21. **PRIORITY QUESTION.** Section 5.7.2, Table 58, page 185. Please clarify how the values in the columns "Predicted in the CEA" have been calculated. Which treatment group(s) do they represent? Why are the values in the table different to those in the actual Markov traces in the model? Please provide an alternative validation analysis split by treatment group and by individual trial.

Sensitivity analyses

B22. Section 5.6.1, Table 55, page 178. Why was the compliance rate for adalimumab not varied in the probabilistic sensitivity analyses?

B23. Section 5.8.4, Figure 28, page 193. Please clarify the value of lambda used to estimate net monetary benefits in the tornado diagram.

Other model assumptions

B24. **PRIORITY QUESTION.** Company's model. Within the model, patients can discontinue adalimumab therapy due to a lack of response during induction or by losing a prior response during maintenance.

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- Please comment on whether the wording of the Summary of Product Characteristics (SmPC) implies that a full or partial HiSCR response is required in order to begin maintenance therapy.

- Please comment on the extent to which the assumption that patients who lose response continue maintenance treatment for a further 12 weeks is in line with the wording of the SmPC.

B25. Section 5.3.1.1, page 138. Please justify why the discontinuation rate was assumed to be independent of response?

B26. Section 5.11, page 196. The submission states: *"… in the real world, patient compliance is likely to be lower than that observed in the clinical trials."* Please comment on the level of compliance that has been observed based on the real-world experience with adalimumab for other clinical indications?

B27. Company's model. In the "Parameters" worksheet, the resource use and cost parameters are characterised using gamma distributions whereby the standard error is defined as 25% of the mean. Please justify the use of these standard errors.

Executable model

B28. The worksheet "GLM" includes cells which refer to the every other week dosing regimen (cells J23:J25). Please confirm that data relating to patients receiving the every other week regimen were not included in the generalised logit model.

B29. **PRIORITY QUESTION.** It is unclear exactly which patient populations have been used to inform the various transition matrices within the model. Please complete the right hand column in Table 1 below. Please provide as much detail as required.

Table 1: Description of patients used to inform model transition matrices

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
Standard care		
Live_SC0to2	S11:V14	PLEASE COMPLETE
Live_SC2to4	S19:V22	PLEASE COMPLETE
Live_SC4to8	S27:V30	PLEASE COMPLETE
Live_SC8to12	S35:V38	PLEASE COMPLETE
Live_SC12to16	S43:V46	PLEASE COMPLETE
Live_SC16to20	S51:V54	PLEASE COMPLETE
Live_SC20to24	S59:V62	PLEASE COMPLETE

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Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
Live_SC24to28	S67:V70	PLEASE COMPLETE
Live_SC28to32	S75:V78	PLEASE COMPLETE
Live_SC32to36	S83:V86	PLEASE COMPLETE
Live_SC36toEnd	S91:V94	PLEASE COMPLETE
Adalimumab		
Live_ADA0to2	G11:J14	PLEASE COMPLETE
Live_ADA2to4	G19:J22	PLEASE COMPLETE
Live_ADA4to8	G27:J30	PLEASE COMPLETE
Live_ADA8to12	G35:J38	PLEASE COMPLETE
Live_all_12to16	G43:N50	PLEASE COMPLETE
Live_all_16to20	G55:N62	PLEASE COMPLETE
Live_all_20to24	G67:N74	PLEASE COMPLETE
Live_all_24to28	G79:N86	PLEASE COMPLETE
Live_all_28to32	G91:N98	PLEASE COMPLETE
Live_all_32to36	G103:N110	PLEASE COMPLETE
Live_all_36toEnd	G115:N122	PLEASE COMPLETE
live_all_48toend	G127:N134	PLEASE COMPLETE
Live_ADAtoSC_12to16	G139:J142	PLEASE COMPLETE
Live_ADAtoSC_16to20	G147:J150	PLEASE COMPLETE
Live_ADAtoSC_20to24	G155:J158	PLEASE COMPLETE
Live_ADAtoSC_24to28	G163:J166	PLEASE COMPLETE
Live_ADAtoSC_28to32	G171:J174	PLEASE COMPLETE
Live_ADAtoSC_32to36	G179:J182	PLEASE COMPLETE
Live_ADAtoSC	G187:J190	PLEASE COMPLETE

Section C: Textual clarifications and additional points

Health condition and position of technology in the treatment pathway

C1. **PRIORITY QUESTION.** Section 3.2, page 42. Please clarify the anticipated position of adalimumab within the treatment pathway.

- Is adalimumab to be used only before surgery (as claimed on page 42), or is adalimumab to be used alongside surgery and/or after surgery?
- In addition, please clarify whether adalimumab would be used before treatments such as dapsone, retinoids and immunomodulators (as suggested on page 42) or

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only after all other treatment options have been exhausted (as suggested on page 140).

- Please also comment on how this anticipated positioning relates to the populations recruited into the PIONEER I and II trials.

C2. Section 2.4, page 29. The submission states that *"only around 37% of patients with diagnosed moderate to severe HS are suitable for biologic treatment."* Please explain why this value is different to the estimates reported in Section 4.13.3 and Table 39?

C3. Section 3.1, page 33. Please explain why the UK prevalence rates (approximately 1million adults) are different from the rates given in Section 4.13.3 and Table 39.

C4. NICE has noted there is a large volume of information marked as confidential in the company submission. A separate request will be sent to the company, however please consider lifting the confidentiality status of the data in the submission in advance of receiving a formal request.

AbbVie response to clarification questions from the Evidence Review Group (ERG), received 10th November 2015

Section A: Clarification on effectiveness data

Systematic literature review

A1. Section 4.1.1, pages 46-47. Please clarify that these inclusion criteria apply to the potential network meta-analysis outlined in Section 4.10 and not to the decision problem or the review that has been conducted and described in Sections 4.2 to 4.9.

AbbVie Response: The inclusion criteria specified in section 4.1.1 apply to both the systematic literature search performed to gather evidence on the comparative efficacy and safety of interventions in HS (as presented in section 4.1) and the potential network meta-analysis as outlined in Section 4.10. The objective of the systematic review was to identify and select all relevant studies for this appraisal as per NICE scope and decision problem.

A2. Section 4.1, page 48. Please provide a description of the methods of synthesis or meta-analysis of the evidence described and reported in sections 4.2-4.9, and the rationale underpinning these.

AbbVie Response: Evidence extracted from the systematic literature review (described in section 4.1) was summarised and then reported in tabulated form. Data extracted included study characteristics, patient's baseline characteristics, efficacy and safety outcomes of interest. Data on study characteristics have already been presented in the submission of evidence. Table 1 provides the baseline characteristics of patients across the selected studies and Table 2 and Table 3 summarize the relevant efficacy and safety outcome data available, respectively, for each included study.

Table 1: Patient's baseline characteristics

Reference	Interventions	Sample size	Age (y)	% Females	Disease duration (y)	Weight (kg)	BMI (kg/m^2)	% Nicotine users	% prior antibiotic users	Race			BMI (kg/m^2)	Modified Sartorius score	HS Severity		CRP (mg/L)	Pain		DLQI
										% Caucasian	% African	% Asian			Criteria	% of patients		VAS	NRS30[a]	
Biologics																				
Error! Reference source not found. 2010	Etanercept	10	40	60			33.5			90.0			34							
	Placebo	10	36.7	70			32.1			100.0			32							
Error! Reference source not found. 2010	Infliximab	15	34	80						53.3	20.0				HSSI#	7/93	20.0	53.3		17.2
	Placebo	23	33.2	60.9						26.1	30.0				HSSI#	22/78	36.0	49.7		16.5
Error! Reference source not found.	Placebo	163	36.1	69.3	11.8	95.7	32.9	67.3	98.2	79.8	12.3	2.5		122.6	Hurley I/II/III	0/55/45	18.3		6.2	14.9
	Adalimumab 40 mg EW	163	34.9	66.3	11.3	90.2	31.3	64.4	99.4	87.7	5.5	3.7		107.5	Hurley I/II/III	0/53/47	13.3		5.7	14.1
Error! Reference source not found.	Placebo	154	37.8	68.2	11.6	99.3	34.5	59.7	100	76.6	18.8	1.9		147.3	Hurley I/II/III	0/53/47	17.4		6	16
	Adalimumab 40 mg EW	153	36.2	59.5	11.3	97.1	33	52.9	100	75.8	21.6	0.7		151	Hurley I/II/III	0/52/48	20.3		6	16.3
Error! Reference source not found.2012	Placebo	51	37.8	70.6	13.4	96.5		56.9	7.8	72.5	15.7				Hurley III vs. I/II	71/29	13.3	57.8		15.4
	Adalimumab 40 mg EOW	52	36.1	73.1	10.9	99.8		50	9.6	69.2	23.1				Hurley III vs. I/II	71/29	17.8	53		13.5
	Adalimumab 40 mg EW	51	35.1	70.6	11.3	95.4		58.8	17.6	72.5	17.6				Hurley III vs. I/II	71/29	22.0	52		16.4
Error! Reference source not found.2011	Adalimumab 40 mg EOW	15	38.7	80		32							32	45.2	Hurley I vs. II/III	0/100		58		16.1
	Placebo	6	40.2	83.3		32.4							32	32.83	Hurley I vs. II/III	0/100		36.2		8.3
Non-biologics (antibiotics only)																				
Error! Reference source not found. 1998	Tetracycline-Systemic	24	31.8^	54											Hurley III vs. I/II	0/100				
	Clindamycin-Topical	22	33.3^	68											Hurley III vs. I/II	0/100				

Surgery																			
Error! Reference source not found. 2009	Laser + topical antibiotics	22	41.0	86.4											Hurley I vs. II/III	0/100			
	Topical antibiotics	22	41.0	86.4											Hurley I vs. II/III	0/100			

HS-PGA: Hidradenitis Suppurativa Physician's Global Assessment; HSSI: Hidradenitis Suppurativa Severity Index; VAS: Visual Analog Scale; NRS30: Global skin pain numerical rating scale; DLQI: Dermatology Life Quality Index Mean values are presented unless specified; Patient skin pain assessment as assessed on VAS; # moderate vs severe; ^median age; [a] NRS30 at worst (≥3)
Note: Table includes baseline parameters reported in ≥2 studies.

Table 2: Reporting of efficacy outcomes of interest across the included studies

Reference	Interventions	% with Clinical Response			Patient Disease Activity Scores (mean/median)					Pain and Quality of life				
		HiSCR	HS-PGA	HSSI	HS-PGA	HS-LASI*	Sartorius	Modified Sartorius	Hurley	Pain-VAS	Pain-NRS30	Pain-Other**	DLQI	MDI
Biologics														
Error! Reference source not found. 2010	Etanercept vs. Placebo				X[#] (wk 12, 24)							X[#] (wk 12, 24)	X[#] (wk 12, 24)	
Error! Reference source not found. 2010	Infliximab vs. Placebo			X (wk 8)	X (wk 8)					X (wk 8)			X (wk 8)	
Error! Reference source not found.	Adalimumab EW vs. Placebo	X (wk 12)						X (wk 12)			X (wk 12)	X (wk 12)	X (wk 12)	
Error! Reference source not found.	Adalimumab EW vs. Placebo	X (wk 12)						X (wk 12)			X (wk 12)	X (wk 12)	X (wk 12)	
Error! Reference source not found. 2012	Adalimumab EW vs. Adalimumab 40 mg EOW vs. Placebo	X (wk 4, 12, 16)	X (wk 12, 16)					X (wk 12)		X (wk 2, 4, 8, 12, 16)			X (wk 16)	
Error! Reference source not found. 2011	Adalimumab EOW vs. Placebo						X (wk 6, 12, 24)		X (wk 6, 12, 24)	X (wk 6, 12, 24)			X (wk 12, 24)	
Non-biologics														
Error! Reference source not found. 1998	Tetracycline- Systemic vs. Clindamycin-Topical				X (wk 4, 8, 12, 16)									
Surgery														
Error! Reference source not found. 2009	Laser + topical antibiotics vs. Topical antibiotics					X (m 1, 2, 3, 6)								

HiSCR: Hidradenitis Suppurativa based Clinical Response; HS-PGA: Hidradenitis Suppurativa-Physician Global Assessment; HSSI: Hidradenitis Suppurativa Severity Index; HS-LASI: Hidradenitis Suppurativa Lesion, Area, and Severity Index; VAS: Visual Analog Scale; NRS30: Global Assessment of Skin Pain numerical rating scale; DLQI: Dermatology Life Quality Index; MDI: Major Depression Inventory X represents the study outcome available for extraction. wk: week; m: month; EW: weekly; EOW: Every other week *Modified HS-LASI score; **HS Pain on a scale of 0 (no pain) to 5 (worst pain) [#] No values reported, only descriptive text and/or bar-graphs were available

Table 3 : Reporting of safety outcomes of interest across the included studies

Reference	Interventions	Safety Outcomes	
		Discontinuations due to Adverse events	Serious adverse events
Biologics			
Adams 2010	Etanercept vs. Placebo		
Error! Reference source not found. 2010	Infliximab vs. Placebo		X (week 8)
Error! Reference source not found.	Adalimumab EW vs. Placebo	X (week 12)	X (week 12)
Error! Reference source not found.	Adalimumab EW vs. Placebo	X (week 12)	X (week 12)
Error! Reference source not found. 2012	Adalimumab EW vs. Adalimumab EOW vs. Placebo	X (week 16)	X (week 16
Miller 2011	Adalimumab EOW vs. Placebo		
Non-biologics			
Jemec 1998	Tetracycline- Systemic vs. Clindamycin-Topical		
Surgery			
Tierney 2009	Laser + topical antibiotics vs. Topical antibiotics		

X represents the study outcome available for extraction.
EW: weekly; EOW: Every other week

A3. Section 4.1, page 48. Please give details of the data extraction process followed by the company. Who conducted the data extraction? What measures were taken to minimise bias in the process? Which data were extracted? Was the data extraction form piloted?

AbbVie Response: Data were extracted for the study characteristics, patient's baseline characteristics, efficacy and safety outcomes of interest, by two independent reviewers for each eligible trial (Table 4). In case of discrepancies between the two reviewers, a third reviewer provided arbitration.

Where more than one report of an individual study existed, reports were grouped together and the report with the most complete data was used in the analyses. Relevant outcomes that were only published in secondary publications were also extracted.

Table 4: Data extraction

Field	Details
Study characteristics	• Study design (e.g. double blind, open label, cross-over, etc.) • Trial name • Location(s) of study • Study duration • Study inclusion criteria • Study exclusion criteria • Outcome definitions
Intervention characteristics	• Drug name • Treatment dose • Route and frequency of administration • Duration • Concomitant/background therapies
Patient's baseline characteristics	• Age • Sex • Race or ethnic group • Smoking status • Disease duration • Body weight and body mass index • C-reactive protein level • Hurley stage • HS severity index (HSSI) • Prior treatment history • DLQI • HS-Physician's global assessment (HS-PGA)
Efficacy outcomes	• Clinical response (HiSCR, HS-PGA, HSSI) • Hurley score • HS-PGA score (overall and components: abscesses, inflammatory nodules and fistulas) • HS-Lesion, activity and severity (HS-LASI) score • Patient skin pain assessment • (Modified) Sartorius score • Dermatology life quality index (DLQI) • Major depression inventory (MDI)
Safety outcomes	• Discontinuations due to adverse events • Serious adverse events

A4. Section 4.1, Figure 4, page 49.

- Please clarify the source of the “additional” 26 citations.

  AbbVie Response: The additional 26 records were retrieved from clinicaltrial.gov searches. The PRISMA flow diagram has been updated to reflect this change (see Figure 1).

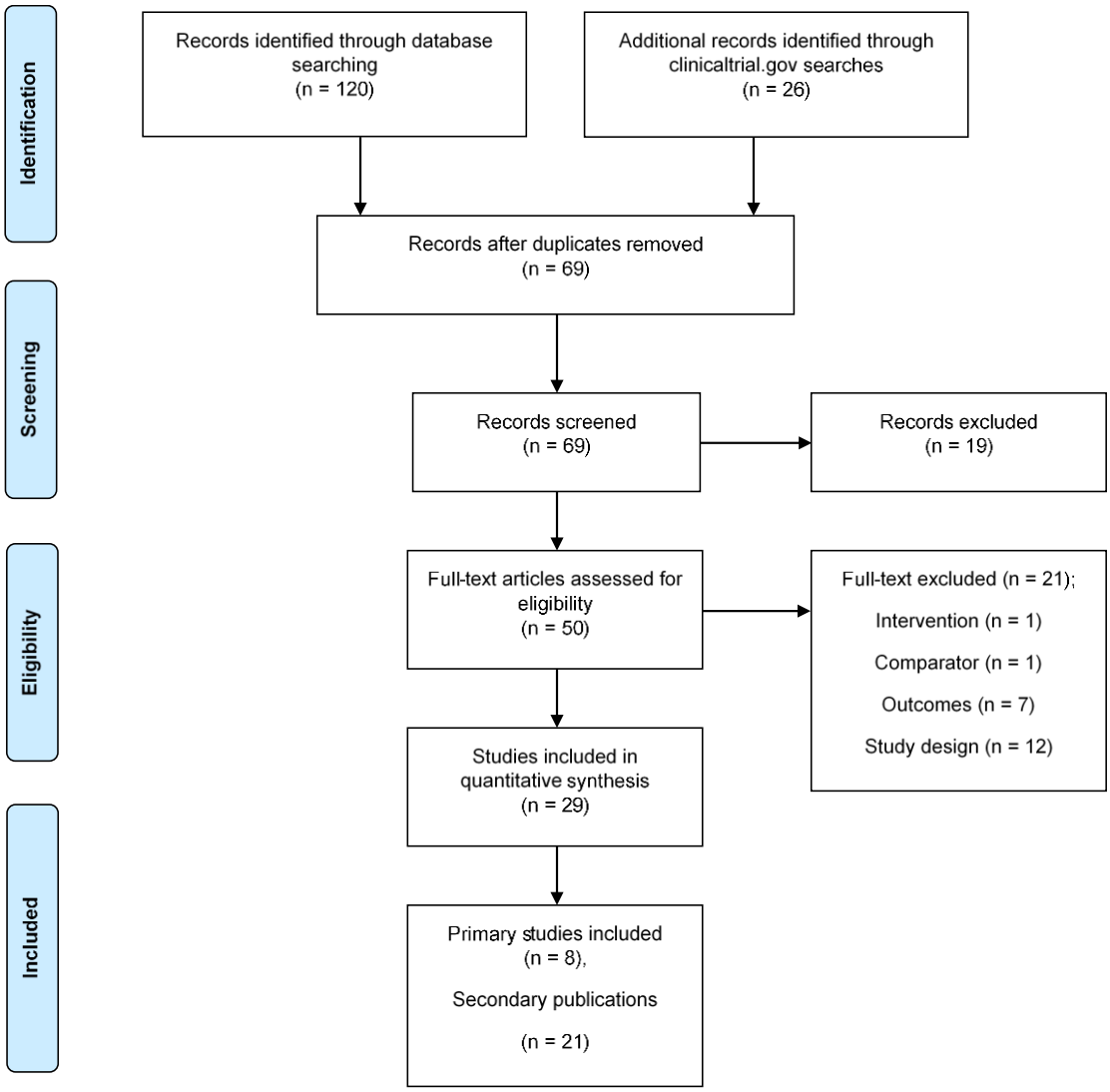
- Please clarify the numbers of full text excluded studies. This is listed as 21, with 1 excluded due to the intervention, 1 the comparator and 7 excluded due to outcomes (total=9/21). Why were the other 12 studies excluded? Please also clarify the details of the outcomes that led to their exclusion (the current tables in the appendices do not report this information).

  AbbVie Response: Studies were excluded due to the following reasons: intervention (n = 1), comparator (n = 1), outcomes (n = 7) and study design (n = 12). The PRISMA flow diagram has been updated to reflect this change (see Figure 1).

- Please clarify how “29 included studies” came to be categorised as “8 studies and 29 secondary publications.”

  AbbVie Response: The text should read "21 secondary publications". The PRISMA flow diagram has been updated to reflect this change (see Figure 1).

Figure 1: Systematic Review PRISMA flow diagram



A5. Appendices 2 and 6. RCT filters have been used in the clinical effectiveness searches and several filters have been used in the searches for economic studies and utilities, however no sources have been cited in the company submission. Please indicate whether published, validated filters have been used in each of these cases and give details of any alterations made to the filters.

AbbVie Response: For clinical effectiveness, a valid RCT filter from the "Cochrane Handbook for Systematic Reviews of Interventions" was used. (http://handbook.cochrane.org/chapter_6/box_6.4.d_cochrane_hsss_2008_sensprec_ovid.htm).

The economic search strategy filter was sourced from SIGN (http://www.sign.ac.uk/methodology/filters.html). This is a validated source of search strategy filters and is recognised and recommended by HTA agencies including NICE. Few terms were added in this filter to further ensure that no important study was missed (see Table 5). No term was omitted from the filter.

Table 5: Additional terms added to the SIGN economic filter

fee:ab,ti OR fees:ab,ti
(value NEXT/2 (money OR monetary)):ab,ti
'quality adjusted life year'/exp
'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR qualy*:ab,ti
'hospitalization'/exp
'consumer satisfaction'/exp
'patient acceptance of health care'
'disease management'
'physician practice patterns'
'health care rationing'
((clinical OR critical OR patient) NEXT/1 path*):ab,ti
(managed NEXT/2 (care OR clinical OR network)):ab,ti
(resource* NEXT/2 allocat*):ab,ti

The quality of life search strategy filter was based on the utility studies search method and terms developed by ScHARR[1].

A6. Appendix 2, Tables A1 and A2. Please clarify which platform was used to run the clinical effectiveness searches (some of the syntax resembles that used on Ovid but when the searches were re-run as presented there appeared to be some errors, such as missing brackets).

AbbVie Response: Embase and Medline were searched through "Ovid" platform. Please see below the updated Tables A1 and A2.

Table A1: Embase search strategy

Database: Embase <1974 to 2015 July 20>
Date of search strategy: 20 July, 2015

No.	Terms	No. of hits
1	exp hidradenitis suppurative/	1539
2	(hidradenitis suppurativa or hidradenitis supportiva or acne inversa or apocrine acne or apocrinitis or fox-den disease or pyodermia fistulans significa or velpeaus disease or verneuils disease).ti,ab.	1393
3	or/1-2	1812
4	randomized controlled trial/	379976
5	exp controlled clinical trial/	517438
6	randomized.ab.	440867
7	placebo.ab.	214380

8	exp "clinical trial topic"/	155274
9	randomly.ab.	297748
10	trial.ti.	186723
11	or/4-10	1219941
12	letter.pt.	898999
13	editorial.pt.	484418
14	exp retrospective studies/	414240
15	cohort studies/	208917
16	cohort analysis/	208917
17	(observational adj3 (study or studies or design or analysis or analyses)).mp.	128675
18	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).mp.	622364
19	(comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence or posters or News or Newspaper article or meeting abstracts or lectures or interview or historical article or handbooks or guidelines or guidebooks or essays or editorial or database or comment or clinical conference or catalogs) not "randomized controlled trial".pt.	5062812
20	animal/	1679151
21	human/	16007806
22	20 not (20 and 21)	1263360
23	or/12-19,22	6880312
24	(3 and 11) not 23	65
25	Limit 24 to english language	62
26	remove duplicates from 25	61

Table A 2: Medline search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present>
Date of search strategy: 20 July, 2015

No.	Terms	No. of hits
1	exp hidradenitis suppurative/	727
2	(hidradenitis suppurativa or hidradenitis supportiva or acne inversa or apocrine acne or apocrinitis or fox-den disease or pyodermia fistulans significa or velpeaus disease or verneuils disease).ti,ab.	1068
3	or/1-2	1166
4	randomized controlled trial.pt.	405925
5	controlled clinical trial.pt.	91275
6	randomized.ab.	328723
7	placebo.ab.	166504
8	clinical trials as topic.sh.	177402
9	randomly.ab.	237142
10	trial.ti.	144799
11	or/4-10	986174
12	letter.pt.	943149

13	editorial.pt.	390976
14	exp retrospective studies/	545626
15	cohort studies/	184404
16	cohort analysis/	184404
17	(observational adj3 study or studies or design or analysis or analyses)).ti,ab.	74500
18	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.	285376
19	((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence or posters or News or Newspaper article or meeting abstracts or lectures or interview or historical article or handbooks or guidelines or guidebooks or essays or editorial or database or comment or clinical conference or catalogs) not "randomized controlled trial").pt.	4020735
20	animal/	5542482
21	human/	14237507
22	20 not (20 and 21)	3988434
23	or/12-19,22	8570458
24	(3 and 11) not 23	28
25	limit 24 to english language	28
26	remove duplicates from 25	27

Network meta-analysis

A7. **PRIORITY QUESTION.** Section 4.9, page 99. Please provide a more complete explanation as to why a meta-analysis is "not applicable." Table 38 (page 123) of the company submission indicates that concomitant antibiotic use was the only key study difference for the Week 12 (Period A) data, thereby suggesting that the trials might be directly comparable for outcomes other than quality of life.

AbbVie Response: Efficacy data from the PIONEER I & II trials has been presented in the submission of evidence both for the individual trial sets and as a pooled analysis where all patients were analysed together as one dataset. As such a pair-wise meta-analysis has not been presented for the efficacy and safety outcomes of the PIONEER I & II trials.

A8. Section 4.9, Page 99. Please clarify which patient and/or study characteristics are known or potential prognostic factors or treatment effect modifiers.

AbbVie Response: Potential effect modifiers within and between direct comparisons as presented in Appendix 5 of the submission include:

- Age: The variation in mean age across the comparisons of biologics was not significant, age was therefore not considered as an effect modifier.
- Gender: Females are associated with a higher risk of HS, but the association with disease severity has not been established, hence not considered as an effect modifier.
- Disease duration: There was a slight variation in the disease duration between trials, however, it was not considered as an effect modifier.

- Race and ethnicity: Due to the absence of evidence on association of race or ethnicity with HS, they were not considered as effect modifiers.
- Weight and body mass index: Albeit obesity being associated with HS severity, due to not substantial variations in the weight and BMI, these were not considered as effect modifiers.
- Prior and concomitant medication: Not possible to draw a meaningful comparison due to prior therapy not uniformly reported across studies.
- Smoking status: Higher proportion of nicotine users in PIONEER II study could contribute to heterogeneity among the adalimumab vs. placebo comparisons.
- C-reactive protein levels: Patients with an elevated CRP will elicit a better response to biologics compared to those with lower levels of inflammation; hence mean CRP at baseline is considered as a potential effect modifier.
- Disease severity: A higher proportion of severe HS disease could contribute to heterogeneity among the adalimumab and infliximab comparisons.
- Patient's skin pain assessment: Due to a moderate variation in the mean pain score at baseline, pain on VAS was not considered as an effect modifier.
- Dermatology Life Quality Index (DLQI): DLQI at baseline was not considered as an effect modifier.

Clinical outcomes

A9. **PRIORITY QUESTION.** Section 4.1.1.4, page 47. Please produce a table to clarify exactly which instruments are being used to measure each of the outcomes specified in the decision problem: disease severity, clinical response, inflammation and fibrosis, discomfort and pain. Please give full details of these outcome measures, including any pre-defined and post-hoc thresholds such as clinical response and discontinuation (loss of response [LOR] and worsening of absence of improvement [WOAI]).

AbbVie Response: Table 6 summarises the instruments used to measure each of the outcomes specified in the decision problem.

Table 6: Instruments used to measure each of the outcomes specified in the decision problem

	Outcomes			
	Disease severity	**Clinical response**	**Inflammation and fibrosis**	**Discomfort and pain**

Instruments	Hurley stage	HiSCR,	Hurley stage,	NRS 30 skin pain (at worst and on average)
	Modified Sartorius Score,	AN counts/lesion counts,	HiSCR,	
	representative lesions,	modified Sartorius Score	AN counts/lesion counts,	
	AN counts/lesion counts		erythema assessments	
			representative lesions	

Loss of response (LOR) was defined as a loss of at least 50% of the improvement (50% reduction) in the AN count achieved from Baseline to Week 12.

Worsening or Absence of Improvement (WOAI) was defined as an Abscess and inflammatory nodule (AN) count greater than or equal to the AN count at Baseline on two consecutive visits (excluding Week 12) occurring at least 14 days apart.

Disease severity was measured by Hurley staging. In addition, lesion severity scores were used to assess lesion severity of baseline representative lesion. Each lesion was evaluated in three categories (erythema, tenderness, and size) with severity scores ranging from 0 – 3 in each category, where higher scores denote worse conditions. Patient's Lesion Severity Score for each subject, the Average Lesion Severity Score for each lesion type, and the Lesion Severity Score in each category (erythema [E], tenderness [T], and size [S]) for each lesion type were evaluated.

A10. **PRIORITY QUESTION.** Section 4.7.2.4, page 89. The hidradenitis suppurativa (HS) Clinical Response (HiSCR) is described in its validation study (reference 38 in the submission) as a “dichotomized clinical response”, i.e. response / no response. Please explain and justify the validity of the HiSCR “partial responder” category. This is the first reference to this group other than in summary sections 1.3.1 and 1.4 in the Executive Summary, and the clinical effectiveness chapter summary on page 45. Is this a *post hoc* analysis group?

AbbVie Response: HiSCR was developed as a dichotomized response/no response endpoint and responders met a pre-specified definition of at least a 50% improvement of abscess and inflammatory nodule (AN) count with no increase in either abscess or draining fistula counts. HiSCR Partial Responders are those patients who achieved a partial response, defined as ≥ 25% reduction in AN count relative to baseline, but did not achieve HiSCR response in the PIONEER trials at week 12. In the PIONEER I and II studies it was noted that subjects in the nonresponder population (those who had not achieved HiSCR at week 12) achieved

a higher rate of HiSCR with continued adalimumab EW treatment, as compared to subjects receiving Adalimumab EOW or placebo. As such in order to identify an appropriate population where continued treatment could be beneficial, a post hoc analysis was performed on the proportion of subjects in the nonresponder population achieving a partial HiSCR, or AN25 (defined as a 25% reduction in AN count relative to Baseline at the end of Period A). The new population defined post-hoc included partial responders and HiSCR responders at the end of Period A. In this population, HiSCR rate at Week 36 with EW/EW dosing [redacted] was higher compared with EW/EOW dosing [redacted] or EW/PBO dosing [redacted] suggesting that continuous weekly dosing is the most efficacious dosing strategy and that this is the most appropriate population for treatment. Results also showed that the utility of continuing adalimumab EW dosing was concentrated among the subset of non-responders who had achieved at least AN25 (partial responders) at the end of Period A [redacted] of partial responders in the EW/EW group achieved HiSCR at Week 36).

Adalimumab trial design

A11. **PRIORITY QUESTION.** Section 4.3.2, page 60. For PIONEER I and PIONEER II, please specify exactly who was blinded in these trials (patients and outcome assessors only?).

AbbVie Response: All enrolled patients, all study site staff (including all sub-Investigators and Investigators), and all Sponsor personnel were blinded to treatment randomisation. An Independent Data Monitoring Committee (IDMC) was established to monitor routine safety and efficacy data and provided AbbVie guidance on the overall conduct of the trial. The IDMC was unblinded in its assessment of safety and efficacy data and ensured that continued exposure to adalimumab during the studies was justified.

A12. **PRIORITY QUESTION.** Section 4.3.2 page 60. For PIONEER I and PIONEER II, did patients in either group (apart from placebo or adalimumab 40mg every week) receive any elements of supportive care?

- If so, what were they and were these comparable between groups?

  AbbVie Response: Patients in the PIONEER I and PIONEER II did not receive any "supportive care" interventions (such as tobacco cessation or weight control counselling).

- Apart from oral antibiotics, were there any other concurrent medications or interventions?

  AbbVie Response: All subjects in both PIONEER I and II were instructed to use a daily antiseptic wash (chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater) to their HS affected body regions. Lesion interventions were also permitted per protocol specified guidelines in either group. Only two types of interventions were allowed: (1) injection with intralesional triamcinolone acetonide suspension and (2) incision and drainage.

A13. **PRIORITY QUESTION.** Section 4.3.2 page 61. Please clarify who determined continuation of treatment by clinical response in PIONEER I and PIONEER II.

AbbVie Response: In both the PIONEER I and II trials, all patients randomised to Adalimumab in Period A were re-randomised at the week 12 visit into one of 3 treatment arms, stratified by treatment response (responder vs. non-responder) and baseline Hurley stage. Subjects who had been randomised to placebo in Period A were (using re-randomisation numbers to maintain the blind) to continue on blinded placebo from week 12 through week 35 (Study M11-810) or to receive adalimumab 160 mg at week 12, adalimumab 80 mg at week 14, matching placebo at Weeks 13 and 15, and adalimumab 40 mg every week from week 16 through week 35 (Study M11-313).

While there were no specific factors that determined continuation of treatment by clinical response at this week 12 visit, patients did have the opportunity to early escape to the open label extension trial (M12-555) as early as the week 16 visit and beyond based on WOAI or LOR protocol definitions. Additionally, any patient could have discontinued treatment at any time during study participation for any reason.

A14. **PRIORITY QUESTION.** Section 4.3.2 page 62. Patients in PIONEER I were excluded if they had received oral antibiotics for HS within 28 days before baseline visit whilst patients in PIONEER II were permitted to have oral antibiotic treatment. What was the reason for excluding patients receiving oral antibiotics in PIONEER I?

AbbVie Response: In the U.S. the FDA requested not to include antibiotics in the study while in Europe the EMA advised that patients should be able to continue antibiotics. Thus, in PIONEER I, which was primarily conducted in the US, antibiotics were excluded and in PIONEER II oral antibiotics were allowed.

A15. **PRIORITY QUESTION.** Section 4.3.2, page 62. Please explain how participants had to be "*unresponsive or intolerant to oral antibiotics*" to be eligible for enrolment, yet were allowed to take doxycycline or minocycline if they were on a stable dose in PIONEER II, and were permitted "rescue therapy" antibiotics in PIONEER I?

AbbVie Response: In both the PIONEER I and II trials patients were required to have inadequately responded to or be intolerant to oral antibiotics in order to qualify for study entry. Inadequate clinical response was based on investigator judgement. HS patients typically cycle through multiple courses of oral antibiotics, prior to progressing to other treatments. Intolerance was defined in the following way:

A subject was defined as intolerant to oral antibiotic when oral antibiotic therapy has been discontinued by a physician as a result of a significant adverse reaction to oral antibiotic administration.

A reaction will be considered significant if the adverse reaction is at least moderately severe (i.e., the adverse event causes the subject discomfort and interrupts the subject's usual activities or function). Examples of significant adverse reactions include, but are not limited to:

- nausea resulting in decreased oral intake;
- macular or papular eruption or erythema associated with pruritus or other associated symptoms;
- dizziness/disequilibrium/lightheadedness/vertigo interfering with function;
- allergic reaction manifesting as rash, flushing, urticaria, dyspnea, or drug fever ≥ 38°C;
- diarrhea manifesting as an increase in stool frequency of at least 4 stools per day over baseline.

Patients were allowed to continue a stable dose of oral antibiotics (PIONEER II) or use oral antibiotics as part of a rescue regimen (PIONEER I) if the treating physician believed there was some benefit associated with this.

A16. Section 4.1.6, Table 6, page 53 and Table 7 page 56. Please explain why the inclusion criteria for Kimball 2012 (Study M10-467) state that only patients with moderate and severe disease were eligible, whilst Table 11 states that approximately 70% of included patients in this study were diagnosed as Hurley Stage I or II (that is, people with mild and moderate disease).

AbbVie Response: Study M10-467 was stratified by Hurley stage I or II vs. Hurley stage III. The study included patients with moderate to severe disease based on the following enrolment criteria:

- Adult patients with HS for at least 6 months
- HS must have been present in 2 anatomic locations
- Patients must have been unresponsive or intolerant to oral antibiotics for treatment for their HS
- HS PGA of at least 3 (moderate). This would require the patient at a minimum to meet one of the following 3 criteria:
  - no abscesses or draining fistulas, and at least 5 inflammatory nodules, or
  - single abscess or draining fistula in the presence of inflammatory nodules, or
  - between 2 and 5 abscesses or draining fistulas with or without inflammatory nodules, up to 10

AbbVie is unaware of any literature reference that states Hurley stage I, II, and III respectively equates to HS disease severity of mild, moderate, and severe.

A17. Section 4.3.2, page 64 and Table 9. Please explain why PIONEER I and II used different instruments to measure quality of life.

AbbVie Response: Both the SF-36 and the EQ-5D are general QOL questionnaires. The EQ-5D is particularly important for cost utility calculations, while the SF-36 is a richer instrument, capturing different aspects of QOL. Ideally both would have been included in both PIONEER trials, however, the patient burden in terms of the sheer number of questions was judged to be unacceptable. Therefore, the decision was made to include one instrument in each study.

The exclusion of HADS in PIONEER II was due to a licensing issue.

A18. Section 4.4, page 68. Please list the pre-specified and *post hoc* subgroup analyses (we acknowledge that some are specified in Sections 4.8.1 and 4.8.2).

AbbVie Response: Please see below a list of pre-specified and post hoc subgroup analyses.

Pre-specified:

1. Baseline concomitant use of oral antibiotics (Y/N)
2. Age group (< 40, 40 – 64, ≥ 65; since < 10% of subjects were in the ≥ 65 group, that group was combined with the 40 – 64 group)
3. Sex (male, female)
4. Race (white, black, and other)
5. Duration of HS (by median)
6. Weight (by median)
7. Body mass index (BMI) category: normal (< 25, overweight (25 – < 30), obese (30 – < 40), morbid obesity (≥ 40)
8. Current smoking status at baseline (Y/N)
9. Baseline CRP level (by median)
10. Baseline AN count category (≤ 5, 6 – 10, ≥ 11)
11. Baseline AN count (< median, ≥ median)
12. Prior HS surgery history (Y/N)
13. Smoking habit change (increase, decrease).
14. Time from prior HS surgery to the first dose of study drug (< median, ≥ median)

Post-hoc:

Combined week 12 partial responders (achieved ≥ 25% reduction in AN count relative to baseline) and HiSCR responders analyzed in period B.

A19. Section 4.13.2, page 120. Please explain why the PIONEER trials did not use HS Physician's Global Assessment (HS-PGA) alongside HiSCR? This would have enabled the trials to be pooled more easily in network meta-analysis and would have provided more robust evidence for the validity of HiSCR.

AbbVie Response: When the PIONEER I and II trials were designed, a decision was made to use a newly developed assessment tool as the primary endpoint, specifically the Hidradenitis Suppurativa Clinical Response, or HiSCR. HiSCR was developed in consultation with regulatory health authorities and has been validated against other measures of response in HS (Hurley stage, MSS and HS-PGA).

Psychometric evaluation of the HiSCR was performed using data from both Phase 2 Study M10-467 and an observational study, which supported HiSCR reliability (both intra and inter-rater reliability), validity (construct and predictive validity), and ability to detect change. The HiSCR is a well-defined endpoint that is a measure of concepts important and relevant to HS (abscesses, inflammatory nodules, and draining fistulas) and is based on trustworthy scores (i.e., reliable and valid) that are interpretable with respect to drawing conclusions regarding clinical benefit among patients with moderate to severe HS. HiSCR has been proven to be more responsive to change and better able to discriminate improvement in ADA-treated patients, compared to HS-PGA[2]. As such HiSCR would be expected to provide a more

dynamic assessment than HS-PGA, and better able to capture changes over the course of the phase III trials[3]. HiSCR was also expected to more accurately predict the non-worsening of key inflammations that would eventually require surgery.[3] Finally, HiSCR is a simpler measure to use, since it only requires counting of the inflammatory nodules, abscesses and draining fistulas. Expert clinical opinion from a UK advisory board held by AbbVie in 2015, revealed that UK clinical experts generally welcomed HiSCR and thought that it allowed appropriate assessment of response to therapy.[4] Introducing another endpoint into the Phase 3 program would have increased investigator/site burden and potential for confusion. For all the above mentioned reasons the HS-PGA was not used in the Phase III trial program.

The proportion of subjects achieving HiSCR at Week 12 was conducted as a post-hoc analysis for Study M10-467 and results can be generally compared to and are supportive of the phase III results. Post-hoc analyses of data from Study M10-467 showed more subjects treated with adalimumab 40 mg EW achieved HiSCR at Week 12 compared with subjects receiving placebo [redacted] and at Week 16 [redacted]

Assessment of bias

A20. **PRIORITY QUESTION.** Section 4.1.7, page 51 and Section 4.6, page 76. Risk of bias assessment.

- Please explain why different judgements of risk of bias are given in Appendix 4 compared with Section 4.6 for the M10-467 trial.
- Please explain why different judgements of risk of bias are given in Appendix 4 compared with 4.6 for the PIONEER trials.

AbbVie Response: The risk of bias and methodological quality of study results were assessed both using the seven domains specified in Cochrane risk of bias assessment tool (as presented in Appendix 4 of the submission) and based on the template presented in section 4.6 of the NICE user guide. Different judgements of risk of bias were given in the two tables due to the different sources used to evaluate the risk (abstracts vs CSRs).

The summary of study quality according to the NICE checklist for the PIONEER I and PIONEER II was based on the published abstracts and as such the judgements of risk of bias was considered intermediate for most domains (as most of the details required for quality assessment were not reported) whereas the tables presented in Appendix 4 were based on the CSRs for PIONEER I and PIONEER II.

The risk of bias based on the PIONEER I and PIONEER II CSRs assessed using the NICE checklist would produce a low risk in all domains and would be more closely aligned to the seven domains specified in Cochrane risk of bias assessment tool.

Table 7: Summary of study quality according to the NICE checklist

	M10-467[5]	**PIONEER I**[6]	**PIONEER II**[7]
Was randomisation carried out appropriately	Low risk	Intermediate risk	Intermediate risk
Was the concealment of treatment	Low risk	Intermediate	Intermediate

allocation adequate		risk	risk
Were the groups similar at the outset of the study in terms of prognostic factors?;	Low risk	Low risk	Low risk
Were the care providers, participants and outcome assessors blind to treatment allocation	Low risk	Intermediate risk	Intermediate risk
Were there any unexpected imbalances in drop-outs between groups?;	Low risk	Intermediate risk	Intermediate risk
Is there any evidence to suggest that the authors measured more outcomes than they reported	Low risk	Intermediate risk	Intermediate risk
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk	Intermediate risk	Intermediate risk

Table 8: Kimball 2012[5]: adalimumab EW vs. adalimumab EOW vs. placebo

Type of bias	Review authors' judgement	Support for judgement
Selection bias	Low risk	Randomized controlled study; method of randomization and allocation concealment were adequate
Performance bias	Low risk in Period A High risk in Period B	Blinding was maintained during the double blind phase for 16 weeks (Period A); placebo and drug were identical in appearance. The double-blind phase was followed by an open label treatment period (Period B)
Detection bias	Low risk in Period A Unclear risk in Period B	The outcome assessor was blinded to treatment assignment.
Attrition bias	Low risk	46/51 patients receiving placebo, all the patients in the adalimumab EOW arm and 45/51 in the adalimumab EW arm completed Period I (16 week double blind placebo-controlled phase) of the study. Non-responder imputation was used for missing values. The three arms were fairly balanced in number of patients completing the Period II of the study
Reporting bias	Low risk	Study protocol was not available; however, results were presented for all the study outcomes listed in methodology section and verified by clinicaltrial.gov description.
Other bias	Unclear risk	The trial was funded by industry, no other details were provided.

Table 9: PIONEER I[8]: adalimumab vs. placebo

Type of bias	Review authors' judgement	Support for judgement
Selection bias	Low risk	Randomized study, method of randomization and allocation concealment were adequate
Performance bias	Low risk	Double blind study, blinding was maintained throughout the study
Detection bias	Low risk	Outcome assessors were blinded to treatment assignment
Attrition bias	Low risk	9 subjects from placebo arm and 8 subjects from the adalimumab arm discontinued the study. In period B (unclear risk), 52/145 in placebo/adalimumab ew arm, 27/ 49 from adalimumab EW/placebo arm, 21/48 from adalimumab EW/EOW arm and 20/48 from adalimumab EW/EW arm discontinued the study. Overall, missing data was imputed using appropriate methods and the analysis was presented for PP and ITT populations.
Reporting bias	Low risk	Results were reported for all the outcomes described in the efficacy and safety variables section of the clinical study report
Other bias	Unclear risk	The trial was funded by Abbvie; however, there was insufficient information to permit judgement

Table 10: PIONEER II[9]: adalimumab vs. placebo

Type of bias	Review authors' judgement	Support for judgement
Selection bias	Low risk	Randomized study, method of randomization and allocation concealment were adequate
Performance bias	Low risk	Double blind study, blinding was maintained throughout the study
Detection bias	Low risk	Outcome assessors were blinded to treatment assignment
Attrition bias	Low risk	12 subjects from placebo arm and 8 subjects from the adalimumab arm discontinued the study. Unclear risk in period B: In period B, 111/151 in placebo/adalimumab ew arm, 28/51 from adalimumab EW/placebo arm, 28/53 from adalimumab EW/EOW arm and 23/51 from adalimumab EW/EW arm discontinued the study. Overall, missing data was imputed using appropriate methods and the analysis was presented for PP and ITT populations.
Reporting bias	Low risk	Results were reported for all the outcomes described in the efficacy and safety variables section of the clinical study report
Other bias	Unclear risk	The trial was funded by Abbvie; however, there was insufficient information to permit judgement

A21. **PRIORITY QUESTION.** Section 4.1.7, page 51 and Section 4.6, page 76.

- Participant flow suggests that the risk of bias might be different between Period A and Period B in all trials (there are possible issues of allocation concealment, blinding and attrition in Period B). Different levels of risk in Period A and Period B of the M10-467 trial are acknowledged in Appendix 4, but only a single level of risk is considered for the PIONEER trials. Please conduct and report a separate risk of bias assessment for both Period A and Period B of the PIONEER trials.

  AbbVie Response: For the PIONEER I and II trials the risk of bias was regarded as low for all seven domains specified in Cochrane risk of bias assessment tool except for attrition bias where the risk was deemed unclear. In both PIONEER trials all subjects who continued to Period B, regardless of the treatment in Period A, were to be re-randomised at Week 12 to maintain the blind. All AbbVie personnel with direct oversight of the conduct and management of the trial, the investigator, study site personnel, and the subject remained blinded to each subject's treatment throughout the blinded periods of the study. As such risks of allocation concealment and blinding were considered low in both studies.

- Please also specify the source of the information being used to make the risk of bias assessments (abstracts or CSR).

  AbbVie Response: The risk of bias using the seven domains specified in Cochrane risk of bias assessment tool are based on the CSR of the PIONEER I and PIONEER II studies.

A22. Section 4.1.4, page 48.

- The proposed risk of bias assessment described here relates only to the Cochrane tool for RCT evidence: the findings of this assessment are given in Appendix 4. However, Section 4.6 “Quality assessment of the relevant randomised controlled trials” uses and reports the findings of the “NICE checklist.” Please explain and justify the use of two different tools.

  AbbVie Response: As part of the systematic review of evidence presented in Section 4.1 the methodological quality of all studies identified in the review (including all the adalimumab studies identified) and the risk of bias were assessed using the Cochrane risk of bias assessment tool. In section 4.6 only the relevant randomised controlled trials were assessed using the checklist recommended in the NICE user guidance (specified in sections 4.6.2–4.6.4).

- The open-label extension study (M12-555) was not randomised as all eligible participants received the adalimumab every week dose; please describe and justify the choice of risk of bias tool used to assess this study in Section 4.11.4.

  AbbVie Response: The open-label extension study was assessed for risk of bias using the quality assessment tool for non RCT from the Centre for Reviews and Dissemination (CRD) at the University of York (www.york.ac.uk/inst/crd)[10] as recommended in the NICE user guidance (specified in sections 4.6.2).

A23. Section 4.6, page 76. Please clarify why several aspects of PIONEER I and II are judged to be at an intermediate risk of bias. Please provide a description on the likely direction and magnitude of bias.

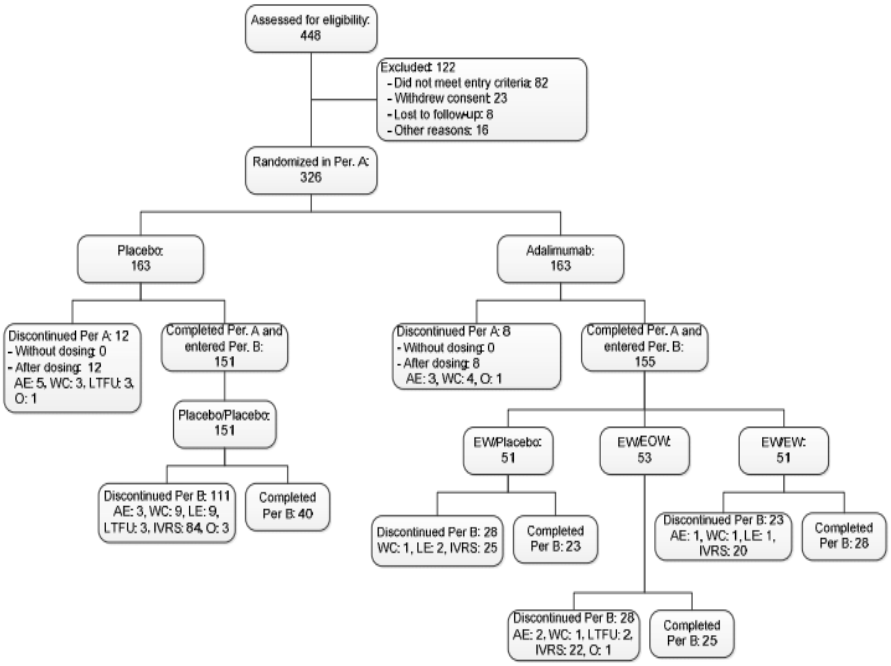
AbbVie Response: Please see answer to question A20.

Adalimumab trials - Participant flow

A24. **PRIORITY QUESTION.** Section 4.5.3, page 72. Please provide the correct participant flow diagram for PIONEER II (Figure 9 is a reproduction of the PIONEER I flow diagram).

AbbVie Response: Figure 2 presents the participant flow for PIONEER II.

Figure 2: Participant flow for PIONEER II



A25. Section 4.3.1, page 57. Please explain the statement for M10-467: "*Patients who had received placebo in period 1 received initial blinded ADA 80 mg at week 16, and patients who had received active therapy in period 1 received blinded placebo at week 16.*" This does not appear to be consistent with the information that precedes it, or in Table 7, or the design described in Figure 5, in which all patients in Period 2 receive adalimumab every other week, irrespective of their initial randomisation.

AbbVie Response: In order to maintain blinding, subjects received different treatments at week 16 (start of Period 2). During Period 2 all patients received 40mg EOW. As they entered Period 2 (week 16), those patients on placebo during Period 1 received a dose of 80mg and then continued on 40mg EOW. Those patients on active adalimumab during Period 1 received placebo at Week 16 and then continued

on their 40mg EOW schedule. It was necessary to preserve blinding at the beginning of Period 2 so as not to unblind Period 1 treatment assignment.

A26. Section 4.3.2, page 60. For PIONEER I and PIONEER II, please clarify at what point it was determined that patients originally randomised to placebo were allocated in Period B to adalimumab every week or placebo for PIONEER I AND II respectively.

AbbVie Response: The week 12 visit was the timepoint when patients on placebo in Period A of PIONEER I and PIONEER II were assigned (using re-randomisation numbers) to receive adalimumab (PIONEER I) every week dosing and placebo (PIONEER II),in Period B. Placebo patient assignment to Period B dosing regimen was planned at the time of the initial study design development. Patients were not allowed to be randomised to period B prior to week 12.

A27. Section 4.3.2, page 61. Please explain the statement: "*In PIONEER I, patients in the placebo arm were re-randomised to ADA mg EW*", as it appears that no randomisation was conducted: these patients were simply switched from placebo to adalimumab every week.

AbbVie Response: Subjects who had been randomised to placebo in Period A were indeed switched to adalimumab weekly dose. Since the switches occurred in real time while some subjects were still ongoing in Period A, in order to maintain the blind of Period A treatment assignments, this switch was done using re-randomisation numbers, therefore were described as "re-randomised".

A28. Section 4.5.2, page 71. In Figures 8 and 9, for those who discontinued treatment in Period B, please define what the "other" category encompasses. Likewise, please give details (numbers and categorisation) of the "per protocol" reasons for discontinuation. For example, what was the reason for the "per protocol" discontinuation of 30/52 in the placebo/every week Period B group?

AbbVie Response: Subjects meeting criteria of LOR or WOAI were requested "per protocol" to discontinue from the study and enter the open-label extension study M12-555.

Table 11: Patients who discontinued treatment in Period B of PIONEER I & II listed as "other"in participant flows

Study M11-313 (PERIOD B)		**Study M11-810 (PERIOD B)**	
Patient treatment arm	**Reason for discontinuation (other)**	**Patient treatment arm**	**Reason for discontinuation (other)**
PBO/EW	Completed < 75% of scheduled doses	PBO/PBO	Returned to country of origin
PBO/EW	Pregnancy	PBO/PBO	Pregnancy
PBO/EW	Wanted to become pregnant	PBO/PBO	Moved location

PBO/EW	Pregnancy		
PBO/EW	Pregnancy		
EW/PBO	Non-compliance with visits		
EW/EOW	Pregnancy		
EW/EW	Pregnancy		
EW/EW	Loss of response		

A29. Section 4.7.2.4, page 90. Please provide full details of the randomisation process after 12 weeks in PIONEER I and II. Were participants stratified by response in Period A?

AbbVie Response: After week 12, all subjects continuing to Period B, regardless of the treatment in Period A were re-randomised to maintain the blind. In both PIONEER I and II, subjects who had been randomised to adalimumab during Period A were re-randomised 1:1:1 to one of three groups: adalimumab 40 mg EW, adalimumab 40 mg EOW, or placebo from week 12 to week 35. The re-randomisation was stratified by week 12 response (HiSCR responder versus non-responder) and by baseline Hurley Stage (II versus III). In PIONEER I, subjects who were randomised to placebo in Period A were assigned (using re-randomisation numbers) to blinded adalimumab 160 mg at week 12, 80 mg at week 14, matching placebo at week 13 and week 15, and adalimumab 40 mg EW from week 16 to week 35. In PIONEER II, subjects who were randomised to placebo in Period A were assigned (using re-randomisation numbers) to blinded placebo.

Clinical effectiveness results

A30. **PRIORITY QUESTION.** Section 4.7.2.1, page 81-82. Please explain the reason for the placebo response (e.g. Figure 12 and Table 15).

AbbVie Response: Hidradenitis suppurativa (HS) is a chronic, inflammatory skin condition known to have periods of quiescence and flare. Limited data on the natural history of the disease are available to fully characterise disease activity in HS and there are no published prospective studies of the clinical course of HS that can provide expected placebo response rates. PIONEER I and II are the first large placebo-controlled Phase III studies that investigated a pharmaceutical intervention and were the first studies to prospectively use a newly validated measure, HiSCR, as the primary efficacy endpoint. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline. As with any placebo-controlled clinical trial, it is expected that some subjects in the placebo group will have a response. Given the fluctuations in the course of HS and considering the definition of achieving HiSCR, some response to placebo would be expected in the study population.

A subgroup analysis of the integrated data from Studies M11-810 and M11-313 by baseline AN count category (≤ 5, 6 – 10, and > 10) showed that response to placebo varied, depending on the baseline AN count (Table 12). Specifically, the HiSCR rate decreases as the baseline AN count increases, reflecting a greater threshold to

achieve at least a 50% decrease in the AN count without adalimumab intervention. In contrast, HiSCR rates for the adalimumab group were similar across the 3 categories; the treatment difference was greatest in the baseline AN count category of > 10. Despite the observed placebo response in both Phase III studies, the percentage of subjects in the adalimumab group who achieved HiSCR at Week 12 was significantly higher than subjects in the placebo group. These results represent a clinically meaningful difference between treatment groups.

Table 12: Proportion of Subjects Achieving HiSCR at week 12 (NRI) by Baseline AN Count Category (ITT_A population)

Treatment	N	Yes n (%)	No n (%)	Missing n (%)	Diff %	p value [A]
BASELINE AN CATEGORY (NUMERIC) : <= 5						
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]		
EW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASELINE AN CATEGORY (NUMERIC) : 6 - 10						
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASELINE AN CATEGORY (NUMERIC) : >= 11						
PLACEBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[A]: P-VALUE WAS CALCULATED FROM THE COCHRAN-MANTEL-HAENSZEL TEST ADJUSTED FOR STUDY AND BASELINE HURLEY STAGE. *, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.**

A31. **PRIORITY QUESTION.** Section 4.12, page 107. The clinical study report for PIONEER II discusses the use of surgery during the trial period (page 282) in relation to adverse events, especially surgery relating to HS. Please provide data on pre-planned and unplanned surgery (which was designated an adverse event) in PIONEER I and II.

AbbVie Response: Surgery for HS, either planned or unplanned, was not allowed during the PIONEER I and II trials. The phase III trials were designed to assess the safety and efficacy of adalimumab for the treatment of patients with HS. Allowing for surgical intervention during the randomized controlled trial would have confounded the study results and limited our ability to understand the safety and efficacy of adalimumab.

The text referenced above from the PIONEER II CSR is standard language included in AbbVie study protocols to describe adverse event collection *"An elective surgery or procedure scheduled to occur during the study was not considered an AE if the surgery or procedure was performed for a pre-existing condition and the surgery or procedure was preplanned (and documented as preplanned) before study entry. However, if the pre-existing condition deteriorated unexpectedly during the study (e.g., surgery performed earlier than planned), the deterioration of the condition for which the elective surgery or procedure was done was considered an AE".*

A32. Sections 4.7.1.1 and 4.7.1.2, pages 76-78 and Section 4.7.2.4, page 89-91. Please explain why the results have been presented for the every other week dose when this is unlicensed and has been described by the cited 2015 Cochrane review as "ineffective"?

AbbVie Response: In sections 4.7.1.1 and 4.7.1.2 of the submission the results of the phase II randomised placebo-controlled dose-finding trial (M10-467) are presented. The phase 2 study included an initial dose ranging period (A) to evaluate adalimumab 40 mg EW or EOW versus placebo, followed by an open-label period (B) with Adalimumab 40 mg EOW treatment.

Section 4.7.2.4 of the submission presents the results of the PIONEER I and PIONEER II trials at week 36. The two phase III studies each included two periods: Period A was designed to assess the efficacy and safety of Adalimumab EW compared to placebo for the first 12 weeks of treatment, and Period B was designed to explore the safety and efficacy of different maintenance regimens (continuation of Adalimumab EW, reduction to Adalimumab EOW, or treatment withdrawal) over 24 weeks.

Since the Adalimumab 40 mg EOW regimen was used as a comparator in period A of study M10-467 and in Period B of studies M11-313 and M11-810 AbbVie has presented in their submission all the available efficacy evidence from the trials, although it acknowledges that the Adalimumab 40 mg EOW regimen is not licensed for HS and that both the results from the Phase 2 and Phase 3 studies support the superior efficacy of adalimumab 40 mg EW vs EOW in the treatment of adult patients with moderate to severe HS.

A33. Section 4.7.2.1, page 81-82. Please explain why the treatment effect in PIONEER II appears to be greater than that in PIONEER I (e.g. Figure 12 and Table 15).

AbbVie Response: The treatment difference between the adalimumab EW and placebo groups was statistically significant and over 15% in both the PIONEER I and PIONEER II trials. The difference in the magnitude of the treatment effect observed can be considered quantitative rather than qualitative, i.e., the direction of the difference is consistent between the two studies.

The magnitude of the treatment effect may partially be explained by baseline differences in the populations enrolled in the 2 studies. The impact of Hurley Stage (II/III), continuation of baseline concomitant antibiotics use (Y/N), weight, smoking status, HS duration, baseline CRP, and baseline lesion counts were examined. Two factors were identified to have an impact on HiSCR: body weight and baseline draining fistula count. The patient population in PIONEER I had slightly higher weight and were slightly more severe. The small imbalance in draining fistula counts between the treatment groups was in reverse direction.

After including baseline weight and baseline draining fistula count (identified by stepwise selection) into a logistic regression model, the treatment-by-study interaction was no longer significant, suggesting that these differences in baseline characteristics accounted for much of the difference in treatment effect between the 2 studies.

A34. Section 4.7.2.3, page 86. Please clarify whether these improvements in Dermatology Life Quality Index (DLQI) satisfy the criteria for Minimum Clinically Important

Difference (MCID) (a difference of at least 4 points) as defined by Basra *et al* (Dermatology 2015;230: 27–33).

AbbVie Response: Statistical significance is the gold standard measure in clinical trials to assess treatment effect; however, statistical evaluation is driven by group level evaluations (i.e., mean, variance) while subject level information provides a better understanding of the impact of a treatment. In order to understand and interpret change in patient reported outcomes within a clinical population, it is important to anchor individual change to a meaningful threshold. This threshold, Minimally Clinically Important Differences (MCID), a within group parameter, is computed as the smallest difference in scores in the domain of interest which patients perceive as beneficial. Meaningful change on the DLQI has been detected in previous clinical studies of patients with dermatologic conditions with improvement in DLQI change from baseline greater than or equal to 3 points[11,12] and in a recent study by Basra et al (2015)[13] of greater than or equal to a 4-point improvement. At the group level, in both the PIONEER I and PIONEER II studies, patients on each treatment arm reported equivalent DLQI scores at baseline. Change from baseline for patients receiving ADA 40 mg EW exceeded each of these thresholds with improvements greater than 5-points compared to mean change from placebo below even the lower threshold. In addition, as stated, meaningful change is a within subject parameter, within these two studies, the proportion of individuals achieving a meaningful improvement was statistically higher for patients receiving ADA 40 mg EW compared to patients receiving placebo.

A35. Section 4.7.2.3, page 86-87. Please clarify whether these improvements in skin pain satisfy the criteria for a MCID.

AbbVie Response: Research on placebo-controlled studies of pain supports a 30% reduction of pain as clinically significant and corresponds to a "much improved" or "very much improved" response.[14] In addition, data from multiple clinical trials suggest that reduction in pain intensity of ≥30% corresponds to patients reporting their change as being at least “moderately better” whereas a reduction of ≥50% corresponds to patients reporting their change as being at least “substantially better” compared to patients reporting increased or no change in pain over the course of treatment.[15,16,17] These thresholds are substantiated as recommendations by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) which includes US FDA Agency member authors.

A36. Section 4.11.1, page 101. Please provide discrete outcomes data for patients who did/did not receive the unlicensed adalimumab every other week dose on account of dose reduction if there were any instances other than the 3 patients mentioned in Section 4.12.3 (page 114).

AbbVie Response: Only three patients had dose reductions as of the last data cut for Study M12-555 (29 April 2014).

Section B: Clarification on cost-effectiveness data

Systematic literature review

B1. Appendix 6. Several filters have been used in the searches for economic studies and utilities, however no sources have been cited in the company's submission. Please indicate whether published validated filters have been used in each of these cases and give details of any alterations made.

AbbVie Response: Please see response to question A5.

Model structure: health states

B2. **PRIORITY QUESTION.** Section 5.2.3, pages 133-136. Please provide justification for the structure of the model, in particular, why the HiSCR response health states are segregated into "high response", "response" and "partial response." Why was the model not based on "response" and "no response" as per the PIONEER trials?

AbbVie Response: The rationale behind the expansion of the number of response health states was to better evaluate the impact of Adalimumab on quality-adjusted life years (QALYs) and costs. The "high response" and "response" constituted the HiSCR response, and the "partial response" and "non-response" constituted the HiSCR non-response in the PIONEER trials. In particular, the selection of four response health states was due to the following considerations: 1) there were statistically significant differences in the response rates of adalimumab and placebo in "high response", "response" and "non-response", and 2) the utility and resource use differed across the four response health states 3) a *post-hoc* analisys of the PIONEER I and II studies identified a population where continued treatment with ADA could be beneficial. Therefore, to evaluate the cost-effectiveness of adalimumab, it was reasonable to segregate the model into four response health states.

Table 13 shows that the rates of high response, response and non-response were significantly different between Adalimumab and placebo at both week 12 and week 36 based on the PIONEER I and PIONEER II trials.

Table 13: Health state distributions at Week 12 and Week 36

Health state[1]	Adalimumab n (%)	Placebo n (%)	P-value[2]	
Week 12[3]	(N=316)	(N=317)		
High response	[redacted]	[redacted]	<0.001	*
Response	[redacted]	[redacted]	0.010	*
Partial response	[redacted]	[redacted]	0.139	
Non-response	[redacted]	[redacted]	<0.001	*
Week 36[4]	[redacted]	[redacted]		
High response	[redacted]	[redacted]	0.014	*
Response	[redacted]	[redacted]	0.006	*
Partial response	[redacted]	[redacted]	0.771	
Non-response	[redacted]	[redacted]	0.000	*

Notes:
1. This analysis was conducted using the non-responder imputation (NRI) data from the clinical trial(s).
2. P-values were calculated using Chi-squared tests (or Fisher's exact tests if ≥25% of the cells had expected counts <5). P-values less than 0.05 are indicated with an asterisk (*).
3. Week 12 health state distributions were evaluated using data from the PIONEER I and PIONEER II trials. The adalimumab arm included patients who received adalimumab every week in Period A (Weeks 0-12); the placebo arm included patients who received placebo in Period A.
4. Week 36 health state distributions were evaluated using data from the PIONEER II clinical trial only. The PIONEER I trial data were not used because all placebo-treated patients in the Period A were crossed-over to adalimumab during Period B (Weeks 12-36). The adalimumab arm included patients who received adalimumab every week in both Period A and B; the placebo arm included patients who received placebo in both Period A and B.

Table 14 indicates that there were statistically significant differences in the mean utilities of high response and response health states, and in the mean utilities of partial response and non-response health states. Therefore, AbbVie believes that for the economic model, where the utility is a key factor, it is justifiable to incorporate four response health states instead of grouping high response and response into HiSCR response health state, and grouping partial response and non-response into HiSCR non-response health state, as per the PIONEER trials.

Table 14: Utility values across four response health states

Health state	Utility value: mean (SE)	P-value[1]
High response	0.782 (0.018)	0.036*
Response	0.718 (0.025)	
Partial response	0.576 (0.032)	0.034*
Non-response	0.472 (0.036)	

Notes:
1. P-values were calculated using two-sample t-test comparing the mean EQ-5D values of high response to response, and mean EQ-5D values of partial response to non-response, respectively. P-values less than 0.05 are indicated with an asterisk (*).

Also, as detailed in Table 51 of the submission report and included below, differences were observed in resource use across the four response health states based on the responses received from the online physician questionnaire.

Table 51 (of the submission report). Resource use rates by health states

Type of visit	Resource use (Average number of units per year)				Source
	High response	Response	Partial response	Non-response	
Number of hospitalisations for HS surgeries	0.13	0.22	0.54	0.80	UK Physician survey
Outpatient visits due to HS surgery	0.22	0.35	0.67	0.94	
Visits to wound-care due to HS surgery (presumed outpatients)	0.12	0.17	0.40	0.85	
Number of hospitalisation non-surgery related	0.11	0.23	0.29	0.45	
Routine outpatient visits	3.10	3.51	4.44	4.68	
Visits to wound-care NOT due to HS surgery (presumed outpatients)	0.67	0.47	0.64	0.45	
A&E visits	0.12	0.20	0.47	0.57	

Furthermore a *post-hoc* analsyis of the PIONEER I and II studies identied a population where continued treatment with ADA could be beneficial (partial HiSCR or AN25 defined as a 25% reduction in AN count relative to baseline at the end of Period A). Results showed that the utility of continuing adalimumab EW dosing was concentrated among the subset of non-responders who had achieved at least AN25 (partial responders) at the end of Period A [redacted] of partial responders in the EW/EW group achieved HiSCR at week 36). For subjects with less than AN25 at week 12 (non-responders), continuing adalimumab therapy in either EW or EOW dosing beyond week 12 yielded outcomes similar to placebo.

Abbvie believes that for all the above mentioned reasons a cost effectiveness model with four response health states would more accurately capture the long term costs and benefit of Adalimumab in moderate to severe HS compared to a two model health state (HiSCR response/non-response) as per the PIONEER trials.

- Please also provide a health economic analysis using only the outcomes of response or no response.

AbbVie Response: Unfortunately due to time constraints AbbVie was not able to make structural changes to the cost effectiveness model (ie. change the structure from a 4 model response state to a 2 model response state), however AbbVie was able to provide a health economic analysis which would use only the outcomes of response or no response as per the PIONEER trials by implementing the following changes to the existing model structure:

1. Assign the same utility value to the High response and Response (HiSCR responders as per the PIONEER trials) health states based on a re-analysis of the EQ-5D data at week 12 and 36 from the PIONEER II trial
2. Assign the same utility value to the Partial response and non-Response (HiSCR non-responders as per the PIONEER trials) health states based on a re-analysis of the EQ-5D data at week 12 and 36 from the PIONEER II trial
3. Assign the same resource use cost to the High response and Response (HiSCR responders as per the PIONEER trials) health states (average the cost across the two health states)
4. Assign the same resource use cost to the Partial response and non-Response (HiSCR non-responders as per the PIONEER trials) health states (average the cost across the two health states)
5. Assign same week 36+ discontinuation rate for partial responders as per non responders based on discontinuation rate using OLE

Table 15 presents an analysis using only the outcomes of response and no response.

Table 15: Incremental cost effectiveness analysis results using only the outcomes of response and no response

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£) Incremental (QALYs)
SC	£113,068	22.73	12.43				
ADA	[redacted]	22.73	13.12				
ADA vs. SC				[redacted]	0.000	0.69	[redacted]

B3. **PRIORITY QUESTION.** Section 5.4.4, page 167. The submission states that *"The differences in utility values between health states were statistically significant."*

However, in Table 47 of the submission, the 95% confidence intervals for HRQoL for the states of partial response and non-response, and the 95% confidence intervals for HRQoL for the states of high response and response, are overlapping. Please provide further justification for including these as separate states in the model.

AbbVie Response: This question seemed to suggest that two statistics with overlapping confidence intervals cannot be significantly different. AbbVie believes that this is a common misconception, which has been well elaborated in the literature.[18] Table 14 in question B2 presents the p-values comparing the mean utility values between the high response and response health states (p-value=0.036), and between the partial response and non-response health states (p-value=0.034). Both p-values are less than 0.05, indicating significant differences.

To help illustrate this point further, we have provided an example below to show significant difference in mean utility values between high response and response health states, despite overlapping confidence intervals. T-test is used for the evaluation.

Example:

Table 16: Utilities of high response and response health states

Health state	**Utility value: mean (SE; $\bar{X}$)**	**Utility value: SD (S^2)**	**Number of observations (n)**	**95% confidence interval of utility mean**
High response	0.782 (0.018)	0.204	130	(0.746, 0.816)
Response	0.718 (0.025)	0.231	83	(0.667, 0.766)

H_0: mean utility value of high response = mean utility value of response

$$t = \frac{\overline{X_1} - \overline{X_2}}{\sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}} = \frac{0.782 - 0.718}{\sqrt{\frac{(130-1)\times 0.204^2 + (83-1)\times 0.231^2}{130+83-2}\left(\frac{1}{130}+\frac{1}{83}\right)}} \approx 2.1129^{\S}$$

$$\text{Degrees of freedom} = 130 + 83 - 2 = 211$$

$$\alpha = 0.05$$

$$\text{Critical value} \approx 1.3971$$

$$\text{P} - \text{value} \approx 0.036$$

n: number of observations; *S*: standard deviation; $\bar{X}$: mean utility value.

§ The calculation used up to 15 decimal places. Only 3 decimal places were shown in the table and the formula for illustration purpose.

With 211 degrees of freedom, the t-test critical value of a two-tailed comparison at a 0.05 significance level was 1.9713. With a t-test statistic of 2.1129, which was larger than 1.9713, the p-value was 0.036 and the null hypothesis (H_0) was rejected.

Therefore, the mean utility values of high response and response health states were significantly different, regardless of their overlapping 95% confidence intervals.

B4. Section 5.5.3, page 174. Given that surgery is a key driver of cost in the model, why did the model structure not include surgery as a health state?

AbbVie Response: Surgery was not included as a health state due to the following considerations:

Surgeries for HS are transient and discrete events, not chronic treatments. Thus, surgery was not suitable to serve as a health state in the current model where one model cycle consisted of four weeks.

Surgeries for HS are not curative and patients can experience multiple surgeries over the disease course. For example, Menderes et al 2010[19] reported 54 operative procedures among 27 HS moderate to severe patients from 2004 to 2009, with a follow-up of at least 6 months. In addition, as discussed in Section 2.5, page 31 of the submission report, an observational cross-sectional study in the UK that reviewed patient notes for 101 patients found that among a total of 41 patients with surgeries, there were 86 surgeries over a 5-year period.[20] The frequent occurrence of surgical procedures over the disease course suggests that it is more efficient to consider surgeries as discrete events that could occur within specific health states, as currently incorporated in the model, instead of considering it as a distinct health state.

Finally, surgeries in HS are heterogeneous. There are a wide range of surgical options, including laser treatment for local excision and radial surgeries for widely spread lesions. Therefore, it would not be feasible to model the diverse types of surgeries as separate health states within one model.

Resource use rates

B5. **PRIORITY QUESTION.** Section 5.5.3, page 174. Please provide data on the number of surgical procedures received by patients allocated to adalimumab or placebo within the PIONEER I and II trials.

AbbVie Response: Surgery was not permitted in the PIONEER I and II studies per protocol. As such a change in the number of surgeries could not be observed.

- Was a reduction in surgery observed in the adalimumab every week groups, compared with the placebo groups?

  AbbVie Response: Data was not available from the PIONEER I and II studies.

- Please provide any available data collected from these studies with respect to the number of surgical procedures received in patients achieving “high response”, “response”, “partial response” and “no response” in each treatment group.

  AbbVie Response: Data was not available from the PIONEER I and II studies.

- Is there any other evidence to suggest that patients achieving response undergo fewer surgical procedures?

  AbbVie Response: To determine whether ADA therapy reduces the need for acute surgical interventions, a *post-hoc* analysis using the integrated data from the PIONEER I and PIONEER II studies was conducted using incision and drainage procedures and intralesional steroid injections as surrogate markers for more surgical interventions. Results showed that at week 12 a greater proportion of patients who received ADA, compared with placebo, experienced elimination of both draining fistulas (33% vs 19%; P < .001) and nondraining fistulas (15% vs 9%; P = .017).[21]

B6. **PRIORITY QUESTION.** Section 5.5.3, page 174. Please provide further information on the UK Physician Survey used to inform the resource use assumptions within the model.

- In particular, please explain how estimates were elicited from experts and how these were aggregated across respondents.

  AbbVie Response:

  AbbVie conducted a physician survey among UK clinicians with experience of treating HS. Initially 11 clinical experts (9 dermatologists and 2 surgeons) completed the online survey. The answers for the resource use questions were based on those respondents who would see a particular type of patient suffering of HS in clinical practice. Each respondent's answer were reviewed individually to check for consistency and outliers. Although there were 11 respondents who answered the questionnaire the answers were based on only those respondents who had patients that would fit into each particular category (ie. high-response, moderate patients, patients who attended A&E for example).

  In order to confirm the initial results an additional 29 dermatologists were approached to complete the online questionnaire. In total 40 completed questionnaires were received, and resource use estimates were derived from these. Estimates elicited from the experts were aggregated across respondents using descpritive statistics, and the mean of the answers provided were fed into the economic model.

- Please provide a copy of the questionnaire document administered to participants in the survey.

  AbbVie Response: A copy of the online questionnaire document administered to the participants in the survey has been provided with these questions.

B7. **PRIORITY QUESTION.** The executable model appears to predict that patients receiving standard care undergo approximately 34 inpatient surgical admissions over their lifetime (this was derived by setting the cost of inpatient surgical admission to 1, setting all other unit costs to zero, setting the discount rate to zero and calculating the total surgery-related cost). Please provide evidence to support the validity of this prediction.

AbbVie Response: The UK physician survey estimated that patients with HS would have between 0.13 and 0.80 inpatient surgical admissions per year related to HS depending on their response status (no-response to high response). Considering that a typical HS patient is diagnosed in its early 20s it is not unreasonable to assume that over a lifetime patients who receive no active treatment could undergo approximately 34 inpatient admissions for surgery.

Furthermore evidence from the literature suggests that patients with moderate to severe HS undergo surgical procedures quite frequently. Menderes et al 2010[19] reported 54 operative procedures among 27 HS moderate to severe patients from 2004 to 2009. In an observational cross-sectional study conducted by AbbVie out of 41 patients with surgeries there were 86 surgeries over a 5-year period.[20]

B8. Section 5.5.3.2, Table 52, page 175. The submission reports the costs of non-surgical inpatient admissions used in the model. Please clarify why patients would require non-surgical inpatient admission. What types of events are these admissions intended to capture?

AbbVie Response: Patients with HS will require surgical inpatient admissions (ie. to perform the surgery itself) as well as non-surgical ones. Non-surgical admissions can be due to infection or surgical complications. Please see below question Q13a from the physician survey.

Q13a

Thinking about the last 12 months, how many of your moderate HS (Hurley Stage II) patients had:

a) At least one in-patient HS surgical procedure
b) At least one out-patient HS surgical procedure
c) At least one HS-related hospitalisation NOT involving an HS surgical procedure (e.g., due to infection or surgical complications)
d) At least one non-surgical HS-related A&E visit
e) At least one attendance at clinic/wound care centre for wound care for abscesses or draining of fistulas

Costs

B9. **PRIORITY QUESTION.** Section 5.5.2, page 173. Please clarify why the costs of concomitant and rescue medications received by patients in the PIONEER trials were not included in the model. Please summarise the use of concomitant and rescue medications in the PIONEER trials.

AbbVie Response: Concomitant medications were used in both the PIONEER I and II trials and a summary of the most commonly used medications (used in > 5% of the population in Period A of both trials) are presented in Table 17. Since the use of concomitant medications was observed to be similar between the placebo and adalimumab EW arm and due to the low cost of these medications (see Table 18) AbbVie decided not to include these into the economic analysis. Likewise antibiotic rescue medications from the PIONEER I trial (antibiotic use was allowed in PIONEER II) were not included as only 4 patients (2 in the placebo arm and 2 in the

adalimumab EW arm) were started on antibiotic rescue medication during period A of PIONEER I.

Table 17: Concomitant medications used in the PIONEER trials in > 5% of the population in Period A

Generic Name	Placebo (N=315) N (%)	Adalimumab EW (N=316) N (%)
Any Concomitant Medication	[redacted]	[redacted]
Chlorhexidine	[redacted]	[redacted]
Ibuprofen	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]
Triclosan	[redacted]	[redacted]
Tramadol	[redacted]	[redacted]
Benzoyl Peroxide	[redacted]	[redacted]
Skinsan	[redacted]	[redacted]
Cyteal	[redacted]	[redacted]
Hypochlorous Acid	[redacted]	[redacted]
Doxycycline	[redacted]	[redacted]

Table 18: Drug price comparing adalimumab and concomitant HS therapies

Description	Unit cost (2015)	Dosing	Drug cost per week (2015)	Source
ADA price per 40 mg dose	£352.14	40 mg every week	£352.14	BNF[22] for drug price and dosing
Chlorhexidine 0.05% 1000 ml (2000 solutions)	£0.77	Sterile water, assuming 1000 ml per week	£0.77	
Ibuprofen 600 mg	£0.07	0.6 -1.2 g daily	£0.71	
Paracetamol 500 mg	£0.03	max 4 g daily	£1.61	

- Please provide an analysis in which the costs of these are included in the model.

AbbVie Response: The costs of concomitant and rescue medications are expected to be relatively low and AbbVie believes that omission of these would most likely not have a major impact on the ICER.

B10. Section 5.5.3.3, Table 54, pages 176-177. The costs of some severe adverse events appear very high (in particular, nasopharyngitis cost=£908.28 and headache cost=£674.21). Please explain which Reference Costs codes were used for these and justify their use in the model.

AbbVie Response: In the PIONEER trials the following definition were used to define a mild, moderate and severe adverse event:

- Mild: The AE is transient and easily tolerated by the subject.
- Moderate: The AE causes the subject discomfort and interrupts the subject'susual activities.
- Severe: The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

Severe adverse events in the base case analysis were assumed to require an inpatient stay (elective, non-elective, day case). As such a weighted average of the total HRGs costs that most closely matched the AE was used to estimate the cost of that particular adverse event.

Please see below a description of the full NHS Reference Costs[23] codes used to estimate severe adverse events in the CE model.

Table 19: Unit cost of severe AE

AE	Cost	Reference
Headache	£674.21	NHS reference costs 2013-2014. [23] Weighted average of Total HRGs AA31C (Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 11+), AA31D (Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 7-10) and AA31E (Headache, Migraine or Cerebrospinal Fluid Leak, with CC Score 0-6)
Hidradenitis	£0.00	Assume no cost
Nasopharingitis	£908.28	NHS reference costs 2013-2014. [23] Weighted average of Total HRGs WA06A (Other Viral Illness with CC Score 2+), WA06B (Other Viral Illness with CC Score 1) and WA06C (Other Viral Illness with CC Score 0)
Gastroenteritis	£1,468.01	NHS reference costs 2013-2014. [23] Weighted average of Total HRGs FZ91A-D (Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with CC Score 0-8+), FZ91E-H (Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 0-9+) and FZ91J-M (Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-11+)
Influenza	£908.28	NHS reference costs 2013-2014. [23] Weighted average of Total HRGs WA06A (Other Viral Illness with CC Score 2+), WA06B (Other Viral Illness with CC Score 1) and WA06C (Other Viral Illness with CC Score 0)
Viral gastroenteritis	£1,345.99	NHS reference costs 2013-2014. [23] Weighted average of Total HRGs FZ36G-H

		(Gastrointestinal Infections with Multiple Interventions, with CC Score 0-4+), FZ36J-L (Gastrointestinal Infections with Single Intervention, with CC Score 0-5+) and FZ36M-Q (Gastrointestinal Infections without Interventions, with CC Score 0-8+)

B11. Section 5.5.2, pages 173-174. Why is the cost of adalimumab treatment applied only to those patients who are compliant? Would some patients receive the drug but not take it? How does the company expect this to affect the cost effectiveness of adalimumab?

AbbVie Response: The cost of Adalimumab in the base case analysis is only applied to those patients who are compliant with treatment since the efficacy data and treatment compliance used in the CE model are both based on the Intent-to-Treat (ITT) analysis of the pooled populations from the pivotal Phase 3 placebo-controlled studies (PIONEER I and II). Any other assumption around the compliance rate (as opposed to that observed in the RCTs) in the CE model would also need to reflect the impact a lower/higher compliance rate would have on the overall efficacy of ADA for the treatment of moderate to severe HS patients.

Due to the controlled setting of the RCTs in clinical practice patient compliance might be lower than that observed in the PIONEER I and II studies, however based on feedback received from the UK clinical experts, consulted during this appraisal treatment compliance is unlikely to be an issue in patient receiving ADA for the treatment of moderate to severe HS. As such AbbVie believes that the compliance rates from the PIONEER I and II are representative of what would be expected in UK clinical practice.

In terms of the impact a different compliance rate would have on the cost effectiveness of Adalimumab this would be difficult to quantify in the absence of both effectiveness and compliance data.

Utility values

B12. Section 5.4, Table 46, page 155. The table footnote "m" states that the *"method of elicitation and valuation of EQ-5D scores was not clearly reported."* Given that the clinical study report was available to the company, please explain why this information could not be ascertained.

AbbVie Response: The systematic literature review was based on published studies. The data was primarily extracted from publications if they were available for a particular study. For the study in question (PIONEER II) where we marked "m" as an endnote, we only had an abstract availble as a publications and the method of elicitation and valuation of EQ-5D scores was not reported in the abstract. [7]

Inputs from trial data

B13. **PRIORITY QUESTION.** Section 5.3.1.1, page 138. The submission states: *"For patients non-responding to ADA at week 36 the discontinuation rate from the OLE clinical trial[32] was only applied up to week 48 in the base case. This was based on input from clinical experts suggesting that patients who do not respond to ADA treatment will be discontinued in clinical practice after a re-assessment period and 12 additional weeks of treatment[40-42 44]."* Please explain the mathematical logic underpinning the implementation of this assumption within the model. Is this assumption of continued adalimumab use assumed to apply only to the 36-48 week time period or is it intended to be applied to all subsequent cycles beyond week 48?

AbbVie Response: The assumption we are making is that patients who are not responding to treatment at or after week 36 and are still not responding to treatment 12 weeks later, discontinue treatment. This assumption is made for all patients from week 36 onwards.

This is applied within the model in "cell N130" where the probability of remaining in the non-response health state for four weeks is cubed, as this gives the probability of remaining in the non-response health state for three consecutive cycles and thus the probability of remaining non-responsive for 12 consecutive weeks.

B14. **PRIORITY QUESTION.** Section 4.13, page 122. The submission states *"There are also differences in study design between PIONEER I and PIONEER II, as shown in Table 38 below, which means that the results of PIONEER I and PIONEER II are not directly comparable."*

- Please comment on the appropriateness of pooling these data within the model.

AbbVie Response: From a clinical perspective, both studies are of very similar study design which allows many direct comparisons as well as pooling of data. Pooled data was selected in the base-case as it maximized the use of the clinical trial information. This was very important in the current case given that the sample size was small. For example, there were only 40 patients who received adalimumab every week during week 12-36 of the PIONEER II trial (after excluding patients who were non-responders at week 12). After pooling the data from the PIONEER I and PIONEER II trials together, the sample size increased to 68.

As detailed in Section 4.5.3 of the submission report, baseline patient characteristics were similar across these two trials. For example, among 307 patients in PIONEER I trial, the mean age was 37.0 years, the mean disease duration was 11.5 years, 63.8% were female, 52.4% were Hurley stage II, and 46.6% Hurley stage III. Similarly, among 326 patients from PIONEER II trial, the mean age was 35.5 years, the mean disease duration was 11.5 years, 67.8% were female, 53.7% were Hurley stage II, and 46.3% were Hurley stage III.

Furthermore, both PIONEER I and PIONEER II trials were double-blinded and placebo-controlled during the induction period, during which patients were randomised to receive either adalimumab or placebo. In the maintenance period in both trials, patients who had been randomised to adalimumab in the induction period were re-randomised to receive either adalimumab or placebo. Patients who had been

randomised to placebo in the induction period were continued on placebo during the maintenance period in the PIONEER II trial, and were all crossed-over to adalimumab in PIONEER I. Therefore, the only difference between the two trials was that the PIONEER II trial included patients receiving placebo in the maintenance period, but the PIONEER I trial did not.

To address the impact of pooling the data across the two PIONEER trials, an alternative data source using only the PIONEER II trial data was evaluated in the scenario analysis. When only PIONEER II data was used, the ICER increased to [redacted] as detailed in Table 63, page 194 of the submission report.

- Please explain how the data were pooled.

AbbVie Response: Patients from both trials were pooled and analysed together as one dataset.

B15. Section 5.3.1, page 138. Please provide a justification for breaking the randomisation and combining responses across treatment arms rather than combining treatment effects across studies.

AbbVie Response: The current model does contain a scenario analysis where only the PIONEER II trial is used to estimate transition probabilities for adalimumab on treatment, adalimumab discontinued and standard care. In this case, all transition probabilities are estimated from the same trial. The ICER was [redacted] under this scenario, as detailed in Table 63, page 194 of the submission report. One drawback with only using PIONEER II trial is the sample size is small (please refer to the response to B14). The small sample size when using only one trial could lead to instabilities in estimating relative treatment effects estimates; therefore, patients were pooled across trials to increase the sample size in the base-case. Patients from both trials were very similar at baseline as noted in response to B14.

Transition probabilities

B16. **PRIORITY QUESTION.** Section 5.3.1.3, page 142. The submission states *"For patients on ADA TPs were estimated using a generalised logit model using week 0-24 data from the OLE trial, which corresponds to week 36-60 if counting from the initiation of the PIONEER phase III trials; LOCF was used when conducting the analysis since less than half of the patients had follow-up up to 24 weeks at the time of the interim data cut."* Please provide an alternative generalised logit model analysis which does not include any imputation for this population. Please also confirm that imputation was not used in the generalised logit models for the standard care group or the group that discontinued treatment with adalimumab.

AbbVie Response: The transition probability (TP) of the alternative generalised logit model from the open label extension (OLE) trial without any imputation is presented in Table 20 and an analysis using these alternative TPs is presented in Table 21.

Table 20: 4-week TP using the observed OLE trial data (adalimumab arm only)

From / To	High responders	Responders	Partial responders	Non-responders
High responders	[redacted]	[redacted]	[redacted]	[redacted]
Responders	[redacted]	[redacted]	[redacted]	[redacted]
Partial responders	[redacted]	[redacted]	[redacted]	[redacted]
Non-responders	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: Incremental cost effectiveness analysis results using the alternative generalised logit model from OLE

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£) Incremental (QALYs)
SC	£128,541	22.73	11.61				
ADA	[redacted]	22.73	12.57				
ADA vs. SC				[redacted]	0.000	0.96	[redacted]

The OLE trial data could only be used to derive TPs for the adalimumab arm for the period beyond week 36, because the placebo arm was not included in the OLE trial. The TPs for patients on supportive care and for patients who discontinued adalimumab were derived from the PIONEER I and II trial data using non-responder imputation (NRI) in the base-case. The current model included a scenario analysis, where PIONEER I and PIONEER II trial data with NRI were also used to estimate the TPs for adalimumab beyond week 36, to be consistent with the data source and imputation method used for supportive care and adalimumab discontinuers. The ICER in this scenario changed to [redacted].

Imputation was needed when we analysed the PIONEER trials, because missing in clinical trials is not at random. We have explored both the NRI and last observation carried forward (LOCF) imputation methods, and they provided similar ICERs in the model (as documented in Table 63, page 194 of the submission report). The ICER would change to [redacted] when LOCF imputation was used, while the base-case ICER was [redacted] when NRI method was used.

B17. **PRIORITY QUESTION.** Company's model. Please explain the matrix presented in worksheet "Transition probabilities" in cells E124:N134. Why is the transition probability in cell N130 cubed?

Abbvie Response: As discussed in the response to question B13, the assumption is made that when patients are in the non-response health state for 12 weeks, they discontinue treatment. 12 weeks equals three model cycles of four weeks. The probability of a patient staying in the non-response health state for three consecutive cycles is the probability of a patient remaining in the non-response health state for 1

cycle cubed. Therefore the transition probability in “cell N130” is the probability of a patient remaining in the non-response health state for 4 weeks cubed.

B18. Section 5.3.1.3, page 142. The submission states that *“Patients who received ADA in the induction period and switched to placebo in the maintenance period in the trials were used to estimate TPs for ADA discontinuers.”* Does this population reflect all adalimumab induction responders who were switched to placebo, or all patients who were initially randomised to adalimumab irrespective of whether they responded at 12 weeks?

AbbVie Response: This reflects all patients who were initially randomised to adalimumab in the induction period (Week 0-12) and who were later randomised to placebo in the maintenance period (Week 12-36), irrespective of their response states at Week 12.

B19. Section 5.3.1.3, page 142. The submission states *“The TPs for the SC arm were estimated using all patients who received placebo in both induction and maintenance periods of the clinical trials.”* However, elsewhere the submission states that patients could only receive placebo in both the induction and maintenance phase of PIONEER II. Please clarify.

Abbvie Response: Both the PIONEER trials were double-blinded and placebo-controlled during the induction period, in which patients were randomised to receive either ADA or placebo. In the maintenance period in both trials, patients who had been randomised to ADA in the induction period were re-randomised to receive either ADA or placebo. Patients who had been randomised to placebo in the induction period were continued on placebo during the maintenance period in the PIONEER II trial, however they were all crossed-over to ADA in the PIONEER I trial.

As a result, the PIONEER II trial included patients receiving ADA in both the induction and maintenance periods, patients receiving ADA in the induction period and switching to placebo in the maintenance period, and patients receiving placebo in both periods. The PIONEER I trial only included patients receiving ADA in both periods (induction and maintenance) and patients receiving ADA in the induction period and switching to placebo in the maintenance period; it did not include patients receiving placebo in both the induction and maintenance periods.

As such the TPs for the SC arm were estimated using all patients who received placebo in the induction (PIONEER I and PIONEER II) and maintenance periods of the clinical trial (only PIONEER II).

B20. Section 5.3.1.3, pages 140-143. With respect to the extrapolation of transition probabilities, why was the generalised logit model chosen over the ordered logit? What alternative approaches were considered and why were they not selected?

AbbVie Response: Ordered logit models were first explored, however, these models were not selected because of invalid proportional odds assumptions (p-value of the proportional odds assumption test was <0.05). As a result, generalized logit models were used instead.

Cost-effectiveness results

B21. **PRIORITY QUESTION.** Section 5.7.2, Table 58, page 185. Please clarify how the values in the columns "Predicted in the CEA" have been calculated. Which treatment group(s) do they represent? Why are the values in the table different to those in the actual Markov traces in the model? Please provide an alternative validation analysis split by treatment group and by individual trial.

Abbvie Response: The values in Table 58, page 185 in the columns "Predicted in the CEA" have been estimated by dividing the proportion of patients in each health state at each time point (week 12 and week 36) by the sum of all health states at each time point. Please see formula below.

= (High Response %) / Sum (High response%, Response%, Partial response %, Non-Response)

Sensitivity analyses

B22. Section 5.6.1, Table 55, page 178. Why was the compliance rate for adalimumab not varied in the probabilistic sensitivity analyses?

AbbVie Response: Compliance data was derived directly from the analysis of the phase III clinical trial. Mean treatment compliance was estimated as: "100 * (NUMBER OF INJECTIONS ACTUALLY RECEIVED)/(TOTAL NUMBER OF INJECTIONS PLANNED)". No information was available on the variance for this parameter and such it was not included in the PSA.

B23. Section 5.8.4, Figure 28, page 193. Please clarify the value of lambda used to estimate net monetary benefits in the tornado diagram.

Abbvie Response: The willingness-to-pay threshold to estimate net monetary benefits in the tornado diagram is £30,000.

Other model assumptions

B24. **PRIORITY QUESTION.** Company's model. Within the model, patients can discontinue adalimumab therapy due to a lack of response during induction or by losing a prior response during maintenance.

- Please comment on whether the wording of the Summary of Product Characteristics (SmPC) implies that a full or partial HiSCR response is required in order to begin maintenance therapy.
- **AbbVie Response:** In the SmPC it is recommended *that "Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period".*

  Evidence from the PIONEER I and II trial demonstrated that in patients who were non-responders at week 12 and who continued to receive treatment with ADA in

period B (up to week 36) no improvement was seen. As such for modelling purpose all patients in the non-response state at week 12 discontinued ADA treatment. Patients in the response health states (including partial responders) continue on ADA treatment from week 12 onwards and all patients discontinue treatment based on the discontinuation rates observed in the PIONEER and OLE trials.

- Please comment on the extent to which the assumption that patients who lose response continue maintenance treatment for a further 12 weeks is in line with the wording of the SmPC.

- **AbbVie Response:** The ADA drug label indicates that "*the benefit and risk of continued treatment should be periodically evaluated after week 12*". The UK clinical experts consulted suggested that patients not responding will be assessed every 12 weeks and discontinued if they had not responded after an additional 12 weeks on ADA treatment. This assumption is implemented in the economic model by discontinuing at week 48 all patients that were not responding at week 36.

B25. Section 5.3.1.1, page 138. Please justify why the discontinuation rate was assumed to be independent of response?

AbbVie Response: During week 12-36, one discontinuation rate was used irrespective of response rate; from week 36 onward, response-specific discontinuation rates were used.

At week 12, non-responders on adalimumab would discontinue. Only responders to adalimumab at week 12 would continue adalimumab. For those patients, even if they lost response during week 12-36, they were likely to be advised to stay on treatment even if they lose response to regain response instead of discontinuation, as advised by experts. Therefore, only one discontinuation rate was used irrespective of response status.

From week 36 onward, response-specific discontinuation rates were used. If a patient failed to regain response after a continuous treatment with adalimumab for up to 24 weeks it would be reasonable to assume they would discontinue.

A scenario analysis was provided to evaluate the impact of the response-specific discontinuation rate of adalimumab during week 12-36 in the current model. In this scenario, two different discontinuation rates were assigned to the non-response health state and to the high response, response and partial response health states, respectively. The ICER was [redacted] in this scenario, which was very similar to the base-case ICER of [redacted] (as detailed in Table 62, page 192 of the submission report).

B26. Section 5.11, page 196. The submission states: *"… in the real world, patient compliance is likely to be lower than that observed in the clinical trials."* Please comment on the level of compliance that has been observed based on the real-world experience with adalimumab for other clinical indications?

AbbVie Response: Results from a systematic review (Fidder et al, 2013)[24] report adherence rates in Crohn's disease (CD) and Rheumatoid Arthritis (RA) of 55% and 67% respectively.

B27. Company's model. In the "Parameters" worksheet, the resource use and cost parameters are characterised using gamma distributions whereby the standard error is defined as 25% of the mean. Please justify the use of these standard errors.

AbbVie Response: The standard error of parameters for which no distribution information was available was assumed to be 25% of the mean. This is a conventional approach often used in the field in the absence of real variance (20% or 25% variance has been assumed in past HTAs)[25].

Executable model

B28. The worksheet "GLM" includes cells which refer to the every other week dosing regimen (cells J23:J25). Please confirm that data relating to patients receiving the every other week regimen were not included in the generalised logit model.

AbbVie Response: A scenario analysis is presented in the DSA in the submission using modelled TP from the week 12-36 data from the PIONEER I and PIONEER II clinical trials using generalised logit models. Patients who received ADA in the induction period, who were week 12 responders, and who continued receiving ADA during week 12-36, were used to estimate the TPs of ADA treatment for the period beyond week 36 in the model. The dependent variable was the current health state, and the independent variables were the previous health state and the ADA dosing regimen (EW or EOW). Both patients receiving ADA EW and patients receiving ADA EOW were included in the generalised logit model, in order to increase the sample size and to maximize the utilised data. ADA EW specific TPs were estimated from the generalised logit model and applied to the CEA model. The worksheet "GLM" presents the model coefficient and matrix-co matrix variance for this analysis.

In the base case analysis the ADA TPs beyond week 36 were estimated using a generalised logit model using week 0-24 (weeks) data from the OLE trial. The dependent variable in the model was the current health state, and the independent variables were the previous health state. The ADA dosing regimen (EW or EOW) was not included as an independent variable in the model. The OLE trial only allows EW dosing.

B29. PRIORITY QUESTION. It is unclear exactly which patient populations have been used to inform the various transition matrices within the model. Please complete the right hand column in Table xx below. Please provide as much detail as required.

AbbVie Response: Please see Table 22.

Table 22 : Description of patients used to inform model transition matrices

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
Standard care (SC)		
Live_SC0to2	S11:V14	• Method: Cross-tabulation based on Week 0 and Week 2 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to placebo (PBO) during Period A • Current treatment: PBO • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; deterministic sensitivity analysis (DSA) PIONEER II only *All patients start from non-response; thus, the values on rows 11-13 are 0.
Live_SC2to4	S19:V22	• Method: Cross-tabulation based on Week 2 and Week 4 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A • Current treatment: PBO • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_SC4to8	S27:V30	• Method: Cross-tabulation based on Week 4 and Week 8 health state distribution; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A • Current treatment: PBO • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_SC8to12	S35:V38	• Method: Cross-tabulation based on Week 8 and Week 12 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A • Current treatment: PBO • Prior treatment: Conventional therapy received before enrollment to the trial

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		• Trials: Base case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_SC12to16	S43:V46	• Method: Cross-tabulation based on Week 12 and Week 16 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO • Trials: Base-case PIONEER II; DSA PIONEER II
Live_SC16to20	S51:V54	• Method: Cross-tabulation based on Week 16 and Week 20 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO • Trials: Base-case PIONEER II; DSA PIONEER II
Live_SC20to24	S59:V62	• Method: Cross-tabulation based on Week 20 and Week 24 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO • Trials: Base-case PIONEER II; DSA PIONEER II
Live_SC24to28	S67:V70	• Method: Cross-tabulation based on Week 24 and Week 28 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO • Trials: Base-case PIONEER II; DSA PIONEER II
Live_SC28to32	S75:V78	• Method: Cross-tabulation based on Week 28 and Week 32 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		• Trials: Base case PIONEER II; DSA PIONEER II
Live_SC32to36	S83:V86	• Method: Cross-tabulation based on Week 32 and Week 36 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO • Trials: Base case PIONEER II; DSA PIONEER II
Live_SC36toEnd	S91:V94	• Method: Generalized logit model based on the PBO data at Week 12, 16, 20, 24, 28, 32 and 36; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to PBO during Period A and continued with PBO during Period B • Current treatment: PBO • Prior treatment: PBO • Trials: Base-case PIONEER II; DSA PIONEER II
Adalimumab (ADA)		
Live_ADA0to2	G11:J14	• Method: Cross-tabulation based on Week 0 and Week 2 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA 40 mg every week (EW) during Period A • Current treatment: ADA EW • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only *All patients start from non-response; thus, the values on rows 11-13 are 0.
Live_ADA2to4	G19:J22	• Method: Cross-tabulation based on Week 2 and Week 4 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A • Current treatment: ADA EW • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADA4to8	G27:J30	• Method: Cross-tabulation based on Week 4 and Week 8 health state distributions; the row header

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A • Current treatment: ADA EW • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADA8to12	G35:J38	• Method: Cross-tabulation based on Week 8 and Week 12 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A • Current treatment: ADA EW • Prior treatment: Conventional therapy received before enrollment to the trial • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_all_12to16	G43:N50	<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Cross-tabulation based on Week 12 and Week 16 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state; a certain proportion of patients would discontinue ADA EW based on the specified discontinuation rate, and be moved to the same row within K-N columns. • Patients: Patients randomized to ADA EW during Period A, who were not Week 12 non-responders and were re-randomized to ADA EW during Period B • Current treatment: ADA EW • Previous treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only <u>Bottom 4 rows in Column K-N:</u> • Same as Live_ADAtoSC_12to16, details provided below
Live_all_16to20	G55:N62	<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Cross-tabulation based on Week 16 and Week 20 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state; In addition, a certain proportion of patients would discontinue ADA EW based on the specified discontinuation rate, and be moved to the same row within K-N columns.

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		• Patients: Patients randomized to ADA EW during Period A, who were not Week 12 non-responders and were re-randomized to ADA EW during Period B • Current treatment: ADA EW • Previous treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only <u>Bottom 4 rows in Column K-N:</u> • Same as Live_ADAtoSC_16to20, details provided below
Live_all_20to24	G67:N74	<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Cross-tabulation based on Week 20 and Week 24 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state; in addition, a certain proportion of patients would discontinue ADA EW based on the specified discontinuation rate, and be moved to the same row within K-N columns. • Patients: Patients randomized to ADA EW during Period A, who were not Week 12 non-responders and were re-randomized to ADA EW every week during Period B • Current treatment: ADA EW • Previous treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only <u>Bottom 4 rows in Column K-N:</u> • Same as Live_ADAtoSC_20to24, details provided below
Live_all_24to28	G79:N86	<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Cross-tabulation based on Week 24 and Week 28 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state; in addition, a certain proportion of patients would discontinue ADA EW based on the specified discontinuation rate, and be moved to the same row within K-N columns. • Patients: Patients randomized to ADA EW during Period A, who were not Week 12 non-responders and were re-randomized to ADA EW during Period B • Current treatment: ADA EW • Previous treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only <u>Bottom 4 rows in Column K-N:</u>

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		• Same as Live_ADAtoSC_24to28, details provided below
Live_all_28to32	G91:N98	<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Cross-tabulation based on Week 28 and Week 32 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state; in addition, a certain proportion of patients would discontinue ADA EW based on the specified discontinuation rate, and be moved to the same row within K-N columns. • Patients: Patients randomized to ADA EW during Period A, who were not Week 12 non-responders and were re-randomized to ADA EW every week during Period B • Current treatment: ADA EW • Previous treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only <u>Bottom 4 rows in Column K-N:</u> • Same as Live_ADAtoSC_28to32, details provided below
Live_all_32to36	G103:N110	<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Cross-tabulation based on Week 32 and Week 36 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state; in addition, a certain proportion of patients would discontinue ADA EW based on the specified discontinuation rate, and be moved to the same row within K-N columns. • Patients: Patients randomized to ADA EW during Period A, who were not week 12 non-responders and were re-randomized to ADA EW every week during Period B • Current treatment: ADA EW • Previous treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only <u>Bottom 4 rows in Column K-N:</u> • Same as Live_ADAtoSC_32to36, details provided below
Live_all_36toEnd		<u>Column G-J and top 4 rows in Columns K-N:</u> • Method: Generalized logit model based on ADA data (patients and trials information are described below); the row header indicates the "From" state, and the column header indicates the "To" state; in addition, a certain proportion of patients would discontinue ADA

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		EW based on the specified discontinuation rate, and be moved to the same row within K-N columns. • Patients and trials: Base-case used the data at Week 0, 12 and 24 from the OLE trial, which corresponds to Week 36, 48 and 60 if counting from the initiation of the PIONEER phase III trials. All patients who received ADA within the PIONEER phase III trials and OLE trials were used for the analyses, i.e. the EW/EW/EW patients (i.e., ADA EW all the time) and EW/EOW/EW patients (i.e., ADA EW in Period A and the OLE trial, and ADA 40 mg every other week [EOW] in Period B). Patients who were Week 12 non-responders in PIONEER phase III trials were excluded. DSA used the data at Week 12, 16, 20, 24, 28, 32 and 36 from the PIONEER I and II trials. Patients who received ADA EW in Period A and EW or EOW in Period B were included. Patients who were Week 12 non-responders in PIONEER phase III trials were excluded. ADA EW specific TPs were estimated from the model. • Current treatment: ADA EW • Previous treatment: ADA EW in Period A, ADA EW or EOW in Period B in the base-case <u>Bottom 4 rows in Column K-N:</u> • Same as Live_ADAtoSC, details provided below
live_all_48toend	G127:N134	• Same as live_all_36toend except for ADA discontinuation rate
Live_ADAtoSC_12to16	G139:J142	• Method: Cross-tabulation based on Week 12 and Week 16 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO • Prior treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADAtoSC_16to20	G147:J150	• Method: Cross-tabulation based on Week 16 and Week 20 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		• Prior treatment: ADA EW • Trials: Base case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADAtoSC_20to24	G155:J158	• Method: Cross-tabulation based on Week 20 and Week 24 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO • Prior treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADAtoSC_24to28	G163:J166	• Method: Cross-tabulation based on Week 24 and Week 28 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO • Prior treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADAtoSC_28to32	G171:J174	• Method: Cross-tabulation based on Week 28 and Week 32 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO • Prior treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADAtoSC_32to36	G179:J182	• Method: Cross-tabulation based on Week 32 and Week 36 health state distributions; the row header indicates the "From" state, and the column header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO • Prior treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only
Live_ADAtoSC	G187:J190	• Method: Generalized logit model based on the data at Week 12, 16, 20, 24, 28, 32 and 36; the row header indicates the "From" state, and the column

Transition matrix reference name	Cell reference in "Transition Probabilities worksheet"	Description of patient population used to derive transition matrix (including information on trial(s), prior response status and previous and currently allocated treatments)
		header indicates the "To" state • Patients: Patients randomized to ADA EW during Period A and re-randomized to PBO during Period B • Current treatment: PBO • Prior treatment: ADA EW • Trials: Base-case PIONEER I and PIONEER II pooled; DSA PIONEER II only

Section C: Textual clarifications and additional points

Health condition and position of technology in the treatment pathway

C1. **PRIORITY QUESTION.** Section 3.2, page 42. Please clarify the anticipated position of adalimumab within the treatment pathway.

AbbVie Response: In the UK a number of different pharmacological treatments are currently used off-label in clinical practice to manage HS including antiseptics, antibiotics, NSAIDs, immunosuppressants, corticosteroids, anti-androgens, retinoids and TNF-α inhibitors.

Adalimumab should be used after all effective conventional systemic HS treatments have been exhausted.

- Is adalimumab to be used only before surgery (as claimed on page 42), or is adalimumab to be used alongside surgery and/or after surgery?

AbbVie Response: An evidence-based approach to the treatment of HS based on the European Guidelines for HS[26] state that: *"The need for surgical intervention should be assessed in all patients depending upon type and extent of scarring, and an evidence-based surgical approach should be implemented".* Further, surgical treatments are rated separately from the medical, and list the order of therapies as: 1) First line medical therapy (including adalimumab), 2) Surgery, 3) Second line medical therapy, 4) Third line therapy.

In addition, results from an UK online clinician survey[27] state that the decision of concomitant treatment alongside surgery should be reserved to the clinician's opinion based on the specific patient's history of disease, severity and needs.

There is no published evidence on treatment with adalimumab alongside surgery for the treatment of moderate to severe HS. However, additional analyses from the PIONEER trials assessing events requiring surgery showed that adalimumab decreased these events by 14%-35%.[21] Further, UK experts' opinion suggest that treatment with a biologic may potentially delay the need for some types of surgery.

Based on the above mentioned reasons AbbVie believes that Adalimumab could be used either before or after surgery.

- In addition, please clarify whether adalimumab would be used before treatments such as dapsone, retinoids and immunomodulators (as suggested on page 42) or only after all other treatment options have been exhausted (as suggested on page 140).

  AbbVie Response: A UK online clinician survey[27] looking at the current HS clinical management in the UK found that the most common treatment in the UK were oral tetracyclines (used as first choice among clinicians), followed by a combination of clindamycin and rifampicin as second choice, with the duration depending on patient response. Other treatments, such as acitretin, isotretinoin, dapsone and ciclosporin were ranked third, fourth, fifth and sixth choice interventions. Respondents from the same survey noted that the use of biologic agents was restricted due to funding issues.

  AbbVie believes that Adalimumab should be used after all effective conventional systemic HS treatments have been exhausted.

- Please also comment on how this anticipated positioning relates to the populations recruited into the PIONEER I and II trials.

  AbbVie Response: In the PIONEER trials patients unresponsive or intolerant to oral antibiotics with moderate-to-severe HS were eligible for enrolment which would represent the population described above. Patients in the PIONEER trials have failed conventional systemic therapies and they are treated either with adalimumab or BSC (placebo). Adalimumab should therefore be positioned after failed conventional systemic HS therapies.

C2. Section 2.4, page 29. The submission states that *"only around 37% of patients with diagnosed moderate to severe HS are suitable for biologic treatment."* Please explain why this value is different to the estimates reported in Section 4.13.3 and Table 39?

AbbVie Response: The statement "*about 37% of patients with diagnosed moderate to severe HS are suitable for biologic treatment"*[28] is based on clinicians opinion and it refers to patients <u>suitable</u> for biologic treatment. This percentage was estimated using market research and calculated as follows:

"In slide 98 the last column shows moderate to severe patients stratified by "not seen by anyone" (15%), "not suitable" (52%), "potentially suitable" (25.8%), "being worked up" (7.4%) and "treated with at biologic" (0.44%)". The 37% is the sum of the last three.

Table 39 shows the calculation of patients treated by a dermatologist and treated with a biologic. The range of treated patients (410-1,417) are AbbVie's own estimation (2.4%-8%) of moderate to severe patients that would be <u>eligible</u> to receive treatment with a biologic.

C3. Section 3.1, page 33. Please explain why the UK prevalence rates (approximately 1million adults) are different from the rates given in Section 4.13.3 and Table 39.

AbbVie Response: The prevalence rate in section 3.1 is based on AbbVie's market research and based on results from an online clinician survey. The survey estimated that 1.94% of the total adult population in the UK might have HS (977,900 people). This number includes both diagnosed and undiagnosed HS patients.

The estimates presented in Table 39 are based on ONS 2016 prognosed adult population in England and Wales, using a 1% prevalence from a publication (Revuz 2008).[29]

C4. NICE has noted there is a large volume of information marked as confidential in the company submission. A separate request will be sent to the company, however please consider lifting the confidentiality status of the data in the submission in advance of receiving a formal request.

AbbVie Response: AbbVie has reviewed the evidence presented in the submission and has amended the confidentiality status of some of this evidence.

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AbbVie response to clarification questions from the Evidence Review Group (ERG), received 27th November 2015

In relation to question B2
Please can the company provide the executable version of the model used to obtain the results presented in Table 15 on page 31 of the company's clarification response?

AbbVie Response: An executable version of the model which uses only the outcomes of response or no response as per the PIONEER trials has been provided.

In relation to question B13
The ERG has concerns regarding the implementation of the company's assumption around the use of 12 additional weeks of adalimumab maintenance therapy in non-responders prior to discontinuation. In particular, cell N130 of the transition probabilities worksheet in the company's model takes the 4-week probability of remaining non-responsive to adalimumab from the M12-555 OLE study and raises this value to the power of 3.

In response to the ERG's clarification questions (question B13), the company states: *"the probability of remaining in the non-response health state for four weeks is cubed, as this gives the probability of remaining in the non-response health state for three consecutive cycles and thus the probability of remaining non-responsive for 12 consecutive weeks."*

The consequence in the model is that during weeks 40-44 and 44-48, the 4-weekly probability of discontinuing adalimumab for non-responders estimated from the OLE study is 0.05. The company's cubing approach, which is applied to week 48 onwards then increases the probability of adalimumab discontinuation for non-responders to 0.56 every 4-weeks. The consequence in the model is that based on the company's approach, patients discontinue from adalimumab treatment considerably faster than the rate observed in the OLE study, despite the fact that the company's description of the continuation rule indicates that patients would remain on adalimumab for longer even if it is not producing a treatment response. The ERG also notes that the cubed probability relates to a 12-week duration rather than the model's 4-week cycle duration.

The ERG believes that applying the company's treatment continuation rule, as described in the submission, requires the incorporation of memory into the model (i.e. additional health states would be required to estimate the probability that patients remain non-responsive for 2 consecutive cycles, 3 consecutive cycles etc.). Patients may also be non-responsive in one cycle, but then obtain a response during the next cycle. The company's approach does not satisfactorily reflect these issues.

Please can the company provide either further justification regarding how their approach reflects the intended continuation rule described in the submission.

AbbVie Response: In the base case analysis the same discontinuation rate is assumed during weeks 12-36 for all ADA patients, regardless of health states, since all patients remaining on ADA during this period were week 12 responders and if a loss of response might occur, an attempt would most likely be made to regain response instead of aggressive discontinuation as suggested by the experts consulted during this submission. However, after week 36 the discontinuation rate is based on the response-specific discontinuation rates since the discontinuation rate of ADA would most likely be driven by loss of response to treatment in the long term, given that patients who remained on ADA treatment for 36 weeks were likely to be those who tolerated the biologic treatment well.

Clinical experts consulted during this submission suggested that patients who do not respond to ADA treatment will most likely be discontinued in clinical practice after a re-assessment period and 12 additional weeks of treatment. Furthermore the ADA drug label also indicates that "the benefit and risk of continued treatment should be periodically evaluated after week 12". As such in the model base case all patients who are in the non-response health state at week 36 discontinue ADA treatment at week 48. In

order to implement this assumption into the model patients who were in a non-response health state at week 36 were assigned the non-response discontinuation rate as per the OLE trial in weeks 36-40, 40-44 and 44-48 (first 12 weeks) and then at week 48 were discontinued using the cubing approach.

Beyond week 48 all patients who move to the non-response health state also discontinue treatment at a rate of 0.56 per cycle, taking in the assumption that patients who have been unresponsive for 12 consecutive weeks should discontinue treatment (the probability of adalimumab discontinuation for non-responders is 0.56 at week 48+). The assumption around the use of a higher discontinuation rate beyond week 48 was necessary in order to stop treatment in all patients who would gain no further benefit with ADA treatment, as was suggested by the clinical experts consulted. Using the discontinuation rates as observed in the OLE trial (annual rate of 44.99%) beyond week 48 would result in some patients not responding at week 36 continuing treatment with ADA for far more than 12 weeks.

The cubed transition probability is used to reflect the assumption that patients that have been unresponsive for 12 consecutive weeks discontinue treatment. This apporah was used in order to avoid introducing multiple tunnel states into the model. The ERG seem to suggest that cubing the probability of remaining unresponsive would overestimate the proportion of patients discontinuing, however the proportion discontinuing will equal out in the long term. AbbVie has provided an example with and without tunnel states to demonstrate the impact of using a model with and withouth tunnel states. From the calculations provided we can notice that there is initailly a difference between the proportion of patients that have discontinued with and without using tunnel states, however this difference becomes smaller in the long term.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: The HS Trust

Your position in the organisation: Founder

Brief description of the organisation: The HS Trust is the leading charity for HS in the UK. It was founded by a HS sufferer in 2009 and became the first registered charity for HS. The HS Trust supports patients emotionally with patients support groups throughout the UK, and has influenced the need for HS clinics and centres of excellence. The HS Trust raises awareness surrounding HS to both the medical community and the general public through printed literature and the internet, including social media. Our facebook group has in excess of 1700 members and our facebook page has a reach to over 4800 individuals worldwide. The HS Trust is funded by general public donations, and sponsored events that members of the public take part in. We have only had 1 grant from a pharmaceutical company (AbbVie – June 2015) and the organisation is run voluntarily by 5 Trustees.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

To live with HS could be extremely devastating. Not only enduring daily physical pain, but to also suffer emotionally as a result. HS is a chronic illness that is disfiguring, and many HS patients report having low self-esteem, low body image and no confidence. HS dictates the life of a patient including what clothes to wear (due to abscess leakage and staining), where they can travel and how far. HS also affects careers, and the emotional wellbeing as many

HS patients often report depression as a direct result of having HS. Social lives of patients are severely affected and patients often lead a life of complete isolation. Relationships can also breakdown as a result as intimacy becomes problematic. HS is a disease that affects patients, but also the lives of those surrounding patients emotionally.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Patients would like treatment outcomes of – better pain management, no leakage from wounds, less odour, less scarring, less abscesses/boils, more confidence, emotional support, better understanding, and acceptance. The most important factor would be to have better pain management. If pain was controlled then HS patients would be mentally stronger to be able to cope and manage other disease symptoms better, and ultimately this will help to have a better quality of life.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Currently care and treatment from the NHS for HS patients is inadequate. There are no pathways for patients to follow and HS patients are not referred to dermatology consultants quickly enough. HS patients often suffer disease progression prior to obtaining any adequate help and support and on average it may take 8 years before patients are referred to dermatology where they obtain the accurate diagnosis. Patients then have to endure a trial and error process of medications as the information surrounding how to treat HS is lacking. The treatments are not acceptable as HS patients endure side effects from medications that are not proven to help HS patients, and before finding a disease control the patient often progresses to levels that affect their jobs, relationships and quality of life. It would be preferable to get an earlier referral to dermatology where there would stand more hope at finding the appropriate disease control. Patients who have moderate to severe HS often need to have biologic intervention which may be the preferred option as they help with inflammatory diseases, but this is often rejected for patients due to funding issues. There is no specific treatment for HS to date which is completely unacceptable.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

There will be less physical symptoms that will decrease pain, decrease the level of disability and improve mental health. Patients may be able to continue or return to work, have increased social activity and self-manage the disease better. Less leakage from wounds, improved confidence and have better relationships with peers and family members. This could benefit the patient as they can self-administer the injection meaning other medications may be able to cease which would save time, and possibly decrease the amount of hospital visits needed. This could also prevent further disease progression and quality of life will be improved.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Patients feel that the advantages are that this medication could provide disease control for a number of years, and even possibly provide a route to disease remission.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None to my knowledge

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Current NHS treatments can be frustrating as they do not provide the desired effect or relieve any symptoms. Some treatments used can make symptoms worse, or introduce new symptoms, and they can be time consuming at home, and also include travel to hospitals frequently. This may affect social lives as patients deal with possible side effects and not having time to get to hospital as often as needed.

Please list any concerns patients or carers have about the treatment being appraised.

Some patients are concerned about possible side effects, particularly in long term use, such as becoming more susceptible to infections. Patients also show concern about having to self-inject.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Some patients are not concerned about the side effects as some medications taken orally have the same or similar side effects.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients with moderate to severe HS will benefit more from the treatment as it is at these stages where quality of life is severely affected, patients often lose their jobs and they become isolated, along with emotional distress. Having this treatment may improve all areas where the patient could potentially lead a relatively normal life.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

None.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes – patients report that they are responding and benefitting from the use of the treatment which reflect the results of the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes – the outcomes captured are of great benefit to the patients with better disease control less flares as a result which improved the quality of life. To my knowledge there are no limitations in how the treatment has been assessed.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but

have emerged during routine NHS care?

No

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

http://www.ncbi.nlm.nih.gov/pubmed/24903313 - HS Priority Setting Partnership – This was a study in which patients/carers/clinicians were all asked about what HS uncertainties were most important to them.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Patients who have needle phobias would find using this treatment difficult.

When discussing the use of this treatment always ensure that patients are

trained on how to use this treatment effectively, and discuss any concerns which will make it evident that patients have these difficulties.

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

By using the self-administration injection method it provides patients a way to self-manage the illness at home and reduces time constraints.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- HS to date has been severely mismanaged.
- HS patients have the desire to be able to lead a relatively normal life.
- HS knowledge among HCP's is inadequate.
- HS affects the physical and emotional wellbeing of a patient.
- HS treatments need to be practical for patients.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] and [redacted] and the British Association of Dermatologists Therapy and Guidelines sub-committee

Name of your organisation: British Association of Dermatologists (BAD)
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? No
- other? (please specify)

[redacted]

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

In the NHS a stepwise approach to treatment is taken, based on disease severity. The medical treatment ladder commences with topical antimicrobial therapy, such as clindamycin 1% solution, for mild disease. The next step is single agent oral antibiotics, most commonly the oral tetracycline group and then combination antibiotic treatment with clindamycin 300mg twice daily and rifampicin twice daily for 10-12 weeks, for moderate disease. For moderate to severe disease unresponsive to these therapies a number of options may be considered, including acitretin for males and non-fertile females, dapsone or other immunomodulators such as ciclosporin. Metformin may be a helpful adjunct. For severe disease unresponsive to other therapy, biologic anti-TNF treatments are considered, including infliximab and adalimumab.

Surgical management is utilised as stand-alone intervention or in combination with medical therapy and include extensive excision of an involved region when only one, or a few regions are involved. Limited surgical procedures include deroofing of sinus tracts and narrow margin excision; however, both are associated with a high rate of recurrence at the surgical margins. In other European countries, STEEP (Skin Tissue Sparing Excision with Electrosurgical Peeling) is performed more often for moderate disease, but is again associated with a high rate of recurrence.

There is a reasonable degree of consensus between UK clinicians regarding the medical treatment pathway, in line with the European guidelines, as demonstrated in a recent UK survey of current practice (Ingram et al 2015). However, there was less consensus regarding the timing of any surgery and the type of surgical procedure. The survey did not highlight any particular geographical variation, although access to plastic surgery expertise may have affected the timing and type of surgery.

The main alternative to adalimumab, in terms of medical therapy, is infliximab. Infliximab has the advantage of being dosed by weight, which is particularly important in the context that many hidradenitis suppurativa (HS) patients are overweight or obese and has potential for rapid onset of action. However, the IV mode of administration makes infliximab less convenient for patients compared to the subcutaneous dosing of adalimumab which can be administered in the patient's own home.

Cost is a very important issue. Based on the RCT evidence available, which is summarised in the recently-published Cochrane review (Ingram et al 2015), adalimumab is only effective when given at a dose of 40 mg weekly. This represents twice the standard dose used for psoriasis and other conditions and, at current prices, will make adalimumab cost nearly twice as much as infliximab.

Long term safety data is currently lacking regarding administration of adalimumab at twice the standard psoriasis dose. However, trials up to 12 months in duration have not raised significant concerns regarding infection rates or other adverse effects, compared with infliximab or the standard dose of adalimumab.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

This is essentially unknown due to a lack of cohort and registry studies.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Adalimumab should be instigated and monitored in secondary care, ideally via specialist HS and/or biologic clinics. This will ensure appropriate patient selection and monitoring. However, some centres may not have dedicated clinics currently. Once established on treatment, administration of adalimumab can take place in the patient's own home.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Current variation in the use of adalimumab mainly relates to local funding issues. Prior to adalimumab obtaining its European licence for HS, funding was sought on an individual patient basis.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

Dr Ingram is currently leading the British Association of Dermatologists UK guideline development group for HS, using GRADE methodology, and the guidelines will take about another 12 months to be finalised. European Dermatology Forum guidelines were published earlier this year (Zouboulis et al 2015). The guidelines are evidence-based but the quality of evidence was not formally assessed and the final treatment algorithm is based on a consensus approach.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Prior to use of anti-TNF therapy for HS, there were no other equivalent medical treatment options for severe, widespread HS. Oral immunomodulators were used with limited success and surgery was the other option, depending on the number of regions involved.

As discussed above, the main alternative biologic to adalimumab is infliximab. Infliximab has the advantage of being dosed by weight and being cheaper than adalimumab weekly therapy. However the evidence base for infliximab in HS is weaker, it is unlicensed for HS, and the IV route of administration is less convenient for patients. In addition, the single RCT investigating infliximab for HS reported primary outcomes after 8 weeks and so we do not know whether infliximab's efficacy is sustained for this chronic condition.

Safety monitoring for biologic therapy in HS is similar to the framework currently used for psoriasis. However, as discussed above, safety data for adalimumab weekly dosing is currently relatively limited.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Using current trial evidence and based on its European licence, adalimumab should be considered for moderate to severe HS unresponsive to standard therapy. The definition of standard therapy may need further discussion, particularly because adalimumab is currently the only systemic therapy licensed for HS in the UK. Standard therapy could be defined as topical therapy, oral tetracyclines, and the clindamycin and rifampicin combination. Acitretin for males and infertile females could also be considered, but this therapy is unlicensed and based on case series evidence only. Surgery may also need to be considered, particularly when disease is localised to only one or two sites.

The rules for starting and stopping adalimumab should be based on both physician and patient reported outcome measures. There is only limited validation data for outcome measures in HS. Hurley staging is a useful physician-reported baseline measure and moderate to severe disease corresponds to Hurley stages 2-3. The Hurley system is unresponsive to change and so HiSCR (Kimball et al 2014), based

on a count of the number of inflammatory lesions, could be used in which a 50% reduction in baseline score represents treatment success. The physician's global assessment (PGA) is an alternative measure that is quicker to perform.

The two standard patient reported outcomes in HS are quality of life and pain. In the adalimumab trials, quality of life was measured using the Dermatology Life Quality Index (DLQI). A DLQI score of 11 or more represents a severe impact on quality of life, while the mean score of patients entering the largest HS adalimumab trial (Kimball 2012) was approximately 15. The minimal clinically important difference for the DLQI scale is 4 points (Basra et al 2015), which could be used as one of the stopping rules. Pain can be measured on a visual analogue scale (VAS) and a 50% reduction in baseline pain is usually considered an adequate response.

The primary outcome in Kimball et al 2012 was measured at 16 weeks and this is an appropriate duration of treatment to assess disease response after commencing adalimumab.

There is no data regarding differential responses in particular subgroups of HS patients. The trial conditions probably do reflect in general how adalimumab would be used in UK clinical practice, however real-life experience is limited because adalimumab has only recently gained its HS licence and approval for its use in HS has been on a named patient basis in severe cases where all other therapies have failed.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The clinical trials and clinical practice have not demonstrated adverse effects that differ from use of adalimumab in psoriasis and other inflammatory conditions. The main issue is that there is only limited data regarding the long term safety profile of weekly adalimumab therapy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The Cochrane review of "Interventions for hidradenitis suppurativa" has just been published in October 2015 (Ingram et al).

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Adalimumab therapy for HS is likely to mirror the systems already in place for psoriasis, including dermatology biologic clinics and biologic specialist nurses in secondary care. An expansion of this service may be required however. Delivery systems to transport adalimumab to the patient's home are already in place for psoriasis and other inflammatory conditions.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No particular equality issues identified.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Anthony Bewley, Consultant Dermatologist

Name of your organisation Barts Health NHS Trust, London,

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

- X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Hidradenitis Suppurativa (HS) is a dermatological condition where patients develop chronic painful inflammatory disease of the skin's apocrine glands. This causes swelling, pain, exudation, pus, sinus formation, weeping, abscesses, scarring, and disfigurement of the areas affected. These areas are usually the axillae, groin and perianal skin, but can also be the skin folds (beneath the breasts), and other apocrine bearing areas of the skin. The disease affects about 1% of the population and can range in severity. The diagnosis is often delayed as patients will seek the help of primary care physicians and A&E departments before being referred to dermatology departments. Many non-dermatologists have limited exposure / experience of treating patients with HS. The British Association of Dermatologists are about to publish guidelines for the management of HS. Other guidelines include J Eur Acad Dermatol Venereol. 2015 Apr;29(4):619-44. doi: 10.1111/jdv.12966. Epub 2015 Jan 30.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa.

Zouboulis CC[1], Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, Lapins J, Matusiak L, Prens EP, Revuz J, Schneider-Burrus S, Szepietowski JC, van der Zee HH, Jemec GB.

Other guidelines include those of the primary care dermatological society (http://www.pcds.org.uk/clinical-guidance/hidradenitis-suppurativa). About 10% of patients with HS do not respond to conventional treatments (cf guidelines above), and require treatment with systemic treatment. There is a literature in the use of adalimumab a TNF-alpha blocking biological treatment in the management of patients with HS who have recalcitrant disease or who do not respond to (or are not eligible for) systemic treatments such as ciclosporin A. These patients can respond to treatment with adalimumab, and in such patients , this treatment can be revolutionary in the management of their physical disease, but also in the associated (often very severe) psycho-social comorbidities.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There is a literature in the use of adalimumab a TNF-alpha blocking biological treatment in the management of patients with HS who have recalcitrant disease or who do not respond to (or are not eligible for) systemic treatments such as ciclosporin A. These patients can respond to treatment with adalimumab, and in such

patients, this treatment can be revolutionary in the management of their physical disease, but also in the associated (often very severe) psycho-social comorbidities.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Dermatology HCPs are familiar with adalimumab and there would be no additional training necessary to implement any guidance from NICE in the management of patients with HS.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Tara Burton
Name of your nominating organisation: The HS Trust
Do you know if your nominating organisation has submitted a statement?

☐ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☐ No

- a patient organisation employee or volunteer?
-

☐ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

Living with Hidradenitis Suppurativa (HS) is extremely difficult and frustrating both emotionally as well as physically. The length of time that it took to correctly diagnose me was approximately 10 years from the onset of disease, and about 7 years from my initial GP diagnosis. I had my first abscess in 1995 when I was 14. Started to see GP when I was 17 in 1998, and was diagnosed when I was 24 in 2005. It was a difficult time to try and get an accurate diagnosis and I was originally diagnosed with Herpes, which was then changed to blame my symptoms on lifestyle by claiming that it was because I smoked and was overweight.

Suffering with HS is extremely stressful which also affects all round health. There is very little support from both the medical community and family/social peers. There is little understanding and it is a difficult route to try and obtain an adequate treatment plan. I also ended up clinically depressed in 2006 due to the lack of knowledge and support, coupled together with the ongoing disease symptoms and continuous pain. The disease, for me, deteriorated extremely rapidly going from stage 1 to stage 3 in the space of 6 months. The pain that I experience is present daily, and just the intensity of pain fluctuates. HS has left me severely scarred and disfigured.

Due to ill health I lost my job in 2006. Having HS is extremely time consuming with having to ensure wounds are kept clean. This entails taking showers regularly and at times 3 or 4 times a day. Then ensuring that all open wounds are dressed accordingly to help prevent any secondary infection from setting in, and then if “leakage” is severe the dressings would need to be changed 3 or 4 times a day. That is without having to contend with new abscesses appearing which also happens, and at times an abscess can occur as quickly as within a few hours, or even overnight. The onset of a flare can be extremely quick, and when in a severe flare state every aspect of daily life is affected. Taking care of yourself is almost impossible as mobility becomes impossible. Walking, bending, moving in general all becomes painful to

endure. So tasks, such as, bending for the oven or to load the washing machine is impossible. Even putting on a pair of socks is impossible to do, and so getting dressed or washing hair can be difficult to say the least. Every aspect of daily living has to be thought about, and due to how quickly a flare state can happen planning ahead rarely happens.

Family life is affected, and my mental health due to this at one point was very strained. I felt extremely guilty at being a wife and a mother. I couldn't even climb the stairs to put my girls to bed, and when they cried at night it was Daddy that went to comfort them as I couldn't get there. I couldn't take my girls out when I was on my own as if they ran off I couldn't catch them. I didn't even share a bed with my own husband for over 5 years as I couldn't get up to the bedroom, so we had to move into a bungalow. I felt guilty at being a wife, and the most simple and mundane tasks that I should have been able to do, I just couldn't. My husband, along with working full time, had to do everything as my HS was out of control.

HS is a life altering illness to endure on a daily basis.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I would like treatment outcomes of improved quality of life with less active flares. Less pain. Reduction in disease activity. Reduction in disability. A control over current disease activity and prevention of further flare states. Improved self-esteem, and body image. Less leaking wounds, and better wound care.

I feel that obtaining a control over current disease is most important. I feel that this would naturally prevent any further deterioration, but it will also enable patients to become self aware, and would naturally lower the amount of pain, which in turn will enable a better quality of life. Plus, would allow time to enable current wounds to possibly heal, and lessen leaking areas, which would lower the risk of any complications due to non-healing abscesses/wounds.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

Current NHS care and treatments is very poor. Referrals to dermatologists are slow which delay adequate diagnosis. The treatment plans are generally trial and error as there are no guidelines to follow, and the pathways for patients are not clear. It generally begins with antibiotic therapies, and then moves on to more harsh medications when a patient shows no signs of improvement or response to medications. At times a combination of oral medication and topical treatments will be used to try and help symptoms. It is not acceptable to be treated this way as it is very time consuming with no real regime, and one that changes frequently, and patients are often left feeling deflated, and defeated, along with possibly being ignored as some doctors do not like to discuss options with patients. Topical treatments are good to try as you can see and feel results and responses, however when trying other oral medications it almost was like a science experiment as there was no clear indications that it was going to help.

Often medications for other skin ailments (with similar patterns) are tried, however, this proves to be a daunting process to follow. Medications for inflammation are also tried, and so I was on oral steroids for over 5 years which were great at calming the disease, but not so great long term due to side effects. This was not an option to be a long term treatment plan and as I also suffer with Crohns disease, biologics were discussed as an option to try. These proved effective for me, and gave me a level of control and enabled me to wean off the steroids. This process for me worked best in my situation.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health

- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

The benefits from using the treatment being appraised would be improved physical symptoms, i.e. less abscesses and open wounds. A lower pain level which would naturally improve mental health and wellbeing. The level of disability may be reduced and all round this will all lead to a better quality of life. This will be an easy to use medication and the convenience would help to free up time elsewhere during the daily lives of patients and lower the time needed to be at hospital. This could also prevent any further disease deterioration and may well improve current situations. It could also offer patients a sense of normality that is often lost with chronic diseases.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

As this is a self-administered injection it has the convenience to be done at the patients own leisure, and at home. Therefore this could be a great way to save time, costs for the patient and any frustrations that may arise from having to travel. Plus, this medication is delivered to a patients choice of address, and therefore it helps to be accessible and can be arranged to meet the needs of the patient. It could also be a way to promote patients to become self-aware, and promotes self-management of the disease.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

The main difference in opinion is the side effects listed. Many patients feel uncomfortable with the fact that the risk of cancer may be increased and some feel these side effects to be harsh. Others do not consider this to be of a concern due to the severe effects that HS has.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

My main concerns are that for HS there is limited knowledge, and so using treatments seem more like a trial and error process and some medications, particularly antibiotics, are prescribed too freely and too easily by doctors. This not only wastes money, but also causes frustrations for patients and families when they see no response, and so further appointments are needed, and yet different antibiotics are used until a list has been exhausted. This then also makes patients feel hopeless, and that they are not being taken seriously as well as having to endure horrendous side effects. All through this trial and error process families, relationships and careers are often stretched and some cease to exist due to the effects of medications or time needed to attend hospital visists.

Please list any concerns you have about the treatment being appraised.

My main concern is to ensure that adequate training is given to patients who embark on this treatment plan. Therefore nurse specialists who are trained to be able to show patients how to use this, and to be able to empower patients where needed, but also what to look out for, and what should happen or could

happen. An all round font of knowledge which would also give patients confidence in healthcare professionals as well as treatment use. Some may be needle phobic and so would need to be handled with extra care.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I think the more severe stage patients (i.e. late stage 2, stage 3) will find a greater benefit. As their lives would be greatly affected by HS, having these symptoms improve would give a better quality of life. Patients with stage 1-early stage 2 generally still maintain a good quality of life without the need for such interventions.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

As stated in question above, those of more mild disease would not benefit greatly as their quality of life would not be as severely affected.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

I can agree that the use of the treatment does reflect the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

I do think that the trials have captured outcomes that are important to patients. Just to have an all round improved quality of life is extremely important to HS patients with severe disease. I am not aware of any limitations.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

None

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

The HS Priority Setting Partnership

http://www.ncbi.nlm.nih.gov/pubmed/24903313

Interventions for HS – Cochrane Review

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010081.pub2/full

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

None really, but special care when dealing with patients who are needle phobic.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It saves time as it's an injection rather than having to adhere to a schedule of taking medications that, at times, have to be juggled around eating. It is done

in the convenience of your own home, and so is more comfortable to use, and it is delivered to an address of choice so saves time at hospitals, and pharmacies.

Is there anything else that you would like the Appraisal Committee to consider?

Please consider the emotional effects that having HS has on a patient, and that at severe stages not only does HS affect the physical wellbeing, as it can be quite an aggressive and disfiguring illness, it also has the capacity to destroy families, and relationships, and careers due to the emotional effects. It is a life changing illness and to date there is no clear patient pathway, and this appraisal is providing hope that patients needs are finally being listened to. To have a medication that would enable to possibly reach a remission state could prove to be life changing.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Lack of disease awareness and education to both the general public and medical professionals.
- No clear patient pathway, including diagnosis tools/treatment plans, which leads to patients being severely mismanaged.
- The need for better and more practical treatments to be made available for HS patients.
- HS severely affects the physical and emotional wellbeing of a patient, therefore finding adequate treatment options is paramount.
- HS patients have the desire to be included and to be understood.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Adalimumab for treating moderate to severe hidradenitis suppurativa [ID812]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Ceri Harris
Name of your nominating organisation: HS Trust
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☐ No

- a patient organisation employee or volunteer?
-

x Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I have known that I had HS for almost 10 years, this was when I started to really notice the cysts and have pain. I was not diagnosed until 2011, at that stage I was already stage 3. Living with HS feels like your on a rollercoaster, with few highs and many low's. From living with constant pain and discomfort being the norm. So much that you have forgotten what it was like before. It impacts on everything from choosing what to wear, dark colours if bad flares and open wounds, to the activities you do. (walking alone becomes painful)

Personal relationships become difficult. I was in a relationship when first noticed the problem, not long after I was single. I found having to have a conversation about my scars very difficult and avoided relationships for a very long time. I'm now with someone who loves me and my scars, but its a constant struggle with self image and self worth.

In work I kept my condition hidden for 8 years, only this January coming out to everyone. That's how it felt, coming out. Struggling to hide my condition during the worst times, but being able to work from home helped. It also helps that I work in the NHS as an equality manager and therefore have a better sense of protection under legislation than most, plus people are less likely to challenge my condition etc.

But you do feel that you have to hide it, try to act normal, whatever that is and carry on.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I am about to start Infliximab treatment tomorrow (29th Oct) it has taken me 2 years for my consultant to agree funding as I live outside the Local Health Board (LHB) and my LHB does not provide it. I had surgery back in February, which was invasive and I needed to take almost 4 months off work. I feel it was only because I had the surgery that I finally had the go ahead to have

biological treatment. I know that if it doesn't work, at least now I have a chance of moving to Humeria.

For me I want to be able to get more mobile again, I feel HS holds me back and make exercise more difficult, which of course leads to the vicious circle of weight loss helping HS. I want to be able to go swimming, without fear of people looking at my scars, bumps or have open wounds.

I want to want to have sex with my partner with the light on, rather than wanting to hide in the shadows, fearing my scars will put him off me. (even though I know that it wont)

I want to be able to go on holiday and walk long distances around cities without being in pain, needing to stop and feeling that people think i need to stop because of my weight rather than the condition.

Finally I want the treatment to work, be as close to a cure as possible, so I don't think of my old age as me needing a wheelchair to be mobile.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

It takes a long time for people to take the condition seriously and not just offer Hipiscrub and antibiotics, which don't work as there is no infection. It is a bit of a postcode lottery, with the treatment choices available in my own LHB not meeting my needs, but then they realised this and refered me to Cardiff. But as I stated above there was a delay in being offered the treatment I had been promised and I had to go through several medicinal hoops and surgery before it was offered.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:
• the course and/or outcome of the condition
• physical symptoms
• pain

- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

Improved course and/or outcome of the condition
Relief from Physical symptoms and Pain
Decreased Level of disability
Improved Mental health
Quality of life(such as lifestyle and work)
Other people (for example, family, friends and employers)
Self esteem and personal relationships

Please explain any advantages that you think this treatment has over other NHS treatments in England.

It has a high satisfaction level and offering this at earier stages and quicker could stop levels of scaring and pain. (medically nipping in the bud. We all for prevention rather than a cure, easier access to this treatment would mean relieve for thousands ion pain.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Fear of side effects have anecdotally stopped many from trying this treatment, as well a fear of needles etc. The treatment also requires a sympathetic employer for time off for appointments etc.

Main disadvantage is the cost and NHS practitioners using this as an excuse to avoid offering it as treatment.

Please list any concerns you have about the treatment being appraised.

None that I can think of

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I'm sure there are many

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Depends of level of condition and severity of outbreaks. Obviously less effective the worse it is.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

x Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Not applicable at the moment

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Unsure

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

not aware of any

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

As stated it has a higher impact on some racial groups, plus many with HS have other medical needs and disabilities. The impact of the condition effects genders differently. I feel that male difficulties over personal appearance and mental health are dismissed more. As if men should not worry about those areas in the same way has women and I worry that the support for me is less as a result. Combined with the known research on men accessing healthcare.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Its the only dedicated treatment for HS

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Physical impact of HS
- Emotional Impact
- Lack of medical knowledge on HS
- Reluctance to dispense biologiocal treatment
- Need for more research and support

Adalimumab for treating moderate to severe hidradenitis suppurativa: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Declared competing interests of the authors

John Ingram is the Cardiff Principal Investigator for a hidradenitis suppurativa (HS) observational study sponsored by Abbvie. He is also currently leading the British Association of Dermatologists HS guideline development group and was lead author for a Cochrane review of interventions for HS.

Fiona Collier is an employee of Forth Valley NHS, who are involved in Abbvie's study of HS demographics and secondary care usage. She is a co-investigator at the site.

The other authors have no declared competing interests.

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Contributions of authors

Christopher Carroll and Eva Kaltenthaler summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden, Andrew Rawdin and Sabine Grimm critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategies. John Stevens critiqued the statistical analysis contained within the company's submission. John Ingram, Fiona Collier and Mohammad Ghazavi provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

TABLE OF CONTENTS

1.	SUMMARY	1
1.1	Critique of the decision problem in the company's submission	1
1.2	Summary of clinical effectiveness evidence submitted by the company	3
1.3	Summary of the ERG's critique of clinical effectiveness evidence submitted	4
1.4	Summary of cost effectiveness submitted evidence by the company	6
1.5	Summary of the ERG's critique of cost effectiveness evidence submitted	7
1.6	ERG commentary on the robustness of evidence submitted by the company	8
2	BACKGROUND	10
2.1	Critique of company's description of underlying health problem	10
2.2	Critique of manufacturer's overview of current service provision	11
3.	CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM	13
3.1	Population	14
3.2	Intervention	14
3.3	Comparators	15
3.4	Outcomes	16
3.5	Economic analysis	17
3.6	Subgroups	17
3.7	Special considerations	17
4.	CLINICAL EFFECTIVENESS	18
4.1	Critique of the methods of review(s)	18
4.2	Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)	31
4.3	Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison	66
4.4	Critique of the indirect comparison and/or multiple treatment comparison	67
4.5	Additional work on clinical effectiveness undertaken by the ERG	67
4.6	Conclusions of the clinical efficacy section	67
5.	COST EFFECTIVENESS	70

5.1	ERG comment on the company's systematic review of cost-effectiveness evidence	70
5.2	Description of the company's model	75
5.3	Critical appraisal of the company's health economic analysis	95
5.4	Additional exploratory analyses undertaken by the ERG	118
5.5	Discussion	128
6.	END OF LIFE	132
7.	OVERALL CONCLUSIONS	133
8.	REFERENCES	137
9.	APPENDICES	139

LIST OF TABLES

Table 1:	Hurley's classification	11
Table 2:	Company's statement of the decision problem	13
Table 3:	Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review	22
Table 4:	Risk of bias assessment - PIONEER I	25
Table 5:	Risk of bias assessment - PIONEER II	26
Table 6:	Company's critical appraisal of m12-555 OLE using CRD non-RCT tool	28
Table 7:	ERG critical appraisal of M12-555 OLE using CASP cohort study checklist	29
Table 8:	Characteristics of included RCTs	33
Table 9:	Final scope outcomes and trial outcome measures	38
Table 10:	HS-PGA scale	39
Table 11:	Participants' baseline characteristics in M10-467, PIONEER I and PIONEER II	42
Table 12:	Patient loss to follow-up in trials in the adalimumab 40mg EW and placebo arms	43
Table 13:	Percentage of patients achieving clinical response measured by HS-PGA relative to baseline at 16 weeks	44
Table 14:	Percentage of patients achieving clinical response by HiSCR relative to baseline at 12 or 16 weeks	45
Table 15:	Percentage of patients achieving clinical response measured by HiSCR relative to baseline at week 12 in PIONEER I and II	45
Table 16:	Proportion of patients in PIONEER I and II (amalgamated data) achieving HiSCR during Period B	47
Table 17:	M10-467: improvement from baseline in individual symptoms in Period 1 (LOCF)	48
Table 18:	Percentage of patients who achieved AN count of 0, 1, or 2 at week 12 in PIONEER I and PIONEER II	49
Table 19:	Improvement from baseline in MSS score at weeks 12 and 16 (LOCF)	49
Table 20:	Mean change in NRS30 skin pain relative to baseline at week 12 in patients with baseline of NRS $\geq$ 3 (LOCF)	50
Table 21:	Percentages of all patients with clinically relevant improvement in pain relative to baseline at weeks 12 and 16	50
Table 22:	Quality of life measured by DLQI scores relative to baseline in weeks 12 and 16 (LOCF)	51

Table 23: Quality of life measured by HSQOL scores relative to baseline at week 12 (LOCF) 51
Table 24: PIONEER I: change in SF-36 physical component score relative to baseline at week 12 52
Table 25: PIONEER II: mean change from baseline in EQ-5D at week 12 (LOCF) 53
Table 26: PIONEER I and PIONEER II secondary outcomes at week 36 relative to week 12 53
Table 27: Primary endpoint analysis subgroups in MI0-467, PIONEER I and PIONEER II 55
Table 28: M10-467 clinical response at week 16 (proportion of patients achieving HS-PGA of clear minimal or mild with at least a 2-grade improvement relative to baseline at week 16) 56
Table 29: Proportion of patients achieving HiSCR over time from the first dose of adalimumab (LOCF) 59
Table 30: Key AE rates in in M10-467, PIONEER I and PIONEER II (weeks 16 and 12) 61
Table 31: Specific AES occurring in >5% of patients in M10-467, PIONEER I and PIONEER II (weeks 16 and 12) 62
Table 32: AEs occurring in >5% of patients in study M10-467 (week 16) 63
Table 33: AEs in PIONEER I and PIONEER II during Period B 64
Table 34: AEs occurring in >5% of patients PIONEER I and PIONEER II during period B 64
Table 35: AEs in M12-555 OLE in all adalimumab groups and in the EW/EW/EW trial population 65
Table 36: AEs occurring in >5% of in patients in M12-555 OLE in all adalimumab groups and in the EW/EW/EW trial population 66
Table 37: Scope of company's health economic analysis 75
Table 38: Categorisation of depth of response in the company's model 78
Table 39: Summary of evidence sources used to inform the company's model parameters 81
Table 40: Sources of transition probabilities used in the company's model 84
Table 41: Probability of discontinuing adalimumab maintenance therapy 85
Table 42: Health utilities used in the company's model 86
Table 43: Resource use by health state 88
Table 44: Annual AE rates assumed in the company's model based on PIONEER I/II 90
Table 45: Costs associated with managing AEs 91
Table 46: Company's base case cost-effectiveness results 92
Table 47: Company's scenario analysis results 95

Table 48: Adherence of the company's economic analysis to the NICE Reference Case 97
Table 49: Results of company's analysis based on HiSCR response/no response 105
Table 50: Number of patients included in transition matrices 108
Table 51: Alternative GLM model excluding imputation 112
Table 52: Comparison of company's base case model and ERGs's rebuilt model 112
Table 53: Modelled time on adalimumab treatment based on ole discontinuation rate and applying company's 12-week continuation approach 114
Table 54: Company's original week 36+ matrix for patients receiving adalimumab 119
Table 55: Week 36+ matrix for patients receiving adalimumab including tunnel states 120
Table 56: Revised HS surgery costing assumptions 121
Table 57: ERG Exploratory Analysis 1 – correction of model errors 123
Table 58: ERG Exploratory Analysis 2 – incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule 123
Table 59: ERG Exploratory Analysis 3 – revised assumptions regarding costs of HS surgery (ERG base case) 124
Table 60: ERG Additional Exploratory Analysis 4 – use of PIONEER II data only 125
Table 61: ERG Additional Exploratory Analysis 5 – alternative assumptions regarding transition probabilities beyond week 36 125
Table 62: ERG Additional Exploratory Analysis 6 – discontinuation of partial responders and non-responders at 12 weeks 126
Table 63: ERG Additional Exploratory Analysis 7 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders 126
Table 64: ERG Additional Exploratory Analysis 8 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12 weeks 127

LIST OF FIGURES

Figure 1: Design of study M10-467 35
Figure 2: Design of the PIONEER I and II trials 36
Figure 3 Company's health economic model structure 78

Figure 4 Cost-effectiveness plane 93

Figure 5: Cost-effectiveness acceptability curves 93

Figure 6: Deterministic sensitivity analysis - tornado diagram 94

Figure 7: Change in pain VAS and DLQI 102

Figure 8 Change in Work Productivity and Activity Impairment Questionnaire – Total Activity Impairment and Total Work Impairment 103

Figure 9 Time to treatment discontinuation using the company's Excel mock-up 117

LIST OF BOXES

Box 1: Inclusion and exclusion criteria for company's review of cost and resource use / utility / economic evaluation studies (adapted from CS Tables 40, 41 and 44) 71

Box 2: Main issues identified within the critical appraisal of the company's model 95

ABBREVIATIONS

A&E	Accident and Emergency
AAD	American Academy of Dermatology
ADA	Adalimumab
AE	Adverse event
AN	Abscess and Inflammatory Nodule
AWMSG	All Wales Medicines Strategy Group
BMI	Body Mass Index
BNF	British National Formulary
CASP	Critical Appraisal Skills Programme
CCRCT	Cochrane Central Register of Controlled Trials
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
CS	Company's submission
CSR	Clinical Study Report
DARE	Database of Abstracts of Reviews of Effectiveness
DLQI	Dermatology Life Quality Index
DSA	Determinstic sensitivity analysis
EMA	European Medicines Agency
EMBASE	Excerpta Medica dataBASE
EOW	Every other week
ERG	Evidence Review Group
ESDR	European Society for Dermatological Research
EW	Every week
FDA	Food and Drug Administration
GLM	Generalised logit model
HADS	Hospital Anxiety and Depression Score
HiSCR	Hidradenitis Suppurativa Clinical Response
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HS	Hidradenitis suppurativa
HS-LASI	HS-lesion, activity and severity
HS-PGA	Hidradenitis Suppurativa Physicians' Global Assessment
HSQoL	Hidradenitis Suppurativa Quality of Life
HSSI	Hidradenitis Suppurativa Severity Index
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
LOCF	Last observation carried forward
LOR	Loss of response

LS	Least squares
LSCF	Last state carried forward
MCID	Minimal clinically important difference
MDI	Major Depression Inventory
MEDLINE	Medical Literature Analysis and Retrieval System Online
MSS	Modified Sartorius Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NRI	Non responder imputation
NRS30	Patient's Global Assessment of Skin Pain
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	Open-label extension
PAS	Patient Access Scheme
PBO	Placebo
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs	Patient Reported Outcome Measures
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
s.c.	Subcutaneous
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short-Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TSQM	Treatment Satisfaction Questionnaire for Medicine
VAS	Visual Analogue Scale
WCD	World Congress of Dermatology
WOAI	Worsening or absence of improvement
WPAI-SHP	Work Productivity and Activity Impairment-Specific Health Problem
WTP	Willingness-to-pay

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory, recurrent, debilitating, skin follicular disease that usually presents after puberty with painful deep-seated, inflamed lesions. In patients with HS, hair follicles in the apocrine gland-bearing regions (axilla, genital area, groin, infra-mammary region, peri-anal region and buttocks) become blocked and inflamed, resulting in painful recurrent deep-seated boils and nodules. Boils and nodules may progress to abscesses, sinus tracts and scarring. In most patients, disease flares occur at varying intervals, often pre-menstrually in women. Disease flares are characterised by increased pain and suppuration with a foul smelling discharge which stains clothing. Studies have suggested that active disease can have a substantial impairment on a patient's health-related quality of life (HRQoL), exceeding that of other skin diseases that are generally perceived to have a high burden and substantial disability, for example, alopecia, acne, mild to moderate psoriasis, vascular anomalies of the face and atopic dermatitis.

The decision problem required an assessment of the clinical effectiveness and cost-effectiveness of adalimumab compared with established clinical management of active moderate to severe HS in adults whose disease has not responded to conventional systemic HS therapy.

Adalimumab is a recombinant human IgG1 monoclonal antibody expressed in Chinese Hamster Ovary cells. Adalimumab inhibits the activity of the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α), a key component in the inflammatory process. Adalimumab has a marketing authorisation for the treatment of active moderate to severe HS in adult patients with an inadequate response to conventional systemic HS therapy. Adalimumab also holds a European marketing authorisation for a number of other conditions including rheumatoid arthritis, psoriasis, Crohn's disease and ulcerative colitis. In the management of HS, the recommended adalimumab dose regimen for adult patients with HS is 160mg initially at Day 1 (four 40mg injections in one day or two 40mg injections per day for two consecutive days), followed by 80mg two weeks later at Day 15 (two 40mg injections on the same day). From Day 29 onwards, the recommended dose regimen is 40mg every week (EW). As of December 2015, the NHS indicative price for adalimumab 40mg/0.8ml solution as two pre-filled syringes or auto-injection pens is £704.28.

The population defined in the final NICE scope relates to *"adults with active moderate to severe HS which has not responded to conventional therapy."* This is in line with the marketing authorisation for adalimumab and reflects the populations of the PIONEER I/II studies which form the main basis of

the clinical evidence presented within the company's submission (CS). The health economic model submitted by the company is largely based on evidence relating to the relative efficacy and safety of adalimumab versus placebo within the PIONEER I/II trials. The model also includes additional data on long-term responders to adalimumab 40mg EW who were initially enrolled into the PIONEER I/II trials and who were subsequently enrolled into the M12-555 open-label extension (OLE) study.

The comparator within all three randomised controlled trials (RCTs) was placebo. No head-to-head data are available for adalimumab versus any other therapy. The CS argues that neither surgery nor antibiotics represent relevant comparators for adalimumab. Surgery is argued to be an inappropriate comparator because adalimumab and surgery are not alternative or exclusive treatment choices and because within the PIONEER I/II trials, patients were allowed to undergo surgery to control symptoms (although it is unclear whether this was actually the case). Antibiotics are argued to be inappropriate comparators because they are used alongside adalimumab and because the use of oral antibiotics was allowed in both the intervention and control arms of the PIONEER II trial and as rescue therapy in the PIONEER I trial. The CS also argues that dapsone, retinoids and immunomodulators are not relevant comparators because these are prescribed before adalimumab. According to the company's network meta-analysis (NMA) feasibility assessment, a comparison with infliximab would not be feasible due to evidence limitations and heterogeneity between studies with respect to C-Reactive Protein (CRP) levels and disease severity. As such, the CS argues that the main comparator for the analysis is standard care, as represented by the placebo arms in the PIONEER I/II trials.

The company's clinical review includes data on a large range of outcomes relating to disease severity, clinical response, inflammation and fibrosis, discomfort and pain, adverse events (AEs) and HRQoL. The ERG notes that the primary efficacy endpoint in the PIONEER trials is the Hidradenitis Suppurativa Clinical Response (HSiCR) measure, which was developed by the company.

The CS highlights that there is little research around the treatment of HS, hence the evidence base supporting existing treatment options is limited. The CS also notes that the use of unlicensed treatments exposes patients to potential safety risks and results in variations in clinical practice and inequities with respect to access to effective HS therapies.

End-of-Life criteria were not relevant to this submission and no Patient Access Scheme (PAS) was submitted by the company. The Evidence Review Group (ERG) considers that the evidence presented in the submission was therefore generally consistent with the decision problem.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS consists of three separate reviews: (1) a review of the clinical efficacy evidence from RCTs of treatments for HS, specifically RCTs comparing adalimumab with placebo; (2) a review of the evidence from an non-controlled OLE study, and; (3) a review of safety evidence from the RCTs of adalimumab versus placebo and the OLE study.

The principal clinical efficacy review included three relevant RCTs comparing adalimumab with placebo in adults with moderate to severe HS: these were a Phase II "dosing" trial, M10-467, and two Phase III trials, PIONEER I and II. The three trials all have two periods: an initial period (weeks 0-12 in the PIONEER I/II trials and weeks 0-16 in the M10-467 trial) comparing adalimumab 40mg EW with placebo, and a second period (weeks 12-36 in the PIONEER trials), initiated by re-randomisation of patients at week 12 to arms of adalimumab 40mg EW, placebo or adalimumab 40mg every other week (EOW, PIONEER trials only). The three RCTs and the OLE study were all found by the company to be at low risk of bias following quality assessment using critical appraisal tools. In the M10-467 trial, significantly more patients in the adalimumab 40mg EW group achieved a clinical response (defined as achieving a HS-PGA score of clear, minimal or mild with at least a 2 grade improvement relative to baseline at week 16) than patients receiving placebo: 17.6% versus 3.9% ($p<0.025$). Significant improvements compared with placebo were also seen at week 16 in individual symptoms, overall disease severity and pain scores with adalimumab 40mg EW.

In PIONEER I and II, significantly more patients in the adalimumab 40mg EW group achieved a clinical response (defined as achieving HiSCR, that is, at least a 50% reduction in the total abscess and inflammatory nodule [AN] count with no increase in abscess count and no increase in draining fistula count relative to baseline at week 12) than patients receiving placebo: 41.8% for adalimumab vs 26.0% for placebo ($p=0.003$) in PIONEER I, and 58.9% for adalimumab vs 27.6% for placebo ($p<0.001$) in PIONEER II.

Significant improvements were also seen in symptoms, disease severity (according to the Modified Sartorius Severity [MSS] score) and pain. All outcomes were significant in PIONEER II. However, in PIONEER I, some of the improvements with adalimumab 40mg EW were numerically but not significantly better than placebo. Subgroup analyses indicated that patients achieved benefit with adalimumab 40mg EW regardless of their baseline characteristics, although some subgroups were subject to small patient numbers. In PIONEER I and II, adalimumab 40mg EW significantly improved quality of life as measured by the EQ-5D, the physical components of the Short-Form 36 (SF-36), and the Dermatology Life Quality Index (DLQI) compared with placebo, but the improvements were not significant across some other components of SF-36. The treatment effect varied between the trials. This might be explained in part by differences in patient demographics and

study design between trials. The company is conducting ongoing analyses of the data from the PIONEER trials and the OLE study to understand these differences. The CS did not include a pairwise meta-analysis of the PIONEER I/II trials. An NMA was not considered feasible.

Some improvements were maintained into the second period of the PIONEER trials up to 36 weeks. The company stated that re-randomisation at week 12, at the beginning of this second period (Period B), and protocol-driven discontinuation during Period B for patients with Loss of Response (LOR) or Worsening or Absence of Improvement (WOAI), accounted for low patient numbers in the group receiving adalimumab 40mg EW for the total study duration (n=21 in PIONEER I and n=20 in PIONEER II). In the second period, there was a loss of effect for patients re-randomised to placebo or adalimumab 40mg EOW. Outcomes were maintained in patients who went on to enter the M12-555 OLE study.

The review of the safety evidence included the three key RCTs and the single OLE cohort study (M12-555 OLE). Adalimumab 40mg EW was well-tolerated in all three RCTs. The proportion of patients experiencing serious adverse events (SAEs) or discontinuing treatment attributable to AEs was low and similar in both the adalimumab and placebo arms. In an integrated summary of PIONEER I and II (n=633), six patients receiving placebo (1.9%) and three receiving adalimumab 40mg EW (0.9%) gave AEs as their primary reason for discontinuation during Period A. The most common AEs were exacerbation of HS, nasopharyngitis and headache. Rates of infectious AEs were similar for patients receiving adalimumab and for those receiving placebo. The CS states that the M12-555 OLE is the only ongoing study of adalimumab in this indication. Final data from this study are expected to be available in 2016.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The principal efficacy review is a poorly-reported systematic review of relevant RCTs (M10-467 and PIONEER I and II). The trials are generally consistent with the final NICE scope. The primary efficacy outcome was clinical response, principally measured using the HiSCR measured developed by the company. Clinical advice received by the ERG confirms that the HiSCR measure has been validated but, in terms of clinical decision-making, its findings must be viewed alongside the results of patient-reported outcome measures, in particular quality of life assessed by the DLQI and a pain measure. In the trials, secondary outcomes included assessments of disease severity and symptoms, using the MSS score and AN counts, pain and quality of life (various measures).

The ERG considers the M10-467 trial to be at low risk of bias across all domains for the relevant Period 1 (up to week 16). The ERG also considers the results from Period A (i.e. up to week 12) in PIONEER I and II to be generally at low risk of bias: only the domains of attrition and reporting have

a low-to-moderate risk of bias. However, the ERG considers there to be a moderate or unclear risk of selection and attrition bias affecting the results of Period B in the PIONEER trials. There is also a low-to-moderate risk of reporting bias in Period B in the two trials. It should also be noted that whilst M10-467 has been published, the PIONEER trials have not.

Across all three RCTs, the percentage of patients achieving clinical response according to the HiSCR measure on adalimumab 40mg EW compared with placebo at week 12 or week 16 was significantly higher than in the placebo groups ($p<0.01$), although the treatment effect varied between the trials. In addition, significant or clinically relevant differences in favour of adalimumab 40mg EW that were reported for secondary outcomes in PIONEER II were not always found for those outcomes in PIONEER I, especially for AN count, MSS score, pain and some components of quality of life measured by the SF-36. An arm-based integrated summary, which breaks randomisation, was conducted for the two PIONEER trials to tabulate Period B response (for all patients and for a group of HiSCR "responders" and "partial responders"). This "partial responder" group (defined as HiSCR responders with ≥25% reduction rather than ≥50% reduction) are a *post hoc* analysis group. This group was not defined in protocols or published descriptions of study design or pre-specified analysis methods for the PIONEER trials. It was also not considered in the published validation study for the HiSCR measure, nor was it justified or explained in the company's clinical review. According to this analysis, improvements in response were maintained or reduced in this second period. A small number of secondary outcomes were reported for Period B of PIONEER I and II, but only for patients who had had a clinical response at week 12. The results were based on analyses with small sample sizes (range of 15 to 22 patients across all outcomes for both PIONEER trials).

These trials were supplemented by a single, unpublished, non-randomised, non-controlled, unblinded cohort study, which was an OLE study of the PIONEER trials (M12-555 OLE). In terms of efficacy, the results suggested [redacted]. Details of the results for secondary outcomes such as MSS and NRS30 were not reported. The ERG considers these efficacy results to be subject to uncertainty because they are drawn from interim analyses of unpublished study data. The study also only potentially offers efficacy data for up to 72 weeks for a drug that might be taken for many years by patients with moderate to severe HS.

The submission of safety evidence was a review of the three generally good quality RCTs, supplemented by the single arm cohort study. There were no obvious safety concerns, with most AEs being balanced across adalimumab 40mg EW and placebo trial arms, and small numbers of SAEs.

Longer-term data are required to determine whether reported AE rates are maintained for patients on long-term maintenance doses of adalimumab 40mg EW; whether or not certain subgroups of patients are at a higher risk of certain events; and to confirm whether or not there are any differences between the interrupted and uninterrupted regimens.

1.4 Summary of cost-effectiveness submitted evidence by the company

The CS includes a systematic review of economic evaluations of treatments for HS together with a *de novo* model-based economic evaluation of adalimumab versus standard care in adult patients with an inadequate response to conventional systemic HS therapy.

The company's systematic review of existing economic evaluations did not identify any relevant studies for inclusion.

The company's *de novo* economic model adopts a Markov approach to estimate costs and health outcomes for adalimumab and standard care from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. All analyses presented in the CS relate to the full population specified in the marketing authorisation for adalimumab; no subgroup analyses are presented within the CS. The company's model includes five mutually exclusive health states, based on depth of HiSCR response: (i) high response; (ii) response; (iii) partial response; (iv) no response, and; (v) dead. The model uses a 2-week cycle length for the first 2 cycles, and a 4-week cycle length thereafter. Health state transitions are modelled up to week 36 using data from PIONEER I/II, including a discontinuation rule for patients who do not achieve at least a partial response by week 12. The long-term HiSCR trajectory of adalimumab responders (including partial responders) beyond 36 weeks is subsequently modelled using a time-invariant generalised logit model (GLM) fitted to last observation carried forward (LOCF)-imputed data from the M12-555 OLE study. The long-term HiSCR trajectories for patients receiving standard care and for those who have previously discontinued adalimumab beyond 36 weeks are modelled using separate time-invariant GLMs fitted to data from weeks 12-36 from the PIONEER I/II trials. Health utilities are modelled according to depth of HiSCR response using a *post hoc* analysis of EQ-5D data collected within PIONEER II. Resource use estimates, which were again differentiated by depth of HiSCR response, were based on a survey of UK physicians and were assumed to include inpatient visits due to HS surgery, outpatient visits due to HS surgery, visits to wound care due to HS surgery, non-surgical inpatient visits, non-surgical outpatient visits, visits to wound care not due to HS surgery, Accident and Emergency (A&E) visits and costs associated with AEs. Unit costs were taken from the British National Formulary (BNF), the Personal Social Services Research Unit (PSSRU) and NHS Reference Costs. AEs are not assumed to have an additional impact on HRQoL.

Based on the probabilistic version of the company's base case model, adalimumab is expected to produce an additional 1.02 quality-adjusted life years (QALYs) at an additional cost of £[redacted] as compared with standard care; the probabilistic incremental cost-effectiveness ratio (ICER) for adalimumab versus standard care is expected to be £[redacted] per QALY gained. The results of the deterministic model are similar, with adalimumab yielding an ICER of £[redacted] per QALY gained compared with standard care. The company's probabilistic sensitivity analysis (PSA) suggests that assuming a willingness-to-pay (WTP) threshold of £20,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately [redacted]. Assuming a WTP threshold of £30,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately [redacted]. Within the company's deterministic scenario analysis, the ICER for adalimumab was greater than £30,000 per QALY gained in four scenarios: (i) when the time horizon was truncated to 20 years; (ii) when the model was based only on data from PIONEER II; (iii) when the last state carried forward (LSCF) imputation rule was used, and; (iv) when the discontinuation rate for adalimumab non-responders after week 36 was based on the OLE study.

[redacted]

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified a number of issues relating to the company's model and analysis. The most pertinent of these relate to: (i) the use of a model structure in which health gains and treatment continuation rules are defined according to depth of response, which does not reflect the pre-planned and validated HiSCR endpoint used in the PIONEER trials; (ii) the likely overestimation of the lifetime costs of HS surgery predicted by the company's model; (iii) the incorrect implementation of a continuation rule for adalimumab non-responders which does not mathematically reflect the actual assumptions stated in the CS; (iv) the use of arm-based aggregate data from the PIONEER I/II trials rather than a meta-analysis of relative treatment effects, and; (v) uncertainty surrounding the long-term transition probabilities derived from the PIONEER I/II trials and the M12-555 OLE study.

The ERG undertook eight sets of exploratory analyses based on the company's submitted model. The first three of these analyses represent the ERG's base case analysis. These include: (i) correction of technical programming errors in the company's model; (ii) applying structural amendments to the model to correctly reflect the company's intended adalimumab non-responder continuation rule during the maintenance phase; (iii) re-estimation of the costs of HS surgery. Further analyses were also undertaken to explore uncertainty surrounding the transition probabilities employed in the model, the likely impact of discontinuing non-responders and partial responders to adalimumab (during the induction phase only) and the potential structural uncertainty around the company's adopted

modelling approach. The latter two analyses could not however be fully implemented due to the limitations of the company's model structure.

The ERG's exploratory analyses indicate that the technical programming errors have only a minor impact on the model results and lead to a small increase in the ICER for adalimumab versus standard care. The incorporation of tunnel states for adalimumab non-responders within the maintenance phase of the corrected model increases the ICER for adalimumab versus standard care more substantially (ICER=£[redacted] per QALY gained). The ERG's base case, which comprises a scenario whereby these two sets of corrections are combined with a lower cost of HS surgery, results in an estimated deterministic ICER for adalimumab versus standard care of £[redacted] per QALY gained. The probabilistic ICER for this analysis is slightly higher (£[redacted] per QALY gained). The ERG's base case ICER for adalimumab versus standard care is markedly less favourable than that presented within the CS.

1.6 ERG commentary on the robustness of evidence submitted by the company

The ERG considers the RCT evidence to be robust for the initial trial periods up to 12 or 16 weeks: it generally satisfied the requirements of the decision problem, with some minor exceptions, and was good quality. The treatment effect did vary between studies, which might be explained by differences in patient characteristics and study design between trials. The efficacy results from the second period of the PIONEER trials are at a higher risk of bias across some domains, and are affected by the merging of "responders" with "partial responders", the latter being a *post hoc* analysis group which is neither justified nor explained in the submission. The safety evidence is generally at low risk of bias but is limited, and several questions remain over AE rates for patients on "continuous" or long-term adalimumab 40mg EW.

The ERG has concerns regarding the company's implemented model structure, in particular, the incorrect implementation of the adalimumab non-responder discontinuation rule during the maintenance phase and the definition of health states and treatment continuation rules based on depth of HiSCR response rather than the ≥50% AN reduction threshold. In addition, the cost savings due to HS surgery avoided predicted by the company's model are likely to be overestimated. The ERG has further concerns regarding the use of arm-based summaries to aggregate data from the PIONEER I/II trials and the uncertainty surrounding the long-term transition probabilities used to inform the model.

1.6.1 Strengths

The ERG recognises that the submission included three RCTs at low risk of bias for the initial study period (up to 12 weeks for the PIONEER trials and 16 weeks for M10-467) comparing the study drug, adalimumab at its licensed dose, with placebo. All of the required outcomes were assessed and

reported: clinical response, , as well as disease severity, symptoms, pain and quality of life. The ERG considers the efficacy results for up to 12 weeks and the safety data for up to 36 weeks to be at a low risk of bias.

1.6.2 Weaknesses and areas of uncertainty

The ERG noted that the principal areas of uncertainty in the clinical evidence related to potential treatment effect modifiers and the short follow-up. These uncertainties exist due to observed differences in certain outcomes or level of outcome between trials, differences in disease severity and other baseline characteristics between trials, and the amount of missing data and imputed results beyond 12 weeks in the PIONEER I/II trials and the OLE study. In addition, the ERG notes that there is uncertainty with respect to whether the achievement of a partial HiSCR represents a clinically meaningful treatment benefit sufficient to warrant continuing adalimumab, and around the expected impact of adalimumab on the use of other healthcare resources (for example surgery and other pharmacological treatments used to manage HS).

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory, recurrent, debilitating, skin follicular disease that usually presents after puberty with painful deep-seated, inflamed lesions. In patients with HS, hair follicles in the apocrine gland-bearing regions (axilla, genital area, groin, infra-mammary region, peri-anal region and buttocks) become blocked and inflamed resulting in painful recurrent deep-seated boils or nodules. Boils and nodules may progress to abscesses, sinus tracts and scarring. In most patients, disease flares occur at varying intervals, often pre-menstrually in women. Disease flares are characterised by increased pain and suppuration with a foul smelling discharge which stains clothing.[1-3]

Several risk factors probably contribute to HS, including smoking, obesity genetic predisposition and endocrine influences. HS affects young adults, with disease onset typically between the second and fourth decades of life.[4, 5] It is likely that HS is a progressive disease, with some patients reporting a progression from Hurley Stage I to II to III over time; the risk factors that predispose patients to progression include smoking and obesity.[6, 7]

The prevalence of HS is not precisely known, but a number of estimates are available in the literature. A prevalence of 1% in the adult Eurpoean population has been reported in several studies,[2] although actual rates are likely to be higher due to problems of under-recognition.[1, 3] There are no published data on prevalence rates in the UK, although it has been suggested that this might be in the region of 1 in 600.[4] HS has higher prevalence in women than men and around one-third of patients have a disease in first-degree relatives.[2] The other important known risk factors for HS are obesity and cigarette smoking.[1-3]

The pathogenesis of HS is largely unknown and it is defined by its clinical features and its chronicity.[2] Diagnosis relies on the presence of: (1): typical lesions, i.e. deep-seated painful nodules: 'blind boils' in early lesions, abscesses, draining sinus, and bridged scars; (2) typical topography, i.e. axillae, groin, perineal and perianal region, buttocks, infra- and inter-mammary folds, and; (3) chronicity and recurrences. These three criteria must be met to establish a diagnosis of HS. The population referred to in the final NICE scope[8] relates to patients with active moderate to severe HS who have failed prior systemic therapy. The CS[9] provides a description of HS in accordance with the terminology used in the NICE scope.

HS is classified according to the Hurley staging system, as shown in Table 1.

Table 1: Hurley's classification[10]

Stage	Clinical features
Grade I	Abscess formation, single or multiple without sinus tracts and cicatrisation
Grade II	Recurrent abscesses with tract formation and cicatrisation. Single or multiple, widely separated lesions
Grade III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across entire area

Hurley's grades are used to classify each disease location in an individual, such as armpit, groin etc. in a disease severity category.[2] It has been suggested that the Hurley classification is a useful guide for baseline severity and for helping to select appropriate treatment options, but that the MSS scoring system offers a more precise means of detailing severity of disease in the context of evaluating improvement.[2] This score has not been formally validated but is frequently used and has been shown to be highly correlated with Hurley's classification, as well as degree of suppuration, which are good markers of inflammation and burden of the disease.[2]

HS is associated with malodorous discharge that stains clothing and is therefore accompanied by embarrassment, disabling social stigma, low self-worth and impacts on interpersonal relationships. Studies have found that active disease can have a substantial impairment on a patient's HRQoL, exceeding that of other skin diseases that are generally perceived to have a high burden and substantial disability, for example, alopecia, acne, mild to moderate psoriasis, vascular anomalies of the face and atopic dermatitis. Given the debilitating impact of HS on a person's life, measures of pain and quality of life, especially the DLQI, are recognised as being useful in the clinical management of HS.[2,3,11]

2.2 Critique of manufacturer's overview of current service provision

The ERG and clinical advisors considered the company's description of current service provision for the treatment of populations with HS to be appropriate and relevant to the decision problem (see CS,[12] pages 29-31 and pages 39-43) and that the recommendations of relevant clinical guidelines have been taken into account.[13]

The CS, literature, guidelines and clinical advice received by the ERG, all indicate that there is no current standard of care for HS in the UK, but that treatment is determined by the specifics of the disease in the individual patient, together with clinical and patient experience. The aim of treatment is usually to control the disease and to reduce the number of outbreaks. Total cure is generally not expected. In addition to lifestyle changes (smoking cessation and weight loss), therapeutic options include topical antiseptics and antibiotics, systemic antibiotics (e.g. oral tetracyclines, clindamycin and rifampicin), antiandrogens, systemic retinoids, immunomodulatory agents, laser treatment,

surgery and anti-TNF-α therapies.[13-15] The choice of therapy typically depends on frequency, severity and spread of lesions and also gender in the case of the retinoid acitretin.

Topical antimicrobials are recommended for Hurley Stage I local disease, whilst systemic antibiotics are typically used for widespread or severe disease. Medical therapy is generally recommended for multiple, widely-spread lesions, and surgery for stable, locally-recurring lesions or severe and advanced disease. There is currently no known effective monotherapy, as confirmed by recent reviews,[13, 14, 16] hence a combination of different treatment modalities is often applied. Clinical advice received by the ERG suggests that surgery is usually an option after the failure of medical treatments and might involve simple local incision and drainage (usually as a response to acute flares, rather than to control the disease or reduce recurrence); narrow margin excision (which might see recurrence at the edge of the excised area) and wide margin excision for patients with advanced disease.[15] All of these interventions are mentioned as possible therapies or potential comparators in the CS.[9]

A survey of current UK practice among dermatologists confirmed that, after topical treatments, oral antibiotics, such as lymecycline or doxycycline, represent the first-line medical treatment of choice, followed by clindamycin and rifampicin, dapsone, acitretin, ciclosporin, depending on response and gender.[15] TNF-α inhibitors, such as etanercept, infliximab and adalimumab are already being used in the treatment of patients with moderate to severe HS, especially infliximab as the dose can be adjusted according to patient weight.[15] The CS states that adalimumab would typically be used after the failure of antibiotic therapy and before other therapies such as dapsone (antibiotic), retinoids and immunomodulators (ciclosporin) or surgery (see CS,[9] page 42). However, in response to a request for clarification from the ERG, the company's initial proposed positioning of adalimumab was amended to a position *"after all effective conventional systemic HS treatments have been exhausted"* and *"before or after surgery"* (see clarification response,[17] question C1). Clinical advisors to the ERG agreed that this was an appropriate place in the pathway. The number of patients who are likely to be suitable or eligible for treatment with adalimumab is unclear (see clarification response,[17] question C2). Adalimumab would only be prescribed in secondary care (see CS,[9] page 28). It is administered via subcutaneous (s.c.) injection, but clinical advice received by the ERG confirmed that initial and ongoing patient training would not be required from secondary care services because this support was to be provided by AbbVie Care (see CS,[9] page 27).

3. CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[9] A summary of the decision problem as outlined in the final NICE scope[8] and addressed in the CS[9] is presented in Table 2.

Table 2: Company's statement of the decision problem (adapted from CS[9] page 14)

Element	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Population	Adults with active moderate to severe HS which has not responded to conventional therapy	Adults with active moderate to severe HS which has not responded to conventional therapy	As specified in the scope
Intervention	Adalimumab	Adalimumab	As specified in the scope
Comparator(s)	Established clinical management without adalimumab	Where the data allows AbbVie has performed comparisons in line with the licence	As per scope where data allows
Outcomes	The outcome measures to be considered include: • Disease severity • Clinical response • Inflammation and fibrosis • Discomfort and pain • AEs of treatment • HRQOL	The outcome measures to be considered include: • Disease severity • Clinical response • Inflammation and fibrosis • Discomfort and pain • AEs of treatment • HRQOL	As specified in the scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.	• Cost-effectiveness will be presented as incremental cost per QALY. • The time horizon for the modelling is a lifetime. • Costs will be considered from an NHS and PSS perspective.	As specified in the scope
Subgroups to be considered	None stated	None stated	As specified in the scope
Special considerations including issues related to equity or equality	None stated		

3.1 Population

The population defined in the final NICE scope[8] relates to *"adults with active moderate to severe HS which has not responded to conventional therapy."* This is in line with the marketing authorisation for adalimumab and reflects the populations of the PIONEER I/II studies[18, 19] which form the main basis of the clinical evidence presented within the CS.[9] The health economic model submitted by the company is largely based on evidence relating to the relative efficacy and safety of adalimumab versus placebo within the PIONEER I/II trials. The model also employs additional data on long-term responders to adalimumab 40mg EW who were initially enrolled into the PIONEER I/II trials[18, 19] who were subsequently enrolled into the M12-555 OLE study.[20]

3.2 Intervention

The intervention defined in the CS is adalimumab 40mg EW administered via subcutaneous (s.c.) injection. Adalimumab is available as either as an auto-injection pen or pre-filled syringe (40mg/0.8ml solution).

Adalimumab is a recombinant human IgG1 monoclonal antibody expressed in Chinese Hamster Ovary cells.[12] Adalimumab inhibits the activity of the pro-inflammatory cytokine TNF-α, a key component in the inflammatory process. Adalimumab binds specifically to TNF-α and blocks its interaction with TNF receptors 1 and 2.

Adalimumab has a marketing authorisation for the treatment of active moderate to severe HS in adult patients with an inadequate response to conventional systemic HS therapy.[12] Adalimumab also holds a European marketing authorisation for the treatment of juvenile idiopathic arthritis, rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, Crohn's disease and ulcerative colitis.

As of December 2015, the NHS indicative price for adalimumab is £704.28. Each pack contains two syringes.

The Summary of Product Characteristics (SmPC)[12] states that the recommended adalimumab dose regimen for adult patients with HS is 160mg initially at Day 1 (four 40mg injections in one day or two 40mg injections per day for two consecutive days), followed by 80mg two weeks later at Day 15 (two 40mg injections on the same day). From Day 29 onwards, the recommended dose regimen is 40mg EW. The SmPC notes that antibiotics may be continued during treatment with adalimumab if necessary and that patients should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with adalimumab. The SmPC advises that continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should

treatment be interrupted, adalimumab 40mg EW may be re-introduced. The SmPC also notes that the benefits and risks of continued long-term treatment should be periodically evaluated.[12]

According to the European Medicines Agency (EMA), treatment with adalimumab should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which adalimumab is indicated and patients treated with adalimumab should be given the special alert card. The SmPC notes that patients require training in injecting after which time patients might self-inject with adalimumab if their physician determines that it is appropriate and with medical follow-up as necessary. The CS[9] states that adalimumab will be administered in the home setting via AbbVie Care (the company's home care service). During treatment with adalimumab, other concomitant therapies should be optimised.

The SmPC[12] notes that the safety and efficacy of adalimumab in children aged 12-17 years with HS have not yet been established and that no data are available. There is no relevant use of adalimumab in children aged below 12 years in this indication.

Contraindications to adalimumab treatment include hypersensitivity to the active substance, the presence of active tuberculosis (TB) or other severe infections such as sepsis, and opportunistic infections, and moderate to severe heart failure (NYHA class III/IV). The administration of adalimumab during pregnancy is not recommended.

3.3 Comparators

Within the clinical section of the company's review, all RCT evidence for adalimumab is drawn from trials which included a placebo control. Within the company's model, the comparator is defined as "standard care"; this is assumed to include surgery and non-surgery related hospital visits and A&E attendances. Whilst the company considered the feasibility and appropriateness of undertaking NMAs for various outcomes, these were not performed for any outcome and the CS does not include any comparison of adalimumab against any specific pharmacological or surgical comparator.

With reference to the decision problem, the CS states that, *"where the data allows AbbVie has performed comparisons in line with the licence."* The relevance of this statement is unclear however as the licence relates to adalimumab rather than any selected comparator. Further, whilst the company argues that there is no effective licensed or NICE-recommended treatment for HS, this does not preclude the consideration of such therapies as potentially relevant comparators to adalimumab.[21]

With respect to currently used therapies for HS, the CS notes that within a survey of 142 patients from 10 UK hospitals funded by the company, patients took an average of 10 medications within the 5-year

retrospective period (range 1-43 medications). The CS[9] also highlights that there are no licensed therapies for the treatment of HS in the UK and that various pharmacological therapies are used off-label (including antiseptics, non-steroidal anti-inflammatory drugs [NSAIDs], immunosuppressants, corticosteroids, anti-androgens, retinoids and TNF-α inhibitors). The CS also notes that there is limited robust evidence to demonstrate the efficacy of any of these therapies in the management of HS.

The CS argues that neither surgery nor antibiotics represent relevant comparators for adalimumab. Surgery is argued to be an inappropriate comparator since adalimumab and surgery are not alternative or exclusive treatment choices and because, within the PIONEER I/II trials,[18,19] patients were allowed to undergo surgery such as incision and drainage to control symptoms (although it is unclear whether this was actually the case – see Section 4.2.1 and Section 5.3). Antibiotics are argued to be inappropriate comparators because they are used alongside adalimumab and because the use of oral antibiotics was allowed in both the intervention and control arms of the PIONEER II trial[19] and as rescue therapy in the PIONEER I trial.[18] The CS also argues that dapsone, retinoids and immunomodulators are not relevant comparators for adalimumab because these are prescribed before adalimumab. According to the company's NMA feasibility assessment,[9] a comparison with infliximab would not be feasible due to evidence limitations and heterogeneity between studies. As such, the CS argues that the main comparator for the analysis is standard care, as represented by the placebo arms in the PIONEER I/II trials.[18,19] Issues surrounding the implementation of this economic comparison is discussed in further detail in Section 5.3.

Clinical advisors to the ERG agree that there are few obvious comparators for adalimumab and that standard care, as defined within the company's model, represents a reasonable comparator. One clinical advisor to the ERG did however note that infliximab and adalimumab are typically used interchangeably, with the choice of treatment often being guided mainly by cost concerns. Whilst the ERG agrees that an indirect comparison based on the HiSCR measure would not be possible for adalimumab versus infliximab, it may have been possible to compare the two treatments using an alternative clinical outcome measure, such as pain. This would however have required a very different model structure to that presented within the CS.

3.4 Outcomes

The company's clinical review includes evidence relating to the following outcomes:

- Clinical response, measured by the HS-PGA or the HiSCR measures, which assess clinical improvement following pre-specified thresholds for reduction or maintenance in the number of a patient's lesions, abscesses, inflammatory nodules and draining fistulae;

- Disease severity and inflammation and fibrosis, which are also assessed by counts of lesions, abscesses, inflammatory nodules and draining fistulae using measures such as the HiSCR, and the MSS and Hurley scores;
- Discomfort and pain, which are measured by specific dermatology and generic pain scores;
- Any AE of treatment, including serious AEs, in particular those which led to discontinuation of the study drug, as well as common AEs such as headache and nasophryngitis, or serious infections associated with adalimumab, such as TB;
- HRQOL, assessed by specific dermatology quality of life measures (e.g. Hidradenitis Suppurativa Quality of Life [HSQOL] and the DLQI) as well as more general measures, such as the SF-36 and the EQ-5D.

3.5 Economic analysis

The CS includes the methods and results of a *de novo* model-based health economic analysis to assess the incremental cost-utility of adalimumab versus standard care for the treatment of adults with active moderate to severe HS which has not responded to conventional therapy. The company's model is detailed and critiqued in Chapter 5. The ERG notes that whilst the efficacy and safety data used within the model are based on the PIONEER I/II trials[18,19] and the OLE study,[20] the resource costs associated with the comparator are instead drawn from a survey on UK physicians funded by the company.[22]

3.6 Subgroups

Within the company's review of clinical effectiveness evidence (see CS,[9] Chapter 4), pre-specified subgroup analyses were undertaken for all three adalimumab RCTs in order to assess the consistency of the primary efficacy endpoint by demographic and baseline characteristics. *Post hoc* analyses were also undertaken in the dose-finding trial (M10-467) in order to compare the clinical response for patients in the adalimumab 40mg EW group compared with those in the placebo group. No specific subgroups are considered within the company's health economic analysis.

3.7 Special considerations

The CS[9] notes that currently no therapies have been approved for the treatment of HS in England and that various therapeutic options are used off-label in clinical practice. The CS highlights that there is little research around the treatment of HS, hence the evidence base supporting existing treatment options is limited. The CS states that the use of unlicensed treatments exposes patients to potential safety risks and also results in variations in clinical practice and inequities in the access to effective HS therapies.

A confidential PAS has not been submitted by the company. End-of-Life criteria are not applicable to this appraisal.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the reviews submitted by the company on the efficacy and safety of adalimumab in adults with moderate to severe HS. The critique was performed following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist.[23]

4.1 Critique of the methods of review(s)

The CS[9] reports the methods and results of three separate reviews:

(i) A review of the efficacy evidence from RCTs (see CS, Sections 4.1-4.10);

(ii) A review of the efficacy and safety evidence from non-randomised and non-controlled studies (see CS, Section 4.11), and;

(iii) A review of safety evidence from RCTs and a non-randomised study (see CS, Section 4.12).

Each review applies different inclusion criteria depending on the intended analysis and the included study designs.

The main review of efficacy evidence from RCTs was a poorly-reported systematic review. Following a request for clarification from the ERG regarding certain process elements adopted by the company, the ERG considered the review to be generally sound (see clarification response,[17] questions A1-A7).

The review of the efficacy evidence from non-randomised and non-controlled studies was limited to a single open-label, non-controlled extension study (M12-555 OLE). This review was not considered to be a systematic review because it was unclear how the evidence was identified, selected and extracted, no inclusion or exclusion criteria were provided, and a list of excluded studies was not reported. Quality assessment of the OLE study was performed by the company using a checklist, but the choice and origin of this was neither justified nor specified. This was clarified by the company in response to a request by the ERG (see clarification response,[17] questions A22).

The review of the safety evidence was also not considered by the ERG to be a systematic review because it was unclear from the original submission how the included non-RCT evidence was identified and selected, no detailed inclusion or exclusion criteria or details of data extraction were provided, and a list of potentially relevant excluded studies was not reported.

4.1.1 Searches

The company conducted a systematic literature review search for evidence on the comparative efficacy and safety of interventions in HS. The ERG notes that, since the searches focussed on treatment of the condition (HS) rather than the specific intervention under review (adalimumab),

studies describing AEs where the drug was used for other conditions would not have been retrieved. Studies were identified by a literature search of MEDLINE, EMBASE and the Cochrane CENTRAL register of clinical trials. Whilst these are the key sources identified by the Cochrane Handbook,[24] many STAs go beyond this and include additional sources in order to increase the coverage of the search and to ensure that all potentially relevant evidence has been taken into account. The CS also reports an additional search of the US National Institutes of Health Ongoing Trials Register (clinicaltrials.gov), but no searches of the equivalent WHO or EU registers (http://www.who.int/ictrp/search/en/ and https://www.clinicaltrialsregister.eu/ respectively) were reported. In addition, standard supplementary methods such as reference tracking were not used.

The ERG queried the interface on which the MEDLINE and EMBASE searches were conducted as there were significant logical errors in the searches as reported (for example, the omission of brackets, without which the search would not function or produce the number of results reported). For example, Line 17 of the EMBASE search strategy (see CS,[9] Appendix 2, Table A1) was written as *"observational adj3 study or studies or design or analysis or analyses.mp"* should read *"observational adj3 (study or studies or design or analysis or analyses).mp"*. Without these brackets, the query would be interpreted as: "*(observational adj3 study) or studies or design or analysis or analyses.mp."* This search would additionally find many instances of the "study" terms occurring without "observational" in proximity. There are also similar problems in lines 17-19 of the EMBASE search and the combinations at lines 22 and 24. The MEDLINE search, which follows a similar structure, also contains the same errors.

When attempting to reproduce and verify the company's searches, the ERG found that, after correcting the syntax, the numbers of results retrieved suggested that the errors had not been made in the company's live search, rather they were present only in the reported version. Whilst this raises some concerns about the accuracy of the reporting, it appears that correct syntax was used in the search itself.

In addition to the syntax errors, the ERG noticed several typographical errors and/or spelling mistakes in the searches, which appear from the very first line of the EMBASE search: *"exp hidradenitis suppurative/"* (the correct heading is *"exp hidradenitis suppurativa/"*). Line 2 also contains a spelling error (*"hidradenitis supportiva"*) and a variant spelling of the archaic term *"pyodermia fistulans significa"* is sometimes found: *"pyodermia fistulans sinifica"*. Another search term which has been omitted is the reversed form of the name for the condition, *"suppurative hidradenitis"*, which the ERG found to be in relatively common use.

Line 19 of the company's EMBASE search includes the phrase: *not "randomized controlled trial".pt.* Unfortunately, "randomized controlled trial" is not a valid publication type in EMBASE, and is present only in MEDLINE, so this clause of the search string will not have any effect.

The MEDLINE search shares many of the above errors and omissions.

The ERG found that, despite these errors, the numbers of results retrieved by the company were in accordance with the results obtained when all terms were entered correctly by the ERG. It would appear that the search strategies have been re-typed for the CS rather than providing a screenshot or a copy-pasted version of the search (as is the convention), and that errors were made during this transcription process. The ERG notes that it is difficult accurately to assess the robustness of searches if they are not presented in a reproducible form. However, after correcting the various errors described above, the ERG found no additional studies over and above those identified by the company.

4.1.2 Inclusion criteria

The inclusion criteria for the reviews are described in Section 4.1.1 of the CS (pages 46-47, see Table 3). These criteria describe RCTs measuring the efficacy and safety of a number of biologic (including adalimumab), antibiotic, steroid, retinoid and surgical interventions (limited to laser only) compared with any of these interventions or placebo in adult patients with HS. These are the inclusion criteria for the potential performance of an indirect comparison, which is discussed in Section 4.10 of the CS[9] (page 99). However, Sections 4.2 to 4.9 of the CS (pages 54-99) report a clinical efficacy review of a subset of studies satisfying the following inclusion criteria: RCTs measuring the efficacy and safety of adalimumab compared with other interventions or placebo in adult HS patients. The four RCTs satisfying these criteria are: M10-467,[25] PIONEER I,[20] PIONEER II,[19] and Miller *et al*.[26] The RCTs include two doses of adalimumab, 40mg EW and 40mg EOW. One study (Miller *et al*[26]) evaluated only an unlicensed dose of adalimumab in the HS population and was therefore correctly excluded using additional inclusion/exclusion criteria described later in Section 4.2 of the CS. It is unclear why the definition of the surgical comparator in the review was restricted to laser treatment only.

The review of the efficacy evidence from non-randomised and non-controlled studies did not specify any inclusion criteria (see Section 4.11). This review reported a single open-label, non-controlled extension study, M12-555 OLE,[20] whose participants were recruited from the PIONEER I and II trials. According to the inclusion criteria outlined in Section 4.1.1 of the CS and the searches described in Appendix 2 of the CS, non-randomised studies were explicitly excluded (an RCT study filter is applied in the reported searches). It is therefore unclear how the included, unpublished non-RCT was identified or whether additional, relevant evidence might have been excluded.

The inclusion criteria for the review of safety evidence from RCTs and non-randomised studies were not specified. The safety review included the three RCTs from the main clinical efficacy review (M10-467, PIONEER I, PIONEER II), as well as the M12-555 OLE trial from the review of non-randomised and non-controlled studies. However, as noted above, the methods by which the non-randomised study was identified and the criteria by which it was selected, and others were excluded, are not clear.

Table 3: Inclusion and exclusion criteria for the broad clinical efficacy/safety systematic literature review (reproduced from CS,[9] Section 4.1.1)

Inclusion criteria	
Population	Adult patients with moderate to severe HS were included. The inclusion criteria were not limited by the definition of HS severity, and hence, severity, as defined by HS severity index (HSSI), HS-Physician's Global Assessment score (HS-PGA) or Hurley score
Intervention	▪ Biologics: adalimumab, etanercept and infliximab ▪ Antibiotics: erythromycin, metronidazole, minocycline, clindamycin, cephalosporins, penicillins, long-term antibiotics (erythromycin, tetracycline etc.) ▪ Steroids: high-dose oral steroids, prednisolone, intralesional corticosteroid injection, oestrogens and dapsone ▪ Retinoids (acitretin) ▪ Surgery: laser
Comparators	The comparators of interest included placebo, any of the interventions of interest mentioned above or standard of care. The choice of comparators matches the commonly used comparators in the trials of HS.
Outcomes	At least one of the following efficacy measures should be reported in the relevant studies identified: ▪ Clinical response as assessed by HiSCR, HS-Physician's global assessment (HS-PGA) or HS severity index (HSSI) ▪ Hurley score ▪ HS-lesion, activity and severity (HS-LASI) score ▪ Patient skin pain assessment ▪ MSS ▪ DLQI ▪ Major Depression Inventory (MDI)
Study design	The study selection was restricted to RCTs conducted in more than 10 patients. Data reported at the end of the first period of randomised crossover studies were considered.
Language	English only

4.1.3 Critique of study selection and data extraction

No information was given in any of the reviews regarding the data extraction process (for example, the number of reviewers involved, or actions taken to minimise error). This was addressed however in response to clarification requests from the ERG, in which the company detailed standard processes for data extraction in systematic review (see clarification response,[17] question A3). Following standard systematic review good practice, trials were independently selected for inclusion by two reviewers, with any discrepancies between reviewers resolved through discussion or the intervention of a third reviewer. Data extraction was also performed by one reviewer and independently checked for errors against the original trial report by a second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer. This is standard good practice for conducting systematic reviews. During the clarification stage, discrepancies and inadequacies in some of the numbers reported in the PRISMA flowchart were acknowledged and addressed by the company, and an updated PRISMA flowchart was provided (see clarification response,[17] question A4).

4.1.4 Quality assessment

For the review of clinical efficacy evidence, the company conducted a critical appraisal of the three adalimumab 40mg EW trials using the NICE risk of bias assessment tool (see CS,[9] Section 4.6) and a critical appraisal of all four adalimumab and relevant comparator studies using the Cochrane risk of bias assessment tool (see CS,[9] Appendix 4). This summary focusses only on the three EW adalimumab trials: M10-467 and PIONEER I and II.

The CS reports that the M10-467 trial was at low risk of bias across all domains using both tools (see CS,[9] Section 4.6, Table 12, page 76). The assessment in Appendix 4 correctly made separate risk of bias assessments for Period 1 (a triple-arm, randomised, blinded study period) and Period 2 (a single arm, open-label extension period). The data from Period 2 are not relevant to this appraisal because all participants received the unlicensed EOW dose of the study drug. The ERG accepts that the data from Period 1 of M10-467 are likely to be subject only to a low risk of bias.

For PIONEER I and II, the CS reports that, *"The results for PIONEER I and PIONEER II are published only as two abstracts. Therefore, most of the details required for quality assessment are not reported for these two studies"* (CS,[9] Section 4.6, page 76). As a result, the company judged the trials to be at "intermediate" or "low risk of bias" across all domains using the NICE tool (see CS,[9] Section 4.6, Table 12, page 76). Given the acknowledged limitations in performing critical appraisal of study design and conduct using the very limited information available in published abstracts, a more

accurate assessment using the NICE tool might have been to categorise the risk of bias as "unclear" across all domains.

Using the Cochrane risk of bias tool, the company then assessed PIONEER I and II to be at low risk of bias across all domains both in Period A and Period B, except for an assessment of "unclear risk of bias" concerning attrition in Period B, and "unclear risk of bias" regarding other, unspecified potential sources of bias (see CS,[9] Appendix 4). There are a number of issues with this assessment. First, different tools are used and the findings are different (the submission used the NICE tool to judge the PIONEER trials to be at "intermediate" risk of bias across most domains, and the Cochrane tool to judge the PIONEER trials to be at "low" risk of bias across most domains). Following a request for clarification on this issue, the company explained that the NICE tool was used for the adalimumab trials in the main efficacy review and the Cochrane tool was used for the trials included in both the efficacy review and the potential indirect comparison (clarification response,[17] question A22). The company also explained that the NICE tool was used for an assessment based on the published M10-467 paper and the published abstracts relating to the PIONEER trials, whilst the Cochrane risk of bias assessment was based on the clinical study reports (CSRs) only (see clarification response,[17] questions A20, A21). There was no reported rationale for this distinction. Second, the two PIONEER trial periods (A and B) were not formally assessed separately, even though there are differences in study design and conduct between these periods (specifically relating to randomisation, attrition and discontinuation). In response to a request for clarification from the ERG on this matter, the company reiterated the findings reported in the CS, in which PIONEER I and II were judged to be at low risk of bias across all domains both in Period A and Period B, except for an assessment of "unclear risk of bias" concerning attrition in Period B (see clarification response,[17] questions A20, A21 and A23). The ERG disagrees with some of the company's risk of bias assessments relating to the PIONEER I and II trials. The differences between the company's assessments and those made by the ERG are detailed in Tables 4 and 5 using the Cochrane risk of bias criteria only, as this is the accepted standard tool for conducting assessments of risk of bias in RCTs. The assessment has had to be made for the PIONEER trials using the CSRs alone because the trials are currently unpublished and have not been subjected to peer review.

Table 4: Risk of bias assessment - PIONEER I

Risk of bias	Period A		Period B	
	CS	**ERG**	**CS**	**ERG**
Selection bias	LOW	LOW	LOW	MODERATE *All are re-randomised to maintain blind, but randomisation is false for some who can only be assigned to placebo for Period B*
Performance bias	LOW	LOW	LOW	LOW-MODERATE *There is no evaluation of blinding to determine whether it was effective*
Detection bias	LOW	LOW	LOW	LOW
Attrition bias	LOW	LOW-MODERATE *NRI for some primary and LOCF for some secondary outcomes due to up to 6% attrition (CS, p.71); imputation might over-estimate effect*	UNCLEAR	MODERATE *NRI for some primary and LOCF for some secondary outcomes due to 45% attrition from 12-week baseline across arms (CS, p.71); imputation might over-estimate effect*
Reporting bias	LOW	MODERATE *The protocol lists original and "current" outcomes, which are different; DLQI, TSQM, HADS, SF-36, CRP, fistulas, AEs are all reported in CS but are not listed in the protocol. However, clinical advice did not specify any other outcomes that were not included. Outcomes are listed in the protocol for 12 weeks only, but a text description of the trial makes mention of the Period B and a study duration of 36 weeks*	LOW	MODERATE *The protocol lists original and "current" outcomes, which are different; DLQI, TSQM, HADS, SF-36, CRP, fistulas, AEs are all reported in CS but are not listed in the protocol. However, clinical advice did not specify any other outcomes that were not included. Outcomes are listed in the protocol for 12 weeks only, but a text description of the trial makes mention of the Period B and a study duration of 36 weeks*
Other bias	UNCLEAR	MODERATE *Manufacturer-funded, some issues with selective reporting*	UNCLEAR	MODERATE *Manufacturer-funded, some issues with selective reporting*

NRI - non-responder imputation; LOCF - last observation carried forward; DLQI - Dermatology Life Quality Index; TSQM - Treatment Satisfaction Questionnaire for Medicine; HADS: Hospital Anxiety and Depression Score; SF-36: Short-Form 36, CRP - C-Reactive Protein; AE - adverse event; CSR - clinical study report

Table 5: Risk of bias assessment - PIONEER II

Risk of bias	Period A		Period B	
	CS	**ERG**	**CS**	**ERG**
Selection bias	LOW	LOW	LOW	MODERATE *All are re-randomised to maintain blind, but randomisation is false for some who can only be assigned to placebo for Period B*
Performance bias	LOW	LOW	LOW	LOW-MODERATE *There is no evaluation of blinding to determine whether it was effective*
Detection bias	LOW	LOW	LOW	LOW
Attrition bias	LOW	LOW-MODERATE *NRI for some primary and LOCF for some secondary outcomes due to 6% attrition (CS, p.71); imputation might over-estimate effect*	UNCLEAR	MODERATE *NRI for some primary and LOCF for some secondary outcomes due to more than 50% attrition across arms (CS, p.71); imputation might over-estimate effect*
Reporting bias	LOW	MODERATE *The protocol lists original and "current" outcomes, which are different; DLQI, TSQM, HADS, SF-36, CRP, fistulas, AEs are all reported in CS but are not listed in the protocol. However, clinical advice did not specify any other outcomes that were not included. Outcomes are listed in the protocol for 12 weeks only, but a text description of the trial makes mention of the Period B and a study duration of 36 weeks*	LOW	MODERATE *The protocol lists original and "current" outcomes, which are different; DLQI, TSQM, HADS, SF-36, CRP, fistulas, AEs are all reported in CS but are not listed in the protocol. However, clinical advice did not specify any other outcomes that were not included. Outcomes are listed in the protocol for 12 weeks only, but a text description of the trial makes mention of the Period B and a study duration of 36 weeks*
Other bias	UNCLEAR	MODERATE *Manufacturer-funded, some issues with selective reporting*	UNCLEAR	MODERATE *Manufacturer-funded, some issues with selective reporting*

NRI - non-responder imputation; LOCF - last observation carried forward; DLQI - Dermatology Life Quality Index; TSQM - Treatment Satisfaction Measure; HADS - Hospital Anxiety and Depression Score; SF-36 - Short-Form 36, CRP - C-reactive protein; AE - adverse events; CSR - clinical study report

With respect to Period A of both trials, the ERG agrees with the company's judgement that the overall risk of bias is low, albeit with the exception of possible low-to-moderate level bias in terms of attrition and reporting. However, the ERG considers there to also be a moderate or unclear risk of selection and attrition bias for the results of Period B, especially given the absence of any evaluation of the blinding, and the high level of attrition. LOCF imputation was used for secondary outcomes to manage missing data; the ERG notes that it has been shown that using LOCF can overestimate efficacy in certain diseases.[27] However, the disease trajectory is difficult to determine for HS, so there is some uncertainty concerning the results based on this method of imputation.

For the non-randomised evidence, a single additional, non-RCT study (M12-555 OLE[20]) was identified and its findings were presented within the CS. A quality assessment was performed for this study using an unspecified tool and no rationale was provided for its selection. In response to a request for clarification from the ERG, the tool was later specified by the company as the Centre for Reviews and Dissemination (CRD) non-RCT tool (see clarification response,[17] question A22). Given that only simple "Yes", "No" or "Not relevant" responses are presented by the company, it is difficult to establish how these judgements were reached. The ERG disagrees with some of the company's risk of bias assessments relating to the M12-555 OLE study (Table 5). The differences between the company's assessments and those made by the ERG are detailed in Table 6.

Table 6: Company's critical appraisal of M12-555 OLE using CRD non-RCT tool (reproduced from CS,[9] Table 27, page 105)

Criterion	Assessment	Response
Bias in results?	Was there significant potential for bias? List the reasons that have led to this conclusion.	No Clear inclusion and exclusion criteria
Study question	Does the study clearly address a specific question? Has the study question been specifically stated?	Yes Yes
Methodology	Were the methods clearly described, with enough detail that you could repeat the study exactly? Were appropriate methods used to answer the specified research question? Were the outcome measures used appropriate? Are the methods sufficiently flawed as to make the results unreliable?	Yes Yes Yes No
Population and data collection	Was the population under study described adequately? Were the inclusion/exclusion criteria sufficiently described? Was the population under study selected/ recruited in an appropriate way? Was the collection of data complete enough (in terms of size of population and follow-up period)?	Yes Yes Yes, OLE Interim results only
Results and confounding factors	Were the results presented in a clear and useful manner? Were the tables/graphs clearly labeled, easily interpretable, and discussed sufficiently to enable understanding of the meaning of the results? Could the results be due to chance or bias (as highlighted by the authors and/or by your own judgment)? Have the authors identified possible confounding factors that may have influenced the results (such as age, gender, ethnicity, socioeconomic status, occupation, etc.)? Have these factors been incorporated into the analysis (i.e. have the results been presented as crude and adjusted ratios)?	Yes Yes No Not relevant Not relevant No
Statistical methods	Were the statistical methods clearly described? Was any rationale given for the methodology of analysis used? Were the factors used to adjust a model (if any) detailed clearly, with reasoning given for their selection? Were any unusual methods used?	Yes Yes Not relevant No
Conclusions	Do the authors provide a clear discussion of the results that leads to a single, specified conclusion in answer to the specified study question? Do the authors relate their results to any previous literature in the field? Is there consistency between the conclusions and the results presented?	Yes, but interim results Yes Yes

Owing to difficulties in qualifying the company's judgements regarding the risk of bias in the OLE study, the ERG conducted its own critical appraisal using the Critical Appraisal Skills Programme (CASP) tool for cohort studies,[28] as this is an accepted standard tool for conducting assessments of risk of bias in studies with this type of design (see Table 7). The ERG identified the following issues: the study was not blinded so there is potential for detection bias; regression analyses have not yet been conducted to control for potentially confounding variables, and; LOCF is used to account for a large amount of missing data. There is therefore a great deal of uncertainty regarding the findings of this single arm, non-controlled, unblinded, unpublished OLE study.

Table 7: ERG critical appraisal of M12-555 OLE using CASP cohort study checklist

Question	Assessment
1. Did the study address a clearly focused issue? HINT: A question can be 'focused' In terms of • The population studied • The risk factors studied • The outcomes considered • Is it clear whether the study tried to detect a beneficial or harmful effect?	Yes
2. Was the cohort recruited in an acceptable way? HINT: Look for selection bias which might compromise the generalisibility of the findings: • Was the cohort representative of a defined population? • Was there something special about the cohort? • Was everybody included who should have been included?	Yes, an extension study of all responders, partial responders and non-responders from two relevant, placebo-controlled RCTs in the same trial
3. Was the exposure accurately measured to minimise bias? HINT: Look for measurement or classification bias: • Did they use subjective or objective measurements? • Do the measurements truly reflect what you want them to (have they been validated)? • Were all the subjects classified into exposure groups using the same procedure	Yes. All subjects were classified into asingle group. Compliance was measured and monitoring conducted at 4-8 week time-points to determine outcomes or discontinuation
4. Was the outcome accurately measured to minimise bias? HINT: Look for measurement or classification bias: • Did they use subjective or objective measurements? Principally PROMs and some investigator assessments (all subjective), plus some objective measures e.g. CRP • Do the measures truly reflect what you want them to (have they been validated)? • Has a reliable system been established for detecting all the cases (for measuring disease occurrence)? • Were the measurement methods similar in the different groups? • Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?	Overall, Yes, clinical and patient-reported outcome measures. Most measures were validated, though the primary outcome measure, HiSCR, has some known correlation and inter-rater reliability issues.[29] Further, there are some concerns about the "partial response" outcome measure, which is *post hoc* and non-validated. Yes, frequent visits; efforts to make sure the same investigator is making judgments each time: CSR, section 9.5.1.1 Yes No, this was an un-blinded, open-label study: there is potential for detection bias
5. (a) Have the authors identified all important confounding factors? **List the ones you think might be important, that the author missed.** **(b) Have they taken account of confounding factors in the design and/or analysis? List:** HINT: Look for restriction in design, and techniques e.g. modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors	Yes. Severity of disease; gender, BMI, antibiotic use, disease duration, CRP, concomitant interventions, smoking status etc. No. Details of subgroups and confounding factors at baseline are given, but the reported results are simply proportions of patients exposed to "continuous" adalimumab who achieved a response: there were no regression or sensitivity analyses (CS, pp.102, 106)
6. (a) Was the follow up of subjects complete enough?	Most of those subjects without data are

Question	Assessment
(b) Was the follow up of subjects long enough? HINT: Consider □ The good or bad effects should have had long enough to reveal themselves □ The persons that are lost to follow-up may have different outcomes than those available for assessment □ In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?	patients who simply have not reported data yet - so LOCF is used - which introduces greater uncertainty into the results
7. What are the results of this study? HINT: Consider □ What are the bottom line results? □ Have they reported the rate or the proportion between the exposed /unexposed, the ratio/the rate difference? □ How strong is the association between exposure and outcome (RR)? □ What is the absolute risk reduction (ARR)?	Results consist of basic proportions of patients in the different groups achieving a response: only results for patients who have experienced "continuous" adalimumab exposure are presented, not all groups
8. How precise are the results? HINT: Look for the range of the confidence intervals, if given.	Basic frequencies, based on LOCF to manage missing data - therefore some uncertainty
9. Do you believe the results? HINT: Consider □ Big effect is hard to ignore! □ Can it be due to bias, chance or confounding? □ Are the design and methods of this study sufficiently flawed to make the results unreliable? □ Bradford Hills criteria (e.g. time sequence, dose-response gradient, biological plausibility, consistency)	Proportions with response - and trends of response - are similar and consistent across groups. However, large numbers of missing patients and data, and the extensive use of LOCF after week 24, renders these findings more uncertain
10. Can the results be applied to the local population? HINT: Consider whether □ A cohort study was the appropriate method to answer this question □ The subjects covered in this study could be sufficiently different from your population to cause concern □ Your local setting is likely to differ much from that of the study □ You can quantify the local benefits and harms	No UK centres, but clinical advice to the ERG suggests that results for the trial patients are generaliseable
11. Do the results of this study fit with other available evidence?	Yes, similar to the main findings of the original two RCTs
12. What are the implications of this study for practice? HINT: Consider □ One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making □ For certain questions observational studies provide the only evidence □ Recommendations from observational studies are always stronger when supported by other evidence	More longer-term RCT evidence with improved follow-up and fewer missing data is needed, with larger numbers to manage any attrition, and more complete sensitivity analyses of confounding factors to address uncertainties. Otherwise, this study offers some limited but useful data on efficacy and useful data on medium-to-long-term safety

For the review of the safety evidence (see CS,[9] Section 4.12), data from four studies were presented: M10-467, PIONEER I/II, and M12-555 OLE. Quality assessment of these studies was performed within the CS. The ERG accepts the overall low risk of bias affecting the safety data from M10-467,

PIONEER I and II, but has identified a number of issues with the conduct and reporting of the M12-555 OLE study (see Table 7).

4.1.5 Evidence synthesis

The synthesis for the review of clinical efficacy was a basic descriptive summary of the evidence from the M10-467, PIONEER I and PIONEER II trials. The selected approach to evidence synthesis was neither described nor justified in the CS, but was described in response to a clarification question from the ERG, as *"evidence extracted … was summarised and then reported in tabulated form"* (see clarification response,[17] question A2). A meta-analysis was not performed. In response to a request for clarification from the ERG, the company stated that a separate meta-analysis was unnecessary because data from the PIONEER trials had been pooled in the efficacy results section (see clarification response,[17] question A7).

An NMA comparing effects across all treatments was not performed by the company. The CS notes that there were substantial differences in trial characteristics in trials comparing different pairs of treatments. The CS argues that trial charcteristics such as smoking status, CRP status, disease severity, and prior and concomitant medication were potential treatment effect modifiers. Therefore, the company argues that because there were insufficient trials to adjust for trial characteristics it was not possible to produce unbiased estimates of treatment effects. In addition, the company argues that trials did not provide data on all outcome measures so that the number of trials with usable data varied with the outcome measure.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Review of clinical efficacy (relevant RCT evidence)

The CS provides a very detailed, extensive description of three trials identified by the company as satisfying the requirements of the final NICE scope,[8] i.e. adalimumab compared with alternative treatments (see Table 8). Three RCTs compared adalimumab 40mg EW with placebo: a Phase II trial, M10-467,[25] and two Phase III trials: PIONEER I,[18] and PIONEER II.[19]

It should be noted that only one of the trials (M10-467) has been published in full in a journal article.[25] Whilst some details of the study design and some of the results of the PIONEER trials have been published as conference abstracts,[19, 30-32] these have not been fully published as journal articles. As a result, these two trials and their results have not been subjected to rigorous peer review. The ERG has therefore conducted its critique principally based on information contained within the CSRs and the data presented in the main text of the CS.

All three included trials were international and multicentre. The inclusion criteria in all three trials were adult patients with moderate or severe HS. Moderate to severe HS requires lesions to be present in at least two distinct anatomical areas, one of which has to be Hurley Stage II or III. Patients had to have an AN count of >3 at the baseline visit. Patients who were unresponsive or intolerant to oral antibiotics were eligible for enrolment, although antibiotics were permitted as concomitant therapy for some or all participants in all trials.

Table 8: Characteristics of included RCTs (reproduced in part from CS,[9] Table 6, pages 52-53)

Study	Interventions	Study duration	Study design	Inclusion criteria	Exclusion criteria
M10-467	ADA 40mg EW vs. ADA 40mg EOW vs. placebo	52 weeks	International, multicentre, 16 week double-blind randomised controlled phase followed by a 36 week open label phase in which all patients received ADA	≥18 years, moderate to severe HS (HS-PGA score of moderate or worse) in at least 2 distinct anatomical areas and were unresponsive or intolerant to oral antibiotics as assessed by the investigator were eligible for enrolment*	Prior treatment with ADA or any other TNF antagonist therapy (e.g., infliximab or etanercept) or had received any systemic nonbiologic therapy within 4 weeks of baseline. Patients were allowed stable doses of oral (tetracycline, doxycycline, or minocycline) or topical (clindamycin) antibiotic treatment for HS
PIONEER I	ADA 40mg EW vs. placebo	36 weeks	International, multicentre, 12 week double-blind randomised controlled phase (Period A) followed by a 24 week double-blind phase (Period B) in which patients treated with ADA EW in Period A were re-randomised to ADA EW or EOW or placebo. Patients who were on placebo in Period A were assigned (using re-randomisation numbers) to receive ADA40 mg EW	Men or women ≥18 years; HS diagnosis >1 year, HS lesions in at least two distinct anatomical areas, one of which must be at least Hurley Stage II or Hurley Stage III, stable HS for at least 60 days prior to screening visit, inadequate response to at least a 90 day treatment of oral antibiotics for treatment of HS, and a count of ≥3 at baseline	Previously treated with ADA or another anti-TNF therapy (e.g., infliximab or etanercept); not on a stable dose of antibiotic (for at least 28 days prior to entry; received oral concomitant analgesics (including opioids) for HS-related pain, on opioid analgesics, not on a stable dose of non-opioid oral analgesics, within 14 days prior to entry
PIONEER II	ADA 40mg EW vs. placebo	36 weeks	International, multicentre, 12 week double-blind randomised controlled phase (Period A) followed by a 24 week double-blind phase (Period B) in which patients treated with ADA EW in Period A were re-randomised to ADA EW or EOW or placebo. Patients who were on placebo in Period A continued on placebo in Period B	Men or women ≥ 18 years; HS diagnosis >1 year, HS lesions in at least two distinct anatomical areas, one of which must be at least Hurley Stage II or Hurley Stage III, stable HS for at least 60 days prior to screening visit, inadequate response to at least a 90 day treatment of oral antibiotics for treatment of HS, and a count of ≥3 at baseline	Previously treated with ADA or another anti-TNF therapy (e.g., infliximab or etanercept); not on a stable dose of antibiotic for at least 28 days prior to the baseline visit; received oral concomitant analgesics (including opioids) for HS-related pain, on opioid analgesics, not on a stable dose of non-opioid oral analgesics, within 14 days prior to baseline visit

ADA – adalimumab; EW - every week; EOW - every other week; HS - hidradenitis suppurativa

More than 600 participants received the licensed 40mg EW dose during the three RCTs and the non-controlled OLE study. The three RCTs were also the only trials to evaluate the licensed 40mg EW dose of adalimumab. The final selection of the three included trials for the main clinical efficacy review was therefore considered to be appropriate by the ERG.

The M10-467 Phase II "dosing" trial recruited adults with moderate to severe HS, according to the HS Physician's Global Assessment [HS-PGA] score, who were "unresponsive or intolerant to oral antibiotics" as assessed by the investigator, using the following definition:

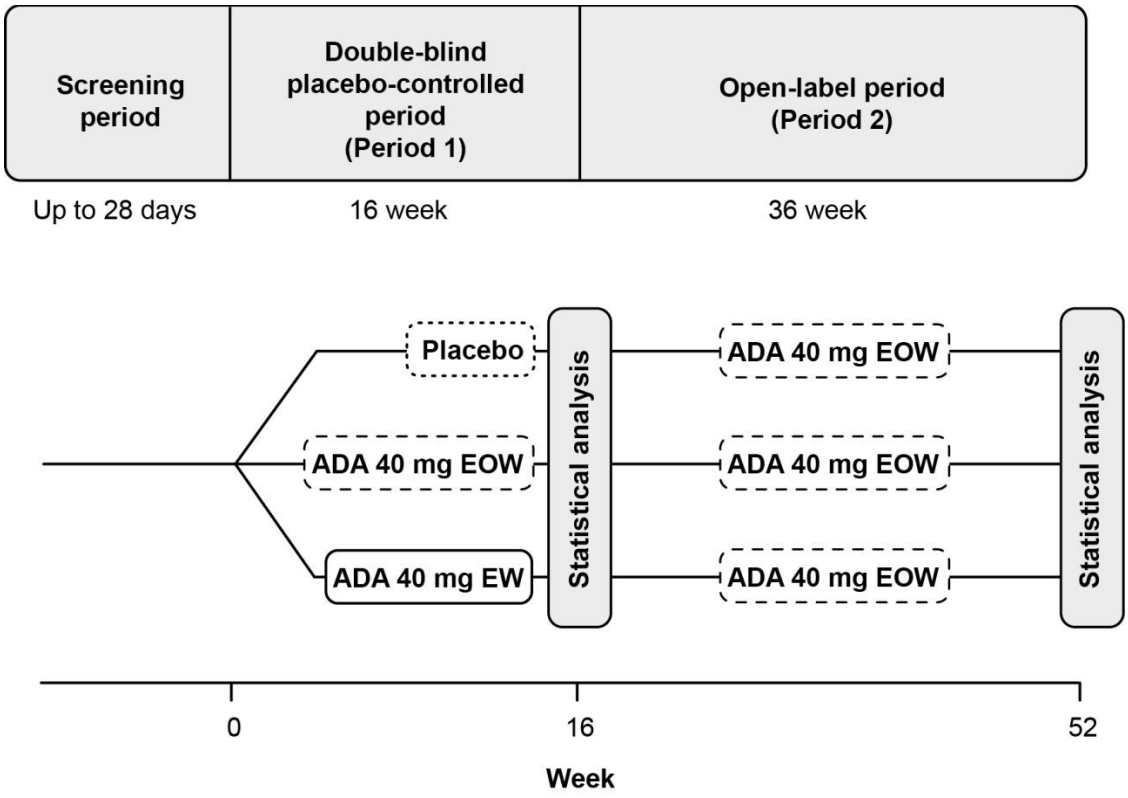
If, after at least 90 days of oral antibiotic therapy, any of the following had occurred, the patient was deemed to have experienced an inadequate response, or loss of response to oral antibiotics:

- Progression of Hurley Stage (i.e., the Hurley Stage of at least one affected anatomic region has progressed from I→II, II→III, or I→III).
- Requirement for at least 1 intervention (e.g., incision and drainage or intra-lesional injection of corticosteroid).
- Pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or paracetamol).
- Pain requiring opioids, including tramadol.
- Drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily)
- An increase in the number of anatomic regions affected by HS
- At least one new abscess or one new draining fistula (CS,[9] page 62).

Patients were ineligible if they had previously received treatment with adalimumab or any other anti-TNF agent or if they had received any systemic non-biologic therapy within 4 weeks of baseline. In Study M10-467, patients were allowed oral (tetracycline, doxycycline, or minocycline) or topical (clindamycin) antibiotic treatment for HS if they had received a stable dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study.

The trial design and patient flow is represented in the CS[9] (see Figure 1).

Figure 1: Design of study M10-467 (reproduced from CS,[9] page 58)



ADA - adalimumab; EW - every week; EOW - every other week

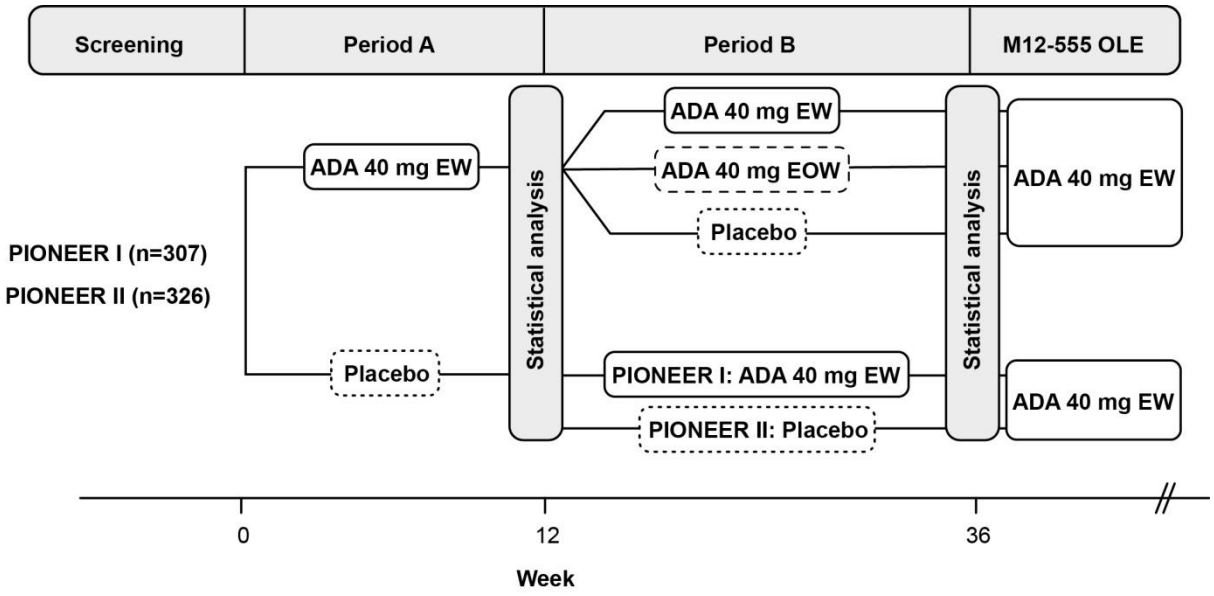
The M10-467 trial directly compared adalimumab in its licensed dose of 40mg EW with placebo in adults with moderate to severe HS. However, only the adalimumab 40mg EW and placebo data from Period 1 (baseline to week 16) are relevant to this efficacy appraisal because the EOW dose received by some participants in Period 1, and by all participants in Period 2, is not licensed for use in HS in the UK.

The PIONEER I and II trials recruited adults with moderate to severe HS, according to the HS-PGA score of moderate or worse, in at least two distinct anatomical areas, who were unresponsive or intolerant to oral antibiotics as assessed by the investigator, as defined above. Patients were ineligible if they had previously received treatment with adalimumab or any other anti-TNF agent or had received any systemic non-biologic therapy within 4 weeks of baseline, but were allowed oral (tetracycline, doxycycline, or minocycline) or topical (clindamycin) antibiotic treatment for HS if they had received a stable dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study.

In PIONEER I, doxycycline or minocycline were permitted as "rescue therapy" if required, and in PIONEER II these two antibiotics were permitted during the trial if participants had received a stable

dose for at least 4 weeks before the baseline visit and were willing to maintain stable dosing during the study (see CS,[9] page 62). The differing use of antibiotics in the two trials is attributed to the principal location of the trial centres: the US Food and Drug Administration (FDA) requested that no antibiotics be used in PIONEER I, whilst the EMA advised that patients should be able to continue on antibiotics in PIONEER II (see clarification response,[17] question A14). The ERG notes that it is unclear why patients who were "unresponsive or intolerant to oral antibiotics" might still receive these treatments as either a background or rescue therapy. The ERG submitted a clarification request on this point and was informed by the company that it depended on whether "the treating physician believed there was some benefit associated with this" (clarification response[17] question A15). The list of other permitted co-interventions for PIONEER trials included: antiseptic wash (chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater) to their HS affected body regions; injection with intralesional triamcinolone acetonide suspension, and; incision and drainage (see clarification response,[17] question A12). The trial design and patient flow is represented in Figure 2 (see CS[9] page 61).

Figure 2: Design of the PIONEER I and II trials (reproduced from CS,[9] page 61)



ADA - adalimumab; EW - every week; EOW - every other week

The PIONEER trials directly compared adalimumab in its licensed dose of 40mg EW with placebo in adults with moderate to severe HS in both Period A and Period B. The adalimumab 40mg EOW data from Period B are not relevant to this appraisal of efficacy because the EOW dose received by some participants in Period B is not licensed for use in HS in the UK.

A list of excluded studies, with reasons, was provided by the company (see CS,[9] Section 4.1 and Appendix 3).

The ERG noted that the three RCTs included in the main clinical efficacy review (CS, Sections 4.2-4.9) compared adalimumab with placebo, which was not a designated comparator in the final NICE scope,[8] which only listed "established clinical management without adalimumab." This was justified by the company, with the CS stating: *"Given that there is no standard of care for moderate to severe HS, placebo is an appropriate comparator for ADA 40 mg"* (see CS,[9] page 56). The ERG accepts that there is no published head-to-head RCT evidence comparing adalimumab with other biologics, steroids, retinoids or surgical intervention for HS, hence a comparison with placebo provides the best available, relevant trial evidence. Antibiotics were available as a possible background therapy in all arms of the PIONEER II trial, whilst incision and drainage of lesions was permitted as required in all three trials[18,19,25] and was reported as being performed in the M10-467 trial on 7%-10% of patients during the trial period.[25] However, it should be noted one of the company's clarification responses suggests the opposite, stating that, *"Surgery was not permitted in the PIONEER I and II studies per protocol"* (Clarification response,[17] question B5), whilst a second included incision and drainage in a list of permitted co-interventions (see clarification response,[17] question A12). The definition and role of surgery in the trials is therefore unclear.

The three trials collected data on several outcomes. The outcome measures for each trial and their relationship to the final NICE scope are summarised in Table 9. This information was compiled by the ERG, with supplementary details provided by the company in response to a request for clarification (see clarification response,[17] question A9).

Table 9: Final scope outcomes and trial outcome measures

NICE final scope outcomes	M10-467	PIONEER I	PIONEER II
Primary outcome			
Clinical response	HS-PGA, HiSCR*, MSS, AN counts/lesion counts	HiSCR, MSS, AN counts/lesion counts	HiSCR, MSS, AN counts/lesion counts
Secondary outcomes			
Disease severity	Hurley, MSS, AN counts/lesion counts, representative lesions	Hurley, MSS, AN counts/lesion counts, representative lesions	Hurley, MSS, AN counts/lesion counts, representative lesions
Inflammation and fibrosis	Hurley, HiSCR, AN counts/lesion counts, representative lesions, erythema lesions	Hurley, HiSCR, AN counts/lesion counts, representative lesions, erythema assessments	Hurley, HiSCR, AN counts/lesion counts, representative lesions, erythema assessments
Discomfort / pain	VAS	PGA- Skin Pain (NRS30)	PGA-Skin Pain (NRS30)
HRQoL	DLQI	DLQI, HSQOL, SF-36	DLQI, HSQOL, EQ-5D
Additional outcomes	WPAI-SHP	WPAI-SHP	WPAI-SHP
	PHQ-9	HADS	

**As a secondary outcome*

Details of the full list of outcomes are given below.

Primary outcomes

- HS-PGA[2,10]
- HiSCR: at least a 50% reduction in the total abscesses and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline[29]

Secondary outcomes

- MSS score: a clinical scoring system that assesses the number of involved anatomical regions, the number and type of lesions, the extent of involvement and the Hurley stage, was used to assess disease activity;
- Pain Visual Analogue Scale (VAS): Pain assessed using a questionnaire with a VAS ranging from 0 mm (no pain) to 100 mm (maximum pain);
- PGA-Skin Pain: Patient Global Assessment of Skin Pain (NRS30: Numeric Rating Scale 0-30);
- Dermatology Life Quality Index questionnaire (DLQI): a questionnaire which measures dermatology specific HRQoL and ranges from 0 to 30, with 0 being no impairment;
- HS Quality of Life (HSQOL);
- Short Form-36 (SF-36) Health Status Survey;

- Euroqol EQ-5D;
- Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) questionnaire (which ranges from 0 to 100, with 0 being no impairment);
- Patient Health Questionnaire-9 (PHQ-9): self-assessment for depression ranging from 0 to 27, with 0 being no depressive symptoms;
- Hospital Anxiety and Depression Scale (HADS).

The primary efficacy outcome in all three trials was clinical response. In the M10-467 trial, this was measured using the standard HS-PGA scale (see Table 10). Response was defined as achieving a HS-PGA score of clear, minimal or mild, with at least a 2 grade improvement relative to baseline, at week 16.

Table 10: HS-PGA scale[1,2] (reproduced in part from CS,[9] Table 8, page 59)

Rating	Description
Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules and 0 non-inflammatory nodules
Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules and presence of non-inflammatory nodules
Mild	0 abscesses, 0 draining fistulas, and 1–4 inflammatory nodules or 1 abscess or draining fistula and 0 inflammatory nodules
Moderate	0 abscesses, 0 draining fistulas, and $\geq$ 5 inflammatory nodules or 1 abscess or draining fistula and $\geq$ 1 inflammatory nodule or 2–5 abscesses or draining fistulas and <10 inflammatory nodules
Severe	2–5 abscesses or draining fistulas and $\geq$10 inflammatory nodules
Very severe	>5 abscesses or draining fistulas

In the PIONEER trials, clinical response was measured using the HiSCR measure. HiSCR is defined as at least a 50% reduction in the total abscesses and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline.[9] This measure was validated using data from the M10-467 but has only been used as a primary endpoint in the PIONEER trials and is untested in other published studies evaluating therapies for HS. The validation study found moderate to strong correlations between HiSCR and MSS, Hurley stage and HS-PGA.[29] Clinical advice received by the ERG suggests that the HiSCR measure is appropriate, but has some limitations: principally that clinical response alone is inadequate for decision-making and that clinically efficacious treatment must also take account of patient reported outcome measures relating to pain and HRQoL. A published clinical commentary also noted that the HiSCR did not achieve moderate levels of correlation (Spearman's rho >0.4) with measures of skin pain or quality of life as measured by the DLQI in the validation study, and that treatment effect must include a separate

assessment of pain and quality of life, as well as HiSCR.[33] The validation study[29] and the commentary[34] both acknowledge that the inter-rater reliability of the measure has not been demonstrated.

The ERG also notes that the CS[9] includes "partial response" as an efficacy outcome in Section 4.7.2.3, page 89; this is defined by the CS as a ≥25% reduction in the total abscesses and AN count with no increase in abscess count and no increase in draining fistula count relative to baseline. However, this was not a pre-specified response category in the PIONEER I/II trials, nor is it explained or justified in the CS, and its clinical validity as a response category has not been demonstrated. Rather, this represents a *post hoc* analysis; this was acknowledged as such in the company's clarification response[17] (question A10). The ERG notes that it is unclear whether a 25% reduction in AN count represents a clinically meaningful difference.

In terms of secondary outcomes, all three trials used the MSS to measure disease activity by scoring the number of involved anatomical regions, the number and type of lesions, the extent of involvement and the Hurley stage. However, clinical advice received by the ERG acknowledges that the application of the MSS is both complex and time consuming.

For pain and quality of life, the trials used a variety of patient-reported outcomes measures (PROMs). Study M10-467 used a standard VAS for pain, whilst the PIONEER I/II trials used the NRS30 specific skin pain tool. Quality of life was assessed across all three trials using the DLQI tool and, in the PIONEER trials, the condition-specific HSQOL tool was also used. In addition, PIONEER I also used the SF-36 and PIONEER II used the EQ-5D. The ERG asked the company to clarify why each PIONEER trial had not used one or both measures. The company responded that the decision was made to include only one instrument in each study, despite measuring different aspects of quality of life, because of the unacceptable patient burden involved in the large number of questions across both measures (see clarification response,[17] question A17). Whilst, the PIONEER trials used different quality of life instruments, the ERG considered the use of all of these measures to be appropriate. The trials also collected data on depression and productivity outcomes, but these were not listed in the final NICE scope and were therefore not considered relevant to this appraisal. Clinical advice received by the ERG also suggests that depression is multifactorial, therefore it is difficult to attribute any improvement in depression scores to changes in the severity of HS. It should also be noted that the CS inclusion criteria specified the HSSI and the HS-LASI score as outcomes (see CS,[9] page 47), neither of which were reported for any of the included trials, although clinical advice to the ERG suggests these are similar measures to the MSS score.

4.2.2 Results

Participants' baseline characteristics

The patients in each of the trials were generally similar in terms of age, gender and disease duration, and were similar between the PIONEER trials in terms of Hurley Stage (see Table 11). The M10-467 trial had a smaller proportion of patients with Hurley Stage III disease (29.4% in M10-467 vs 46.6% in PIONEER I and 46.3% in PIONEER II).

There were some notable differences in patient characteristics between the trials in terms of potential treatment effect modifiers, such as AN count and MSS score, especially between the PIONEER trials. PIONEER I participants appear to have had more severe disease based on these criteria. In the PIONEER trials there were higher proportions of participants with prior surgery in the adalimumab arms compared with the placebo arms (13.7% vs 8.4% in PIONEER I and 16.6% vs 11.0% in PIONEER II), which might be suggestive of more severe disease. PIONEER II included a higher proportion of smokers than the other trials. However, clinical advice received by the ERG suggested that the trial patients were broadly representative of the patients that are encountered in usual clinical practice.

Table 11: Participants' baseline characteristics in M10-467, PIONEER I and PIONEER II (reproduced from CS,[9] Table 11, pages 74-75)

Baseline characteristic	M10-467		PIONEER I			PIONEER II		
	Placebo (n=51)	ADA EW (n=51)	Placebo (n=154)	ADA EW (n=153)	Total (n=307)	Placebo (n=163)	ADA EW (n=163)	Total (n=326)
Female, n (%)	36 (70.6)	36 (70.6)	105 (68.2)	91 (59.5)	196 (63.8)	113 (69.3)	108 (66.3)	221 (67.8)
White, n (%)	37 (72.5)	37 (72.5)	118 (76.6)	116 (75.8)	234 (76.2)	130 (79.8)	143 (87.7)	273 (83.7)
Black, n (%)	8 (15.7)	9 (17.6)	29 (18.8)	33 (21.6)	62 (20.2)	20 (12.3)	9 (5.5)	29 (8.9)
Other	6 (11.7)	5 (9.8)	7 (4.5)	4 (2.6)	11 (3.6)	13 (7.9)	11 (6.7)	24 (7.3)
Age, years; mean [SD]	37.8 [12.1]	35.1 [10.7]	37.8 [11.33]	36.2 [10.83]	37.0 [11.10]	36.1 [12.18]	34.9 [9.96]	35.5 [11.13]
Hurley stage I, n (%)	36 (70.6)	36 (70.6)		-				
Hurley stage II, n (%)			81 (52.6)	80 (52.3)	161 (52.4)	89 (54.6)	86 (52.8)	175 (53.7)
Hurley stage III, n (%)	15 (29.4)	15 (29.4)	73 (47.4)	73 (47.7)	146 (46.6)	74 (45.5)	77 (47.2)	151 (46.3)
Disease duration, years; mean [SD]	13.4 [10.4]	11.3 [9.1]	11.6 [8.86]	11.3 [9.00]	11.5 [8.92]	11.8 [9.41]	11.3 [8.66]	11.5 [9.03]
AN count; mean [SD]			14.4 [14.80]	14.3 [11.92]	14.3 [13.42]	11.9 [11.02]	10.7 [8.10]	11.3 [9.68]
MSS; mean [SD]			147.3 [97.16]	151.0 [131.17]	149.1 [115.19]	122.6 [88.00]	107.5 [80.03]	115 [84.32]
NRS skin pain at worst; mean [SD]			(n=146) 4.8 [2.68]	(n=151) 5.1 [2.51]	(n=297) 5.0 [2.60]	(n=155) 4.8 [2.73]	(n=159) 4.3 [2.62]	(n=314) 4.5 [2.69]
BMI, kg/m^2; mean [SD]			(n=154) 34.5 [7.94]	(n=152) 33.0 [7.62]	(n=306) 33.8 [7.80]	32.9 [7.94]	31.3 [7.41]	32.1 [7.71]
Body weight, kg, mean [SD]	96.5 [24.8]	95.4 [22.9]						
Prior surgery for HS, n (%)			13 (8.4)	21 (13.7)	34 (11.1)	18 (11)	27 (16.6)	45 (13.8)
HS-CRP (C-reactive protein), mg/L; mean [SD]	13.3 [15.0]	21.5 [33.1]	17.4 [20.2]	20.3 [25]	18.9 [22.75]	18.3 [30.72]	13.3 [17.96]	15.8 [25.25]
Current smokers, n (%)	29 (56.9)	30.0 (58.8)	92 (59.7)	81 (52.9)	173 (56.4)	109 (67.3)	105 (64.4)	214 (65.8)

ADA - adalimumab; EW - every week; HS - hidradenitis suppurativa; BMI - body mass index; CRP - C-reactive protein; SD - standard deviation; MSS score - Modified Sartorius Severity score; NRS - numerical rating scale

Participant flow and numbers

The trials all experienced substantial loss of patients to follow-up (see Table 12). Clinical advice received by the ERG suggests that this is expected in trials of HS because patients who do not experience a response are unlikely to be motivated to continue on the trial. The loss to follow-up in the three trials was reported in the participant flow figures in the CS (pages 70-72), although the company had to provide, at the request of the ERG, the correct flowchart for the PIONEER II trial because this was erroneously a duplicate of the PIONEER I flowchart in the original submission (see clarification response,[17] question A24). Patient loss to follow-up in Period B was produced in part by protocol-driven discontinuation. This was based on either LOR, defined as a loss of 50% or more of the improvement gained during Period A among patients who achieved response according to HiSCR at week 12, or WOAI, defined as the second incidence of two consecutive visits with AN count higher than the baseline AN count in patients randomised to adalimumab 40mg EW in Period A who were week-12 HiSCR non-responders.[9]

Table 12: Patient loss to follow-up in trials in the adalimumab 40mg EW and placebo arms

Time endpoint (weeks)	**M10-467 n (%)**		**PIONEER I n (%)**		**PIONEER II n (%)**	
	ADA	PBO	ADA	PBO	ADA	PBO
Baseline total	51 (100)	51 (100)	153 (100)	154 (100)	163 (100)	163 (100)
12			145 (95)	145 (94)	155 (95)	151 (93)
16	45 (88)	46 (90)				
36			170 (55)*		116 (40)*	
52	31 (69)	34 (74)				

ADA - adalimumab; EW - every week; PBO – placebo
**Pooled numbers because of crossover between periods A and B*

According to the CS, clinical response data for the first period in each study (12 or 16 weeks) were analysed according to the intention-to-treat (ITT) principle, so that all patients randomised at week 0 were included (see CS,[9] pages 68 and 69). The primary approach for managing missing values was non-responder imputation (NRI). However, many of the results for the secondary endpoints, as presented in the CS, were based on LOCF imputation, which has particular implications for the results beyond weeks 12 or 16 as the level of attrition was more than 40% (see Table 12). Consequently, when this approach has been used, it was specified in CS and is also specified in this ERG report. In other instances, when the imputation approach has not been specified in the CS, it is assumed that NRI was used for binary outcomes.

4.2.2.1 Primary outcome: Clinical response

Results for the primary outcome for all three trials were reported in the CS. The M10-467 dosing study measured this outcome using both HS-PGA (see Table 13) and HiSCR, whilst PIONEER I and

II both used the HiSCR (Table 14). Response using the HS-PGA scale was defined as a HS-PGA score of clear, minimal or mild, with at least a 2-grade improvement relative to baseline.

The trials each had two separate periods of treatment. Period 1 (M10-467) and Period A (PIONEER I, II) evaluated whether adalimumab induces clinical response in patients with moderate or severe HS. The duration of this period was 16 weeks in Study M10-467, and 12 weeks in PIONEER I and II. M10-467 had a Period 2, for weeks 16-52, but this period only assessed the unlicensed 40mg EOW dose and so these data are not relevant to this appraisal. The PIONEER trials also included a Period B, covering weeks 12 to 36.

Weeks 12 and 16 (Period A in the PIONEER I/II trials and Period 1 in Study M10-467)

In Study M10-467, using the HS-PGA outcome measure, significantly more patients in the adalimumab 40mg EW group achieved clinical response compared with placebo at week 16 (17.6% vs 3.9%, $p<0.025$).

Table 13: Percentage of patients achieving clinical response measured by HS-PGA relative to baseline at 16 weeks (data reproduced from CS,[9] pages 76-77)

Trial	n	Follow-up (weeks)	Adalimumab EW	Placebo	Percentage difference relative to placebo (95% CI)	*p*-value
M10-467	102	16	17.6	3.9	13.7% (1.7 to 25.7)	<0.025

ADA - adalimumab; EW - every week

Across all three trials, the percentages of patients experiencing clinical response using HiSCR, defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline, are reported in Table 14. Across all three RCTs, the percentage of patients achieving clinical response according to the HiSCR measure at week 12 or week 16 was significantly higher for patients receiving adalimumab 40mg EW compared with placebo ($p<0.01$).

Table 14: Percentage of patients achieving clinical response by HiSCR relative to baseline at 12 or 16 weeks (data reproduced from CS,[9] pages 78-79, and Table 14, page 80)

Trial	n	Follow-up (weeks)	ADA EW	Placebo	Percentage difference relative to placebo (95% CI)	*p*-value
M10-467*	102	16	54.5	25.6	38.9 (NR)	<0.007
M10-467*	102	12	59.1	16.3	42.8 (NR)	<0.001
PIONEER I†	307	12	41.8	26.0	15.9 (5.3, 26.5)	0.003
PIONEER II†	326	12	58.9	27.6	31.5 (20.7, 42.2)	0.001

ADA - adalimumab; EW - every week; NR - not reported.
Note: the figures here are reproduced from the CS; the percentage differences in PIONEER I and II are inaccurate, and should be 15.8% and 31.3% respectively
**Secondary outcome; † ITT population (using NRI);*

The rate of absolute clinical response using the HiSCR was similar across the placebo arms of the three trials at 12 weeks (25.6%, 26% and 27.6% for M10-467, PIONEER I and PIONEER II, respectively). The rate of absolute clinical response using the HiSCR was numerically different across the adalimumab arms of the three trials at 12 weeks (42.8%, 15.9% and 31.5% for M10-467, PIONEER I and PIONEER II, respectively, see Table 15).

Table 15: Percentage of patients achieving clinical response measured by HiSCR relative to baseline at week 12 in PIONEER I and II† (reproduced from CS,[9] Table 14, page 80)

	Adalimumab EW	Placebo	Difference (95% CI)	p-value
PIONEER I	**64/153 (41.8%)**	**40/154 (26.0%)**	**15.9 (5,3, 26.5)**	**0.003**
Hurley stage II	37/83 (44.6%)	25/84 (29.8%)	14.8 (0.3, 29.3)	0.048
Hurley stage III	27/70 (38.6%)	15/70 (21.4%)	17.1 (22, 32.1)	0.027
PIONEER II	**96/163 (58.9%)**	**45/163 (27.6%)**	**31.5 (20.7, 42.2)**	**<0.001**
Antibiotic use	20/31 (64.5%)	7/32 (21.9%)	42.6 (17.8, 67.5)	<0.001
No antibiotic use	76/132 (57.6%)	38/131 (29.0%)	28.6 (16.9, 40.6)	<0.001
Hurley stage II	53/85 (62.4%)	32/87 (36.8%)	25.5 (10.5, 40.5)	< 0.001
-Antibiotic use	7/11 (63.6%)	3/12 (25.0%)	38.6 (1.1, 76.2)	0.004
-No antibiotic use	46/74 (62.2%)	29/75 (38.7%)	23.5 (7.9, 39.1)	<0.001
Hurley stage III	43/78 (55.1%)	13/76 (17.1%)	38.1 (22.8, 53.3)	<0.001
-Antibiotic use	13/20 (65.0%)	4/20 (20.0%)	45.0 (17.7, 72.3)	0.004
-No antibiotic use	30/58 (51.7%)	9/56 (16.1%)	35.7 (19.6, 51.7)	<0.001

ADA - adalimumab; EW - every week
† ITT population (using NRI)

Differences in the rate of absolute clinical response between the adalimumab groups across the PIONEER trials might be explained by potential treatment effect modifiers such as differences in patient characteristics at baseline: PIONEER II participants appear to have had less severe disease based on AN count (11.3 for PIONEER II vs 14.3 for PIONEER I) and MSS score (115 for PIONEER II vs 149.1 for PIONEER I, see Table 11), as well as a higher BMI and a higher draining

fistula count (see clarification response,[17] question A33). It might also be explained in part by study design differences between the two PIONEER trials: concomitant antibiotic use – permitted according to differences in the inclusion criteria between PIONEER I and II - was also substantially higher among responders in the adalimumab 40mg EW arm in PIONEER II compared with the placebo arm (64.5% vs 21.9%) with a higher percentage difference compared with placebo for those responders continuing to take antibiotics (42.6% vs 28.6%, see Table 15). The extent to which patients' baseline characteristics and co-interventions modify the treatment effect remains unclear and are the subject of further analyses by the company (see CS,[9] page 118).

Weeks 12-36 (Period B in the PIONEER trials)

The outcomes for clinical response in Period B in PIONEER I and II (Weeks 12-36), after re-randomisation, are reported below. Participants are categorised according to exposure to the licensed dose of adalimumab of 40mg EW (e.g. Period A and Period B exposure is categorised as EW/EW; Period A placebo, and Period B adalimumab exposure is categorised as PBO/EW). The data for the unlicensed adalimumab 40mg EOW dose are not reported here.

The results for clinical response in Period B are reported in the CS and in a poster presentation.[9] Numerical data on clinical response were not provided separately for the two trials (only graphs were provided, see CS,[9] page 89). An arm-based integrated summary, which breaks randomisation, was conducted for the two PIONEER trials to tabulate Period B response (HiSCR "full response" according to the definition of response used elsewhere) for, first, all patients and, second, for a subgroup of responders and "partial responders" from week 12 at the end of Period A. Separate numerical data were therefore not provided for the Period A week 12 responders: this group was combined with week 12 "partial responders". This "partial responder" group (defined as HiSCR responders with ≥25% rather than ≥50% AN reduction) represents a *post hoc* analysis group. This group was not defined in the trial protocols or published or unpublished descriptions of study design or pre-specified analysis methods for the PIONEER trials. It was also not considered in the published validation study for the HiSCR measure.[29] It was neither justified nor explained in the CS, but was confirmed by the company, in response to a request for clarification, as a trial outcome group defined *post hoc* in the PIONEER trials through analysis of response (see clarification response,[17] question A10). The categories of "response" and "partial response" are both included in the company's model; this is discussed in further detail in Section 5.3. Issues relating to the arm-based integrated summary are also discussed in Section 5.3.

Participants were stratified by response and Hurley Stage across the adalimumab 40mg EW and the placebo arms at week 12 re-randomisation for Period B. By week 36, the percentage of patients experiencing clinical response had reduced over time in both trial arms, but the reduction was greatest

in the placebo arm compared with the adalimumab 40mg EW arm (from 53% to 28% for placebo vs 53.5% to 43.4% for adalimumab, *p*-value not reported, see Table 16).

By week 36, the percentage of patients experiencing clinical response, who were categorised as responders or partial responders at week 12, reduced over time in both trial arms, but the reduction was greatest in the placebo arm compared with the adalimumab 40mg EW arm (from 72.6% to 30.1% for placebo vs 75.7% to 55.7% for adalimumab, *p*-value not reported, see Table 16).

Table 16: Proportion of patients in PIONEER I and II (amalgamated data) achieving HiSCR during Period B (reproduced from CS,[9] Table 20, page 90)

PIONEER I and II	Period B intervention	n	HiSCR rate at week 12 n (%)	HiSCR rate at week 24 n (%)	HiSCR rate at week 36 n (%)
All patients*	Placebo	100	53 (53%)	30 (30%)	28 (28%)
	ADA 40mg EW	99	53 (53.5%)	44 (44.4%)	43 (43.4%)
Week 12 responders and partial responders†	Placebo	73	53 (72.6%)	24 (32.9%)	22 (30.1%)
	ADA 40mg EW	70	53 (75.7%)	40 (57.1%)	39 (55.7%)

HiSCR – hidradenitis suppurativa complete response; ADA – adalimumab; EW – every week
**ITT analysis; †ITT_B_R (Period B Responders) analysis*

The CS states that the reduction in HiSCR rate over time in Period B might be explained by the study design, according to which any patient who experienced protocol-defined LOR, during Period B relative to week 12 at the end of Period A (which may have been explained by temporary exacerbation of disease), was discontinued from the study and imputed as a non-responder for this period. LOR was defined as a loss of 50% or more of the improvement gained during Period A among patients who achieved response according to HiSCR at week 12.

[redacted] However, data were not provided to support this statement. [redacted] Again, data were not provided by the company to support this statement.

4.2.2.2 Secondary outcomes

Results for the secondary outcomes for all three trials were reported in the CS[9] (pages 77-79 and pages 81-88). The trials had two separate periods of treatment, but secondary outcomes were only reported for the first period of each trial.

Weeks 12 and 16 (Period A in the PIONEER trials and Period 1 in M10-467)

Abscesses and inflammatory nodule counts

In Study M10-467, patients receiving adalimumab 40mg EW demonstrated a significant improvement in inflammatory nodules (p=0.019) and draining fistulae (p=0.05), but not in abscesses (p=0.22, see Table 17).

Table 17: M10-467: Improvement from baseline in individual symptoms in Period 1 (LOCF) (reproduced in part from CS,[9] Table 13, page 78)

M10-467	n	Follow-up (weeks)	Percentage difference ADA EW versus placebo (95% CI)	*p*-value
Inflammatory nodules	[redacted]102	16	37.0 (6.2 , 67.8)	0.019
Abscesses			26.8 (-16.0, 69.5)	0.22
Draining fistulae			36.9 (0.1, 73.7)	0.050

LOCF - last observation carried forward; ADA – adalimumab; EW – every week; CI – confidence interval
** per protocol analysis*

In PIONEER I, at week 12, there was no significant difference between placebo and adalimumab 40mg EW in the proportion of patients achieving an AN count of 0, 1, or 2, either in patients with Hurley Stage II at baseline or in all patients (see Table 18). In PIONEER II, there was a significant difference between placebo and adalimumab 40mg EW in the proportion of patients achieving an AN count of 0, 1, or 2 at week 12, both in patients with Hurley Stage II at baseline (p=0.01) and in all patients (p<0.001, see Table 18). It is not clear why separate data are presented on Hurley Stage II patients alone and there are no separate data on Hurley Stage III patients. It is also not specified in the CS whether these results are from observed or imputed data and, if the latter, whether the imputation was based on LOCF.

Table 18: Percentage of patients who achieved AN count of 0, 1, or 2 at week 12 in PIONEER I and PIONEER II (reproduced from CS,[9] Table 15, page 82)

Trial and patients	n	Follow-up (weeks)	ADA EW	Placebo	Percentage difference relative to placebo (95% CI)	*p*-value
[redacted]	167	12	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	307		[redacted]	[redacted]	[redacted]	[redacted]
PIONEER II (Hurley II only)	172		44/85 (51.8%)	28/87 (32.2%)	19.6 (4.7, 34.2)	0.01
[redacted]	325		[redacted]	[redacted]	[redacted]	[redacted]

ADA – adalimumab; EW – every week; CI – confidence interval

Modified Sartorius Severity Score (MSS score)

Adalimumab 40mg EW was only associated with a statistically significant improvement in MSS score compared with placebo at week 12 in the PIONEER II trial ($p<0.001$). The change from baseline was not significantly different between the adalimumab and placebo groups in the M10-467[25] or PIONEER I trials (see Table 19). It has been argued that this might be because the MSS score includes elements that are not expected to change with adalimumab therapy, such as the number of fistulas.[25]

Table 19: Improvement from baseline in MSS score at weeks 12 and 16 (LOCF) (reproduced in part from CS,[9] Table 13, page 78, and Figure 14, page 84)

Trial	n	Follow-up (weeks)	ADA EW	Placebo	Percentage difference relative to placebo (95% CI)	*p*-value
Change from baseline: mean (±SE)						
M10-467*	102	16	-40.2 (9.8)	17.2 (9.8)	-22.0 (-50.1, 4.2)	0.097
PIONEER I	304	12	24.4	15.7	8.7 (NR)	NS
PIONEER II	325	12	28.9	9.5	19.4 (NR)	<0.001

LOCF - last observation carried forward; NR - not reported; NS - not significant; ADA – adalimumab; EW – every week; CI – confidence interval; SE – standard error
**Data from Kimball 2012 (not the CS)*

Pain

The PIONEER trials used the Patient's Global Assessment of Skin Pain (NRS30) score. The Patient's Global Assessment of Skin Pain is a numerical rating scale ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). The PIONEER trials measured the mean change in skin pain in all patients and in those with a baseline of NRS≥3. In both PIONEER trials, it was reported that patients with a baseline of NRS≥3 taking adalimumab 40mg EW had statistically significant improvements in

this pain score compared with such patients taking placebo (p=0.016 for PIONEER I, and p<0.001 for PIONEER II, see Table 20).

Table 20: Mean change in NRS30 skin pain relative to baseline at Week 12 in patients with baseline of NRS ≥ 3 (LOCF) (reproduced from CS,[9] Table 18, page 87)

Trial	Within group change (LS mean ± SE)		Between group change	*p*-value
	Placebo	ADA EW	LS mean difference (95% CI)	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LOCF - last observation carried forward; LS - least squares ADA – adalimumab; EW – every week; CI – confidence interval; SE – standard error

Data reported in the CS enabled an assessment as to whether these improvements in pain were clinically meaningful. The M10-467 trial used a VAS measure. According to this measure, a clinically relevant response requires at least a 30% reduction and 10mm reduction in pain relative to baseline (see CS,[9] page 78). A statistically significant percentage of patients achieved a clinically relevant reduction in pain at week 16 (47.9% on adalimumab versus 27.1% on placebo, p=0.037). According to the Patient's Global Assessment of Skin Pain (NRS30), as used in the PIONEER trials, a clinically meaningful response requires at least a 30% reduction and at least a 1 unit reduction from baseline pain score among patients with baseline NRS≥3 (see CS,[9] page 82). In PIONEER I, there was a non-significant numerical improvement in pain using this measure in Period A. However, there was a statistically significant difference at earlier timepoints (see Table 21). In PIONEER II, there was a statistically significant difference in the percentage of patients achieving the clinically relevant endpoint at all timepoints up to and including week 12. It is not specified in the CS whether these results are from observed or imputed data and, if the latter, whether the imputation was based on LOCF (see CS,[9] pages 78 and 82).

Table 21: Percentages of all patients with clinically relevant improvement in pain relative to baseline at weeks 12 and 16 (reproduced from CS,[9] Table 13, page 78, and Figure 13, page 83)

Trial	n	Follow-up (weeks)	Adalimumab EW	Placebo	*p*-value relative to placebo
VAS					
M10-467	103	16	47.9	27.1	0.037
NRS30					
PIONEER I†	231	12	27.9	24.8	NS
PIONEER II†	216	12	45.7	20.7	<0.001

ADA – adalimumab; EW – every week; VAS – visual analogue scale; NRS – numerical rating scale; NS – not significant
† ITT population; NS: Not significant

Quality of life

Several measures were used across the three trials, but the principal recognised measure is the DLQI. DLQI scores range from 0 to 30, with higher scores indicating a more impaired quality of life (see Table 22). Across all three RCTs, adalimumab 40mg EW was associated with a statistically significant improvement in DLQI compared with placebo at week 12 and week 16 (p<0.001).

Table 22: Quality of Life measured by DLQI scores relative to baseline in Weeks 12 and 16 (LOCF) (reproduced from CS,[9] Table 13, page 78, and Table 17, page 86)

Trial	Within group change (LS mean ± SE)		Between group change	*p*-value
	ADA EW	Placebo	LS mean difference (95% CI)	
M10-467	-6.0 ± 0.9	-1.9 ± 0.9	-4.2 (-6.6, 1.8*)	<0.001
PIONEER I	-5.4 ± 0.5	-2.9 ± 0.5	-2.5 (-3.0,-1.8)	<0.001
PIONEER II	-5.1 ± 0.53	-2.3 ± 0.53	-2.8 (-4.1,-1.5)	<0.001

LOCF - last observation carried forward; ADA - adalimumab; EW - every week; LS - least squares; SE – standard error; CI – confidence interval
**This figure from CS, Table 13, page 78*

The CS states that, in all trials, the within arm mean change from baseline in DLQI at week 12 (Period A) or week 16 (Period 1) for patients in the adalimumab 40mg EW group exceeded the minimum clinically important difference (MCID) of 5 (see CS,[9] page 86). It also exceeded the MCID of 4 established by Basra *et al* 2015.[34] However, the ERG notes that the between arm mean change from baseline for the adalimumab arm compared with the placebo arm did not meet this MCID threshold in either PIONEER I or II. In PIONEER I, the CS states that the percentage of patients with a clinically relevant change in DLQI at week 12 was [redacted] in the adalimumab 40mg EW group compared with [redacted] in the placebo group [redacted] and 49% versus 34% (p=0.011) in PIONEER II.

The condition-specific HSQOL scale was also used. Clinical advice received by the ERG suggests that this is a new measure which has not been published. Ratings range from 0 (worst possible) to 10 (best possible). In PIONEER I and PIONEER II, patients receiving adalimumab 40mg EW had significantly improved HSQOL scores compared with placebo patients [redacted] (see Table 23).

[redacted]Table 23: Quality of life measured by HSQOL scores relative to baseline at week 12 (LOCF) (reproduced from CS,[9] Table 17, page 86)

Trial	Within group change (LS mean ± SE)		Between group change	*p*-value
	Placebo	ADA EW	LS mean difference (95% CI)	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LOCF - last observation carried forward; ADA - adalimumab; EW - every week; LS - least squares; SE – standard error; CI – confidence interval

For the HSQOL, the MCID is defined as an increase in HSQOL of 50% or greater than the standard deviation of HSQOL for all patients at baseline (see CS,[9] page 86). The CS states that, in PIONEER I, numerically more patients in the adalimumab 40mg EW arm than the placebo arm achieved the MCID [redacted] however this was not statistically significant (*p*-value and 95% CIs were not reported in the submission). In PIONEER II, the difference was statistically significant [redacted]

PIONEER I assessed overall quality of life using the SF-36, and demonstrated a significant benefit in the overall physical component with adalimumab 40mg EW compared with placebo ($p<0.05$, see Table 24). The CS states that significantly more patients receiving adalimumab 40mg EW achieved a MCID in SF-36 than patients receiving placebo: [redacted] respectively [redacted] In terms of specific components, patients on adalimumab 40mg EW reported clinically relevant statistically significant improvements in general health compared with placebo, and significant but not clinically meaningful improvements in physical functioning compared with placebo, but reported no significant difference compared with placebo in physical functioning or bodily pain (Table 24). It should be noted that 95% confidence intervals were not reported in the CS. The differences in the mental component of the SF-36 were also not significantly different between the two groups (actual data were not reported in the submission). It was not stated in the CS whether these results were based on LOCF, as the other quality of life results, or data as observed.

[redacted]Table 24: PIONEER I: Change in SF-36 physical component score relative to baseline at week 12 (reproduced from CS,[9] Figure 15, page 85)

SF-36	n	Follow-up (weeks)	Placebo	ADA EW	MCID	*p*-value
Physical component summary	325	12	1.5	4.2	>2.5	<0.05
Physical functioning			1.6	3.2	>2.5	NS
Role physical			2.2	4.5	>2.5	<0.05
Bodily pain			2.4	4.9	>5	NS
General health			-0.4	3	>2.5	<0.001

SF-36 – Short Form 36; ADA - adalimumab; EW - every week; MCID - minimum clinically important difference

PIONEER II assessed overall quality of life using the EQ-5D (using both the health state questionnaire and the VAS). There was a baseline difference in the mean EQ-5D health state scores between the adalimumab and placebo arms (0.6 [SE=0.33] and 0.5 [SE=0.36] respectively), but an apparent significant benefit in both health state and VAS for adalimumab 40mg EW compared with placebo ($p<0.001$, see Table 25).

Table 25: PIONEER II: Mean change from baseline in EQ-5D at week 12 (LOCF) (reproduced in part from CS,[9] Table 16, page 84)

Instrument	Within group change (LS mean ± SE)		Between group change	*p*-value
	Placebo	ADA EW	LS mean difference (95% CI)	
Health state	0 ± 0.02	0.1 ± 0.02	[redacted]	<0.001
VAS	0.5 ± 1.87	9.2 ± 1.88	[redacted]	<0.001

ADA - adalimumab; EW - every week; VAS – visual analogue scale; LOCF - last observation carried forward; LS - least squares

Weeks 12-36 (Period B in the PIONEER trials)

A small number of secondary outcomes were reported for PIONEER I and II only for participants who had achieved a clinical response at week 12 (see Table 26). By week 36 of Period B, there were higher percentages of responders with an AN count of 0, 1 or 2 and a clinically relevant NRS30 score in the adalimumab group compared with the placebo group, and improved MSS scores in the adalimumab group compared with the placebo group. However, it should be noted that some of these differences were not large and the results were based on some very small numbers of patients (range of 15 to 22 patients across all outcomes for both PIONEER trials).

Table 26: PIONEER I and PIONEER II secondary outcomes at week 36 relative to week 12 (reproduced from CS,[9] Table 21, page 91)

Outcome	PIONEER I		PIONEER II	
	EW/EW (n=21)	EW/placebo (n=22)	EW/EW (n=20)	EW/placebo (n=20)
AN count of 0/1/2	9 (42.9%)	5 (22.7%)	10 (32.3%)	9 (29%)
NRS30*	(n=16) 5 (31.3%)	(n=15) 1 (6.7%)	(n=19) 3 (15.8%)	(n=20) 1 (5%)
MSS (LS change from baseline ± SE)	-47.7 ± 9.99	-41.9 ± 9.76	-37.1 ± 11.8	-33.8 ± 13.19

EW – every week; NRS – numerical rating score; MSS – Modified Sartorius Score; SE – standard error; LS – least squares; AN - abscess and inflammatory nodule

** Proportion of patients who achieved at least 30% reduction and at least 1 unit reduction from baseline in Patient's Global Assessment of Skin Pain (NRS30) – at worst at week 12 among patients with baseline NRS ≥ 3*

The CS does not specify whether these results are from observed or imputed data and, if the latter, whether the imputation method was appropriate to generate unbiased estimates of treatment effect or whether sensitivity analyses were used to assess the robustness of the results (see CS,[9] page 91). It is only noted that this was an ITT analysis conducted on Period B data for responders (ITT_B_R).

Other measures

The CS also reports results for depression, treatment satisfaction and WPAI; these data are not reported here as they were not included in the final NICE scope.[8]

Pre-specified subgroups

Pre-planned analyses in the three studies are shown in Table 27. The variables considered within these analyses were chosen to assess the consistency of the primary efficacy endpoint by demographic and baseline characteristics.

The CS concludes that the distribution of patients within each subgroup was similar across treatments, with the exception of baseline AN count (≤ 5, 6-10, 11+) which was significantly different in PIONEER I between the adalimumab 40mg EW and placebo arms: more patients were in the <5 and >11 bands in the placebo group than in the adalimumab 40mg EW group (p=0.018). However, there was no significant difference between treatments in AN count by median (see CS,[9] page 95). The CS found that AN count by median was a treatment effect modifier using an interaction test. However, the ERG notes that AN count by median is data-dependent and is not based on clinical relevance; consequently, this finding may have occurred by chance. Nevertheless, the CS highlights that baseline balance does not mean that a variable is not prognostic of outcome nor a modifier of treatment effect. Similarly, an imbalance in a baseline characteristic does not mean that it affects outcome or treatment effect. Ideally, relevant covariates should be pre-specified.

Table 27: Primary endpoint analysis subgroups in MI0-467, PIONEER I and PIONEER II (reproduced from CS,[9] Table 22, page 93)

Subgroup	M10-467	PIONEER I	PIONEER II
Baseline concomitant use of oral antibiotics (yes/no)	✓		✓
Age group (< 40; 40-64; ≥ 65, if less than 10% of patients were in the ≥ 65 group, that group was combined with the 40-64 group)		✓	✓
Sex (male, female)		✓	✓
Race (white, non-white)		✓	✓
Duration of HS (by median)		✓	✓
Weight (by median)		✓	✓
BMI category: normal (< 25), overweight (25 – < 30), obese (30 – < 40), morbid obesity(≥ 40)		✓	✓
BMI (by median)	✓		
Current smoking status (Y/N)	✓	✓	✓
Baseline hs-CRP level (by median)		✓	✓
Baseline AN count (≤ 5, 6-10, 11+)	✓	✓	✓
Baseline AN count (< median, ≥ median)		✓	✓
Hurley stage (I or II, III)	✓		
Prior HS surgery history (yes, no)		✓	✓
Smoking habit change (increase, decrease)*.		✓	✓
Time from prior HS surgery to the first dose of study drug (by median)		✓	✓

HS – hidradenitis suppurativa; BMI – body mass index; AN - abscess and inflammatory nodule; CRP – C-reactive protein
**Increase in smoking habit was defined as an at least 25% increase from baseline in both the urine cotinine and the urine nicotine level. Decrease in smoking habit was defined as patients with at least 25% decrease from baseline in both the urine cotinine and the urine nicotine level. A change from ND (not detectable) to detectable (< 2 ng/ml or any value ≥ 2 mg/ml) was considered as an increase in smoking habit; and a change from detectable to not detectable was considered as a decrease in smoking habit. Note: This is a reproduction of CS, Table 22, page 93.*

The CS states that response according to the HiSCR criteria was generally not affected by baseline characteristics (patients were stratified by response and Hurley Stage when re-randomised at week 12), but notes also that, [redacted] (see CS,[9] page 97). [redacted]

[redacted]

Post hoc subgroups

A *post hoc* analysis of subgroups based on clinical response measured by the HS-PGA tool was conducted for the M10-467 trial (see Table 28). This analysis found that larger proportions of patients in the adalimumab group, compared with placebo, achieved clinical response in the following subgroups: those with more mild disease (based on Hurley stage) compared with those with more severe disease; those who were current smokers; those who were taking concomitant antibiotics, and; those who had a BMI greater than or equal to the median. The CS notes that these results should be treated with caution because some of the subgroups contained few people (see CS,[9] page 94).

Table 28: M10-467 clinical response at week 16 (proportion of patients achieving HS-PGA of clear minimal or mild with at least a 2-grade improvement relative to baseline at week 16) (reproduced from CS,[9] Table 23, page 95)

Variable	Adalimumab EW (n=51)	Placebo (n=51)	Difference (95% CI) EW vs. placebo
Hurley Stage			
I or II, n/N (%)	8/36 (22.2%)	2/36 (5.6%)	16.7 (1.2, 32.2)
III, n/N (%)	1/15 (6.7%)	0/15 (0)	6.7 (-6.0,19.3)
Current smokers			
Yes, n/N (%)	7/30 (23.3%)	1/29 (3.4%)	18.4 (0.7, 36.1)
No, n/N (%)	2/21 (9.5%)	1/22 (4.5%)	7.2 (-8.8, 23.1)
Received concomitant oral antibiotics for HS			
Yes, n/N (%)	4/9 (44.4%)	0/4 (0)	39.4 (-2.2, 81.0)
No, n/N (%)	5/42 (11.9%)	2/47 (4.3%)	8.0 (-3.1, 19.1)
BMI			
>median, n/N (%)	5/22 (22.7%)	0/25 (0)	26.2 (8.5, 44.0)
<median, n/N (%)	4/29 (13.8%)	2/26 (7.7%)	5.4 (-11.5, 22.4)
CRP level			
>median, n/N (%)	3/18 (16.7%)	1/21 (4.8%)	13.1 (-5.6, 31.8)
<median, n/N (%)	4/20 (20.0%)	1/18 (5.6%)	14.3 (-8.0, 36.6)

ADA - adalimumab; EW - every week; BMI - body mass index; CRP - C-reactive protein

4.2.3 Review of clinical efficacy (non-randomised and non-controlled evidence)

The CS presents findings from a single ongoing, non-randomised, non-controlled, open-label, unpublished study: M12-555 OLE.[20] The ERG notes that the company did not perform a systematic review of the non-randomised and non-controlled evidence. The inclusion criteria for this review were not specified, the methods by which this study was identified, and the criteria by which it was selected, and any others excluded, are not reported. The only searches reported for the clinical effectiveness section of the CS contain an RCT filter (see CS,[9] Appendix 2). Furthermore, no information was given about the data extraction process, as required by standard systematic review guidelines.

The M12-555 OLE study is a continuation study for patients enrolled in PIONEER I and PIONEER II in which all participants receive adalimumab 40mg EW. The aim of the study was to generate longer-term safety, tolerability and efficacy data on adalimumab 40mg EW in patients with moderate or severe HS. The CS justifies the inclusion of this study on the basis that it provided long-term data (see CS,[9] page 100).

Approximately 600 patients from PIONEER I and PIONEER II were eligible to enrol in M12-555 OLE, of which 497 were enrolled. Patients were evaluated for entry into the OLE at the final study visit of the PIONEER trial in which they participated. Starting at baseline, all patients received open-label adalimumab 40mg EW, regardless of treatment assignment in the PIONEER I and II studies. The dose could be reduced to adalimumab 40mg EOW at any time on or after week 24 of the OLE if patients achieved clinical response according to HiSCR criteria during M12-555 OLE, relative to the baseline at week 12 of the initial PIONEER trials, and achieved an AN count of 0 or 1 on at least two consecutive study visits, and the clinician and patient decided that the risk/benefit of reducing the dose of adalimumab was favourable. This reduced dose is currently not licensed for use in patients with moderate or severe HS in the UK.[12] The dose could be increased back up to adalimumab 40mg EW if required by the clinician or patient, although the dose could only be increased once. Study visits occurred at baseline, week 4, week 8, week 12, week 18, week 24, week 36 and every 12 weeks thereafter, at least to week 60. If after week 24, there was no clinically relevant response, then the clinician and the patient explored the risk/benefit of remaining on treatment.

The following concomitant drugs were not allowed: use of oral antibiotics for HS within 28 days of baseline (except those used in prior PIONEER studies), use of prescription topical therapies for HS within 14 days of baseline, use of systemic non-biologic therapies for HS <28 days before baseline,

use of oral concomitant analgesia (including opioids) for HS-related pain within 14 days of baseline or received any other investigational drug for HS within 30 days or five half-lives of baseline.

Patients who prematurely discontinued from the trial, or who completed the trial and did not initiate adalimumab therapy outside the context of the clinical trial, had study visits 4 and 8 weeks after the last administration of study drug to collect blood samples for the measurement of serum adalimumab concentrations and anti-adalimumab antibody.

The results presented in the CS are from an interim data cut, as of 29 April 2014, for 497 patients who received at least one dose of the study drug. The study is ongoing and there were missing data for a total of 368 subjects (74.0%) at the data cut. In other words, only data on 129 (26%) of enrolled patients are reported.

Efficacy results

In terms of efficacy, the primary outcome was the proportion of subjects achieving HiSCR. The unpublished results for those participants who received adalimumab in at least one period (A or B, or A and B) in PIONEER I and II, and who continued into the OLE, are presented in Table 29. The CS reported that [redacted] The numbers listed in Table 29 are the baseline number of patients in each of the groups providing some data on "continuous" exposure to adalimumab 40mg EW, however [redacted] Consequently, these data have been imputed using LOCF, which might overestimate the true level of HiSCR for these later timepoints. Details of the results for secondary outcomes such as MSS and NRS30 were not reported (see CS,[9] page 106).

Table 29: Proportion of patients achieving HiSCR over time from the first dose of adalimumab (LOCF) (reproduced from CS,[9] Table 28, page 106)

Weeks of adalimumab treatment (relative to the first dose in the PIONEER studies)	EW/EW/EW (n=84)	EW/EOW/EW (n=90)	EW/PBO/EW (n=91)
[redacted]	[redacted]	[redacted]	[redacted]

ADA - adalimumab; EW - every week; EOW - every other week; LOCF - last observation carried forward

Summary

The CS states that the OLE study was of "a good standard" following appraisal using a quality assessment tool (see CS,[9] page 105). However, the source of the tool used was not given within the CS, and its selection was not justified, although this was addressed in a clarification from the company (see clarification response,[17] question A22). The ERG conducted a separate appraisal using the CASP tool[28] – a recognised critical appraisal tool for single-arm, cohort studies such as this. The ERG's critical appraisal identified the following issues: the study was not blinded so there is potential for detection bias; regression analyses have not yet been conducted to control for potentially confounding variables, and; sensitivity analyses have not been performed to assess the robustness of the results to different methods for accounting for the large amount of missing data.

The ERG therefore considers the efficacy results in the follow-up phase to be subject to a high degree of uncertainty because they are the result of interim analyses of unpublished study data from a single-arm, non-controlled, un-blinded study with the risk of bias inherent to that design, as well as other methodological issues such as the methods used to account for missing data. The study also only potentially offers efficacy data for up to 72 weeks for a drug that might be taken for many years by patients with moderate to severe HS.

4.2.4 Review of safety (randomised and non-randomised trial evidence)

The submitted review of the safety evidence for adalimumab was extensive; all key AEs are included and particular events are addressed in detail. This review of the safety evidence from the RCTs included the same studies as the main efficacy reviews, thus the ERG has assumed that the description of the inclusion criteria and methods employed for the adalimumab RCT efficacy review also applied to the identification and extraction of the safety data (see CS,[9] Section 4.1.1-4.1.5, pages 46-48).

M10-467, PIONEER I and II (Weeks 12 and 16)

There were no deaths during the studies in any patients who received adalimumab. The rates of AEs leading to discontinuation, any AE, SAEs, and any infectious AEs were all higher in the adalimumab 40mg EW arm in the M10-467 trial than the placebo arm as well as the adalimumab arms in the PIONEER trials. The CS (page 107) states that most of the excess AEs in the adalimumab arms were attributable to headache, which was typically described as being mild or moderate in severity; that the majority of AEs were grade 1 or 2 or similar across all treatment groups, and that AEs were consistent with those seen with adalimumab in previous studies in other indications (see Tables 30 and 31).

However, across the PIONEER trials, the rates of these categories of AE were generally either comparable between the adalimumab and placebo arms, or the rates were actually lower in the adalimumab treatment arms compared with the placebo arms. For example, for the outcome of any AEs, in PIONEER I, the rate was 52.9% for adalimumab 40mg EW versus 61.8% for placebo, whilst in PIONEER II, the rate was 57.7% for adalimumab 40mg EW versus 66.9% for placebo. The ERG suggests that this is because exacerbations of HS were questionably classified as an AE, when such exacerbations might equally reflect the absence or failure of treatment to control HS: rates of exacerbations were higher in the placebo group, leading to higher AE rates in that group. This is supported by the data on specific AEs, which list the most common AEs across the three trials as exacerbation of HS, nasopharyngitis and headache. AEs which occurred in >5% of patients are shown in Table 30.

For the first 12-week period, therefore, the pattern of AEs was generally consistent throughout the three studies and similar tolerability was reported for both PIONEER trials. With the exception of some higher rates in the M10-467 trial, the AEs for the groups treated with adalimumab 40mg EW were comparable with placebo and were reported as being consistent with the known adalimumab safety profile.

Table 30: Key AE rates in in M10-467, PIONEER I and PIONEER II (weeks 16 and 12) (reproduced from CS,[9] Table 29, page 108)

AE, n(%)	M10-467			PIONEER I			PIONEER II		
	ADA EW (n=51)	Placebo (n=51)	Difference EW versus placebo Relative risk (95% CI)	ADA EW (n=153)	Placebo (n=152)	Difference EW versus placebo Relative risk (95% CI)	ADA EW (n=163)	Placebo (n=163)	Difference EW versus placebo Relative risk (95% CI)
Death	0	0		0	0		0	0	
Any AE leading to discontinuation of study drug	2 (3.9%)	0		1 (0.7%)	3 (2%)	0.33 (0.03, 3.15)	4 (2.5%)	7 (4.3%)	0.57 (0.17, 1.91)
Any AE	36 (70.6%)	30 (58.8%)	1.2 (0.9, 1.6)	81 (52.9%)	94 (61.8%)	0.86 (0.7, 1.04)	94 (57.7%)	109 (66.9%)	0.86 (0.73, 1.02)
SAE	4 (7.8%)	2 (3.9%)	2 (0.38. 10.44)	3 (2%)	5 (3.3%)	0.6 (0.14, 2.45)	3 (1.8%)	6 (3.7%)	0.5 (0.13, 1.97)
Any infectious AE	17 (33.3%)	18 (35.3%)	0.94 (0.55, 1.62)	38 (24.8%)	43 (28.3%)	0.88 (0.6, 1.28)	41 (25.2%)	53 (32.5%)	0.77 (0.55, 1.09)
Infectious SAE	1 (2.0%)	0		1 (0.7%)	0		1 (0.6%)	2 (1.2%)	0.5 (0.005, 5.46)
Cancer	0	0		0	1 (0.7%)		0	0	

ADA – adalimumab; EW – every week; AE – adverse event; SAE – serious adverse event; CI – confidence interval

Table 31: Specific AEs occurring in >5% of patients in M10-467, PIONEER I and PIONEER II (weeks 16 and 12) (reproduced from CS,[9] Table 30, page 109 and Table 34, page 114)

AE	M10-467			PIONEER I			PIONEER II		
	ADA EW (n=51)	Placebo (n=51)	Difference EW versus placebo Relative risk (95% CI)	ADA EW (n=153)	Placebo (n=152)	Difference EW versus placebo Relative risk (95% CI)	ADA EW (n=163)	Placebo (n=163)	Difference EW versus placebo Relative risk (95% CI)
Exacerbation of HS	4 (7.8%)	6 (11.8%)	0.67 (0.2, 2.22.)	14 (9.2%)	20 (13.2%)	0.7 (0.36, 1.33)	7 (4.3%)	21 (12.9%)	0.33 (0.15, 0.76)
Nasopharyngitis	6 (11.8%)	6 (11.8%)	1 (0.35, 2.89)	9 (5.9%)	16 (10.5%)	0.56 (0.25, 1.23)	9 (5.5%)	10 (6.1%)	0.9 (0.38, 2.16)
Headache	8 (15.7%)	2 (3.9%)	4 (0.89, 17.93)	14 (9.2%)	15 (9.9%)	0.93 (0.46, 1.86)	21 (12.9%)	21 (12.9%)	1 (0.57, 1.76)
Upper respiratory tract infection	4 (7.8%)	2 (3.9%)	2 (0.38,10.44)				8 (4.9%)	9 (5.5%)	0.89 (0.35, 2.25)
Diarrhoea	0	2 (3.9%)					9 (5.5%)	4 (2.5%)	2.25 (0.71, 7.16)

ADA – adalimumab; EW – every week; HS – hidradenitis suppurativa; CI – confidence interval

Other specific AEs occurring in >5% of patients in the M10-467 trial are listed in Table 32.

Table 32: AEs occurring in >5% of patients in study M10-467 (week 16) (reproduced from CS,[9] Table 30, page 109)

AE	ADA EW (n=51)	Placebo (n=51)	Difference EW versus placebo Relative risk (95% CI)
Arthralgia	3 (5.9%)	1 (2.0%)	3 (0.2, 27.89)
Back pain	1 (2.0%)	1 (2.0%)	1 (0.06, 15.56)
Cellulitis	0	1 (2.0%)	
Cough	3 (5.9%)	0	
Fatigue	2 (3.9%)	2 (3.9%)	1 (0.15, 6.83)
Folliculitis	0	3 (5.9%)	
Gastroenteritis	0	0	
Gastroesophageal reflux disease	3 (5.9%)	0	
Influenza	2 (3.9%)	0	
Nausea	4 (7.8%)	1 (2.0%)	4 (0.46, 35.57)
Oropharyngeal pain	1 (2.0%)	1 (2.0%)	1 (0.06, 15.56)
Pruritus	1 (2.0%)	0	
Sinusitis	2 (3.9%)	1 (2.0%)	2 (0.19, 21.37)
Vomiting	1 (2.0%)	3 (5.9%)	0.33 (0.04, 3.10)

ADA – adalimumab; EW – every week; CI – confidence interval

PIONEER 1 and II (Weeks 12-36)

AE rates were similar for weeks 12-36 (Period B) to those seen at week 12 (Period A) (see Table 33 and Table 34).

[redacted]

Table 33: AEs in PIONEER I and PIONEER II during Period B[34, 35](reproduced from CS,[9] Table 33, page 113)

AE	PIONEER I				PIONEER II			
	Placebo/EW (n=145)	EW/placebo (n=49)	EW/EOW (n=48)	EW/EW (n=48)	Placebo/placebo (n=151)	EW/placebo (n=51)	EW/EOW (n=53)	EW/EW (n=51)
[redacted]								

EW – every week; EOW – every other week; AE – adverse event; SAE – serious adverse event

Table 34: AEs occurring in >5% of patients PIONEER I and PIONEER II during Period B (reproduced from CS,[9] Table 34, page 113)

AE	PIONEER I				PIONEER II			
	Placebo/EW (n=145)	EW/placebo (n=49)	EW/EOW (n=48)	EW/EW (n=48)	Placebo/placebo (n=151)	EW/placebo (n=51)	EW/EOW (n=53)	EW/EW (n=51)
[redacted]								

EW – every week; EOW – every other week; HS – hidradenitis suppurativa

M12-555 OLE

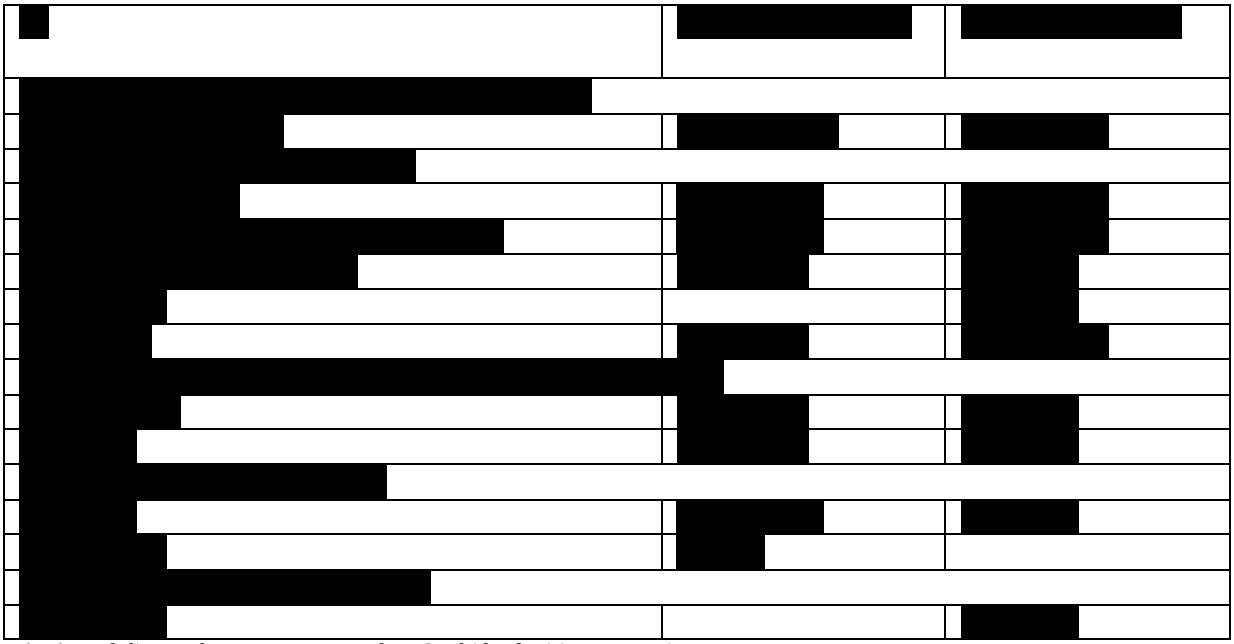
[redacted] from an interim data cut (29th April 2014) [redacted]

The ERG also notes that the OLE study only potentially offers safety data for up to 72 weeks for some participants (given the high levels of attrition) for a drug that might be taken for many years by patients with moderate or severe HS.

Table 35: AEs in M12-555 OLE in all adalimumab groups and in the EW/EW/EW trial population (reproduced from CS,[9] Table 35, page 115)

ADA – adalimumab; EW – every week; AE – adverse event; SAE – serious adverse event

Table 36: AEs occurring in >5% of in patients in M12-555 OLE in all adalimumab groups and in the EW/EW/EW trial population (reproduced from CS,[9] Table 36, page 115)



ADA – adalimumab; EW – every week; HS – hidradenitis suppurativa

Overall summary

On the basis of the evidence presented withn the CS, adalimumab appears to have a generally acceptable safety profile. However, longer-term data are required to determine whether AE rates are maintained for patients on long-term maintenance doses of adalimumab 40mg EW, whether or not certain subgroups of patients are at higher risk of certain AEs, and to confirm whether or not there are any differences between the interrupted and uninterrupted regimens.

4.2.5 Ongoing studies

The CS indicates that the M12-555 OLE[20] is the only ongoing study of adalimumab for HS. Final data from this study are expected to be available in 2016.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

An NMA comparing effects across all treatments was not performed. The company noted that there were substantial differences in baseline characteristics in trials comparing different pairs of treatments. The company argues that trial charcteristics such as smoking status, CRP status, disease severity, and prior and concomitant medication were potential treatment effect modifiers. Therefore, they argue that because there were insufficient trials to adjust for trial characteristics it was not possible to produce unbiased estimates of treatment effects. However, the company did not find any evidence that the specified subgroups were treatment effect modifiers in PIONEER I and that AN count by median was the only potential treatment effect modifier in PIONEER II. Neverthless, there

may be other trial characteritstics that are treatment effect modifiers. The CS does not discuss the potential to perform a simulated treatment comparison or a matching-adjusted treatment comparison.

In addition, the CS argues that trials did not provide data on all outcome measures, hence the number of trials with usable data varies between outcome measures. In principle, it might be possible to perform a multivariate NMA and borrow strength about treatment effects on different outcome measures across trials, although the CS does not consider this option. The ERG notes that even if an indirect comparison had been deemed suitable using one or more secondary outcomes measured in the PIONEER trials, such evidence could not have been used within the response-based health economic model structure developed by the company (see Chapter 5).

4.4 Critique of the indirect comparison and/or multiple treatment comparison

As discussed in Section 4.3, an NMA comparing effects across all treatments was not performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional analyses for the clinical effectiveness review.

4.6 Conclusions of the clinical efficacy section

The CS consisted of three separate reviews: (1) a review of the clinical efficacy evidence from RCTs of treatments for HS, specifically RCTs comparing adalimumab with placebo; (2) a review of the evidence from a non-controlled, OLE study; and (3) a review of safety evidence from the RCTs of adalimumab versus placebo and the non-controlled, OLE study.

The principal clinical efficacy review is a poorly-reported systematic review of three relevant RCTs comparing adalimumab with placebo in adults with moderate to severe HS: these were a Phase II "dosing" trial, M10-467, and two Phase III trials, PIONEER I and II. The three trials all have two periods: an initial period (weeks 0-12 in the PIONEER I/II trials and weeks 0-16 in the M10-467 trial) comparing adalimumab 40mg EW with placebo, and a second period (weeks 12-36 in the PIONEER trials), initiated by re-randomisation of patients at Week 12 to arms of adalimumab 40mg EW, placebo or adalimumab 40mg EOW (PIONEER trials only). The included trials are generally consistent with the final NICE scope. The primary efficacy outcome was clinical response to treatment using two measures: the HS-Physicians' Global Assessment (HS-PGA) and the company's own HiSCR. Clinical advice received by the ERG confirms that the HiSCR measure has been validated but, in terms of clinical decision-making, its findings must be viewed alongside the results of patient-reported outcome measures, in particular quality of life assessed by the DLQI and a pain measure. Secondary outcomes in the trials included assessments of disease severity and symptoms, using the MSS score and AN counts, pain and quality of life (various measures).

The ERG considers the M10-467 trial to be at low risk of bias across all domains for the relevant Period 1 (up to week 16). The ERG also considers the results from Period A (i.e. up to week 12) in PIONEER I and II to be generally at low risk of bias. However, the ERG considers there to be a moderate or unclear risk of selection and attrition bias for the results of Period B in the PIONEER trials. There is also a low-to-moderate risk of reporting bias in Period B in the two trials. It should also be noted that whilst M10-467 has been published, the PIONEER trials have not.

In PIONEER I and II, significantly more patients in the adalimumab 40mg EW group achieved a clinical response (defined as achieving HiSCR [at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline] at week 12) than patients receiving placebo: 41.8% for adalimumab vs 26.0% for placebo, p=0.003 in PIONEER I, and 58.9% for adalimumab vs 27.6% for placebo, p<0.001 in PIONEER II. Subgroup analyses indicated that patients achieved benefit with adalimumab 40mg EW regardless of their baseline characteristics, although some subgroups had small patient numbers. Significant or clinically relevant differences in favour of adalimumab 40mg EW that were reported for secondary outcomes in PIONEER II were not always found in PIONEER I, especially for AN count, MSS score, pain and some components of quality of life measured by the SF-36. The treatment effect varied between the trials. This might be explained by differences in patient demographics and study design between trials. The company is conducting ongoing analyses of the data from the PIONEER trials and the OLE study to understand these differences. An NMA was not considered feasible.

An arm-based integrated summary, which breaks randomisation, was conducted for the two PIONEER trials to tabulate Period B response (12-36 weeks) for all patients and for a group of HiSCR "responders" and "partial responders." According to this analysis, improvements in response were maintained or reduced in this second period. However, the "partial responder" group (defined as HiSCR responders with ≥25% reduction rather than ≥50% reduction) are a *post hoc* analysis group. This group was not defined in protocols or published descriptions of study design or pre-specified analysis methods for the PIONEER trials. It was also not considered in the published validation study for the HiSCR measure, nor was it justified or explained in the company's clinical review. A small number of secondary outcomes were reported for PIONEER I and II for weeks 12-36, but only for patients who had had clinical response at week 12. However the results were based on analyses with small sample sizes (range of 15 to 22 patients across all outcomes for both PIONEER trials).

These trials were supplemented by a single, unpublished, non-randomised, non-controlled, un-blinded cohort study, which was an OLE study of the PIONEER trials (M12-555 OLE). In terms of efficacy, the results suggested

[redacted]

[redacted].

Details of the results for secondary outcomes such as MSS and NRS30 were not reported. The ERG considers these efficacy results to be affected by a large degree of uncertainty because they are drawn from interim analyses of unpublished study data, and a sizeable amount of data was missing. The study also only potentially offers efficacy data for up to 72 weeks for a drug that might be taken for many years by patients with moderate or severe HS.

The submission of safety evidence was a review of the three RCTs, supplemented by the single arm cohort study. There were no obvious safety concerns, with most AEs being balanced across adalimumab 40mg EW and placebo trial arms, and small numbers of SAEs. Longer-term data are required to determine whether reported AE rates are maintained for patients on long-term maintenance doses of adalimumab 40mg EW; whether or not certain subgroups of patients are at higher risk of certain events; and to confirm whether or not there are any differences between the interrupted and uninterrupted regimens. The submission states that the M12-555 OLE is the only ongoing study of adalimumab in this indication. Final data from this study are expected to be available in 2016.

5. COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The CS[9] presents the methods and results of systematic reviews of existing health economic evaluations of treatments for patients with moderate to severe HS, HS cost and resource use studies and HRQoL studies in patients with HS. The searches for the economic evaluation review and the cost and resource use review were run together in order to avoid potential duplicates, whilst the HRQoL search was run separately. According to the CS, the purpose of the combined search was *"to identify healthcare resource use, costs, cost drivers, previous economic evaluations and health technology assessment (HTA) economic models of treatments for patients with moderate to severe HS"* (CS[9] page 127).

Search strategy

All searches were undertaken across the following electronic databases:

- MEDLINE
- MEDLINE In-Process
- EMBASE (using EMBASE.com)
- Econlit (using EBSCO.com)
- The Cochrane Library including the following:
    - The Cochrane Database of Systematic Reviews
    - The Database of Abstracts of Reviews of Effectiveness (DARE)
    - The Cochrane Central Register of Controlled Trials (CCRCT)
    - The Health Technology Assessment (HTA) Database.

Both the combined search and the HRQoL search were restricted to studies which were published in English in the last 15 years (up to 30th July 2015).

In addition to the searches of electronic databases, key HTA websites (NICE, the Scottish Medicines Consortium [SMC] and the All Wales Medicines Strategy Group [AWMSG]) were searched for

relevant HTA evaluations and models from the last two years (precise dates of the searches are not specified in the CS). Conference posters and abstracts were also searched within the following conferences over the last two years:

- American Academy of Dermatology (AAD)
- European Society for Dermatological Research (ESDR)
- World Congress of Dermatology (WCD)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Precise dates for these searches are not specified in the CS.

Inclusion and exclusion criteria

The company's inclusion and exclusion criteria for the three searches are summarised in Box 1. Inclusion and exclusion criteria relating to outcomes and study design differed between each of the three reviews, although all other criteria were the same.

Box 1: Inclusion and exclusion criteria for company's review of cost and resource use / utility / economic evaluation studies (adapted from CS[9] Tables 40, 41 and 44)

Inclusion criteria

- **Population:** Treated and/or untreated adult patients with moderate to severe HS.
- **Interventions:** Any treatment for HS, including antibiotics, retinoids, dapsone, ciclosporin, biologics, surgical options, oral prednisolone, intralesional triamcinolone injections, oral contraceptive pills, incision/drainage and analgesia.
- **Outcomes:** Cost and resource use studies: Any study quantifying costs or resource use requirements of HS and its management or quantifying the costs or resource use associated with disease- or treatment-related AEs / Utility studies: Utility values produced using generic preference-based measures of patient utility, disease-specific measures or vignettes / Economic evaluation studies: Studies with a comparison of costs between the intervention and comparator arms with results reported in terms of cost per QALY gained, cost per life year gained or just cost if accompanied by a cost-minimisation argument.
- **Study design:** Cost and resource use studies: Cost studies or resource use studies or economic evaluations reporting costs or resource use / Utility studies: QoL studies, economic studies or observational studies reporting utility values / Economic evaluation studies: Full economic evaluations, comparing at least two interventions.
- **Other criteria:** Studies providing sufficient detail regarding methods used and studies which provided extractable results, studies must present cost and resource use data (preferably for the UK).

Exclusion criteria

- **Population:** Patients with any skin disease other than HS, healthy volunteers, children only.
- **Outcomes:** Cost and resource use studies: Studies that do not report either cost or resource use / Utility studies: Disease-specific and non-preference-based measures not converted to utilities / Economic evaluation studies: Cost-only outcomes without a cost-minimisation argument.
- **Study design:** Reviews, letters, comments / Economic evaluation studies: burden of illness studies.
- **Other criteria:** Studies that failed to present sufficient methodological detail or failed to present extractable results.

Study selection

The CS[9] (page 132) presents a PRISMA flow diagram for all three searches combined. Results of all three searches were screened together. The PRISMA diagram indicates that after studies were identified through the searches, they were subject to primary screening followed by secondary

screening of those studies that had not been excluded thus far, based on the inclusion/exclusion criteria presented in Box 1. No details were provided regarding the difference between primary and secondary screening or the number of researchers involved in the screening process.

Results of the company's review of cost-effectiveness evidence

The company's electronic searches yielded a total of 400 potentially relevant unique citations. Of these, 143 articles were economic and cost/resource use studies, whilst 212 articles were HRQoL studies. Forty-five citations were also identified through "published ahead of print" searches. Of the 400 potentially relevant citations, 276 publications were excluded at the primary screening stage following a review of titles and abstracts. Following secondary screening, 92 of the remaining 124 studies were excluded.

A total of 21 studies reported across 32 publications were included in the company's reviews of economic evaluations, resource use and cost studies and HRQoL studies. Of these, five studies reported resource use data for patients with moderate to severe HS and 20 reported HRQoL data. The CS[9] notes that no relevant HTAs were identified through searching the NICE, SMC or AWMSG websites and no economic evaluations or modelling studies were identified for HS patients from any of the company's searches.

The CS notes that a Cochrane review[35] was published in October 2015; owing to the time of its publication, this study was not included in the company's review. The Cochrane review did not identify any additional studies that were not identified by the company's systematic review.

The results of the reviews are summarised in the CS in Table 45 (study characteristics) and Table 46 (relevant outcomes reported) for utility studies, and Table 48 (study characteristics) and Table 49 (resource use outcomes reported) for cost and resource use studies.[9] The included studies of the HRQoL review are summarised on pages 164 to 167 of the CS and the included cost and resource use studies are summarised on pages 172 to 173 of the CS.[9]

5.1.2 ERG critique of company's systematic review of cost-effectiveness evidence

The searches undertaken by the company were of a reasonable quality; however, there were some errors in the search strategies which, if executed as reported in the CS, may have led to results being missed or irrelevant results being retrieved. The economic evaluation and utility searches were designed for the Embase.com platform, whereas the ERG uses Ovid to access this database. On attempting to translate the searches to the Ovid interface, the ERG was unable to reproduce the searches exactly as presented within the CS.[9] For example, the same number of results was not retrieved with the string in line 48 of the economic evaluations search of Medline/EMBASE (*"patient*

acceptance of health care"); this was the case both when the search string was defined as a subject heading search and when it was defined as a phrase search. Some lines were confusing and appeared to include redundant repetition or duplication; for example, in line 1 of the EMBASE search: "*hidradenitis suppurativa'/exp OR 'hidradenitis suppurativa' OR 'hidradenitis' OR 'hidradenitis'/exp OR hidradenitis OR suppurativa OR hidradeniti* NEAR/1 suppurativ**". This appears to include exploded and unexploded forms of the same subject headings as well as searches for individual terms "suppurativa" and "hidradenitis" irrespective of whether they occur in proximity.

The ERG queried the source of the filters used to identify relevant studies (see clarification response,[17] question A5). In response, the company clarified that the cost-effectiveness searches were based on filters published by the Scottish Intercollegiate Guidelines Network (SIGN). It should be noted that SIGN filters are not always validated prior to publication, but the ERG acknowledges that this is a reputable source and one which is endorsed by NICE. The company did make some modifications to the SIGN filters (in the form of additional terms) but as they did not remove any of the existing terms this would not have had any detrimental effect on the search results.

The utility searches used terms taken from a paper by Papaioannou *et al*,[36] however, this contained several typographical errors (for example, in line 20 of the utility search on EMBASE, "*shorform thirtysix"* should have been written as *"shortform"* or *"short form"*; in line 23 of the same search, *"shortfrom sixteen"* should read *"shortform sixteen"*). When a corrected version of the utility search was run by the ERG, the number of results was not markedly different from that reported in the CS.[9]

The single search for "ahead of print" studies in PubMed was deemed by the ERG to be a valuable complement to the searches. However, the CS failed to include "PreMEDLINE" (MEDLINE-in-Process) citations in PubMed as well (i.e. those studies which have been printed and will be added to MEDLINE, but are not yet fully indexed). The ERG notes that there can be a backlog of several months between the print publication of an article and its appearance in MEDLINE.

The ERG also notes that imposing a restriction to include only studies published in English introduces a risk of missing relevant foreign language studies.

The ERG notes that the Cochrane systematic review[35] did not identify any cost-effectiveness studies. However, it should be noted that the Cochrane search had been designed to identify RCTs whereas this restriction on study design would not normally be applied for a cost-effectiveness search.

Despite the limitations described above, the ERG is satisfied that the company's searches are unlikely to have missed any relevant economic evaluation studies.

5.2 Description of the company's model

5.2.1 Health economic evaluation scope

As part of their submission to NICE,[9] the company submitted a fully executable health economic model programmed in Microsoft Excel. The scope of the company's economic analysis is summarised in Table 37. The company's model assesses the cost-effectiveness of adalimumab versus standard care for the treatment of patients with active moderate to severe HS who have had an inadequate response to conventional systemic therapy. The incremental health gains, costs and cost-effectiveness of adalimumab are evaluated over a lifetime horizon from the perspective of the UK NHS and PSS, although the ERG notes that no relevant PSS costs are included in the company's model. All costs and health outcomes are discounted at a rate of 3.5% per annum. Unit costs are valued at 2013/14 prices.

Table 37: Scope of company's health economic analysis

Population	Patients with active moderate to severe HS who have had an inadequate response to conventional systemic therapy
Intervention	Induction: Adalimumab 160mg at week 0, 80mg at week 2 and 40mg EW from week 4 onwards. Maintenance (week 12 responders* only): Adalimumab 40mg EW
Comparator	Standard care
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	Lifetime
Discount rate	3.5% per year

HS – hidradenitis suppurativa; EW – every week; NHS – Naitonal Health Service; PSS – Personal Social Services; QALY – quality-adjusted life year
**Including high response, response and partial response*

Population

All clinical efficacy data used in the company's model are based on the PIONEER I/II trials[18, 19] and the M12-555 OLE study,[20] hence the population represented within the model reflects the populations of patients recruited into these studies. At model entry, the population is assumed to be 35 years of age; this is broadly reflective of the mean age of patients in the PIONEER I/II trials. 65.9% of patients are assumed to be female. 44.7% are assumed to have moderate disease, whilst the remainder are assumed to have severe disease; this variable is used only to determine expected resource use in each health state. The economic analysis presented in the CS does not include any subgroup analyses.

Interventions

The intervention under consideration is adalimumab administered subcutaneously via an auto injection pen or pre-filled syringe.[12] Adalimumab is given at a dose of 160mg at week 0, 80mg at week 2 and 40mg EW from week 4 onwards. The company's model assumes that at 12 weeks, patients who achieve high response, response or partial response, based on the HiSCR measure, will

continue to receive adalimumab maintenance therapy. Patients who do not achieve at least a partial HiSCR response at 12-weeks are assumed to discontinue adalimumab treatment and subsequently receive standard care. During weeks 12-36 of the maintenance phase, patients are assumed to discontinue adalimumab at a constant rate irrespective of response status, based on the PIONEER I/II studies;[18, 19] thereafter differential withdrawal rates are applied to patients achieving at least a partial response and non-responders based on the OLE study.[20] This approach to handling adalimumab discontinuation is not fully justified in the CS. It is also noteworthy that according to the CS, the model assumes that from week 36 onwards, patients who are non-responders will continue to receive adalimumab and will discontinue if a further 12 weeks of adalimumab treatment fails to achieve at least a partial response (i.e. from week 48 onwards). The implementation of this continuation rule within the company's model is discussed in detail in Section 5.3.

Comparators

The comparator in the company's economic analysis is defined as "standard care." According to the CS[9] (page 139), surgery was not considered to be an appropriate comparator as surgery and adalimumab are not alternative or exclusive treatment choices. The CS also states that patients in the PIONEER trials were allowed surgery for symptom control and that an online survey of members of the UK Dermatology Trials Network and British Association of Dermatologists revealed that extensive surgery was generally used later in the treatment pathway.[9] However, the ERG notes that in response to a request for clarification (see clarification response,[17] questions A31 and B5), the company later stated that patients were not permitted to undergo either planned or unplanned surgery in the PIONEER I/II trials (see Section 4.2.1). The CS states that antibiotics were not considered to represent a relevant comparator, as antibiotics are typically used throughout the treatment pathway and these may be used concomitantly with adalimumab. The CS further notes that a comparison of adalimumab versus dapsone, retinoids and immunomodulators was not performed since UK clinical experts consulted in the preparation of the CS suggested that these therapies would currently be prescribed before adalimumab, noting also that there is currently a lack of efficacy evidence for these therapies in HS.[9] The company also considered that a comparison of adalimumab versus infliximab was not appropriate as infliximab is used in very specific subgroups of patients (for example, those who are very overweight) and such a comparison was not possible given the limited evidence base and heterogeneity between the infliximab and adalimumab trials. Clinical advisors to the ERG disagree that infliximab is only used in specific subgroups and a 2015 survey of UK clinicians suggests that that despite funding constraints, infliximab is currently used more widely in HS than adalimumab.[15]

Given the arguments presented by the company, the CS states that the relevant comparator is standard care, based on the placebo groups within the PIONEER I/II trials.[18, 19] The ERG notes that whilst the

placebo group data from PIONEER I/II are used to characterise the efficacy of standard care, resource use associated with standard care is instead based on expert opinion and is predominantly driven by the usage and costs of surgical inpatient admissions in both the adalimumab and placebo groups.

5.2.2 Description of the company's health economic model structure and logic

The general structure of the company's model is presented diagrammatically in Figure 3. The model adopts a simple Markov approach based on depth of HiSCR response. The model structure is comprised of five discrete mutually exclusive health states: (i) high response; (ii) response; (iii) partial response; (iv) non-response, and; (v) death. Table 38 presents the definitions for the categorisation of these different levels of response applied within the model. Within the adalimumab group, separate health states are used to define whether the patient is currently receiving adalimumab or whether they have discontinued and are currently receiving standard care. Within the standard care group, fewer discrete health states are required as all patients remain on standard care from the point of model entry. The model adopts a 2-weekly cycle length for the first 2 cycles and a 4-weekly cycle length thereafter; the CS[9] states that these cycle durations were selected to reflect the dosing schedule of adalimumab[12] and the timing of assessments within the PIONEER I/II trials.[18, 19] The model is evaluated over a total of 859 cycles (equating to a total time horizon of 66 years), although all surviving patients are forced into the death state at age 100 (at cycle 846, that is, after 65 years). A half-cycle correction is partially applied to account for the timing of events (see Section 5.3).

Figure 3 Company's health economic model structure (reproduced from CS[9] page 134)

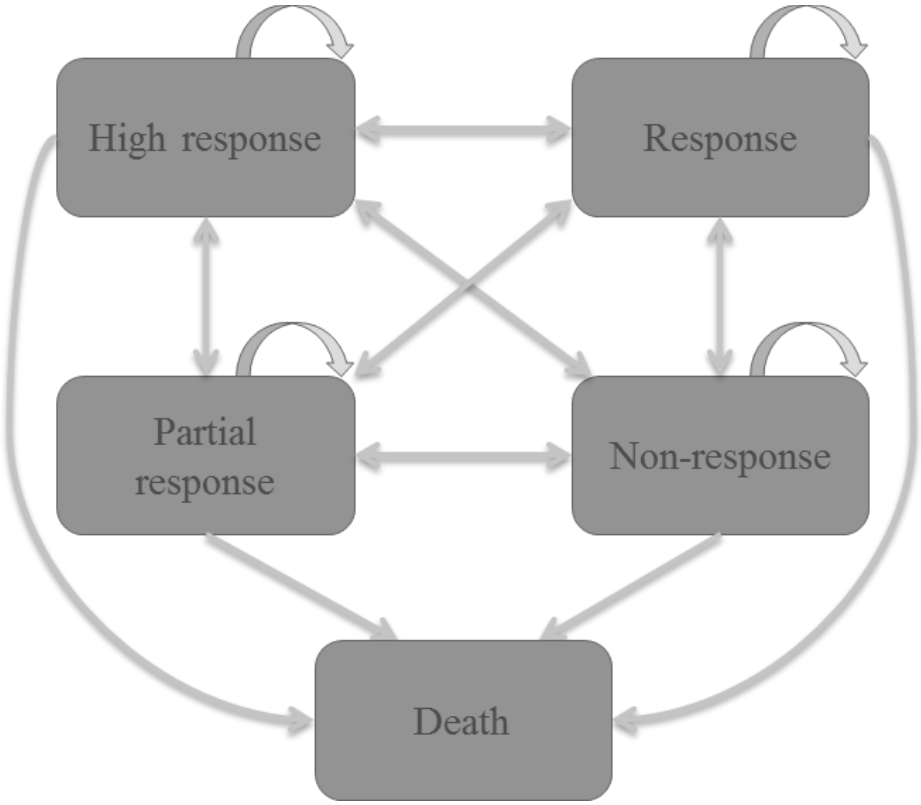


Table 38: Categorisation of depth of response in the company's model

HiSCR-based state definition	HiSCR-based state description
High response	At least 75% total AN count reduction, with no increase in abscesses or draining fistulas from baseline
Response	At least 50% but less than 75% AN reduction, with no increase in abscesses or draining fistulas from baseline
Partial response	At least 25% but less than 50% AN reduction, with no increase in abscesses or draining fistulas from baseline; or at least 25% AN reductions, with an increase in abscesses and/or draining fistulas
No response	Defined as less than 25% AN reduction

HiSCR - Hidradenitis Suppurativa Clinical Response; AN - abscess and inflammatory nodule

Model logic - adalimumab group

All patients enter the model in the no response state. Cycle-specific time-variant transition matrices based on cross-tabs of observed HiSCR outcomes pooled from the PIONEER I/II trials[18, 19] are used to determine health state populations for each cycle up to week 12 using simple matrix multiplication. All surviving patients remain on adalimumab induction therapy up to week 12. At 12 weeks, the model cohort separates into four discrete Markov submodels, each of which is defined according to the patients' 12-week HiSCR response (achievement of high response, response, partial response and no response at the end of induction); this distribution of patients is then used to define the initial vector for each of the maintenance submodels. Patients who do not achieve at least a partial response

during the first 12 weeks of adalimumab induction therapy are assumed to discontinue and subsequently receive standard care. Up to week 36, patients who have previously achieved an adalimumab induction response transit through the model health states based on cycle-specific time-variant probabilities based on cross-tabs of observed HiSCR outcomes for patients initially randomised to the adalimumab 40mg EW group who were subsequently re-randomised to receive adalimumab 40mg EW in the PIONEER I/II trials.[18, 19] Beyond week 36, a single time-invariant transition matrix is used to extrapolate the trajectory of patients through the health states, based on a GLM fitted to data from the M12-555 OLE study[20] (note that from week 48, the adalimumab non-responder discontinuation rate is increased, although the underlying HiSCR transition data remain the same). During each maintenance cycle, patients have a probability of discontinuing adalimumab treatment; these patients discontinue adalimumab, transit to the equivalent response state and subsequently receive standard care.

During weeks 12-36, cycle-specific time-variant transition matrices for patients discontinuing adalimumab therapy are based on cross-tabs of observed HiSCR outcomes for patients who were initially randomised to adalimumab 40mg EW induction therapy in PIONEER I/II[18, 19] who subsequently switched to placebo during the maintenance period (Period B). Beyond week 36, transition probabilities for adalimumab discontinuers are based on a single time-invariant transition matrix derived from a GLM fitted to the week 12-36 data for this population.

During each Markov cycle, a cycle-specific age-dependent probability of death is modelled to reflect the risk of all-cause mortality.

Model logic - standard care group

Within the standard care group, the model logic is similar to that for the adalimumab arm, albeit without the possibility of treatment discontinuation. Rather, patients continue treatment with standard care during induction and maintenance irrespective of their level of response. Patients enter the model in the no response state. Cycle-specific time-variant transition matrices based on cross-tabs of observed HiSCR response outcomes pooled from the PIONEER I/II trials[18, 19] are used to determine health state populations for each cycle up to week 12 using simple matrix multiplication. From week 12 to week 36, cycle-specific time-variant transition probabilities are based on cross-tabs of observed HiSCR outcomes for patients initially randomised to placebo in PIONEER II[19] who subsequently continued on placebo during Period B (note that data from PIONEER I[18] are not used in this portion of the model as the design of the trial did not allow for placebo group patients to be re-randomised to placebo during Period B). Beyond week 36, a single time-invariant transition matrix is applied for all subsequent Markov cycles based on a GLM fitted to the week 12-36 data from PIONEER II[19] described above.

During each Markov cycle, a cycle-specific age-dependent probability of death is modelled to reflect the risk of all-cause mortality.

Model logic – modelling health gains, costs and cost-effectiveness

Health utility is differentiated according to the patient's level of HiSCR outcome, with higher values applied to better response states. State-specific utilities are assumed to be the same for adalimumab and standard care. The model does not include disutilities to account for the impact of AEs in either treatment group.

The model includes the acquisition costs associated with adalimumab treatment (taking into account reductions in costs incurred due to imperfect compliance), inpatient admissions for HS surgeries, outpatient visits due to HS surgery, outpatient visits for wound care due to HS surgery, non-surgery related hospitalisations, routine outpatient visits, outpatient visits for wound care which are not due to HS surgery, A&E visits, and costs associated with managing AEs. The costs of adalimumab administration are assumed to be zero; the CS[9] states that adalimumab will be administered in the patient's home via AbbVie Care (homecare). The costs of concomitant pharmacological therapies used to manage HS are not included in the model.

The application of different transition matrices for the adalimumab and standard care groups leads to different trajectories of patients through the model's health states, thereby producing different profiles of costs and health outcomes for the two groups. Incremental cost-effectiveness is calculated as the difference in costs divided by the difference in QALYs for the two options.

Key structural assumptions employed within the company's model

The company's model makes the following structural assumptions:

- All patients enter the model in the no response health state.
- HRQoL and health care resource use are assumed to differ according to depth of response, defined according to the HiSCR measure.
- Patients who are non-responders at 12 weeks discontinue treatment with adalimumab. Patients who achieve at least a partial response continue to receive adalimumab as a maintenance therapy.
- During weeks 12-36, the probability of discontinuing adalimumab is assumed to be independent of the patient's current state of response. The company's model applies the discontinuation rates observed within Period B of the PIONEER I/II trials[18, 19] to patients irrespective of their level of HiSCR response.

- During weeks 40-48, the probability of discontinuing adalimumab is applied based on the discontinuation rate observed in the OLE study;[20] the same discontinuation rate is applied to patients in the high response, response and partial response states, with a higher discontinuation rate applied to non-responders.
- According to the CS,[9] the company's model assumes that patients who lose response to adalimumab will continue to receive a further 12-weeks of therapy before discontinuing adalimumab treatment. The ERG notes problems in the implementation of this continuation rule (see Section 5.3).
- Up to week 36, transition probabilities are assumed to be time-variant.
- Beyond week 36, transition probabilities are assumed to be time-invariant. Separate matrices are applied to (a) patients who are currently receiving adalimumab maintenance therapy; (b) patients who have received adalimumab but have subsequently discontinued, and (c) patients who are receiving standard care.
- The impact of AEs is reflected in the HiSCR-based utility values used in the model.
- Neither the disease itself, nor its treatment, is assumed to impact upon the life expectancy of patients.
- All adalimumab administration costs will be borne by the AbbVie homecare service.

5.2.4 Evidence used to inform the company's model parameters

Table 39 summarises the evidence sources used to inform the company's model parameters. These are discussed in more detail in the following sections.

Table 39: Summary of evidence sources used to inform the company's model parameters

Parameter/group	Source(s)
Patient characteristics (start age, proportion cohort who are female, percent of patients with moderate disease)	PIONEER I/II[18, 19]
HiSCR response transition probabilities	PIONEER I/II[18, 19] and M12-555 OLE study[20]
Probability of discontinuation	PIONEER I/II[18, 19] and M12-555 OLE study[20]
HiSCR state utilities	PIONEER II[18, 19]
Adverse event rates	PIONEER I/II[18, 19]
Health state resource use (inpatient/outpatient visits related/unrelated to HS surgery and A&E)	UK Physician Survey[22]
Adalimumab compliance (induction and maintenance periods)	PIONEER I/II[18, 19]
Adalimumab acquisition costs	BNF[37]
Resource use costs	NHS Reference Costs 2013/14[38]
Adverse event costs	NHS Reference Costs 2013/14,[38] and Curtis *et al*[39]

HS – hidradenitis suppurativa; HiSCR - Hidradenitis Suppurativa Clinical Response; OLE – open-label extension

5.2.4.1 Patient characteristics

The model includes three patient characteristics: patient age, gender and the percentage of the cohort that has moderate disease. Patients are assumed to enter the model aged 35 years; this is broadly in line with the mean age of patients in the PIONEER I/II trials[18, 19] (weighted mean=36.2 years). 65.9% of patients are assumed to be female; this is based directly on the characteristics of the populations recruited into PIONEER I/II.[18, 19] 44.7% patients are assumed to have moderate disease.

5.2.4.2 Transition probabilities

Transition probabilities – patients receiving standard care

Transition probabilities in the model were sourced from the PIONEER I/II trials[18, 19] and the M12-555 OLE study,[20] either using cross-tabs of observed trial outcomes relating to the specific time period in which the matrix is applied, or using GLMs fitted to outcomes from assessments at multiple timepoints. In the company's base case, a non-responder imputation rule was applied to all data from the PIONEER trials, whilst an LOCF imputation rule was used for the OLE data. The sources of the HiSCR transition matrices are summarised in Table 40; the full set of matrices employed within the company's base case analysis is presented in Appendix 1.

Within the standard care group, transition probabilities during weeks 0-12 are based directly on cross-tabs of observed HiSCR outcomes for patients who were initially randomised to the placebo groups during Period A within the PIONEER I/II trials.[18, 19] Cycle-specific time-variant transition matrices are used for the periods 0-2 weeks, 2-4 weeks, 4-8 weeks and 8-12 weeks.

For the period 12-36 weeks, transition probabilities for the standard care group are based on cross-tabs of observed HiSCR outcomes for patients who were initially randomised to the placebo group during Period A within the PIONEER II trial[19] who subsequently continued to receive placebo during Period B of the trial. Cycle-specific time-variant transition matrices are used for the periods 12-16 weeks, 16-20 weeks, 20-24 weeks, 24-28 weeks, 28-32 weeks and 32-36 weeks.

Beyond week 36, a single time-invariant transition matrix is used to model HiSCR outcomes for the standard care group. This matrix was based on a GLM of all transitions observed for patients initially randomised to placebo during Period A within the PIONEER II who subsequently continued on placebo during maintenance during Period B of the trial (i.e. the week 12-36 maintenance data described above).

Transition probabilities – patients receiving adalimumab

Within the adalimumab group, transition probabilities during the induction phase of the model are based on cross-tabs of observed HiSCR outcomes for patients initially randomised to the adalimumab

40mg EW groups during Period A within the PIONEER I/II trials.[18, 19] Cycle-specific time-variant transition matrices are used for the periods 0-2 weeks, 2-4 weeks, 4-8 weeks and 8-12 weeks.

For the period 12-36 weeks, transition probabilities for patients remaining on adalimumab are based on cross-tabs of HiSCR outcomes for patients initially randomised to adalimumab 40mg EW during Period A within the PIONEER I/II trials[18, 19] who were 12-week responders and were subsequently re-randomised to receive adalimumab 40mg EW during Period B of the trial. Cycle-specific time-variant transition matrices are used for the periods 12-16 weeks, 16-20 weeks, 20-24 weeks, 24-28 weeks, 28-32 weeks and 32-36 weeks.

Transitions during the period from week 36-48 within the company's model are based on a GLM of HiSCR outcomes for weeks 0-24 within the M12-555 OLE study.[20] According to the CS,[9] LOCF imputation was used as fewer than 50% of patients had 24-weeks of follow-up data. A single cycle-specific time-invariant matrix is used for cycles beginning at week 40 and week 44. Transitions for all cycles from week 48 onwards are based on the same GLM described above; however, the transition from the adalimumab no response state to the standard care no response state is raised to the power of three (i.e. cubed) and is assumed to reflect a situation whereby patients continue to receive a further 12-weeks of adalimumab treatment despite remaining non-responsive for this period. All other transitions out of the non-response state are adjusted accordingly. The justification for this mathematical approach is unclear from the CS (see Section 5.3).

Transition probabilities – patients who have discontinued adalimumab

For patients who previously received adalimumab and either failed to achieve a 12-week induction response, or who achieved an induction response but subsequently lost that response whilst receiving adalimumab maintenance therapy, transition probabilities during weeks 12-36 are based on cross-tabs of HiSCR outcomes for patients randomised to adalimumab 40mg EW in PIONEER I/II[18, 19] who switched to placebo during Period B (irrespective of whether they had previously achieved an induction response on adalimumab). Cycle-specific time-variant transition matrices are applied for the periods 12-16 weeks, 16-20 weeks, 20-24 weeks, 24-28 weeks, 28-32 weeks and 32-36 weeks.

Beyond week 36, a single time-invariant transition matrix is applied based on a GLM of all transitions observed for patients initially randomised to adalimumab in PIONEER I/II[18, 19] who subsequently switched to placebo during Period B (i.e. the 12-36 week data described above).

Table 40: Sources of transition probabilities used in the company's model

Matrix description	Source
Standard care – induction phase	
Week 0-12	Cross-tabs of outcomes based on pooling of patients initially randomised to the placebo groups within PIONEER I/II
Standard care – maintenance phase	
Week 12-36	Cross-tabs of outcomes for patients initially randomised to the placebo group in PIONEER II who subsequently continued on placebo during maintenance.
Week 36+	GLM based on 12-36 week data described above
Adalimumab – induction phase	
Week 0-12	Cross-tabs of outcomes based on pooling of patients initially randomised to adalimumab 40mg EW groups within PIONEER I/II.
Maintenance phase – adalimumab 12-week responders	
Week 12-36	Cross-tabs of adalimumab 40mg EW patients re-randomised to adalimumab 40mg EW after responding at 12-weeks in PIONEER I/II.
Week 36-48	GLM based on weeks 0-24 of M12-555 OLE study (including LOCF imputation as <50% patients had 24-weeks follow-up data).
Week 48+	Same as above except the probability of transiting from adalimumab no response state to standard care no response state is cubed.
Maintenance phase – adalimumab 12-week non-responders and subsequent discontinuers	
Week 12-36	Cross-tabs of patients randomised to adalimumab 40mg EW in PIONEER I/II who switched to placebo in the maintenance period (irrespective of whether they achieved an induction response on adalimumab).
Week 36+	GLM based on week 12-36 data described above

OLE – open-label extension; EQ- every week; LOCF – last observation carried forward

The ERG's concerns regarding the use of these pooled data from the PIONEER trials, particularly with respect to breaking randomisation, are detailed in Section 5.3.

5.2.4.3 Probability of discontinuing adalimumab treatment

The company's model applies two types of discontinuation for patients receiving adalimumab: (i) discontinuation due to a lack of induction response, and (ii) general discontinuation during the maintenance phase (this presumably reflects discontinuation due to loss of treatment response, although given that the discontinuation rate is greater than zero for the response states, this may include other reasons such as the incidence of treatment-related AEs).

In line with the wording of the marketing authorisation for adalimumab,[12] the model assumes that patients who do not achieve treatment benefit 12 weeks after initiating therapy will discontinue adalimumab. This discontinuation rule is applied in the model only to those patients who are in the no response state at the end of the induction phase (after 12 weeks). Patients who achieve full response,

response, or partial response according to the HiSCR measure are assumed to continue adalimumab as maintenance therapy.

During weeks 12-36 within the company's model, patients receiving adalimumab are assumed to discontinue adalimumab according to a constant discontinuation rate based on the rate observed in the PIONEER I/II trials.[18, 19] The company's model applies a constant 4-week probability of discontinuation during each cycle; this discontinuation rate is assumed to be independent of HiSCR state (see Table 41).

Beyond week 36, adalimumab discontinuation rates are based on data from the M12-555 OLE study,[20] calculated using the person-year approach. Patients were assumed to remain in their prior HiSCR response state until a change occurred and patients' health states at the time of discontinuation were used to derive response-specific discontinuation events.[9] According to the CS,[9] the estimation of discontinuation rates from the M12-555 OLE study was based on all adalimumab-treated patients who were week 12 responders, who received adalimumab during the maintenance periods of PIONEER I/II[18, 19] and who were subsequently enrolled into the OLE study.[20] Within the model, this is applied as the same discontinuation rate for the states of high response, response and partial response, with a higher discontinuation rate applied to patients in the no response state (see Table 41). The ERG notes that the company's assumption regarding the continued use of adalimumab for a further 12-weeks for non-responding patients is applied in the model as a 4-weekly probability of discontinuation of 0.56.

Table 41: Probability of discontinuing adalimumab maintenance therapy

Treatment period / states	Annual rate	4-weekly rate	Source
Maintenance period (weeks 12-36)			
All states (full response, response, partial response and no response)	20.48%	1.75%	PIONEER I/II[18, 19]
Maintenance period (week 36+)			
High response, response and partial response	7.47%	0.60%	M12-55 OLE study[20]
No response	44.99%	4.49%	

5.2.4.4 Health-related quality of life

Health utilities were based on EQ-5D valuations obtained from the PIONEER II trial.[19] The PIONEER I trial[18] did not include the use of a preference-based measure of HRQoL. The company assumes differential HRQoL according to depth of HiSCR outcome, based on data from week 12 and week 36 data from the trial (see Table 42). The model does not consider the separate impact of disutilities due to AEs or surgical intervention over and above those already reflected in the HiSCR-based health utility scores.

Table 42: Health utilities used in the company's model

Response state	Mean value	Upper 95% CI	Lower 95% CI
High response	0.782	0.816	0.746
Response	0.718	0.766	0.667
Partial response	0.576	0.639	0.512
Non-response	0.472	0.542	0.402

CI – confidence interval

5.2.4.5 Resource use and costs

The company's model includes the following resource components:

- Drug acquisition
- Health state resource use
    - Inpatient admissions for HS surgeries
    - Outpatient visits due to HS surgery
    - Visits to wound-care due to HS surgery (which are assumed by the company to take place in the outpatient setting)
    - Hospitalisations which are non-surgery related
    - Routine outpatient visits
    - Visits to wound-care not due to HS surgery (which are assumed by the company to take place in the outpatient setting)
    - A&E visits
- Management of AEs

Drug acquisition

The acquisition cost of 40mg adalimumab was assumed to be £352.14 per dose, based on the BNF list price.[37] The model also includes small reductions in the costs of adalimumab due to imperfect compliance. Patient compliance with the dosing schedule was estimated from the PIONEER I/II trials.[18, 19] During the induction period (weeks 0-12), adalimumab compliance was estimated to be 98.8%. Subsequently, adalimumab compliance during the maintenance phase was estimated to be slightly lower at 97.4%.

Health state resource use

The company's model includes health state costs associated with hospital admissions for HS surgery, hospital admissions for non-surgical reasons, outpatients visits related to surgery, outpatient visits unrelated to surgery, visits for wound care related to surgery, visits for wound care unrelated to surgery and visits to A&E departments. Estimates of resource use per cycle are assumed to be dependent on HiSCR outcome and are not directly related to whether the patient receives adalimumab

or standard care, although the ERG notes that the model assumes that spending more time in better response states results in lower estimates of total resource use.

The company's model does not use data from the PIONEER I/II studies to inform estimates of resource use; instead, the company undertook a survey of 40 physicians who actively treat patients with moderate to severe HS in the UK.[22] The survey involved the separate elicitation of estimates of resource use for patients with moderate disease and for those with severe disease. Estimates elicited from the respondents were aggregated and the mean of the responses provided were used as inputs into the model;[17] aggregate estimates of resource use per year were weighted according to the proportion of patients with moderate or severe disease in the PIONEER I/II trials[18, 19] and then adjusted to reflect the 2- or 4- week cycle length used in the model. All resource estimates were valued using NHS Reference Costs 2013/14.[38] Annual health state resource use estimates used in the model are summarised in Table 43.

Table 43: Resource use by health state

Resource	Resource use (mean number of units per year)				Cost per event	Source
	High response	Response	Partial response	Non-response		
Hospital admissions for HS surgery	0.13	0.22	0.54	0.80	£5,488.32	NHS Reference Costs 2013/14[38] – elective inpatient, JC41Z (major skin procedures)
Hospital admissions not for HS surgery	0.11	0.23	0.29	0.45	£2,202.14	NHS Reference Costs 2013/14[38] – elective inpatient, weighted mean of codes JD07D and JD07K
Outpatient visits associated with surgery	0.22	0.35	0.67	0.94	£97.63	NHS Reference Costs 2013/14[38] – outpatient service codes 330
Outpatient visits not associated with surgery	3.10	3.51	4.44	4.68	£97.63	
Outpatient wound care visits associated with surgery	0.12	0.17	0.40	0.85	£97.63	
Outpatient wound care visits not associated with surgery	0.67	0.47	0.64	0.45	£97.63	
A&E visits	0.12	0.20	0.47	0.57	£123.67	NHS Reference Costs 2013/14[38] – weighted mean of total HRG for all emergency medicine procedures

HS – hidradenitis suppurativa; A&E – accident and emergency; HRG – Healthcare Resource Group

Adverse event rates and costs

The company's model includes the costs associated with treatment-emergent adverse events (TEAEs) if they occurred in at least 5% of patients in the PIONEER I/II trials.[18, 19] Separate AE estimates were applied for the induction and maintenance phases of the model. During the maintenance phase, AE rates were estimated separately for patients receiving adalimumab, for those who have discontinued adalimumab and for patients receiving standard care. The source of the proportion of AEs which were classified as being severe is unclear from both the CS and the model. The costs associated with managing AEs were valued using 2013/14 NHS Reference Costs,[38] together with GP costs sourced from the PSSRU.[39] AE rates and costs used in the company's model are summarised in Tables 44 and 45, respectively.

Table 44: Annual AE rates assumed in the company's model based on PIONEER I/II[18, 19]

Adverse event	Induction period		Maintenance period			Percentage events severe
	Adalimumab	Standard care	Adalimumab	Standard care	Following discontinuation	
Headache	0.486	0.505	[redacted]	[redacted]	[redacted]	3%
Nasopharyngitis	0.250	0.365	[redacted]	[redacted]	[redacted]	1%
Influenza	0.069	0.084	[redacted]	[redacted]	[redacted]	5%
Gastroenteritis	0.069	0.056	[redacted]	[redacted]	[redacted]	6%
Viral gastroenteritis	0.000	0.028	[redacted]	[redacted]	[redacted]	20%
Diarrhoea	0.167	0.084	[redacted]	[redacted]	[redacted]	0%
Upper respiratory tract infection	0.180	0.182	[redacted]	[redacted]	[redacted]	0%
Bronchitis	0.028	0.084	[redacted]	[redacted]	[redacted]	0%
Toothache	0.028	0.028	[redacted]	[redacted]	[redacted]	0%
Hidradenitis*	0.291	0.575	[redacted]	[redacted]	[redacted]	11%

** As discussed in Section 4.2.4, exacerbations of HS were classified as an AE*

Table 45: Costs associated with managing AEs

Adverse event	Cost (severe)	Cost (mild/moderate)	Cost (per event)*	Source
Headache	£674.21	-	£20.03	NHS Reference Costs 2013/14,[38] - weighted mean of total HRGs for codes AA31C, AA31D and AA31E.
Nasopharingitis	£908.28	-	£12.62	NHS Reference Costs 2013/14,[38] - weighted mean of total HRGs for codes WA06A, WA06B and WA06C.
Influenza	£908.28	-	£43.25	
Gastroenteritis	£1,468.01	£46.00	£125.00	Severe - NHS Reference Costs 2013/14,[38] - weighted mean of total HRGs for codes FZ91A to FZ91M. Mild/moderate - PSSRU[39] - GP visit lasting less than 11.7 minutes.
Viral gastroenteritis	£1,345.99	£46.00	£306.00	Severe - NHS Reference Costs 2013/14[38] - weighted mean of total HRGs for codes FZ36G to FZ36Q. Mild/moderate - PSSRU[39] - GP visit lasting less than 11.7 minutes.
Diarrhoea	-	£46.00	£46.00	Mild/moderate - PSSRU[39] - GP visit lasting less than 11.7 minutes.
Upper respiratory tract infection	-	£147.22	£147.22	NHS Reference Costs 2013/14[38] - weighted mean of outpatient codes 340 and 341.
Bronchitis	-	£147.22	£147.22	
Toothache	-	-	-	Assumed to be zero
Hidrahentitis	-	-	-	Assumed to be zero

NHS – National Health Service; PSSRU – Personal Social Services Research Unit; GP – general practitioner; HRG – healthcare resource group
** Weighted by severity*

5.2.5 Methods for model evaluation

The CS[9] presents the results of the economic evaluation in terms of the incremental cost per QALY gained for adalimumab versus standard care. The base case results are presented deterministically, based on point estimates of parameters. The CS[9] also includes the results of probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSA). The results of the PSA are presented in the form of cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), based on 5,000 Monte Carlo simulations. The CS[9] presents the results of the DSA in the form of a tornado diagram. A number of alternative scenario analyses are presented to explore the impact of truncating the model time horizon, using different discount rates for costs and health gains, using alternative data sources for transition probabilities and discontinuation rates (including removing the assumption of 12-weeks continued use of adalimumab in non-responders), using alternative imputation rules for missing data and varying the adalimumab compliance rate.

5.2.6 Cost-effectiveness results presented within the CS

5.2.6.1 Base case cost-effectiveness results

Table 46 presents the company's base case results. Based on the probabilistic version of the company's base case model, adalimumab is expected to produce an additional 1.02 QALYs at an additional cost of £[redacted] compared with standard care; the ICER for adalimumab versus standard care is expected to be £[redacted] per QALY gained. The results of the deterministic model are similar, with adalimumab yielding an ICER of £[redacted] per QALY gained compared with standard care.

Table 46: Company's base case cost-effectiveness results

Probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Adalimumab	12.63	£[redacted]	1.02	£[redacted]	£[redacted]
Standard care	11.61	£128,674	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Adalimumab	12.61	[redacted]	1.00	£[redacted]	[redacted]
Standard care	11.61	£128,541	-	-	-

QALY – quality-adjusted life year
** derived from company's model*

5.2.6.2 Probabilistic sensitivity analysis results

Figures 4 and 5 present the cost-effectiveness plane and CEACs for adalimumab versus standard care, respectively. Assuming a WTP threshold of £20,000 per QALY gained, the company's base case model suggests that the probability that adalimumab produces more net benefit than standard care is approximately [redacted]. Assuming a WTP threshold of £30,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately [redacted].

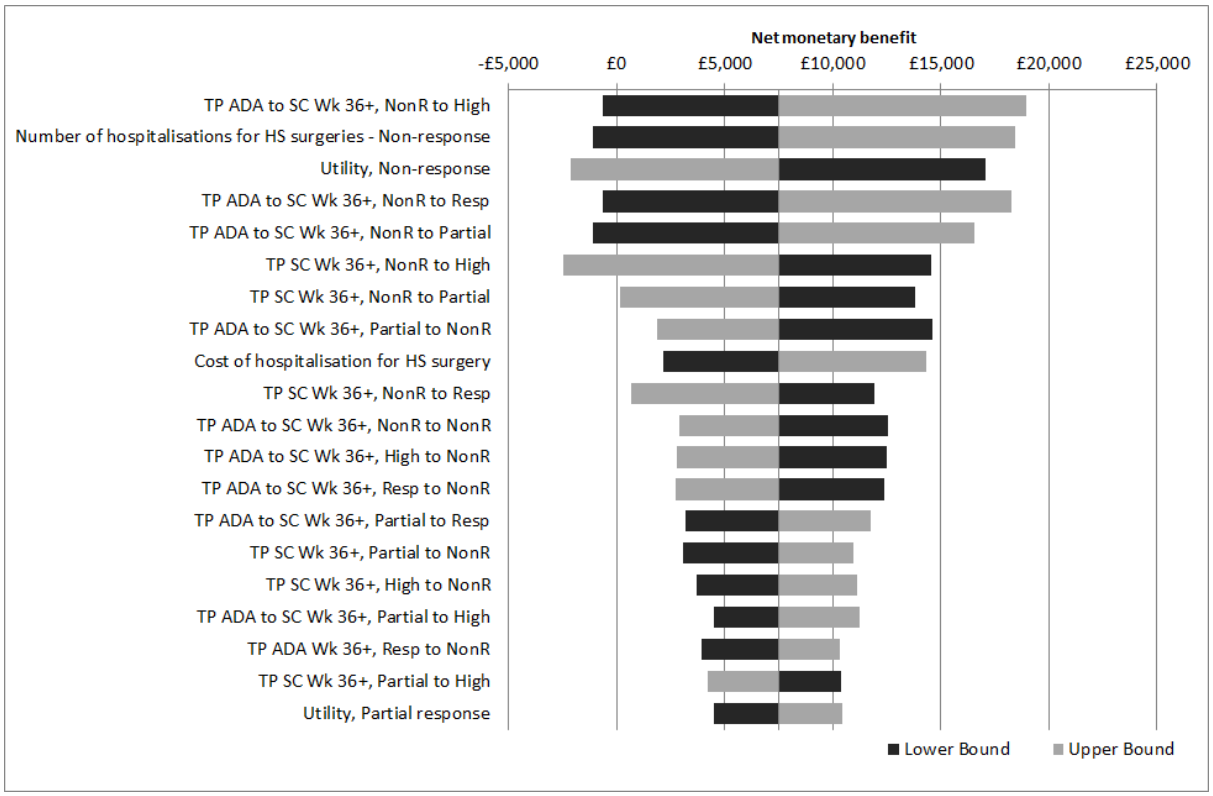
Figure 4 Cost-effectiveness plane (redrawn by the ERG)

Figure 5: Cost-effectiveness acceptability curves (redrawn by the ERG)

5.2.6.3 Deterministic sensitivity analysis results

Figure 6 presents the results of the company's DSA in the form of a tornado diagram using net monetary benefit as the economic outcome measure assuming a WTP threshold of £30,000 per QALY gained.

Figure 6: Deterministic sensitivity analysis - tornado diagram (redrawn by the ERG)



The company's DSA indicates that the key groups of uncertain parameters within the model relate to the long-term transition probabilities (from week 36 onwards, based on the GLMs), the number of HS surgeries assumed in the no response state, and the utility value applied to the no response state. When considered individually, the bounds of the 95% confidence intervals for these parameters produce a negative net benefit for adalimumab versus standard care at a WTP threshold of £30,000 per QALY gained.

5.2.6.4 Scenario analysis results

Table 47 presents the results of the company's scenario analyses.

Table 47: Company's scenario analysis results

Scenario	Incremental – adalimumab versus standard care		
	QALYs	Cost	ICER
Company's base case (deterministic)	1.00	[redacted]	[redacted]
Time horizon 20 years	0.74	[redacted]	[redacted]
Time horizon 30 years	0.86	[redacted]	[redacted]
Discount rate=0%	1.78	[redacted]	[redacted]
Discount rate=5%	0.84	[redacted]	[redacted]
Model based on PIONEER II[19] only for both adalimumab and standard care arms during induction, PIONEER II[19]only for both adalimumab and standard care arms during maintenance	0.90	[redacted]	[redacted]
LSCF extrapolation	0.90	[redacted]	[redacted]
Mean transition probability extrapolation	1.09	[redacted]	[redacted]
Transition probabilities for the adalimumab arm after week 36 estimated based on PIONEER I/II trial data[18, 19]	Model analysis unclear*		[redacted]
LOCF missing value imputation	1.32	[redacted]	[redacted]
Response specific discontinuation rates for adalimumab during weeks 12-36 from PIONEER I/II[18, 19]	0.99	[redacted]	[redacted]
Response specific discontinuation rates for adalimumab for week 36+ from PIONEER I/II[18, 19]	0.94	[redacted]	[redacted]
Discontinuation rate of adalimumab non-responders after week 36 based on OLE study[20]	1.34	[redacted]	[redacted]
Maintenance compliance rate of adalimumab (week 12+) equal to 100%	1.00	[redacted]	[redacted]

LOCF – last observation carried forward; LSCF – last state carried forward; OLE – open-label extension; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Across most of the scenarios considered, the ICER for adalimumab versus standard care remains below £30,000 per QALY gained and in some instances the ICER is below £20,000 per QALY gained. The ICER for adalimumab is greater than £30,000 per QALY gained in the following scenarios: (i) when the time horizon is truncated to 20 years; (ii) when the model uses only data from PIONEER II;[19] (iii) when the LSCF imputation rule is used, and; (iv) when the discontinuation rate for adalimumab non-responders after week 36 is based on the OLE study.[20] The ERG notes that removing the company's approach to modelling 12 further weeks of adalimumab in non-responding patients, and instead basing this on the observed estimate in the OLE study, increases the ICER to £[redacted] per QALY gained.

5.3 Critical appraisal of the company's health economic analysis

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These approaches included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[40, 41] to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of correspondence between the description of the model reported within the CS[9] and the company's executable model.
- Replication of the base case results, PSA and scenario analysis presented within the CS.[9]
- Where possible, checking of parameter values used in the company's model against the original data sources.
- The use of expert clinical input to judge the clinical credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.2 Summary of main issues identified within the critical appraisal

Box 2 summarises the main issues identified within the ERG's critical appraisal of the company's economic analysis. These issues are discussed in further detail in the subsequent sections.

Box 2: Main issues identified within the critical appraisal of the company's model

1. Deviations from the NICE Reference Case
2. Disconnect between evidence for the efficacy and cost of the comparator
3. Modelling treatment effects according to depth of response
4. Modelling treatment continuation rules
5. Potential overestimation of number of surgical inpatient admissions
6. Uncertainty surrounding transition probabilities
7. Appropriateness of pooling data from PIONEER I and II trials
8. Conceptual inconsistency in handling time-variance in transition probabilities
9. Potential bias in the use of OLE study data for long-term adalimumab responders
10. Model errors and other issues surrounding model implementation

(1) Deviations from the NICE Reference Case

Table 48 summarises the extent to which the company's model adheres to the NICE Reference Case.[21]

Table 48: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The scope of the company's model is generally in line with the final NICE scope.[8] The population considered directly relates to the populations of the PIONEER I/II trials.[18,19] Clinical advice received by the ERG suggests that this is likely to be reflective of the UK HS population who may be eligible for treatment using adalimumab.
Comparator(s)	As listed in the scope developed by NICE	The final NICE scope[8] defines the comparator as *"established clinical management without adalimumab."* Whilst the placebo arms of the PIONEER I/II trials[18, 19] are used to model efficacy, costs are based on estimates of surgical and non-surgical resource use from an online survey of UK physicians undertaken by the company.[22] It is unclear whether the elicited survey estimates as applied in the model truly reflect standard care in the UK. The ERG notes that there is no established pathway of care for patients with active moderate to severe HS after the failure of systemic conventional therapy in the UK.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains for patients are modelled in terms of QALYs gained.
Perspective on costs	NHS and PSS	The CS[9] states that an NHS and PSS perspective was adopted, although no relevant PSS costs are included in the company's model. Excluding the management of certain AEs, all costs are assumed to be incurred in the secondary care setting.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of the incremental cost per QALY gained for adalimumab versus standard care.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a lifetime horizon. Scenario analyses are also presented for shorter time horizons (20 years and 30 years).
Synthesis of evidence on health effects	Based on systematic review	The model is largely based on data collected within the PIONEER I/II trials.[18, 19] Long-term extrapolation of transitions for adalimumab responders beyond 36 weeks are based on the M12-555 OLE study.[20] The company's use of arm based summaries to aggregate data from the PIONEER I/II trials breaks randomisation and may lead to bias.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health utilities were based on EQ-5D estimates from the PIONEER II trial.[19]

Element	Reference case	ERG comments
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Health utilities were based on EQ-5D estimates from the PIONEER II trial.[19]
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use estimates according to depth of response were elicited via a survey of UK physicians. Cost estimates were based on the BNF,[37] NHS Reference Costs[38] and the PSSRU.[39]
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	All costs and QALYs are discounted at a rate of 3.5%

QALY – quality-adjusted life year; EQ-5D – Euroqol 5D; NHS – National Health Service; PSS – Personal Social Services; NICE – National Institute for Health and Care Excellence

The company's model is generally in line with the final NICE scope.[8] The company's model is principally based on data collected within the PIONEER I/II trials and therefore reflects the populations of patients recruited into these trials. Clinical advisors to the ERG considered that these patients generally reflect the population who may be considered eligible for treatment using biologic therapy in England. The ERG notes that there is a lack of clarity within the CS with respect to the comparator, particularly since standard care is assumed to relate only to secondary care resource use, and the costs of pharmacological therapies are not included in the model. The ERG also has some concerns regarding whether the elicited estimates of surgical resource use applied in the model truly reflect the typical experience of patients with HS in England. Clinical advisors to the ERG were satisfied that the types of resource use included in the model were generally relevant, but noted that some treatments (e.g. wound dressings, where needed) may be given in a primary care setting and that some patients will be prescribed antibiotics by their GPs for several years, yet these costs are not included in the model. The clinical advisors also noted that a comparison of adalimumab against infliximab may have been useful, but could not have been based on the HiSCR measure. The time horizon, perspective and discount rate used in the company's analysis are appropriate. No additional

equity weighting is applied to estimated QALY gains. Issues surrounding the appropriateness of the company's approach to modelling treatment benefits are detailed in the subsequent sections.

(2) Disconnect between evidence for the efficacy and cost of the comparator

The CS[9] highlights that until recently there were no published guidelines to help clinicians and patients determine potential treatment choices. The CS[9] also states that there are no licensed effective therapies for the treatment of HS in the UK and that various pharmacological therapies are commonly used off-label (including antiseptics, NSAIDs, immunosuppressants, corticosteroids, anti-androgens, retinoids and TNF-α inhibitors). The ERG considers that this in itself is an insufficient justification for excluding these options as potential comparators. The CS does however also note that there is limited robust evidence to demonstrate the efficacy of any of these therapies in the management of HS.

The CS argues that surgery does not represent a relevant comparator for adalimumab since adalimumab and surgery are not alternative or exclusive treatment choices and because within the PIONEER I/II trials,[18,19] patients were allowed to undergo surgery to control symptoms. Page 139 of the CS states that *"Patients receiving ADA in the clinical trials were allowed surgery for symptom control",* whilst the company's clarification response[17] suggests the opposite, stating that *"Surgery was not permitted in the PIONEER I and II studies per protocol. As such a change in the number of surgeries could not be observed"* and a second clarification response included incision and drainage in a list of permitted co-interventions (see clarification response,[17] question A12) and this was reported to have taken place in the M10-467 trial[25] (see Section 4.2.1). Consequently, the ERG remains unclear whether surgery was, or was not, allowed in the PIONEER trials. The CS further argues that antibiotics, dapsone, retinoids, immunomodulators and other biologics are not suitable comparators to adalimumab. As such, the CS argues that the main comparator for the analysis is standard care, as represented by the placebo arms in the PIONEER I/II trials.[18,19]

However, the ERG notes that there is a disconnect with respect to how the treatment benefits and costs of standard care are represented within the company's model. The progression of patients receiving standard care, which is characterised in terms of transitions between HiSCR-defined health states, are based directly on either cross-tabs of observed trial data or GLMs fitted to observed HiSCR outcomes for patients randomised to the placebo groups within the PIONEER I/II trials.[18, 19] In contrast, resource use estimates are instead based on the predicted use of surgery-related and non-surgery-related secondary care resources (inpatient admissions, outpatient appointments and A&E visits), estimated from a survey of UK physicians.[22] These estimates of resource use are assumed to differ according to depth of HiSCR response, which in turn, produces different health state costs for each HiSCR state. Higher resource use is assumed for patients achieving a weaker response or no response (see Table 43).

The ERG has several concerns regarding this approach:

(i) In general, the ERG considers it inconsistent to model the benefits of treatment using one source and the resources required to achieve these benefits using another source. From the evidence presented within the CS,[9] it is unclear whether the company's modelled predictions of overall resource use reflects the experience of patients enrolled into the PIONEER I/II trials.[18, 19] Whilst the CS[9] (page 118) makes the assertion that adalimumab may lead to the delay or reduction in the need for surgery, and this assertion flows through to the company's model to produce surgery-related cost savings for adalimumab, this potential treatment benefit is not substantiated by empirical evidence presented in the CS. In response to a request from the ERG for clarification on this matter (see clarification response,[17] question B5), the company undertook a *post hoc* analysis using combined data from the PIONEER I/II studies to assess the use of incision and drainage procedures and intralesional steroid injections as surrogate markers for surgical interventions. The results of the company's analysis showed that at week 12, a greater proportion of patients who received adalimumab, compared with placebo, experienced elimination of both draining fistulas (33% vs 19%; $p<0.001$) and non-draining fistulas (15% vs 9%; $p=0.017$). The ERG notes however that it is unclear whether this fully reflects an overall reduction in surgery, particularly inpatient surgical admissions, which are a key cost driver in the company's model (see critical appraisal point 5). Clinical advisors to the ERG noted that whilst the use of adalimumab could reduce the extent to which limited surgical procedures are required for patients with previously uncontrolled disease, in some instances adalimumab may be used as a preadjuvant "bridge" to more definitive surgery, thereby increasing the use of surgery. Consequently, there remains uncertainty regarding whether adalimumab will increase or decrease the lifetime costs of surgery for HS patients.

(ii) The company's approach ignores the costs of other concomitant pharmacological therapies. The CS[9] (page 173) claims that the costs of conventional therapies were likely to have been lower in the adalimumab groups relative to the placebo groups in PIONEER I/II,[18, 19] and that excluding these costs from the model is "conservative." This assertion is not however supported by any evidence within the CS.[9] In response to a request for clarification by the ERG (see clarification response,[17] question B9), the company provided estimates of the use of concomitant medications in >5% patients in Period A of the PIONEER I/II trials. On the basis of this additional information provided by the company, the ERG is satisfied that the proportions of patients receiving each therapy are broadly similar between the adalimumab and placebo groups. However, this information relates only to the first 12 weeks of treatment within the RCTs; it remains unclear whether the inclusion of the costs of concomitant medications would substantially impact upon the cost-effectiveness of adalimumab over a lifetime horizon.

(iii) Specifying resource use according to depth of response, whereby resource use is lower for better HiSCR outcomes, may induce a spurious (or at least an unproven) relationship within the model between the time spent receiving adalimumab, the time spent in a state of better response and resource use avoided. Within the PIONEER I/II trials,[18, 19] it is unclear whether the use of health care resources was lower in the adalimumab groups.

(iv) The ERG remains unclear whether estimates of surgery-related and non-surgery-related resource use could or could not have been drawn directly from the PIONEER I/II trials.[18, 19] If certain types of surgery were indeed allowed in the PIONEER I/II trials, using estimates from this source may have allowed for a greater degree of consistency between the modelled estimates of QALYs gained and the resources required to generate such health gains. The ERG notes however that if this information was not adequately collected in the trials, the company would have had no alternative but to use an alternative evidence source to inform resource use estimates within the model.

(3) Modelling treatment benefits according to depth of response

As detailed in Section 5.2, the company's model structure is based on four main health states, defined according to the depth of HiSCR response: (i) high response; (ii) response; (iii) partial response, and; (iv) no response. With respect to the company's decision to adopt this depth-based structure, the CS[9] (page 135) states: *"Preliminary analyses of the EuroQol (EQ-5D) data collected in the PIONEER II trial[30] indicated that there was a statistically significant difference in the utility values between the high response and response state, and between the values of the partial response and non-response health states. Therefore, to better evaluate the impact of treatment on HRQOL, the analysis considered four separate response health states."*

With the exception of data from the poster presented at WCD 2015 reported in Section 4.2.7.4 of the CS,[9] the company's systematic review of clinical evidence reports only on the full HiSCR measure, as pre-specified in the final statistical analysis plans of the PIONEER I/II trials. This leads to a degree of discordance between the evidence presented in the company's clinical efficacy review and the way in which evidence from the included studies is used within the company's model. Consequently, the ERG requested further clarification regarding the justification of the company's model structure (see clarification response,[17] question B2). In response, the company stated: *"...the selection of four response health states was due to the following considerations: 1) there were statistically significant differences in the response rates of adalimumab and placebo in "high response", "response" and "non-response", and 2) the utility and resource use differed across the four response health states 3) a post-hoc analysis of the PIONEER I and II studies identified a population where continued treatment with ADA could be beneficial. Therefore, to evaluate the cost-effectiveness of adalimumab, it was reasonable to segregate the model into four response health states."*

The ERG considers that disaggregating the full HiSCR measure (which is a dichotomous outcome) according to depth of response (which is an ordered categorical outcome), represents a *post hoc* analysis of a pre-planned endpoint. The ERG also notes that the Kimball *et al*[29] validation study of the HiSCR measure relates only to the full HiSCR threshold (≥50% reduction in ANs, with no increase in abscesses or draining fistulas from baseline). Kimball *et al*[29] report that patients with worsening disease or minimal improvement in ANs (<30% reduction) did not have a meaningful improvement on the DLQI and reported some worsening in pain despite demonstrating some improvement in total work impairment and total activity impairment (see Figures 7 and 8). Kimball *et al* also report that no substantial incremental benefits were observed on patient reported outcomes beyond the ≥50% AN reduction threshold for HiSCR.

Figure 7: Change in pain VAS and DLQI (reproduced from Kimball *et al*[29])

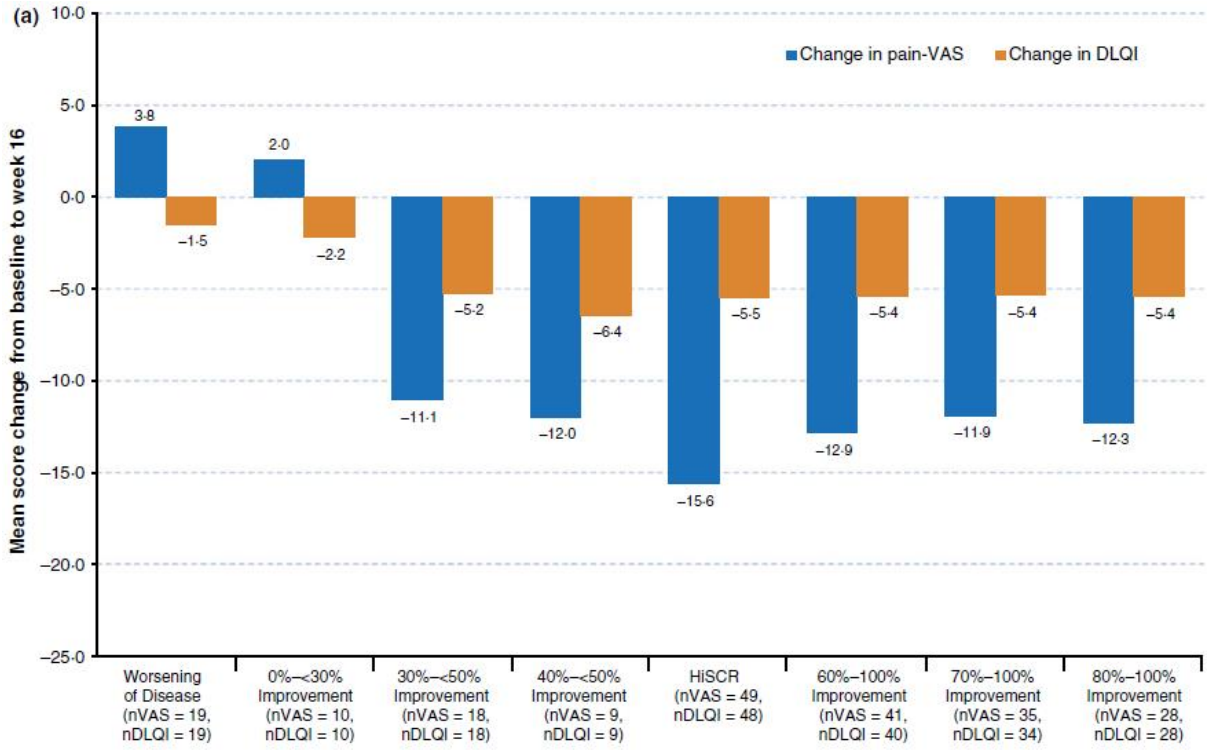
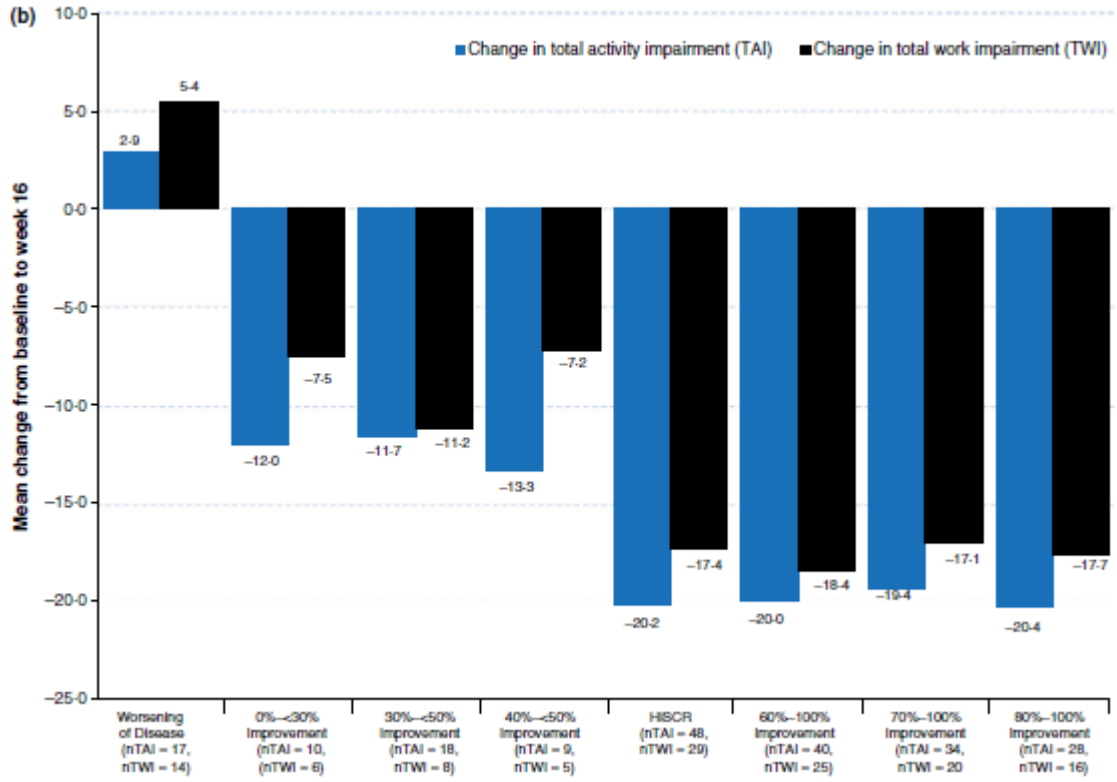


Figure 8 Change in Work Productivity and Activity Impairment Questionnaire – Total Activity Impairment and Total Work Impairment (reproduced from Kimball *et al*[29])



With respect to the PIONEER II EQ-5D valuations, the CS states that the differences in HRQoL between no response and partial response, and high response and response, were statistically significant, but does not provide evidence to support this statement. In response to a request for clarification, the company provided *p*-values for these comparisons which confirm the company's original claim ($p<0.05$ for both comparisons). Whilst the instruments used in these two sets of analyses are not the same, the apparent distinction between health states evident in the *post hoc* analysis of the PIONEER II EQ-5D data does not appear to be entirely consistent with the analyses reported by Kimball *et al.*[29]

From the perspective of model structuring, splitting the HiSCR outcome data according to depth of response within the model would allow for a more granular representation of EQ-5D benefits over time, and in principle, the consideration of alternative discontinuation rules for patients achieving different levels of treatment benefit (although this has not been done). There are however also some negative consequences associated with this approach: (i) the available efficacy data are "stretched" across four rather than two states, hence several cells in the transition matrices are populated with small numbers of patients (see Appendix 1); (ii) patients who would be classed as partial responders in the model would have been considered to be non-responders in the clinical analysis based on the

pre-specified HiSCR threshold, thereby producing some inconsistency in the interpretation of the data from the PIONEER I/II trials,[18, 19] and; (c) the definition of health states in the model is not consistent with the aims and findings of the Kimball *et al* validation study.

The ERG notes also that within the company's model, the criterion for continuing treatment with adalimumab at 12-weeks and during subsequent maintenance therapy requires patients to achieve only a partial response, rather than a full HiSCR response. Had the company's model been structured according to the full HiSCR ≥50% AN reduction threshold, this would have necessarily led to the use of different treatment continuation rules during induction and thereafter, as only patients achieving and maintaining this level of response would continue adalimumab therapy. Clinical advisors to the ERG noted that it was unclear whether patients achieving a partial HiSCR response would obtain a clinically meaningful benefit sufficient to warrant continuing adalimumab treatment. The advisors also noted that some patients may achieve a level of benefit which is only slightly below the threshold for response, whilst at the other end of the spectrum, some patients may accrue little benefit from continued adalimumab treatment.

Based on the definition of health states and the treatment continuation rules assumed in the company's model, it could be argued that the model implicitly suggests that the 50% AN reduction threshold determined in the Kimball validation study, and later pre-specified as the primary endpoint in the PIONEER I/II trials, has been set at the wrong level for clinical practice.

Given the above discussion, there are arguments both for and against structuring the model according to depth of HiSCR response. The ERG therefore considers this to be an area of structural uncertainty. In light of this, the ERG requested that the company undertake a separate analysis in which the modelled costs and health outcomes for adalimumab and standard care were based only on HiSCR responders and non-responders at the ≥50% AN reduction threshold (see clarification response,[17] question B2). In response, the company stated the following:

"Unfortunately due to time constraints AbbVie was not able to make structural changes to the cost effectiveness model (ie. change the structure from a 4 model response state to a 2 model response state), however AbbVie was able to provide a health economic analysis which would use only the outcomes of response or no response as per the PIONEER trials by implementing the following changes to the existing model structure:

1. *Assign the same utility value to the High response and Response (HiSCR responders as per the PIONEER trials) health states based on a re-analysis of the EQ-5D data at week 12 and 36 from the PIONEER II trial*

2. *Assign the same utility value to the Partial response and non-Response (HiSCR non-responders as per the PIONEER trials) health states based on a re-analysis of the EQ-5D data at week 12 and 36 from the PIONEER II trial*
3. *Assign the same resource use cost to the High response and Response (HiSCR responders as per the PIONEER trials) health states (average the cost across the two health states)*
4. *Assign the same resource use cost to the Partial response and non-Response (HiSCR non-responders as per the PIONEER trials) health states (average the cost across the two health states)*
5. *Assign same week 36+ discontinuation rate for partial responders as per non responders based on discontinuation rate using OLE"* (Clarification response,[17]question B2).

The results of the company's re-analysis of the model based on the ≥50% AN reduction threshold are presented in Table 49.

Table 49: Results of company's analysis based on HiSCR response/no response (deterministic model, taken from company's clarification response[17])

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.12	£[redacted]	0.69	£[redacted]	£[redacted]
Standard care	12.43	£113,068	-	-	-

QALY – quality-adjusted life year; HSiCR - Hidradenitis Suppurativa Clinical Response

Within this re-analysis, the incremental QALY gain for adalimumab versus standard care is reduced considerably (from 1.00 QALYs in the company's base case to 0.69 QALYs in the HiSCR-based analysis) whilst the incremental cost is increased (from £[redacted] in the company's base case to £[redacted] in the HiSCR-based analysis). Consequently, the ICER is increased to £[redacted] per QALY gained. The ERG notes that ideally the analysis should also have included the re-estimation of all transition matrices to reflect the HiSCR ≥50% AN reduction threshold. More importantly, the ERG notes that whilst the company's re-analysis assumes that there is no difference in utility or resource use between partial responders and non-responders, patients who achieve only a partial response at the end of induction or during maintenance are assumed to continue adalimumab as a maintenance therapy. This is somewhat inconsistent given that within this analysis, these patients are assumed to gain the same health utility as non-responders. Consequently, the value of the company's re-analysis is limited. Had the company's re-analysis extended the continuation rules at induction and maintenance to apply only to those patients achieving a full HiSCR response, this would have likely improved the ICER for adalimumab. This cannot however be confirmed given the company's model structure.

(4) Modelling treatment continuation rules

The company's model assumes that at the end of the induction phase (week 12), patients receiving adalimumab who achieve high response, response or partial response will go on to receive adalimumab as a maintenance therapy. In addition, according to the CS,[9] beyond week 36, patients who are non-responsive to adalimumab are assumed to receive an additional 12 weeks adalimumab therapy prior to discontinuation.

The SmPC for adalimumab states: *"Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Humira 40 mg every week may be re-introduced (see section 5.1). The benefit and risk of continued long-term treatment should be periodically evaluated (see section 5.1)."*[12]

Given that the PIONEER I/II trials[18, 19] used the full HiSCR ≥50% AN reduction threshold as their primary endpoints, this might be reasonably inferred to reflect the definition of improvement within the SmPC. However, the company's model differs in that patients with only a partial response are also assumed to continue to receive adalimumab treatment into the maintenance phase. It is unclear whether the achievement of a partial response would lead to a health gain which is sufficient to warrant the continuation of adalimumab treatment and indeed whether the modelled continuation rule reflects what would typically occur in usual practice.

The ERG also notes that the SmPC does not stipulate how the balance of benefits and risks of continued long-term treatment with adalimumab should be assessed; the wording of the marketing authorisation is not in disagreement with the company's assumption of a further 12 weeks therapy for non-responders, yet it does not specifically recommend such a treatment approach. Whilst the clinical advisors to the ERG were satisfied with the company's assumption that, in practice, clinicians may continue to use adalimumab for a further time period (up to 3 months) if patients have lost a prior response to treatment, they did have concerns that using the HiSCR alone (particularly the achievement of only a partial response) may not represent a sufficiently broad assessment of whether the treatment is working. As discussed in Section 4.2.1, commentators on the validity of the HiSCR measure have highlighted the need to capture other aspects of treatment benefit such as pain and improvements on the DLQI.[33]

(5) Potential overestimation of number of surgical inpatient admissions

Within the company's model, the incidence and costs of surgical inpatient admissions are key drivers of the total costs in both the adalimumab and standard care groups. As detailed in Section 5.2, annual surgical inpatient admissions according to HiSCR response state were based on the company's survey of UK physicians,[22] whilst the costs were based on NHS Reference Costs 2013/14[38] (elective inpatient

code JC41Z - major skin procedures). The ERG has some concerns regarding the estimated lifetime costs associated with inpatient admissions predicted by the company's model. Within the standard care group, the model predicts that the average patient will require approximately 33.87 inpatient surgical admissions over their remaining lifetime. The equivalent number in the adalimumab group is approximately 29.78 admissions. The tariff cost applied to each inpatient admission is £5,488.32 and is assumed to be associated with a length of stay of 5.1 days; this might be considered to be broadly reflective of a wide excision procedure. The costs of these inpatient surgical admissions account for 69.47% of the total discounted lifetime costs in the standard care group and 50.86% of the total discounted lifetime costs in the adalimumab group. As discussed earlier, the CS[9] does not report any evidence to demonstrate that adalimumab reduces the requirement for overall surgical admissions relative to standard care. The ERG notes also that the questionnaire elicited information from respondents on their patients' average use of surgery over the past 12 months and did not consider an upper limit on the number of inpatient surgical admissions per patient.

Clinical advisors to the ERG suggested that excluding the management of surgical complications, the maximum number of sites which may require wide excision for a patient with very extensive disease would be 6-10 (including breasts, groin, the perineum, armpits and buttocks). Patients with less extensive disease would require fewer wide excisions than this maximum number and in some cases more than one region can be treated in the same surgical episode. The ERG's clinical advisors also suggested that patients may undergo a comparatively higher number of smaller procedures such as incision and drainage and narrow margin excision. Incision and drainage may not require inpatient admission and narrow margin excisions are likely to require a shorter length of stay thereby resulting in a comparatively lower cost than that assumed within the company's model. Lowering the cost of surgical inpatient admissions reduces the total costs for both the standard care and adalimumab groups, although given that the company's model suggests that adalimumab will reduce the number of inpatient admissions relative to standard care, this would ultimately lead to a less favourable ICER for adalimumab.

During the clarification process, the ERG queried the number of inpatient surgical admissions predicted using the model (see clarification response,[17] question B7). Within their response, the company stated:

"Considering that a typical HS patient is diagnosed in its early 20s it is not unreasonable to assume that over a lifetime patients who receive no active treatment could undergo approximately 34 inpatient admissions for surgery. Furthermore evidence from the literature suggests that patients with moderate to severe HS undergo surgical procedures quite frequently. Menderes et al 2010[42] reported 54 operative procedures among 27 HS moderate to severe patients from 2004 to 2009. In an

observational cross-sectional study conducted by AbbVie out of 41 patients with surgeries there were 86 surgeries over a 5-year period.[22]*"*

The ERG notes that the starting age assumed in the model is 35 years of age (not early 20s). In addition, in both of the sources cited by the company,[22, 42] the crude surgery rate is around 2 procedures over approximately 5 years (~0.4 procedures per year). This is lower than the estimates predicted by the company's model. Furthermore, the ERG notes that several alternative surgical procedures may be used in the treatment of HS (for example, local destruction, incision and drainage, and narrow margin excision) which require fewer health resources than an inpatient length of stay of 5.1 days and a cost of £5,488 per procedure. Clinical advisors to the ERG noted also that wide excision surgery has a low recurrence rate and does not usually need to be repeated. Overall, the ERG accepts that the true lifetime cost of HS surgery for the population under consideration is highly uncertain, but considers that the assumed cost of each procedure is likely to have been overestimated within the company's model.

(6) Uncertainty surrounding transition probabilities

There is considerable uncertainty surrounding the long-term transition probabilities for adalimumab responders, for patients discontinuing adalimumab and for patients receiving standard care. The company's DSA (see Figure 6) indicates that altering some of these probabilities individually has the potential to considerably worsen the cost-effectiveness of adalimumab. This issue is recognised in the CS[9] (page 122): *"… the main limitation is the paucity of data for the licensed dose beyond 12 or 16 weeks due to re-randomisation at 12 or 16 weeks and protocol-driven discontinuation during period B for patients with LOR or WOAI in the PIONEER studies."* The number of patients with available data for each period are summarised in Table 50.

Table 50: Number of patients included in transition matrices

Time period	Adalimumab responders	Adalimumab discontinuers	Standard care
Weeks 0-12	316	N/a	317
Weeks 12-36	68	100	151
Weeks 36+	Unclear	100 (6 observations per patient)	151 (6 observations per patient)

As shown in Table 50, whilst the number of patients with available HiSCR data during induction is fairly large (adalimumab n=316; standard care n=317), the available dataset during the maintenance phase is notably smaller. In particular, only 68 patients were used to model the time-dependent transition matrices for adalimumab responders during weeks 12-36. Whilst this is not a criticism of the model itself, it does suggest considerable uncertainty in the cost-effectiveness estimates produced

from it. The ERG notes also that there are no data on long-term outcomes for patients who have discontinued adalimumab or for patients receiving standard care alone.

(7) Appropriateness of pooling data from PIONEER I and II trials

Where relevant data are available (see Table 40), the company model uses arm-based aggregate data from the PIONEER I/II trials[18, 19] to inform the transition matrices. Within the CS, the company argues against conducting a conventional NMA of trials of all treatments because of differences between trials in baseline characteristics that are potential treatment effect modifiers. The ERG notes that there are methods available which may enable such comparisons to be made, for example, matching-adjusted treatment comparisons or simulated treatment comparisons. However given that only the adalimumab trials assessed response according to the HiSCR measure, the value of using such comparisons to inform the company's model would be limited (or an entirely different model would be required).

The CS also argues against conducting a pairwise meta-analysis of the placebo-controlled adalimumab trials because, in addition to differences in baseline characteristics between PIONEER I and PIONEER II that are potential treatment effect modifiers, *"There are also differences in study design between PIONEER I and PIONEER II … which means that the results of PIONEER I and PIONEER II are not directly comparable."* (CS,[9] page 122). The differences in study design that the company alludes to are the use of concomitant oral antibiotics at study entry and subsequently, and the inclusion of concomitant oral antibiotics as a stratification factor within PIONEER II[19] but not PIONEER I.[18] Nevertheless, the company did combine the data from PIONEER I and PIONEER II and the ERG requested clarification regarding this approach (see clarification response,[17] questions B14 and B15). In their response[17] (question B14), the company focusses largely on the similarities in study design, the limited sample size within the individual studies and the similarities in baseline characteristics between the two trials, stating that: *"From a clinical perspective, both studies are of very similar study design which allows many direct comparisons as well as pooling of data."* This inconsistency in perspective ignores the fact that we expect heterogeneity in treatment effect between trials because the two trials included patients with different baseline characteristics that are potential or known treatment effect modifiers.

Whether it is appropriate to combine the evidence from PIONEER I and PIONEER II given the issue of antibiotic use raises some important issues. Firstly, it is never appropriate to perform an arm-based synthesis of data from different trials because this breaks the randomisation within trials; an appropriate analysis involves combining trial-specific treatment effects. Secondly, if variation in treatment effect is expected between trials, then this should be acknowledged in the analysis, ideally by conducting a random effects meta-analysis. Thirdly, consideration should be given to the

appropriate estimate of the treatment effect in the target patient population. If PIONEER I and PIONEER II estimate different treatment effects, then neither trial provides an estimate of the treatment effect in the target patient population. In addition, the mean of a random effects distribution does not relate to any specific patient population and the predictive distribution of a new trial is generally recommended as an estimate of treatment effect. Interestingly, the company performed a sensitivity analysis using only the data from PIONEER II and reported that the ICER for adalimumab versus standard care was £[redacted] per QALY gained (see Table 47). The ERG considers that the implications of these issues are that the estimate of treatment effect provided by the company is likely to be biased, understates uncertainty and lacks clarity regarding the population for whom the decision is being made.

The ERG notes that these same issues also apply to the company's estimates of the AE incidence rates during the induction and maintenance phases of the model (see Table 44).

(8) Conceptual inconsistency in handling time-variance in transition probabilities

The ERG considers that the company's approach to handling time dependency in the health state transition probabilities is conceptually inconsistent. Within the company's model, up to week 36, 2- or 4-week time-dependent transition matrices are used to characterise the trajectories of patients receiving adalimumab and standard care. Thereafter, the company's model uses a single time-independent transition matrix for: (a) adalimumab responders; (b) adalimumab discontinuers, and; (c) patients receiving standard care, based on separate GLMs for each of these three groups. For the adalimumab discontinuers and standard care group, the logit models are each based on all transitions previously observed during the maintenance phase (weeks 12-36), which were treated as being time-variant during the earlier cycles in the model. The ERG considers this approach to be somewhat inconsistent as time-dependency is assumed for one portion of the model, but is then ignored for the remainder of the time horizon, even though the time-variant and time-invariant matrices are based on the same data. The company's decision to adopt this approach was likely driven by the limitations of the available evidence. The ERG notes that whilst the company's scenario analyses consider the use of alternative methods for projecting long-term HiSCR outcomes, the impact of incorporating time-variance in the post-36 week transition matrices is unclear.

(9) Potential biases in the use of OLE study data for long-term adalimumab responders

Within the company's model, long-term HiSCR outcomes for adalimumab responders beyond week 36 are modelled using a GLM based on the M12-555 OLE study.[20] The populations recruited into the OLE study included people not achieving a response by or after week 16 in PIONEER I/II[18, 19] and those who achieved response and completed the PIONEER trials.

The ERG has some concerns regarding the use of these data in the model.

(i) The population recruited into the M12-555 OLE study includes a mix of patients who achieved and maintained a response to adalimumab within the PIONEER trials, as well as non-responders. This is not directly in line with the experience of the patient group for whom the matrix is applied in the model as these patients are specifically those who have achieved at least a partial response to adalimumab up to week 36. The impact of including patients with a history of response or non-response to adalimumab, rather than only long-term adalimumab responders, is unclear. The ERG notes that including only the specific group of patients with a prior response to adalimumab would reduce the available sample size for the GLM further, thereby increasing uncertainty.

(ii) Whilst patients in the M12-555 OLE study were previously enrolled within the PIONEER I/II trials,[18, 19] the OLE study adopted an unblinded observational design. Since the use of the OLE data in the model is not based on relative treatment effects drawn from a randomised blinded study design, there is a risk of bias and confounding.

(iii) The data from the OLE study used in the model have been derived from an interim analysis. Given the immaturity of these data, particularly in terms of length of follow-up for the overall OLE cohort, these transition probabilities are subject to further uncertainty.

(iv) The company used an LOCF imputation rule, whereby patients' final observations are carried forward to the final timepoint, to account for missing data in the OLE cohort, noting specifically that *"less than half of the patients had follow-up up to 24 weeks at the time of the interim data cut"* (see CS,[9] page 142). The ERG notes that the single imputation LOCF approach only produces unbiased estimates of treatment effect in certain situations. In particular, the approach may produce optimistic estimates of treatment effect if the patient's condition is expected to worsen following withdrawal from treatment. The ERG has further concerns about the use of LOCF without adequate justification or an assessment of the robustness of results based on sensitivity analyses using alternative approaches.[12] At the request of the ERG, the company provided the results of an alternative GLM which did not include imputation (see Table 51). As shown in the table, the GLM-derived transition probabilities are affected by the LOCF imputation, although this impact does not appear to be substantial. Based on these additional data, the company's deterministic ICER for adalimumab versus standard care was decreased slightly to £[redacted] per QALY gained. The company's clarification response also notes that when the PIONEER I/II trial data are used instead of the OLE study, the ICER for adalimumab versus standard care was reduced to £[redacted] per QALY gained.[17]

(v) The ERG considers the use of the OLE study to model the trajectory of long-term adalimumab responders beyond 36 weeks to be somewhat inconsistent with the approach

used for all other clinical parameters within the model (which are all based on PIONEER I/II[18,19]), but accepts the company's reasons for using these data.

Table 51: Alternative GLM model excluding imputation

OLE study GLM-derived transition matrix including LOCF imputation (base case)				
From/to state	High response	Response	Partial response	Non-response
High response	0.91	0.04	0.04	0.00
Response	0.23	0.70	0.02	0.05
Partial response	0.08	0.09	0.81	0.02
Non-response	0.03	0.03	0.12	0.82
OLE study GLM-derived transition matrix excluding LOCF imputation				
From/to state	High response	Response	Partial response	Non-response
High response	0.88	0.04	0.06	0.01
Response	0.28	0.63	0.02	0.07
Partial response	0.11	0.10	0.75	0.04
Non-response	0.04	0.05	0.14	0.77

OLE – open-label extension; LOCF – last observation carried forward; GLM – generalised logit model

(10) Model errors and other issues surrounding model implementation

The ERG rebuilt the deterministic version of the company's model in order to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model. Table 52 presents a comparison of total QALYs and costs for adalimumab and standard care, as estimated using the company's model and the ERG's rebuilt model. As shown in Table 52, the ERG was able to produce very similar estimates of costs, health gains and cost-effectiveness to those estimated using the company's model.

Table 52: Comparison of company's base case model and ERG's rebuilt model

Option	**Company's model**			**ERG's rebuilt model**		
	QALYs	**Costs**	**ICER**	**QALYs**	**Costs**	**ICER**
Adalimumab	12.61	[redacted]	[redacted]	12.61	[redacted]	[redacted]
Standard care	11.61	£128,541	-	11.61	£128,541	-

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

During the model double-programming exercise, the ERG identified four errors in the implementation of the company's model, as detailed below.

(i) Inconsistent handling of time

The company's model is inconsistent with respect to the number of days per year. For example, the QALY calculations correctly divide the cycle duration by 365.25 days; however, the weekly discount rate, the per-cycle mortality calculations, the age tracker and the cost calculations all assume that there

are exactly 52 weeks per year (364 days). These minor errors produce a small bias for both the adalimumab and standard care groups.

(ii) The cost of adalimumab is implemented incorrectly

Within the company's model, the health state costs and AE costs are applied from the first cycle (weeks 0-2); however the model only includes the costs of adalimumab from the beginning of the second cycle (during weeks 2-4). This is incorrect, as the initial dose of 160mg should have been included during the first cycle (for the period week 0-2) and an additional cost of maintenance therapy should have been applied to all patients except discontinuing non-responders for the cycle beginning at week 12.

(iii) Incorrect implementation of half-cycle correction

The implementation of the half-cycle correction within the company's model is incorrect. Whilst the company correctly subtract half of the QALY gain and cost for the final cycle from the unadjusted totals, the model includes the full QALY gains and cost for the first model cycle (at cycle 0). Only half of this QALY gain and cost should have been included in the cycle-corrected totals.

(iv) Incorrect implementation of the adalimumab non-responder continuation rule during the maintenance phase

According to the CS,[9] the company's model includes an assumption whereby patients receiving adalimumab who continue to achieve no response from treatment receive an additional 12 weeks of adalimumab treatment prior to discontinuation. The CS[9] (page 138) states that this assumption was based on input from clinical experts who suggested that patients who do not respond to adalimumab treatment will be discontinued in clinical practice after a re-assessment period and 12 additional weeks of treatment. Clinical advisors to the ERG were satisfied that the principle of continuing adalimumab treatment in these patients for a short period is reasonable.

However, the ERG notes that the implementation of this assumption within the company's model is incorrect. In the model, the probability of transiting from the adalimumab no response state to the adalimumab no response state drawn from the OLE GLM (probability = 0.82) is raised to the power of 3 (leading to a probability of 0.56) and is assumed to reflect the probability of discontinuing adalimumab (i.e. transiting to the standard care no response state). All other transitions in the row of the matrix are then adjusted accordingly. The model then applies the first unadjusted matrix to the cycles beginning at weeks 40 and 44, followed by the adjusted matrix from week 48 onwards. The impact of the company's assumption is that the use of this higher discontinuation rate leads to patients discontinuing adalimumab more quickly, thereby substantially reducing the total adalimumab treatment costs.

The ERG sought clarification regarding the mathematical logic underpinning the company's approach (see clarification response,[17] questions B3 and B17). In their response, the company stated: *"…the assumption is made that when patients are in the non-response health state for 12 weeks, they discontinue treatment. 12 weeks equals three model cycles of four weeks. The probability of a patient staying in the non-response health state for three consecutive cycles is the probability of a patient remaining in the non-response health state for 1 cycle cubed. Therefore the transition probability in "cell N130" is the probability of a patient remaining in the non-response health state for 4 weeks cubed."*

The ERG does not consider the company's approach of cubing the discontinuation probability to be mathematically correct. The cubed probability reflects the 12-week probability of consistently remaining in the no response state for three 4-week cycles. As shown in Table 53, the ICER for adalimumab versus standard care is increased substantially as the discontinuation rate is reduced.

Table 53: Modelled time on adalimumab treatment based on OLE discontinuation rate and applying company's 12-week continuation approach

Model scenario	Mean time spent receiving adalimumab (years)	ICER (adalimumab versus standard care)
Model including company's 12-week continuation approach	2.47	£[redacted]
Model based on observed OLE discontinuation rate	5.51	£[redacted]

OLE – open-label extension; ICER – incremental cost-effectiveness ratio

The mathematically correct approach to modelling the company's intended adalimumab continuation rule for non-responding patients would be to include tunnel states to reflect the number of prior cycles in which adalimumab non-responders have remained non-responsive before discontinuing treatment, whilst also accounting for the probability that a patient regains a response within the 12-week period.

Following receipt of the company's clarification response,[17] the ERG asked NICE to request further clarification from the company regarding their implementation of this continuation rule for non-responding patients. In response to this further request, the company sent an additional brief explanation together with a mock-up Excel file[43] which compares their implemented approach against an alternative approach in which 3 consecutive non-response tunnel states are modelled using aggregate HiSCR response/non-response data from the OLE GLM. The company's documented response is reproduced in full below:

"In the base case analysis the same discontinuation rate is assumed during weeks 12-36 for all ADA patients, regardless of health states, since all patients remaining on ADA during this period were

week 12 responders and if a loss of response might occur, an attempt would most likely be made to regain response instead of aggressive discontinuation as suggested by the experts consulted during this submission. However, after week 36 the discontinuation rate is based on the response-specific discontinuation rates since the discontinuation rate of ADA would most likely be driven by loss of response to treatment in the long term, given that patients who remained on ADA treatment for 36 weeks were likely to be those who tolerated the biologic treatment well.

Clinical experts consulted during this submission suggested that patients who do not respond to ADA treatment will most likely be discontinued in clinical practice after a re-assessment period and 12 additional weeks of treatment. Furthermore the ADA drug label also indicates that "the benefit and risk of continued treatment should be periodically evaluated after week 12". As such in the model base case all patients who are in the non-response health state at week 36 discontinue ADA treatment at week 48. In order to implement this assumption into the model patients who were in a non-response health state at week 36 were assigned the non-response discontinuation rate as per the OLE trial in weeks 36-40, 40-44 and 44-48 (first 12 weeks) and then at week 48 were discontinued using the cubing approach.

Beyond week 48 all patients who move to the non-response health state also discontinue treatment at a rate of 0.56 per cycle, taking in the assumption that patients who have been unresponsive for 12 consecutive weeks should discontinue treatment (the probability of adalimumab discontinuation for non-responders is 0.56 at week 48+). The assumption around the use of a higher discontinuation rate beyond week 48 was necessary in order to stop treatment in all patients who would gain no further benefit with ADA treatment, as was suggested by the clinical experts consulted. Using the discontinuation rates as observed in the OLE trial (annual rate of 44.99%) beyond week 48 would result in some patients not responding at week 36 continuing treatment with ADA for far more than 12 weeks.

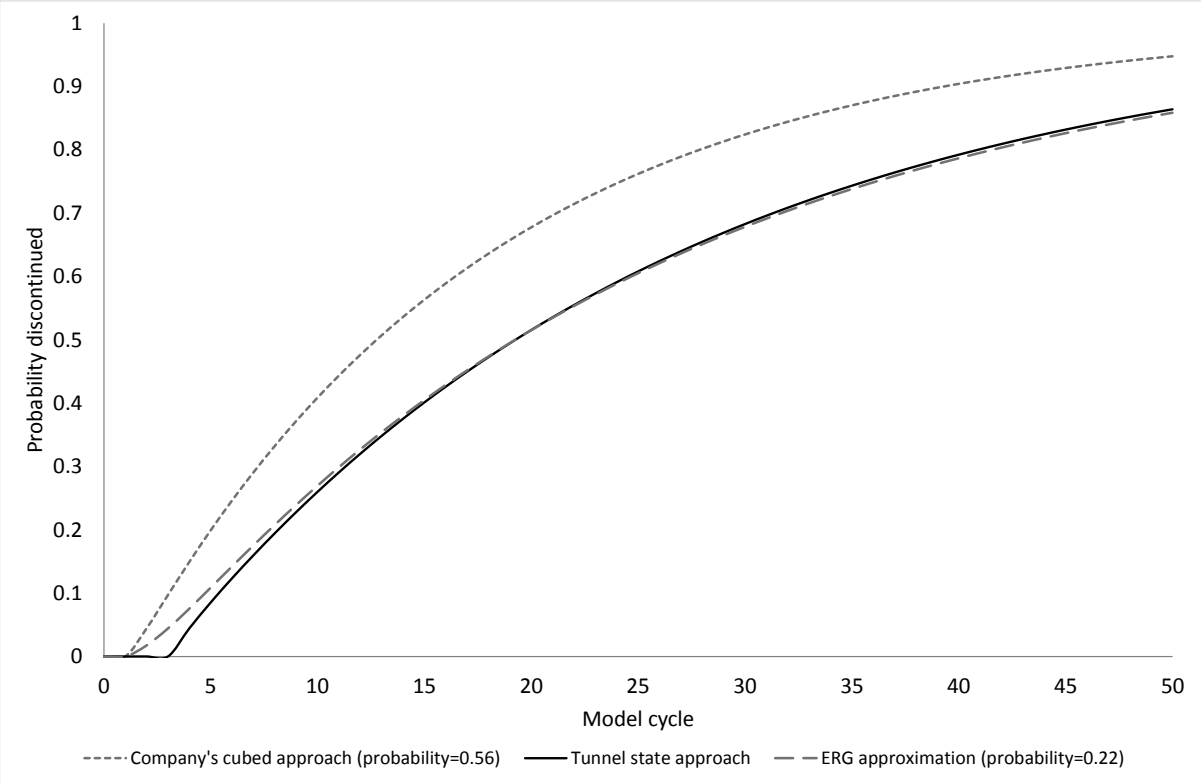
The cubed transition probability is used to reflect the assumption that patients that have been unresponsive for 12 consecutive weeks discontinue treatment. This approach was used in order to avoid introducing multiple tunnel states into the model. The ERG seem to suggest that cubing the probability of remaining unresponsive would overestimate the proportion of patients discontinuing, however the proportion discontinuing will equal out in the long term. AbbVie has provided an example with and without tunnel states to demonstrate the impact of using a model with and without tunnel states. From the calculations provided we can notice that there is initially a difference between the proportion of patients that have discontinued with and without using tunnel states, however this difference becomes smaller in the long term."[43]

With respect to the company's additional response, the ERG notes the following:

- The justification for attempting to incorporate a continuation rule for adalimumab non-responders is reasonable. Clinical advisors to the ERG were satisfied that this is likely to reflect how adalimumab may be used in clinical practice. The ERG's concerns relate to the mathematical implementation of this continuation rule.
- The ERG also agrees that using the observed discontinuation probability for non-responders beyond week 36 may result in an unrealistic proportion of patients remaining on adalimumab yet deriving no further benefit from it.
- The company's response appears to accept that using tunnel states is appropriate, but attempts to justify not using this approach due to the increased complexity associated with its implementation. This is not a satisfactory justification. The use of such an approach may lead erroneous model results.
- The company's approach of cubing the 4-week probability of transiting from non-response to non-response produces a 12-week probability of remaining non-responsive; this cannot be directly used in a model which uses a 4-weekly cycle length. Whilst the ERG understands how the probability of 0.56 has been derived, its use in the model reflects an error of logic.
- The company's Excel mock-up differs slightly from the company's model with respect to how the other transition probabilities from the no response state are normalised. In the Excel mock-up model, the probability of remaining on treatment is calculated as the probability of being non-responsive minus the probability of discontinuing adalimumab. In the company's submitted economic model, all transitions from the non-response state to the high response, response and partial response states are normalised by multiplying the transition probability by one minus the probability of discontinuation.
- The company's Excel mock-up demonstrates that using the cubed probability of 0.56, the probability of adalimumab discontinuation is consistently and substantially overestimated relative to the tunnel state approach. Whilst the company's response indicates that this difference diminishes over time, this is only because there are few patients left on treatment by that point. The ERG notes that within the company's Excel mock-up, manually reducing the 4-week probability of adalimumab discontinuation to a value of 0.22 (estimated by trial and error) produces a much closer approximation of the correct tunnel state approach (see Figure 9). It is also noteworthy that converting the company's cubed (12-week) probability of 0.56 to a rate and then converting this back to a 4-week probability gives an estimated discontinuation probability of 0.24, which is similar to the ERG's manually derived estimate (the slight difference is likely to be due to the small probability of non-responders regaining response during each cycle). The ERG considers the value of 0.22 to be a more reasonable,

but not ideal, approximation of the company's assumed 12-week adalimumab non-responder continuation rule during the maintenance phase of the model.

Figure 9 Time to treatment discontinuation using the company's Excel mock-up



Overall, the ERG considers that the company should have adopted a model structure which includes tunnel states to account for the assumed maintenance phase continuation rule. Based on the evidence presented within the CS and subsequent clarification responses, the impact of the company's approach on the expected ICER for adalimumab versus standard care is unclear.

5.4 Additional exploratory analyses undertaken by the ERG

This section presents additional exploratory analyses using the company's model undertaken by the ERG.

5.4.1 Methods for exploratory analyses

Based on the issues discussed in the ERG's critical appraisal of the company's model (see Section 5.3), eight sets of additional analyses were undertaken. The first three sets of analyses reflect the ERG's base case, whilst the subsequent five sets of analyses were undertaken to examine remaining uncertainties using the ERG's base case. Specific amendments made to the company's model within these analyses are detailed in Appendix 2.

ERG Exploratory Analysis 1 - Correction of model errors

As detailed in Section 5.3, the ERG identified several minor errors in the implementation of the company's model. Within this exploratory analysis, the ERG corrected the inconsistencies in the number of days in a year, resolved the issues surrounding the implementation of the half-cycle correction and altered the timing of the adalimumab acquisition costs to reflect the licensed dosing schedule.[12] The issues surrounding the 12-week adalimumab non-responder continuation rule during the maintenance phase of the model are not addressed within this analysis.

ERG Exploratory Analysis 2 – Incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule

The company's base case model attempts to apply a continuation rule during the maintenance phase whereby patients who are non-responsive to adalimumab continue to receive an additional 12-weeks of adalimumab therapy prior to withdrawing from treatment. The mathematical implementation of this assumption within the company's model is flawed and leads to a rapid withdrawal rate for patients receiving adalimumab (see Figure 9). In this analysis, major structural changes were made to the company's model to implement the company's adalimumab non-responder continuation rule from week 40 onwards, as described in the CS and subsequent clarification responses. This involved the following steps:

1. Restructuring the 36+ week adalimumab transition matrix to include three tunnel states for adalimumab non-responders.
2. Re-calculating the transition probabilities based the original 36+ week matrix whereby the probability of transiting from each tunnel state to the next tunnel state (or eventually discontinuing) is defined as the complement of each row of probabilities. The original and amended week 36+ adalimumab transition matrices are shown in Tables 54 and 55, respectively.

3. Re-generating the Markov trace for the high response, response and partial response maintenance phase submodels using a looping approach to account for state transitions followed by adjustments to account for other-cause mortality.
4. Condensing the new Markov trace for each submodel back to the original states defined in the company's model, whereby health state occupancy in the no response state is calculated as the sum of the health state occupancy in all three no response tunnel states in each cycle.
5. Replacing the entire Markov trace for each submodel with the new trace generated by the ERG from week 40 onwards. The ERG notes that whilst this is in line with the assumptions of the company's model, in practice, this continuation rule may apply immediately following the start of adalimumab maintenance therapy (from week 16 onward).

Table 54: Company's original week 36+ matrix for patients receiving adalimumab

			To state							
			ADA				SC			
			High response	Response	Partial response	No response	High response	Response	Partial response	No response
From state	ADA	High response	[redacted]							
		Response								
		Partial response								
		No response								
	SC	High response								
		Response								
		Partial response								
		No response								

Table 55: Week 36+ matrix for patients receiving adalimumab including tunnel states

			To state									
			On adalimumab						On standard care			
			High response	**Response**	**Partial response**	**No response1**	**No response 2**	**No response3**	**High response**	**Response**	**Partial response**	**No response**
From state	ADA	High response										
		Response										
		Partial response										
		No response 1										
		No response2										
		No response3										
	SC	High response										
		Response										
		Partial response										
		No response										

** Calculated as complement of all other transitions in the row*
† In line with the transitions from the high response, response and partial response states, spontaneous discontinuation from each tunnel state is also assumed

This analysis also includes the minor model amendments detailed in ERG Exploratory Analysis 1.

ERG Exploratory Analysis 3 - Use of alternative assumptions regarding the costs of HS surgery inpatient admissions (ERG-preferred base case)

As discussed in Section 5.3, the ERG has concerns that the costs of HS surgical inpatient admissions are likely to be considerably overestimated. An exploratory analysis was therefore undertaken based on revised HS surgery costings developed by the ERG in conjunction with the clinical advisors involved in the assessment. Within this analysis, the following assumptions were made:

(i) The company's modelled estimate of total lifetime HS surgeries (33.87 procedures) for patients receiving standard care, based on the company's resource use survey, is reasonable;

(ii) Based on the company's retrospective cohort study using HES data described in the CS[9] (page 30), [redacted] of all HS surgeries are intermediate procedures which are undertaken in a day case setting;

(iii) Of the remaining [redacted] of HS surgeries, patients on average have 2 wide excisions over their lifetime;

(iv) All other remaining surgeries are comprised of an equal mix of elective and non-elective intermediate skin procedures with an average length of stay (LOS) of 2 days.

Table 56 presents revised estimates of the average cost of HS surgery, valued using 2013/14 NHS Reference Costs.[38] These alternative assumptions result in an estimated cost of £1,525.74 per surgical procedure. Within the economic analysis, this cost is applied as the unit cost for all HS surgical admissions.

Table 56: Revised HS surgery costing assumptions

Parameter	Value	Source
Lifetime number of surgeries for patients receiving standard care	33.87	Company's model prediction
Average number of wide excisions over patient's lifetime	2	Expert opinion (JRI)
Proportion of all surgeries which are undertaken in day case setting	[redacted]	Company's survey (page 30)
Proportion of all surgeries which are wide excisions	[redacted]	Assumption
Proportion of all surgeries which are intermediate procedures requiring inpatient admission (including procedure plus 24 hours i.v. antibiotics)	[redacted]	Assumption
Cost day case intermediate procedure	£943.17	NHS Reference Costs 2013/14 - JC42A (day case)
Cost wide excision	£5,488.32	NHS Reference Costs 2013/14 - JC41Z (inpatient elective)
Cost intermediate skin procedure requiring admission	£2,102.73	NHS Reference Costs 2013/14 - (average of JC42A elective and JC42A non-elective assuming length of stay=2 days)
Mean HS surgery cost	**£1,525.74**	-

HS – hidradenitis suppurativa

This analysis also includes the model corrections and incorporation of tunnel states for non-responders detailed in ERG Analyses 1 and 2.

ERG Additional Exploratory Analysis 4 – Use of PIONEER II data only

As discussed in Section 5.3, the CS presents contradictory arguments regarding whether PIONEER I and II should be pooled. Within this analysis, the ERG presents a scenario which includes data only from the PIONEER II trial.

This additional exploratory analysis also includes the amendments detailed in ERG Exploratory Analyses 1-3.

ERG Additional Exploratory Analysis 5 – Alternative assumptions regarding transition probabilities beyond week 36

Within this analysis, two alternative scenarios were considered to explore the uncertainty surrounding the long-term extrapolation of health state transitions within the company's model. The first analysis uses the GLM transition matrix derived from the M12-555 OLE study but excludes the use of LOCF

imputation (see Table 51). The second scenario uses the alternative transition matrices for adalimumab discontinuers and patients receiving standard care based on the mean transition probabilities for weeks 12-36 derived from the PIONEER I/II trials.

This additional exploratory analysis also includes the amendments detailed in ERG Exploratory Analyses 1-3.

ERG Additional Exploratory Analysis 6 – Discontinuation of partial responders and non-responders at 12-weeks

Within this analysis, patients who achieve a response or a high response on adalimumab at 12 weeks are assumed to continue adalimumab treatment, whilst those achieving only a partial response or no response are assumed to discontinue at this timepoint. It should be noted that due to the structural limitations of the model, it was not possible to apply the company's intended maintenance continuation rule to both partial responders and non-responders as this would require a further set of tunnel states for partial responders.

This additional exploratory analysis also includes the amendments detailed in ERG Exploratory Analyses 1-3.

ERG Additional Exploratory Analysis 7 – Assumption of no difference in utility, resource use or discontinuation rates for non-responders and partial responders, and for high responders and responders

Within this analysis, the utility values, resource use estimates and discontinuation rates for the high response and response states, and for the partial response and no response states, are assumed to be the same based on the alternative model submitted by the company during the clarification stage (see Table 49). The ERG notes however that within this analysis, partial responders are assumed to continue adalimumab treatment, yet they derive no more benefit than non-responders.

This additional exploratory analysis also includes the amendments detailed in ERG Exploratory Analyses 1-3.

ERG Additional Exploratory Analysis 8 – Assumption of no difference in utility, resource use or discontinuation rates for non-responders and partial responders, and for high responders and responders, including the discontinuation of partial responders and non-responders at 12-weeks

This analysis is the same as the previous analysis, except that patients who achieve a partial response at 12 weeks are assumed to discontinue adalimumab induction therapy. This provides some indication of the impact of discontinuing adalimumab in both partial responders and non-responders, but only at

the end of induction. It would have been preferable to apply a consistent continuation rule to partial responders during the maintenance phase, however, this was not possible within the company's model structure.

This additional exploratory analysis also includes the amendments detailed in ERG Exploratory Analyses 1-3.

5.4.2 Results of the ERG's additional exploratory analyses

ERG Exploratory Analysis 1: Correction of model errors

Table 57 presents the results of ERG Exploratory Analysis 1 which includes only the correction of model errors discussed in Section 5.3 (see critical appraisal point 10 and Appendix 2).

Table 57: ERG Exploratory Analysis 1 – correction of model errors

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.64	£[redacted]	1.00	£[redacted]	**£**[redacted]
Standard care	11.64	£128,430	-	-	-

HiSCR – Hidradenitis Suppurativa Clinical Response; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Based on the corrected version of the company's model, the deterministic ICER for adalimumab is estimated to be £[redacted] per QALY gained; this is marginally higher than the company's base case estimate presented within the CS[9] (original ICER=£[redacted] per QALY gained).

ERG Exploratory Analysis 2: Incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule (including ERG Exploratory Analysis 1)

Table 58 presents the results of the company's model which includes the addition of tunnel states to better reflect the proposed adalimumab non-responder continuation rule during the maintenance phase. The analysis also includes the model corrections presented in ERG Exploratory Analysis 1.

Table 58: ERG Exploratory Analysis 2 – incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.72	£[redacted]	1.07	£[redacted]	**£**[redacted]
Standard care	11.64	£128,430	-	-	-

HiSCR – Hidradenitis Suppurativa Clinical Response; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

The results presented in Table 58 demonstrate that the incorporation of tunnel states within the company's model increases both the incremental QALY gains and the incremental costs of

adalimumab relative to the company's base case estimates. The incorporation of tunnel states for adalimumab non-responders in the corrected version of the model increases the ICER for adalimumab versus standard care to £[redacted] per QALY gained.

The ERG notes that using the corrected version of the company's submitted model together with an adalimumab non-responder 4-week discontinuation probability of 0.22 (see Figure 9) produces a similar ICER to the results presented in Table 58 (ICER=£[redacted] per QALY gained).

ERG Exploratory Analysis 3: Revised assumptions regarding costs of HS surgery (including ERG Exploratory Analyses 1 and 2)

Table 59 presents an exploratory analysis in which the cost of surgical inpatient admissions is assumed to be £1,525.74 per procedure (see Table 56). This analysis also incorporates the model corrections applied in ERG Exploratory Analysis 1 and the tunnel states applied in ERG Exploratory Analysis 2. This analysis represents the ERG's preferred base case (given the constraints of the company's adopted model structure).

Table 59: ERG Exploratory Analysis 3 – revised assumptions regarding costs of HS surgery (ERG base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Probabilistic model					
Adalimumab	12.75	£[redacted]	1.09	£[redacted]	**£**[redacted]
Standard care	11.66	£63,909	-	-	-
Deterministic model					
Adalimumab	12.72	£[redacted]	1.07	£[redacted]	**£**[redacted]
Standard care	11.64	£64,018	-	-	-

HiSCR – Hidradenitis Suppurativa Clinical Response; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

As shown in Table 59, the estimated QALY gains for adalimumab and standard care are the same as those estimated within ERG Analysis 2. However, the total discounted lifetime costs in both treatment groups are reduced considerably. Since the ERG's preferred estimate of the costs of HS surgery are lower than those used in the company's model, and because the company's base case analysis suggests that adalimumab produces cost savings by avoiding HS surgery due to patients spending more time in the better response states, this analysis produces a higher incremental cost for adalimumab versus standard care. Within this analysis, the deterministic ICER for adalimumab versus standard care is estimated to be £[redacted] per QALY gained. Based on the probabilistic version of the model, the ICER for adalimumab versus standard care is expected to be £[redacted] per QALY gained.

ERG Additional Exploratory Analysis 4: Use of PIONEER II data only (using the ERG-preferred base case)

Table 60 presents an exploratory analysis using only the PIONEER II data. This analysis uses the ERG's base case version of the model (ERG Exploratory Analysis 3).

Table 60: ERG Additional Exploratory Analysis 4 – use of PIONEER II data only

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.63	£[redacted]	0.99	£[redacted]	**£[redacted]**
Standard care	11.64	£64,007	-	-	-

HiSCR – Hidradenitis Suppurativa Clinical Response; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

The results presented in Table 60 suggest that deriving the transition matrices and AE probabilities only from the PIONEER II trial increases the ICER for adalimumab versus standard care to £[redacted] per QALY gained. This is partly a consequence of patients remaining on adalimumab for a longer period of time compared with the ERG's base case analysis.

ERG Additional Exploratory Analysis 5 – Alternative assumptions regarding transition probabilities beyond week 36

Table 61 presents the results of two exploratory analyses using alternative long-term transition probabilities.

Table 61: ERG Additional Exploratory Analysis 5 – alternative assumptions regarding transition probabilities beyond week 36

OLE GLM for adalimumab responders (excluding imputation), PIONEER I/II GLMs for adalimumab discontinuers and patients receiving standard care					
Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.68	£[redacted]	1.04	£[redacted]	**£[redacted]**
Standard care	11.64	£64,018	-	-	-
OLE GLM for adalimumab responders (including LOCF), mean of week 12-36 data from PIONEER I/II for adalimumab discontinuers and patients receiving standard care					
Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.58	£[redacted]	1.17	£[redacted]	**£[redacted]**
Standard care	11.41	£65,650	-	-	-

As shown in Table 61, the results of these analyses suggest that the cost-effectiveness of adalimumab versus standard care is slightly reduced when alternative long-term transition matrices are used to project HiSCR outcomes. When LOCF imputation is removed from the GLM for patients receiving adalimumab beyond week 36, the ICER for adalimumab versus standard care is estimated to be

£[redacted] per QALY gained. When the transition matrices for patients who have discontinued adalimumab and for patients receiving standard care are based on the mean of week 12-36 data from the PIONEER I/II trials, the ICER is reduced to £[redacted] per QALY gained.

ERG Additional Exploratory Analysis 6: Discontinuation of partial responders and non-responders at 12-weeks (using the ERG-preferred base case)

Table 62 presents the results of an analysis in which only patients achieving response or high response are assumed to continue adalimumab treatment beyond 12 weeks.

Table 62: ERG Additional Exploratory Analysis 6 – discontinuation of partial responders and non-responders at 12 weeks

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.62	£[redacted]	0.98	£[redacted]	**£[redacted]**
Standard care	11.64	£64,018	-	-	-

HiSCR – Hidradenitis Suppurativa Clinical Response; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Relative to the ERG's preferred base case, the discontinuation of patients who have achieved only a partial response at 12-weeks results in an estimated ICER for adalimumab versus standard care of £[redacted] per QALY gained. This is more favourable than the ERG's base case analysis. The ERG notes however that the impact of discontinuing treatment for partial responders during the maintenance phase is unclear.

ERG Additional Exploratory Analysis 7: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders (using the ERG-preferred base case)

Table 63 presents the results of an analysis in which the model corrections, non-responder tunnel states and lower surgery cost (ERG Exploratory Analyses 1, 2 and 3) are applied to a version of the model in which health utilities, resource use and discontinuation rates are assumed to be the same for partial responders and non-responders, and high responders and responders.

Table 63: ERG Additional Exploratory Analysis 7 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.25	£[redacted]	0.79	£[redacted]	**£[redacted]**
Standard care	12.46	£57,065	-	-	-

The results of this analysis suggest a considerably higher ICER than both the ERG's base case and the company's base case. However, it is important to note that whilst partial responders are assumed to continue adalimumab as maintenance therapy, their health utility is assumed to be the same as that for non-responders, hence this analysis assumes that these patients remain on treatment without obtaining further benefit from it. The ERG would have preferred that the company had incorporated adalimumab continuation rules based on the 50% HiSCR AN reduction threshold.

ERG Additional Exploratory Analysis 8: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12-weeks (using the ERG-preferred base case)

Table 61 presents the results of the scenario described in ERG Additional Exploratory Analysis 7, combined with an additional assumption that both non-responders and partial responders discontinue adalimumab at 12 weeks.

Table 64: ERG Additional Exploratory Analysis 8 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12 weeks

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.17	£[redacted]	0.71	£[redacted]	£[redacted]
Standard care	12.46	£57,065	-	-	-

The results presented in Table 63 indicate that assuming no difference in utility, resource use and discontinuation rates for no response and partial response, and for high response and response, together with the discontinuation of partial responders and non-responders at 12-weeks, the ICER for adalimumab versus standard care is estimated to be £[redacted] per QALY gained. This is lower than the previous scenario in which only non-responders discontinue at 12-weeks (ERG Additional Exploratory Analysis 7, Table 63). As noted above, due to its structure, it was not possible to apply the company's assumed discontinuation rule to partial responders within the maintenance phase of the model. The ERG does however note that increasing the discontinuation rate for partial responders lowers the ICER for adalimumab. However, the true impact of applying the discontinuation rules to both adalimumab non-responders and adalimumab partial responders in both the induction and maintenance phases of the model is unclear. This represents an important uncertainty which cannot be fully addressed given the evidence provided within the CS.

5.5 Discussion

The CS includes a systematic review of economic evaluations of treatments for HS together with a *de novo* model-based economic evaluation of adalimumab versus standard care in adult patients with an inadequate response to conventional systemic HS therapy.

The company's systematic review of existing economic evaluations did not identify any relevant studies for inclusion.

The company's *de novo* economic model adopts a Markov approach to estimate costs and health outcomes for adalimumab and standard care from the perspective of the NHS and PSS over a lifetime horizon. All analyses presented in the CS relate to the full population specified in the marketing authorisation for adalimumab; no subgroup analyses are presented within the CS. The company's model includes five mutually exclusive health states, based on depth of HiSCR response: (i) high response; (ii) response; (iii) partial response; (iv) no response, and; (v) dead. The model uses a 2-week cycle length for the first 2 cycles, and a 4-week cycle length thereafter. Health state transitions are modelled up to week 36 using data from PIONEER I/II, including a discontinuation rule for patients who do not achieve at least a partial response by week 12. The long-term HiSCR trajectory of adalimumab responders (including partial responders) beyond 36 weeks is subsequently modelled using a time-invariant GLM fitted to LOCF-imputed data from the M12-555 OLE study. The long-term HiSCR trajectories for patients receiving standard care and for those who have previously discontinued adalimumab beyond 36 weeks are modelled using separate time-invariant GLMs fitted to data from weeks 12-36 from the PIONEER I/II trials. Health utilities are modelled according to depth of HiSCR response using a *post hoc* analysis of EQ-5D data collected within PIONEER II. Resource use estimates, which are also differentiated by depth of HiSCR response, were based on a survey of UK physicians and were assumed to include inpatient visits due to HS surgery, outpatient visits due to HS surgery, visits to wound care due to HS surgery, non-surgical inpatient visits, non-surgical outpatient visits, visits to wound-care not due to HS surgery, A&E visits and costs associated with AEs. Unit costs were taken from the BNF, the PSSRU and NHS Reference Costs. AEs are not assumed to have an additional impact on HRQoL.

Based on the probabilistic version of the company's base case model, adalimumab is expected to produce an additional 1.02 QALYs at an additional cost of £[redacted] as compared with standard care; the probabilistic [redacted] for adalimumab versus standard care is expected to be £[redacted] per QALY gained. The results of the deterministic model are similar, with adalimumab yielding an ICER of £[redacted] per QALY gained compared with standard care. The company's PSA suggests that assuming a WTP threshold of £20,000 per QALY gained, the probability that adalimumab produces

more net benefit than standard care is approximately [redacted]. Assuming a WTP threshold of £30,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately [redacted]. Within the company's deterministic scenario analysis, the ICER for adalimumab was greater than £30,000 per QALY gained in four scenarios: (i) when the time horizon was truncated to 20 years; (ii) when the model was based only on data from PIONEER II; (iii) when the LSCF imputation rule was used, and; (iv) when the discontinuation rate for adalimumab non-responders after week 36 was based on the OLE study.

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified a number of issues relating to the company's model and analysis. The most pertinent of these relate to: (i) the use of a model structure in which health gains and treatment continuation rules are defined according to depth of response, which does not reflect the pre-planned and validated HiSCR endpoint used in the PIONEER trials; (ii) the likely overestimation of the lifetime costs of HS surgery predicted by the company's model; (iii) the incorrect implementation of a continuation rule for adalimumab non-responders which does not mathematically reflect the actual assumptions stated in the CS; (iv) the use of arm-based aggregate data from the PIONEER I/II trials rather than a formal meta-analysis, and; (v) uncertainty surrounding the long-term transition probabilities derived from the PIONEER I/II trials and the M12-555 OLE study.

The ERG undertook eight sets of exploratory analyses based on the company's submitted model. The first three of these analyses relate to: (i) correction of technical programming errors in the company's model; (ii) applying structural amendments to the model to correctly reflect the company's intended adalimumab non-responder continuation rule during the maintenance phase, and; (iii) re-estimation of the costs of HS surgery. The combination of these three exploratory analyses represent the ERG's preferred base case. Five additional sets of analyses were undertaken using this base case to explore uncertainty surrounding the transition probabilities employed in the model, the likely impact of discontinuing non-responders and partial responders to adalimumab (during the induction phase only) and the potential structural uncertainty around the company's adopted modelling approach. The latter two analyses could not however be fully implemented due to the limitations of the company's model structure.

The ERG's exploratory analyses indicate that the technical programming errors have only a minor impact on the model results and lead to a small increase in the ICER for adalimumab versus standard care. The incorporation of tunnel states for adalimumab non-responders within the maintenance phase of the corrected model increases the ICER for adalimumab versus standard care more substantially (ICER=£[redacted]per QALY gained). The ERG's base case, which comprises a scenario whereby

these two sets of corrections are combined with a lower cost of HS surgery, results in an estimated deterministic ICER for adalimumab versus standard care of £[redacted] per QALY gained. The probabilistic ICER for this analysis is slightly higher (£[redacted] per QALY gained). The ERG's base case ICER for adalimumab versus standard care is markedly less favourable than that presented within the CS.

The additional exploratory analyses undertaken using the ERG's base case model suggest the following:

- Using only PIONEER II to inform the model increases the ICER for adalimumab to £[redacted] per QALY gained. The ERG notes however that this analysis excludes the PIONEER I data; this is not ideal. The ERG would have preferred an analysis whereby treatment effects are based on a formal meta-analysis which maintains the randomised design of the PIONEER trials.
- The exclusion of LOCF imputation within the M12-555 OLE GLM for patients receiving adalimumab and using the mean transition data from the maintenance phase of PIONEER I/II for adalimumab discontinuers and patients receiving standard care, may reduce the ICER for adalimumab versus standard care.
- The discontinuation of partial responders as well as non-responders at the end of induction improves the ICER for adalimumab versus standard care. This can be partly explained in that high responders and responders are assumed to accrue greater benefits than partial responders, yet all three groups incur the same cost of adalimumab whilst receiving treatment. Importantly, owing to the structure of the company's model, this analysis does not apply the company's maintenance phase discontinuation rule to partial responders. Increasing the rate of discontinuation for this group may improve the ICER for adalimumab, however the ERG is unable to fully demonstrate this due to the limitations of the company's model structure.
- Based on the approach used in the company's clarification response, assuming that health utility, resource use and discontinuation rates are the same for partial responders and non-responders, and for high responders and responders, increases the ICER for adalimumab versus standard care to £[redacted] per QALY gained. It is important to note however that this analysis only applies the discontinuation rule to non-responders; whilst partial responders are assumed to continue on adalimumab beyond induction and thereafter, these patients are assumed to accrue the same utility as non-responders. Withdrawing partial responders and non-responders at the end of induction improves the ICER for adalimumab, however, the ERG was unable to apply a consistent continuation rule during the maintenance phase of the company's model. Consequently, it is not possible to fully assess the impact of this uncertainty within the company's model.

There remain several potentially important areas of uncertainty:

1. The impact of using relative treatment effects for adalimumab versus placebo based on a formal meta-analysis of data from PIONEER I and II within the model is unclear. Further, there is no comparative evidence regarding the long-term benefits of adalimumab relative to any other therapy.
2. The company's implemented model is subject to structural uncertainty, in particular around the definition of health states and the use of evidence to populate these. An alternative simpler model would have involved defining health utility, resource use, discontinuation rates, baseline transitions, relative treatment effects and adalimumab continuation rules according to the HiSCR ≥50% AN reduction threshold validated by Kimball *et al* and used as the primary endpoint in the PIONEER I/II trials.
3. The impact of adalimumab on the subsequent requirement or opportunity for surgical intervention is unclear. There is uncertainty around whether reductions in the overall costs of surgery predicted by the company's model will manifest in clinical practice. The impact of taking into account the use of other pharmacological therapies on the cost-effectiveness of adalimumab is also unknown.

6. END OF LIFE

End of life criteria are not relevant to this submission.

7. OVERALL CONCLUSIONS

The CS consisted of three separate reviews: (1) a review of the clinical efficacy evidence from RCTs of treatments for HS, specifically RCTs comparing adalimumab with placebo; (2) a review of the evidence from a non-controlled, OLE study, and; (3) a review of safety evidence from the RCTs of adalimumab versus placebo and the non-controlled, open-label extension study.

The principal clinical efficacy review is a poorly-reported systematic review of three relevant RCTs comparing adalimumab with placebo in adults with moderate to severe HS: these were comprised of a "dosing" Phase II trial, M10-467, and two Phase III trials, PIONEER I and II. The three trials all have two periods: an initial period (Weeks 0-12 in the PIONEER I/II trials and Weeks 0-16 in the M10-467 trial) comparing adalimumab 40mg EW with placebo, and a second period (Weeks 12-36 in the PIONEER trials and Weeks 16-52 in the M10-467 trial), initiated by re-randomisation of patients to arms of adalimumab 40mg EW, placebo or adalimumab 40mg EOW (PIONEER trials only). The included trials are generally consistent with the final NICE scope. The primary efficacy outcome was clinical response to treatment, principally using the company's own HiSCR measure. Clinical advice received by the ERG confirms that the HiSCR measure has been validated but, in terms of clinical decision-making, its findings must be viewed alongside the results of patient-reported outcome measures, in particular quality of life assessed by the DLQI and a pain measure. The trials' secondary outcomes included assessments of disease severity and symptoms, using the MSS score and AN counts, pain and quality of life (various measures).

The ERG considers the M10-467 trial to be at low risk of bias across all domains for the relevant Period 1 (up to week 16). The ERG also considers the results from Period A (i.e. up to week 12) in PIONEER I and II to be generally at low risk of bias. However, the ERG considers there to be a moderate or unclear risk of selection and attrition bias affecting the results of Period B in the PIONEER trials. There is also a low-to-moderate risk of reporting bias in Period B in the two trials. It should also be noted that whilst M10-467 has been published, the PIONEER trials have not.

In PIONEER I and II, significantly more patients in the adalimumab 40mg EW group achieved a clinical response (defined as achieving HiSCR [at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline] at week 12) than patients receiving placebo: 41.8% for adalimumab vs 26.0% for placebo, $p=0.003$ in PIONEER I, and 58.9% for adalimumab vs 27.6% for placebo, $p<0.001$ in PIONEER II. Subgroup analyses indicated that patients achieved benefit with adalimumab 40mg EW regardless of their baseline characteristics, although for some subgroups had small patient numbers. Significant or clinically relevant differences in favour of adalimumab 40mg EW that were reported for secondary outcomes in

PIONEER II were not always found in PIONEER I, especially for AN count, MSS score, pain and some components of quality of life measured by the SF-36. The treatment effect varied between the trials. This might be explained in part by different patient demographics across trials. The company is conducting ongoing analyses of the data from the PIONEER trials and the OLE study to understand these differences. An NMA was not considered feasible.

An arm-based integrated summary, which breaks randomisation, was conducted for the two PIONEER trials to tabulate Period B response (12-36 weeks) for all patients and for a group of HiSCR "responders" and "partial responders." According to this analysis, improvements in response were maintained or reduced in this second period. However, the "partial responder" group (defined as HiSCR responders with ≥25% reduction rather than ≥50% reduction) are a *post hoc* analysis group. This group was not defined in protocols or published descriptions of study design or pre-specified analysis methods for the PIONEER trials. It was also not considered in the published validation study for the HiSCR measure, nor was it justified or explained in the company's clinical review. A small number of secondary outcomes were reported for PIONEER I and II only for patients who had had clinical response at week 12, but the results were based on analyses with small sample sizes (range of 15 to 22 patients across all outcomes for both PIONEER trials).

These trials were supplemented by a single, unpublished, non-randomised, non-controlled, un-blinded cohort study, which was an OLE study of the PIONEER trials (M12-555 OLE). In terms of efficacy, the results suggested that [redacted]

[redacted] Details of the results for secondary outcomes such as MSS and NRS30 were not reported. The ERG considers these efficacy results to be uncertain because they are the result of interim analyses of unpublished study data with a sizeable amount of missing data. The study also only potentially offers efficacy data for up to 72 weeks for a drug that might be taken for many years by patients with moderate or severe HS.

The submission of safety evidence was a review of the three generally good quality RCTs, supplemented by the single arm cohort study. There were no obvious safety concerns, with most AEs being balanced across adalimumab 40mg EW and placebo trial arms, and small numbers of SAEs. Longer-term data are required to determine whether reported AE rates are maintained for patients on long-term maintenance doses of adalimumab 40mg EW, whether or not certain subgroups of patients are at higher risk of certain events, and to confirm whether or not there are any differences between the interrupted and uninterrupted regimens. The submission notes the M12-555 OLE is the only

ongoing study of adalimumab in this indication. Final data from this study are expected to be available in 2016.

Based on the probabilistic version of the company's base case model, adalimumab is expected to produce an additional 1.02 QALYs at an additional cost of £[redacted] as compared with standard care; the probabilistic ICER for adalimumab versus standard care is expected to be £[redacted] per QALY gained. The results of the deterministic model are similar, with adalimumab yielding an ICER of £[redacted] per QALY gained compared with standard care. The company's PSA suggests that assuming a WTP threshold of £20,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately [redacted]. Assuming a WTP threshold of £30,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately [redacted]. Within the company's DSA, the ICER for adalimumab was greater than £30,000 per QALY gained in four scenarios: (i) when the time horizon was truncated to 20 years; (ii) when the model was based only on data from PIONEER II; (iii) when the LSCF imputation rule was used, and; (iv) when the discontinuation rate for adalimumab non-responders after week 36 was based on the OLE study.

The ERG's critical appraisal identified a number of issues relating to the company's model and analysis. The most pertinent of these relate to: (i) the use of a model structure in which health gains and treatment continuation rules are defined according to depth of response, which does not reflect the pre-planned and validated HiSCR endpoint used in the PIONEER trials; (ii) the likely overestimation of the lifetime costs of HS surgery predicted by the company's model; (iii) the incorrect implementation of a continuation rule for adalimumab non-responders which does not mathematically reflect the actual assumptions stated in the CS; (iv) the use of arm-based aggregate data from the PIONEER I/II trials rather than a formal meta-analysis of relative treatment effects, and; (v) uncertainty surrounding the long-term transition probabilities derived from the PIONEER I/II trials and the M12-555 OLE study.

The ERG undertook eight sets of exploratory analyses based on the company's submitted model. The first three of these analyses represent the ERG's base case analysis. These include: (i) correction of technical programming errors in the company's model; (ii) applying structural amendments to the model to correctly reflect the company's intended adalimumab non-responder continuation rule during the maintenance phase; (iii) re-estimation of the costs of HS surgery. Further analyses were also undertaken to explore uncertainty surrounding the transition probabilities employed in the model, the likely impact of discontinuing non-responders and partial responders to adalimumab (during the induction phase only) and the potential structural uncertainty around the company's adopted modelling approach. The latter two analyses could not however be fully implemented due to the limitations of the company's model structure.

The ERG's base case analysis suggests that the probabilistic ICER for adalimumab versus standard care is expected to be £[redacted] per QALY gained. This is less favourable than the company's base case ICER. Additional analyses undertaken using this revised base case model indicate that: (i) using only PIONEER II to inform the model increases the ICER for adalimumab to £[redacted] per QALY gained; (ii) the exclusion of LOCF imputation using the M12-555 OLE GLM for patients receiving adalimumab and using the mean transition data from the maintenance phase of PIONEER I/II for adalimumab discontinuers and patients receiving standard care may reduce the ICER for adalimumab versus standard care, and; (iii) the discontinuation of partial responders at induction improves the ICER for adalimumab versus standard care. Owing to limitations in the structure of the company's model, the ERG was not fully able to assess the impact of modelling health gains, costs and adalimumab continuation rules according to the HiSCR ≥50% AN reduction threshold.

With respect to the company's economic analysis and the ERG's additional exploratory analyses, there remain several potentially important areas of uncertainty:

1. The impact of using relative treatment effects for adalimumab versus placebo based on a formal meta-analysis of data from PIONEER I and II within the model is unclear. Further, there is no comparative evidence regarding the long-term benefits of adalimumab relative to any other therapy.
2. The company's implemented model is subject to structural uncertainty, in particular around the definition of health states and the use of evidence to populate these. An alternative simpler model would have involved defining health utility, resource use, discontinuation rates, baseline transitions, relative treatment effects and adalimumab continuation rules according to the HiSCR ≥50% AN reduction threshold validated by Kimball *et al* and used as the primary endpoint in the PIONEER I/II trials.
3. The impact of adalimumab on the subsequent requirement or opportunity for surgical intervention is unclear. There is uncertainty around whether reductions in the overall costs of surgery predicted by the company's model will manifest in clinical practice. The impact of taking into account the use of other pharmacological therapies on the cost-effectiveness of adalimumab is also unknown.

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9. APPENDICES

Appendix 1 – Transition probabilities used in the company's model

(1) Adalimumab transition matrices

Table A1: Transition probabilities, weeks 0-2, adalimumab induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A2: Transition probabilities, weeks 2-4, adalimumab induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Partial-response	[redacted]		[redacted]		[redacted]		[redacted]	
Non-response	[redacted]		[redacted]		[redacted]		[redacted]	

Table A3: Transition probabilities, weeks 4-8, adalimumab induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]		[redacted]		[redacted]		[redacted]	
Response	[redacted]		[redacted]		[redacted]		[redacted]	
Partial-response	[redacted]		[redacted]		[redacted]		[redacted]	
Non-response	[redacted]		[redacted]		[redacted]		[redacted]	

Table A4: Transition probabilities, weeks 8-12, adalimumab induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]		[redacted]		[redacted]		[redacted]	
Response	[redacted]		[redacted]		[redacted]		[redacted]	
Partial-response	[redacted]		[redacted]		[redacted]		[redacted]	
Non-response	[redacted]		[redacted]		[redacted]		[redacted]	

Table A5: Transition probabilities, weeks 12-16, adalimumab maintenance (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response	[redacted]				
Partial-response	[redacted]				
Non-response	[redacted]				

Table A6: Transition probabilities, weeks 16-20, adalimumab maintenance (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response	[redacted]				
Partial-response	[redacted]				
Non-response	[redacted]				

Table A7: Transition probabilities, weeks 20-24, adalimumab maintenance (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response	[redacted]				
Partial-response	[redacted]				
Non-response	[redacted]				

Table A8: Transition probabilities, weeks 24-28, adalimumab maintenance (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response	[redacted]				
Partial-response	[redacted]				
Non-response	[redacted]				

Table A9: Transition probabilities, weeks 28-32, adalimumab maintenance (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response	[redacted]				
Partial-response	[redacted]				
Non-response	[redacted]				

Table A10: Transition probabilities, weeks 32-36, adalimumab maintenance (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A11: Transition probabilities, weeks 36+, adalimumab maintenance (GLM. PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				NR
Response					NR
Partial-response					NR
Non-response					NR

** not reported*

(2) Adalimumab discontinuation transition matrices

Table A12: Transition probabilities, weeks 12-16, post-discontinuation (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A13: Transition probabilities, weeks 16-20, post-discontinuation (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A14: Transition probabilities, weeks 20-24, post-discontinuation (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A15: Transition probabilities, weeks 24-28, post-discontinuation (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A16: Transition probabilities, weeks 28-32, post-discontinuation (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A17: Transition probabilities, weeks 32-36, post-discontinuation (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A18: Transition probabilities, weeks 36+, post-discontinuation (GLM, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

(3) Standard care transition matrices

Table A19: Transition probabilities, weeks 0-2, standard care induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]				
Response					
Partial-response					
Non-response					

Table A20: Transition probabilities, weeks 2-4, standard care induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A21: Transition probabilities, weeks 4-8, standard care induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A22: Transition probabilities, weeks 8-12, standard care induction (cross-tab, PIONEER I and II)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A23: Transition probabilities, weeks 12-16, standard care maintenance (cross-tab, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A24: Transition probabilities, weeks 16-20, standard care maintenance (cross-tab, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A25: Transition probabilities, weeks 20-24, standard care maintenance (cross-tab, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A26: Transition probabilities, weeks 24-28, standard care maintenance (cross-tab, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A27: Transition probabilities, weeks 28-32, standard care maintenance (cross-tab, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A28: Transition probabilities, weeks 32-36, standard care maintenance (cross-tab, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table A29: Transition probabilities, weeks 36+, standard care maintenance (GLM, PIONEER II only)

From	To				N observations
	High response	Response	Partial response	Non-response	
High response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix 2: Technical details of amendments to company's model within the ERG's exploratory analyses

ERG Exploratory Analysis 1: Correction of model errors

Item no.	Worksheet reference	Cell reference	Description of amendment	Rationale for amendment
1	Life Table	N10:N80 and O10:O80	Amended to reflect number of days in year	Model previously assumed 364 days per year
2	Base Case Results	O11	Weekly discount rate amended to reflect number of days in year	Model previously assumed 364 days per year
3	Markov Trace – ADA	DR10:DR13, DR15:DR869	Amended to reflect number of days in year	Model previously assumed 364 days per year
4	Markov Trace – SC	BQ10:BQ13, BQ15:BQ869	Amended to reflect number of days in year	Model previously assumed 364 days per year
5	Markov Trace – ADA	BK9:BK13, BL9:BL13, BM9:BM13, BN9:BN13, BP9:BP13, BQ9:BQ13, BR9:BR13, BS9:BS13, BK15:BK869, BL15:BL869, BM15:BM869, BN15:BN869, BP15:BP869, BQ15:BQ869, BR15:BR869, BS15:BS869, DU9:DU13, DU15:DU869	Amended to reflect number of days in year	Model previously assumed 364 days per year
6	Markov Trace – SC	S9:S13, T9:T13, U9:U13, V9:V13, X9:X13, Y9:Y13, Z9:Z13, AA9:AA13, S15:S869, T15:T869, U15:U869, V15:V869, X15:X869, Y15:Y869, Z15:Z869, AA15:AA869, BT9:BT13, BT15:BT869	Amended to reflect number of days in year	Model previously assumed 364 days per year
7	Markov Trace – ADA	BK876:BY876, CG876:CU876	Half of cycle 0 costs subtracted from total costs	Half-cycle correction applied incorrectly
8	Markov Trace – ADA	CX876:DG876	Half of cycle 0 QALYs subtracted from total QALYs	Half-cycle correction applied incorrectly
9	Markov Trace – SC	S876:AG876, AK876:AY876	Half of cycle 0 costs subtracted from total costs	Half-cycle correction applied incorrectly

Item no.	Worksheet reference	Cell reference	Description of amendment	Rationale for amendment
10	Markov Trace – SC	BB876:BK876	Half of cycle 0 QALYs subtracted from total QALYs	Half-cycle correction applied incorrectly
11	Markov Trace - ADA	BE9:BH13	Additional 4-weeks of adalimumab included for patients in high response, response and partial response states	Adalimumab costs applied in wrong cycle
12	Markov Trace - ADA	BE876:BI876, CA876:CE876	Lifetime costs of treatment to include treatment received in cycle 0	Lifetime costs of treatment only included costs beginning in cycle 1

ERG Analysis 2: Incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule (including ERG Exploratory Analysis 1)

Structural amendments not shown in appendix; see "ERG_tunnels" worksheet in ERG base case model.

ERG Exploratory Analysis 3: Revised assumptions regarding costs of HS surgery (including ERG Exploratory Analyses 1 and 2)

Including the amendments detailed above, apply a cost of £1525.74 to worksheet "Costs & Resource Use" cell J53.

ERG Additional Exploratory Analysis 4: Use of PIONEER II data only

Using ERG base case model, select "M11-810 only" option in worksheet "Base Case Results" cells J17 and J18.

ERG Additional Exploratory Analysis 5: Alternative assumptions regarding transition probabilities beyond week 36

(i) Using ERG base case model, apply lower transition matrix shown in Table 51 to worksheet "ADA – TP" cells H104:K107.

(ii) Using ERG base case model, select "Mean TP of Weeks 12-36 applied forward" option in worksheet "Base Case Results" cell J19.

ERG Additional Exploratory Analysis 6: Discontinuation of partial responders and non-responders at 12-weeks

Using ERG base case model, set worksheet "Markov Trace – ADA" cell AR14=0 and BA14=I14.

ERG Additional Exploratory Analysis 7: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders

Using the ERG base case model, apply amendments to utilities, resource use and discontinuation rates as per the company's re-analysis provided in response to clarification question B2.

ERG Additional Exploratory Analysis 8: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12-weeks

Using the ERG base case model, apply amendments to utilities, resource use and discontinuation rates as per the company's re-analysis provided in response to clarification question B2. Set worksheet "Markov Trace – ADA" cell AR14=0 and BA14=I14.

Adalimumab for treating moderate to severe hidradenitis suppurativa: A Single Technology Appraisal

ERG response to company's fact check

Issue number	Description of issue	ERG response
1	Page 2 states that "within the PIONEER I/II trials, patients were allowed to undergo surgery to control symptoms (although it is unclear whether this was actually the case)". In the PIONEER I/II trials only 2 types of interventions were allowed: injection with intralesional triamcinolone acetonide suspension and incision and drainage. Narrow margin excision and wide margin excision for patients with advanced disease were not allowed in the PIONEER I/II trials in order not to confound the final study results. As such in the PIONEER I/II trials patients were allowed to only have acute surgical procedures but not extensive ones. Page 98 states that "Consequently, the ERG remains unclear whether surgery was, or was not, allowed in the PIONEER trials".	No change: no explicit definition of surgery as it related to the trials was provided in either the submission or clarification response.
2	Page 2 states that "The ERG notes that the primary efficacy endpoint in the PIONEER trials is the Hidradenitis Suppurativa Clinical Response (HSiCR) measure, which was developed by the company". Page 66 states that "The primary efficacy outcome was clinical response to treatment using two measures: the HS-Physicians' Global Assessment (HS-PGA) and the company's own HiSCR". HiSCR was developed by AbbVie in consultation with regulatory health authorities.	No change: The Kimball 2014 validation study makes no mention of the role of "regulatory authorities" and the authors of the validation study are academic and industry experts: no representative of regulatory authorities appears either as an author or in the acknowledgements.

3	Page 4 and 113 state that "The company is conducting ongoing analyses of the data from the PIONEER trials and the OLE study to understand these differences". The analyses have now been completed by AbbVie and no specific reasons were identified.	No change: This appears to be additional information which has not been provided by the company within the submission or in subsequent correspondence in response to the ERG's clarification questions.
4	Page 5 states that "It should also be noted that whilst M10-467 has been published, the PIONEER trials have not". Results of the PIONEER I/II trials have been published as abstract and posters.	The text has been changed to: "It should also be noted that whilst M10-467 has been published as a full peer-reviewed journal article, the PIONEER trials have not."
5	Page 5, 27, 67 and Tables 4 and 5 suggest that there was a moderate risk of selection bias in Period B of the PIONEER I/II trials due to randomization being false for some who can only be assigned to placebo for Period B. Period B of the PIONEER I/II Phase 3 controlled studies, began at Week 12, when subjects who had been randomized to adalimumab during Period A were re-randomized to 1 of 3 treatment groups in a 1:1:1 ratio: adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo from Week 12 to Week 36. Subjects who had been randomized to placebo in Period A were assigned (using re-randomization numbers to maintain the blind) to continue on blinded placebo from Week 12 through Week 35 (Study M11-810) or to receive adalimumab 160 mg at Week 12, adalimumab 80 mg at Week 14, matching placebo at Weeks 13 and 15, and adalimumab 40 mg ew from Week 16 through Week 35 (Study M11-313).	No change. The appraisal is partly a process of interpretation. Two ERG reviewers conducted this process independently and both judged the study to be at the same risk of bias for this element. The reason, that blinding was not evaluated, has not been addressed by the company.
6	Page 67 states that "However, the "partial responder" group (defined as HiSCR responders with ≥25% reduction rather than ≥50% reduction) are a *post hoc* analysis group". Partial responders in the PIONEER I/II trials were defined as "those subjects achieving at least a 25% reduction in AN count relative to	The suggested change is inaccurate. The text has been changed to: "However, the "partial responder" group (defined as HiSCR responders with ≥25% reduction but less than a 50% reduction) are a *post hoc* analysis group."

	Baseline [AN25])".	
7	Page 13 Table 2. There is missing data in the last row of the table. Page 51 Table 23. The results presented in the Table refer to the wrong trial treatment arm. Page 69 states that "Both the combined search and the HRQoL search were restricted to studies which were published in English in the last 15 years (up to 30th July 2015)". The search date is incorrect.	Not a factual inaccuracy. These cells were blank in the company's submission. Change: Swap around the Placebo and ADA EW headings in Table 23. Based on the appendices, the correct date is actually 30th June. Some supplementary searches were run on 3rd July but the bulk of the utility searches covered the period up to the end of June. The text has been amended.
8	Page 27 states that "LOCF imputation was used for secondary outcomes to manage missing data". In the PIONEER I/II trials missing data for secondary outcomes were analysed using both the non-responder imputation (NRI) and the Last observation carried forward (LOCF) imputation methods. Page 38 Table 9 for study M10-467 HiSCR is defined as a secondary outcome in the footnote. HiSCR was a *post hoc* analysis in study M10-467 not a secondary outcome. Representative lesions are listed in Table 9 for study M10-467 under secondary outcomes. This data was not collected in study M10-467. Page 38 under secondary outcomes the text reads as "PGA-Skin Pain: Patient Global Assessment of Skin Pain (NRS30: Numeric Rating Scale 0-30). Numeric Rating Scale should be 0-10. Page 43 states that "The M10-467 dosing study measured this outcome using both HS-PGA (see Table 13) and HiSCR". The HiSCR was a *post-hoc* analysis in study the M10-467.	Change to: "LOCF imputation was used for some secondary outcomes to manage missing data" Change to: "a *post hoc* analysis" No change: This is not a factual inaccuracy. This outcome was provided by the company as an Instrument in the Outcomes list: Clarification response, A9, Table 6 Change to: "PGA-Skin Pain: Patient Global Assessment of Skin Pain (NRS30: Numeric Rating Scale 0-10)". Change to: "The M10-467 dosing study measured response as a primary this outcome using HS-PGA (see Table 13) and in a *post hoc* analysis using HiSCR".

	Page 44 states that "Across all three RCTs, the percentage of patients achieving clinical response according to the HiSCR measure at week 12 or week 16 was significantly higher for patients receiving adalimumab 40mg EW compared with placebo ($p<0.01$). In Table 14, the largest p-value is $p<0.007$.	This was not a factual inaccuracy, though the number could be more precise: change to: "$p<0.007$"
	Page 47 states that "The CS also states that in PIONEER I and PIONEER II, time to WOAI, which is defined as the second incidence of the two-consecutive visits with AN count higher than the baseline AN count in patients randomised to adalimumab 40mg EW in Period A who were week-12 HiSCR non-responders". The definition of WOAI was not specific to the patients randomised to adalimumab 40mg EW in Period A who were week-12 HiSCR non-responders.	No change: This text is an exact reproduction of the company's own wording: CS, p.92 and CS,Table 9, pp.66-67, Comparative summary of trial methodology for M10-467, PIONEER I and PIONEER II: "Time to WOAI in patients randomised to ADA in period A who were week12 HiSCR non-responders."
	Page 43 Table 12 foot note text reads as "*Pooled numbers because of crossover between periods A and B".	No change: This explanation is required to justify the move from arm-based numbers.
	Page 57 states that "The study is ongoing and there were missing data for a total of 368 subjects (74.0%) at the data cut. In other words, only data on 129 (26%) of enrolled patients are reported". At the cut-off date of 29 April 2014 there were 368 subjects (74.0%) still ongoing in the OLE study. All subject data was analysed together at the cut-off date.	Change to: "Full data were only available for 26% of enrolled patients; missing data imputation methods were used for the remaining subjects who had not completed the study by the data cut-off date."
	Page 57 states that "however [redacted] <u>Visit week should be 36 rather than 26.</u>	No change: This text was an exact reproduction of the company's own wording, CS, p.106.
	Page 64 the text reads as "AEs leading to discontinuation were experienced by [redacted] of patients during M12-555 OLE, with the principal reasons being exacerbation or HS and psoriasis". Replace	Change to: "with the principal reasons being exacerbation of HS and psoriasis".

	"or" with "of". Page 64 states that "The ERG notes, however, that the rates of specific AEs were higher in the EW/EW/EW group compared with the general adalimumab group (see Table 36)". Table 36 does not report rates but reports number of patients and proportions (%).	Change to: "The ERG notes, however, that the number of specific AEs were higher in the EW/EW/EW group compared with the general adalimumab group (see Table 36)".
9	Page 75 states that "During weeks 12-36 of the maintenance phase, patients are assumed to discontinue adalimumab at a constant rate irrespective of response status, based on the PIONEER I/II studies; thereafter differential withdrawal rates are applied to patients achieving at least a partial response and non-responders based on the OLE study". In the cost effectiveness analysis differential withdrawal rates for responders (including high responders, responders and partial responders) and non-responders were considered in the extrapolation period	No amendment has been made. The ERG's original wording was already clear and the company's suggested rewording implies that a partial response is part of a broader response group (implying a 50% AN reduction threshold)
10	Page 97 and Table 48 state that "The ERG also has some concerns regarding whether the elicited estimates of surgical resource use applied in the model truly reflect the typical experience of patients with HS in England." In absence of direct data on resource utilisation from the PIONEER I/II trials AbbVie estimated resource use based on inputs from a survey of physicians (n=40) who actively treat moderate to severe HS	This is not a factual inaccuracy. Our concern is about how those elicited estimates are used in the model (i.e. as annual probabilities applied indefinitely) rather than the estimates themselves.

	patients in the UK. AbbVie believes that the estimates provided by the UK physician survey are from a robust sample (N=40) and that they reflect the experience of patients with HS in England.	
11	Page 75 states that "This approach to handling adalimumab discontinuation is not fully justified in the CS". The approach is described in Table 56 page 183 of the CS. Page 99 states that "However, this information relates only to the first 12 weeks of treatment within the RCTs; it remains unclear whether the inclusion of the costs of concomitant medications would substantially impact upon the cost-effectiveness of adalimumab over a lifetime horizon". Comment regarding the impact of including additional data on the cost-effectiveness of adalimumab in HS not supported by evidence. Page 103 "the definition of health states in the model is not consistent with the aims and findings of the Kimball et al validation study". The study results by Kimball et al 2014 presented in Figure 7 demonstrate that patients with worsening disease or minimal improvement in ANs (<30% reduction) did not experience a meaningful improvement in DLQI however above the 30% threshold a clinically meaningful improvement can be observed from Figure 7 (ie., MCID of 5). This tends to suggest that patients above the 30% threshold (similar to the partial responders as defined in the AbbVie analysis (25% to 50%) experience an improvement in QOL. This would support the model categorization of response into different health states.	We agree. This sentence has been deleted This is not a factual inaccuracy. No amendment has been made to the ERG report. This is not a factual inaccuracy. The ERG consider the original wording in the ERG report to be fair. The definition of health states is not consistent with the aims and findings of the Kimball study (which would imply two living health states – "response" and "non-response"). The Kimball study identified one threshold for differential improvement, not three.
12	Page 109 states that "If PIONEER I and PIONEER II estimate different treatment effects, then neither trial provides an estimate of the treatment effect in the target patient population". The marketing authorization in the EU for adalimumab in HS is based on the results of the PIONEER I/II trial. As such it would be expected that the treatment effect observed in the PIONEER I/II trials	This is not a factual inaccuracy and no amendment has been made. This matter is specifically related to the methods used to synthesise the evidence from the two trials (i.e. simple pooling). A correct synthesis of the evidence from each trial would be to combine estimates of relative treatment effects on an appropriate scale (e.g. log

	provide an accurate estimate of the treatment effect in the target patient population.	relative risks or log odds ratios for adalimumab versus standard care) and to allow for heterogeneity of treatment effects between studies.
13	Page 109 states that "(i) The population recruited into the M12-555 OLE study includes a mix of patients who achieved and maintained a response to adalimumab within the PIONEER trials, as well as non-responders. This is not directly in line with the experience of the patient group for whom the matrix is applied in the model as these patients are specifically those who have achieved at least a partial response to adalimumab up to week 36". Although the population recruited in the OLE trial included patients who achieved and maintained a response to adalimumab within the PIONEER trials, as well as non-responders the data used in the CE model and on which the transition matrix for the extrapolated period was developed excluded patients who were Week 12 non-responders in the PIONEER phase III trials.	The ERG is unsure whether this is a factual inaccuracy. As detailed in the company's clarification response, the OLE data used in the model excluded week 12 non-responders but does appear to include patients who have not maintained at least a partial response up to week 36 (i.e. they could be secondary non-responders). Therefore the wording in the ERG report appears to be correct.
14	Page 112 states that "The implementation of the half-cycle correction within the company's model is incorrect. Whilst the company correctly subtract half of the QALY gain and cost for the final cycle from the unadjusted totals, the model includes the full QALY gains and cost for the first model cycle (at cycle 0). Only half of this QALY gain and cost should have been included in the cycle-corrected totals". AbbVie believes that this is not an error. Please note the first 2 cycles of the model are 2 weeks, and the rest are 4 weeks. The costs and QALY presented at Cycle 0 (Row 9 of the "Markov Trace – ADA" tab) in the model are already for half-cycle (i.e. 2 weeks). Thus, there is no need to further multiply by 0.5 when calculating the total costs or QALYs (Row 874-876 of the "Markov Trace" tabs).	The company is incorrect. It does not matter whether a different cycle duration is applied in the first cycle, it should still be half-cycle corrected. The ERG notes that this amendment does not have a material impact on the model results.

Adalimumab for treating moderate to severe hidradenitis suppurativa: A Single Technology Appraisal. Erratum

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Introduction

Errata for pages 126–7 of the ERG report

Following the submission of the ERG report, an error was identified relating to the implementation of the ERG's additional exploratory analyses 7 and 8 (excluding the PAS for adalimumab). The error arose through the application of the discontinuation rate for partial responders in the model from week 36 onwards. This erratum presents corrected results for these two exploratory analyses. None of the other results presented in the ERG report are affected by this issue.

Other changes to the ERG report

As part of the standard appraisal process, the company was asked to check the ERG report to ensure there are no factual inaccuracies contained within it. Based on the company's response, the ERG made changes to pages 5, 27, 38, 43, 44, 51, 58, 65, 68, 70 and 75 of its report. The corrected pages are presented in this document.

a low-to-moderate risk of bias. However, the ERG considers there to be a moderate or unclear risk of selection and attrition bias affecting the results of Period B in the PIONEER trials. There is also a low-to-moderate risk of reporting bias in Period B in the two trials. It should also be noted that whilst M10-467 has been published as a full peer-reviewed journal article, the PIONEER trials have not.

Across all three RCTs, the percentage of patients achieving clinical response according to the HiSCR measure on adalimumab 40mg EW compared with placebo at week 12 or week 16 was significantly higher than in the placebo groups ($p<0.01$), although the treatment effect varied between the trials. In addition, significant or clinically relevant differences in favour of adalimumab 40mg EW that were reported for secondary outcomes in PIONEER II were not always found for those outcomes in PIONEER I, especially for AN count, MSS score, pain and some components of quality of life measured by the SF-36. An arm-based integrated summary, which breaks randomisation, was conducted for the two PIONEER trials to tabulate Period B response (for all patients and for a group of HiSCR "responders" and "partial responders"). This "partial responder" group (defined as HiSCR responders with ≥25% reduction rather than ≥50% reduction) are a *post hoc* analysis group. This group was not defined in protocols or published descriptions of study design or pre-specified analysis methods for the PIONEER trials. It was also not considered in the published validation study for the HiSCR measure, nor was it justified or explained in the company's clinical review. According to this analysis, improvements in response were maintained or reduced in this second period. A small number of secondary outcomes were reported for Period B of PIONEER I and II, but only for patients who had had a clinical response at week 12. The results were based on analyses with small sample sizes (range of 15 to 22 patients across all outcomes for both PIONEER trials).

These trials were supplemented by a single, unpublished, non-randomised, non-controlled, unblinded cohort study, which was an OLE study of the PIONEER trials (M12-555 OLE). In terms of efficacy, the results suggested [redacted].
Details of the results for secondary outcomes such as MSS and NRS30 were not reported. The ERG considers these efficacy results to be subject to uncertainty because they are drawn from interim analyses of unpublished study data. The study also only potentially offers efficacy data for up to 72 weeks for a drug that might be taken for many years by patients with moderate to severe HS.

The submission of safety evidence was a review of the three generally good quality RCTs, supplemented by the single arm cohort study. There were no obvious safety concerns, with most AEs being balanced across adalimumab 40mg EW and placebo trial arms, and small numbers of SAEs. Longer-term data are required to determine whether reported AE rates are maintained for patients on long-term maintenance doses of adalimumab 40mg EW; whether or not certain subgroups of patients

With respect to Period A of both trials, the ERG agrees with the company's judgement that the overall risk of bias is low, albeit with the exception of possible low-to-moderate level bias in terms of attrition and reporting. However, the ERG considers there to also be a moderate or unclear risk of selection and attrition bias for the results of Period B, especially given the absence of any evaluation of the blinding, and the high level of attrition. LOCF imputation was used for some secondary outcomes to manage missing data; the ERG notes that it has been shown that using LOCF can overestimate efficacy in certain diseases.[27] However, the disease trajectory is difficult to determine for HS, so there is some uncertainty concerning the results based on this method of imputation.

For the non-randomised evidence, a single additional, non-RCT study (M12-555 OLE[20]) was identified and its findings were presented within the CS. A quality assessment was performed for this study using an unspecified tool and no rationale was provided for its selection. In response to a request for clarification from the ERG, the tool was later specified by the company as the Centre for Reviews and Dissemination (CRD) non-RCT tool (see clarification response,[17] question A22). Given that only simple "Yes", "No" or "Not relevant" responses are presented by the company, it is difficult to establish how these judgements were reached. The ERG disagrees with some of the company's risk of bias assessments relating to the M12-555 OLE study (Table 5). The differences between the company's assessments and those made by the ERG are detailed in Table 6.

Table 9: Final scope outcomes and trial outcome measures

NICE final scope outcomes	M10-467	PIONEER I	PIONEER II
Primary outcome			
Clinical response	HS-PGA, HiSCR*, MSS, AN counts/lesion counts	HiSCR, MSS, AN counts/lesion counts	HiSCR, MSS, AN counts/lesion counts
Secondary outcomes			
Disease severity	Hurley, MSS, AN counts/lesion counts, representative lesions	Hurley, MSS, AN counts/lesion counts, representative lesions	Hurley, MSS, AN counts/lesion counts, representative lesions
Inflammation and fibrosis	Hurley, HiSCR, AN counts/lesion counts, representative lesions, erythema lesions	Hurley, HiSCR, AN counts/lesion counts, representative lesions, erythema assessments	Hurley, HiSCR, AN counts/lesion counts, representative lesions, erythema assessments
Discomfort / pain	VAS	PGA- Skin Pain (NRS30)	PGA-Skin Pain (NRS30)
HRQoL	DLQI	DLQI, HSQOL, SF-36	DLQI, HSQOL, EQ-5D
Additional outcomes	WPAI-SHP	WPAI-SHP	WPAI-SHP
	PHQ-9	HADS	

**As a post hoc analysis*

Details of the full list of outcomes are given below.

Primary outcomes

- HS-PGA[2,10]
- HiSCR: at least a 50% reduction in the total abscesses and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline[29]

Secondary outcomes

- MSS score: a clinical scoring system that assesses the number of involved anatomical regions, the number and type of lesions, the extent of involvement and the Hurley stage, was used to assess disease activity;
- Pain Visual Analogue Scale (VAS): Pain assessed using a questionnaire with a VAS ranging from 0 mm (no pain) to 100 mm (maximum pain);
- PGA-Skin Pain: Patient Global Assessment of Skin Pain (NRS30: Numeric Rating Scale 0-10);
- Dermatology Life Quality Index questionnaire (DLQI): a questionnaire which measures dermatology specific HRQoL and ranges from 0 to 30, with 0 being no impairment;
- HS Quality of Life (HSQOL);
- Short Form-36 (SF-36) Health Status Survey;
- Euroqol EQ-5D;

Participant flow and numbers

The trials all experienced substantial loss of patients to follow-up (see Table 12). Clinical advice received by the ERG suggests that this is expected in trials of HS because patients who do not experience a response are unlikely to be motivated to continue on the trial. The loss to follow-up in the three trials was reported in the participant flow figures in the CS (pages 70-72), although the company had to provide, at the request of the ERG, the correct flowchart for the PIONEER II trial because this was erroneously a duplicate of the PIONEER I flowchart in the original submission (see clarification response,[17] question A24). Patient loss to follow-up in Period B was produced in part by protocol-driven discontinuation. This was based on either LOR, defined as a loss of 50% or more of the improvement gained during Period A among patients who achieved response according to HiSCR at week 12, or WOAI, defined as the second incidence of two consecutive visits with AN count higher than the baseline AN count in patients randomised to adalimumab 40mg EW in Period A who were week-12 HiSCR non-responders.[9]

Table 12: Patient loss to follow-up in trials in the adalimumab 40mg EW and placebo arms

Time endpoint (weeks)	**M10-467 n (%)**		**PIONEER I n (%)**		**PIONEER II n (%)**	
	ADA	PBO	ADA	PBO	ADA	PBO
Baseline total	51 (100)	51 (100)	153 (100)	154 (100)	163 (100)	163 (100)
12			145 (95)	145 (94)	155 (95)	151 (93)
16	45 (88)	46 (90)				
36			170 (55)*		116 (40)*	
52	31 (69)	34 (74)				

ADA - adalimumab; EW - every week; PBO – placebo
**Pooled numbers because of crossover between periods A and B*

According to the CS, clinical response data for the first period in each study (12 or 16 weeks) were analysed according to the intention-to-treat (ITT) principle, so that all patients randomised at week 0 were included (see CS,[9] pages 68 and 69). The primary approach for managing missing values was non-responder imputation (NRI). However, many of the results for the secondary endpoints, as presented in the CS, were based on LOCF imputation, which has particular implications for the results beyond weeks 12 or 16 as the level of attrition was more than 40% (see Table 12). Consequently, when this approach has been used, it was specified in CS and is also specified in this ERG report. In other instances, when the imputation approach has not been specified in the CS, it is assumed that NRI was used for binary outcomes.

4.2.2.1 Primary outcome: Clinical response

Results for the primary outcome for all three trials were reported in the CS. The M10-467 dosing study measured this outcome using both HS-PGA (see Table 13) and in a *post hoc* analysis using HiSCR, whilst PIONEER I and

II both used the HiSCR (Table 14). Response using the HS-PGA scale was defined as a HS-PGA score of clear, minimal or mild, with at least a 2-grade improvement relative to baseline.

The trials each had two separate periods of treatment. Period 1 (M10-467) and Period A (PIONEER I, II) evaluated whether adalimumab induces clinical response in patients with moderate or severe HS. The duration of this period was 16 weeks in Study M10-467, and 12 weeks in PIONEER I and II. M10-467 had a Period 2, for weeks 16-52, but this period only assessed the unlicensed 40mg EOW dose and so these data are not relevant to this appraisal. The PIONEER trials also included a Period B, covering weeks 12 to 36.

Weeks 12 and 16 (Period A in the PIONEER I/II trials and Period 1 in Study M10-467)

In Study M10-467, using the HS-PGA outcome measure, significantly more patients in the adalimumab 40mg EW group achieved clinical response compared with placebo at week 16 (17.6% vs 3.9%, $p<0.025$).

Table 13: Percentage of patients achieving clinical response measured by HS-PGA relative to baseline at 16 weeks (data reproduced from CS,[9] pages 76-77)

Trial	n	Follow-up (weeks)	Adalimumab EW	Placebo	Percentage difference relative to placebo (95% CI)	*p*-value
M10-467	102	16	17.6	3.9	13.7% (1.7 to 25.7)	<0.025

ADA - adalimumab; EW - every week

Across all three trials, the percentages of patients experiencing clinical response using HiSCR, defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline, are reported in Table 14. Across all three RCTs, the percentage of patients achieving clinical response according to the HiSCR measure at week 12 or week 16 was significantly higher for patients receiving adalimumab 40mg EW compared with placebo ($p<0.007$).

Quality of life

Several measures were used across the three trials, but the principal recognised measure is the DLQI. DLQI scores range from 0 to 30, with higher scores indicating a more impaired quality of life (see Table 22). Across all three RCTs, adalimumab 40mg EW was associated with a statistically significant improvement in DLQI compared with placebo at week 12 and week 16 (p<0.001).

Table 22: Quality of Life measured by DLQI scores relative to baseline in Weeks 12 and 16 (LOCF) (reproduced from CS,[9] Table 13, page 78, and Table 17, page 86)

Trial	Within group change (LS mean ± SE)		Between group change	*p*-value
	ADA EW	Placebo	LS mean difference (95% CI)	
M10-467	-6.0 ± 0.9	-1.9 ± 0.9	-4.2 (-6.6, 1.8*)	<0.001
PIONEER I	-5.4 ± 0.5	-2.9 ± 0.5	-2.5 (-3.0,-1.8)	<0.001
PIONEER II	-5.1 ± 0.53	-2.3 ± 0.53	-2.8 (-4.1,-1.5)	<0.001

LOCF - last observation carried forward; ADA - adalimumab; EW - every week; LS - least squares; SE – standard error; CI – confidence interval
**This figure from CS, Table 13, page 78*

The CS states that, in all trials, the within arm mean change from baseline in DLQI at week 12 (Period A) or week 16 (Period 1) for patients in the adalimumab 40mg EW group exceeded the minimum clinically important difference (MCID) of 5 (see CS,[9] page 86). It also exceeded the MCID of 4 established by Basra *et al* 2015.[34] However, the ERG notes that the between arm mean change from baseline for the adalimumab arm compared with the placebo arm did not meet this MCID threshold in either PIONEER I or II. [redacted] 49% versus 34% (p=0.011) in PIONEER II.

The condition-specific HSQOL scale was also used. Clinical advice received by the ERG suggests that this is a new measure which has not been published. Ratings range from 0 (worst possible) to 10 (best possible). [redacted]

[redacted]Table 23: Quality of life measured by HSQOL scores relative to baseline at week 12 (LOCF) (reproduced from CS,[9] Table 17, page 86)

Trial	Within group change (LS mean ± SE)		Between group change	*p*-value
	ADA EW	Placebo	LS mean difference (95% CI)	
[redacted]				

LOCF - last observation carried forward; ADA - adalimumab; EW - every week; LS - least squares; SE – standard error; CI – confidence interval

Patients who prematurely discontinued from the trial, or who completed the trial and did not initiate adalimumab therapy outside the context of the clinical trial, had study visits 4 and 8 weeks after the last administration of study drug to collect blood samples for the measurement of serum adalimumab concentrations and anti-adalimumab antibody.

The results presented in the CS are from an interim data cut, as of 29 April 2014, for 497 patients who received at least one dose of the study drug. Full data were only available for 26% of enrolled patients; missing data imputation methods were used for the remaining subjects who had not completed the study by the data cut-off date.

Efficacy results

In terms of efficacy, the primary outcome was the proportion of subjects achieving HiSCR. The unpublished results for those participants who received adalimumab in at least one period (A or B, or A and B) in PIONEER I and II, and who continued into the OLE, are presented in Table 29. The CS reported that [redacted] The numbers listed in Table 29 are the baseline number of patients in each of the groups providing some data on "continuous" exposure to adalimumab 40mg EW, however [redacted] Consequently, these data have been imputed using LOCF, which might overestimate the true level of HiSCR for these later timepoints. Details of the results for secondary outcomes such as MSS and NRS30 were not reported (see CS,[9] page 106).

M12-555 OLE

[redacted]

The ERG also notes that the OLE study only potentially offers safety data for up to 72 weeks for some participants (given the high levels of attrition) for a drug that might be taken for many years by patients with moderate or severe HS.

Table 35: AEs in M12-555 OLE in all adalimumab groups and in the EW/EW/EW trial population (reproduced from CS,[9] Table 35, page 115)

[redacted]

ADA – adalimumab; EW – every week; AE – adverse event; SAE – serious adverse event

The ERG considers the M10-467 trial to be at low risk of bias across all domains for the relevant Period 1 (up to week 16). The ERG also considers the results from Period A (i.e. up to week 12) in PIONEER I and II to be generally at low risk of bias. However, the ERG considers there to be a moderate or unclear risk of selection and attrition bias for the results of Period B in the PIONEER trials. There is also a low-to-moderate risk of reporting bias in Period B in the two trials. It should also be noted that whilst M10-467 has been published, the PIONEER trials have not.

In PIONEER I and II, significantly more patients in the adalimumab 40mg EW group achieved a clinical response (defined as achieving HiSCR [at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline] at week 12) than patients receiving placebo: 41.8% for adalimumab vs 26.0% for placebo, p=0.003 in PIONEER I, and 58.9% for adalimumab vs 27.6% for placebo, p<0.001 in PIONEER II. Subgroup analyses indicated that patients achieved benefit with adalimumab 40mg EW regardless of their baseline characteristics, although some subgroups had small patient numbers. Significant or clinically relevant differences in favour of adalimumab 40mg EW that were reported for secondary outcomes in PIONEER II were not always found in PIONEER I, especially for AN count, MSS score, pain and some components of quality of life measured by the SF-36. The treatment effect varied between the trials. This might be explained by differences in patient demographics and study design between trials. The company is conducting ongoing analyses of the data from the PIONEER trials and the OLE study to understand these differences. An NMA was not considered feasible.

An arm-based integrated summary, which breaks randomisation, was conducted for the two PIONEER trials to tabulate Period B response (12-36 weeks) for all patients and for a group of HiSCR "responders" and "partial responders." According to this analysis, improvements in response were maintained or reduced in this second period. However, the "partial responder" group (defined as HiSCR responders with ≥25% reduction but less than a 50% reduction) are a *post hoc* analysis group. This group was not defined in protocols or published descriptions of study design or pre-specified analysis methods for the PIONEER trials. It was also not considered in the published validation study for the HiSCR measure, nor was it justified or explained in the company's clinical review. A small number of secondary outcomes were reported for PIONEER I and II for weeks 12-36, but only for patients who had had clinical response at week 12. However the results were based on analyses with small sample sizes (range of 15 to 22 patients across all outcomes for both PIONEER trials).

These trials were supplemented by a single, unpublished, non-randomised, non-controlled, un-blinded cohort study, which was an OLE study of the PIONEER trials (M12-555 OLE). In terms of efficacy, the results suggested [redacted].

5. COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The CS[9] presents the methods and results of systematic reviews of existing health economic evaluations of treatments for patients with moderate to severe HS, HS cost and resource use studies and HRQoL studies in patients with HS. The searches for the economic evaluation review and the cost and resource use review were run together in order to avoid potential duplicates, whilst the HRQoL search was run separately. According to the CS, the purpose of the combined search was *"to identify healthcare resource use, costs, cost drivers, previous economic evaluations and health technology assessment (HTA) economic models of treatments for patients with moderate to severe HS"* (CS[9] page 127).

Search strategy

All searches were undertaken across the following electronic databases:

- MEDLINE
- MEDLINE In-Process
- EMBASE (using EMBASE.com)
- Econlit (using EBSCO.com)
- The Cochrane Library including the following:
    - The Cochrane Database of Systematic Reviews
    - The Database of Abstracts of Reviews of Effectiveness (DARE)
    - The Cochrane Central Register of Controlled Trials (CCRCT)
    - The Health Technology Assessment (HTA) Database.

Both the combined search and the HRQoL search were restricted to studies which were published in English in the last 15 years (up to 30th June 2015).

continue to receive adalimumab maintenance therapy. Patients who do not achieve at least a partial HiSCR response at 12-weeks are assumed to discontinue adalimumab treatment and subsequently receive standard care. During weeks 12-36 of the maintenance phase, patients are assumed to discontinue adalimumab at a constant rate irrespective of response status, based on the PIONEER I/II studies;[18, 19] thereafter differential withdrawal rates are applied to patients achieving at least a partial response and non-responders based on the OLE study.[20] It is also noteworthy that according to the CS, the model assumes that from week 36 onwards, patients who are non-responders will continue to receive adalimumab and will discontinue if a further 12 weeks of adalimumab treatment fails to achieve at least a partial response (i.e. from week 48 onwards). The implementation of this continuation rule within the company's model is discussed in detail in Section 5.3.

Comparators

The comparator in the company's economic analysis is defined as "standard care." According to the CS[9] (page 139), surgery was not considered to be an appropriate comparator as surgery and adalimumab are not alternative or exclusive treatment choices. The CS also states that patients in the PIONEER trials were allowed surgery for symptom control and that an online survey of members of the UK Dermatology Trials Network and British Association of Dermatologists revealed that extensive surgery was generally used later in the treatment pathway.[9] However, the ERG notes that in response to a request for clarification (see clarification response,[17] questions A31 and B5), the company later stated that patients were not permitted to undergo either planned or unplanned surgery in the PIONEER I/II trials (see Section 4.2.1). The CS states that antibiotics were not considered to represent a relevant comparator, as antibiotics are typically used throughout the treatment pathway and these may be used concomitantly with adalimumab. The CS further notes that a comparison of adalimumab versus dapsone, retinoids and immunomodulators was not performed since UK clinical experts consulted in the preparation of the CS suggested that these therapies would currently be prescribed before adalimumab, noting also that there is currently a lack of efficacy evidence for these therapies in HS.[9] The company also considered that a comparison of adalimumab versus infliximab was not appropriate as infliximab is used in very specific subgroups of patients (for example, those who are very overweight) and such a comparison was not possible given the limited evidence base and heterogeneity between the infliximab and adalimumab trials. Clinical advisors to the ERG disagree that infliximab is only used in specific subgroups and a 2015 survey of UK clinicians suggests that that despite funding constraints, infliximab is currently used more widely in HS than adalimumab.[15]

Given the arguments presented by the company, the CS states that the relevant comparator is standard care, based on the placebo groups within the PIONEER I/II trials.[18, 19] The ERG notes that whilst the

Corrected exploratory analyses results

ERG Additional Exploratory Analysis 7: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders (using the ERG-preferred base case)

Table 63 presents the results of an analysis in which the model corrections, non-responder tunnel states and lower surgery cost (ERG Exploratory Analyses 1, 2 and 3) are applied to a version of the model in which health utilities, resource use and discontinuation rates are assumed to be the same for partial responders and non-responders, and high responders and responders.

Table 63: ERG Additional Exploratory Analysis 7 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.20	£[redacted]	0.74	£[redacted]	**£**[redacted]
Standard care	12.46	£57,065	-	-	-

The results of this analysis suggest a considerably higher ICER than both the ERG's base case and the company's base case. However, it is important to note that whilst partial responders are assumed to continue adalimumab as maintenance therapy, their health utility is assumed to be the same as that for non-responders, hence this analysis assumes that these patients remain on treatment without obtaining further benefit from it. The ERG would have preferred that the company had incorporated adalimumab continuation rules based on the 50% HiSCR AN reduction threshold.

ERG Additional Exploratory Analysis 8: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12-weeks (using the ERG-preferred base case)

Table 64 presents the results of the scenario described in ERG Additional Exploratory Analysis 7, combined with an additional assumption that both non-responders and partial responders discontinue adalimumab at 12 weeks.

Table 64: ERG Additional Exploratory Analysis 8 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12 weeks

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.13	£[redacted]	0.67	£[redacted]	**£**[redacted]
Standard care	12.46	£57,065	-	-	-

The results presented in Table 64 indicate that assuming no difference in utility, resource use and discontinuation rates for no response and partial response, and for high response and response, together with the discontinuation of partial responders and non-responders at 12-weeks, the ICER for adalimumab versus standard care is estimated to be £[redacted] per QALY gained. This is lower than the previous scenario in which only non-responders discontinue at 12-weeks (ERG Additional Exploratory Analysis 7, Table 63). As noted above, due to its structure, it was not possible to apply the company's assumed discontinuation rule to partial responders within the maintenance phase of the model. The ERG does however note that increasing the discontinuation rate for partial responders lowers the ICER for adalimumab. However, the true impact of applying the discontinuation rules to both adalimumab non-responders and adalimumab partial responders in both the induction and maintenance phases of the model is unclear. This represents an important uncertainty which cannot be fully addressed given the evidence provided within the CS.

Adalimumab for treating moderate to severe hidradenitis suppurativa: A Single Technology Appraisal. Addendum

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1. Introduction

1.1 Overview of addendum

In December 2015, the company submitted a Patient Access Scheme (PAS) application for adalimumab,[1] specifically in the hidradenitis suppurativa (HS) indication. The analysis was later updated in January 2016 to include the costs of implementing the PAS. This addendum summarises the company's base case cost-effectiveness results and the ERG's exploratory analyses including the company's PAS. Unless otherwise stated, all cost-effectiveness results presented in this addendum include the PAS.

1.2 Description of PAS

The company's PAS is designed to provide patients with moderate to severe HS with adalimumab at a fixed cost which is lower than the NHS list price. The proposed PAS will apply only to adalimumab pre-filled pens or syringes in the HS indication, that is, adult patients with moderate to severe HS with an inadequate response to conventional systemic HS therapies. The scheme will not apply to any other current and future indications for adalimumab. The proposed PAS takes the form of a simple price discount whereby the cost for each pack of 2x40mg pre-filled syringes or pens of adalimumab will be reduced from the list price of £704.28.to [redacted] (exclusive of VAT).

According to the company's PAS application,[1] the proposed scheme has the following advantages:

1. The concept of the discounted price is simple for customers to understand.
2. The NHS in England and Wales is immediately in receipt of the benefits of managing the scheme, rather than potentially waiting for the benefits with other potential schemes.
3. The benefit of the discount will apply to the patient throughout the duration of their treatment.
4. No rebates will be required.
5. No additional clinical intervention is required in administrating the scheme, and no additional testing of patients is required.

The company's PAS application[1] reports estimated set-up costs for the PAS of £79.07; this cost is assumed to reflect the cost to each NHS trust operating the scheme. The costs associated with operating the PAS (per order) are estimated to be £21.53 for direct orders, and £15.07 homecare orders. Further details relating to the design and implementation of the company's proposed PAS are contained on pages 5-14 of the company's PAS application.[1]

2. Implementation of the PAS in the company's model

The ERG confirms that the price reduction associated with the proposed PAS has been applied correctly within the company's model. This has been implemented by reducing the parameter relating to the price per unit of adalimumab by [redacted]. The costs of implementation have been included by

adding a one-off PAS set-up cost of £0.70 per patient (applied in the second model cycle) and operational costs of £8.21 per 4-week cycle. The ERG was able to reproduce the company's base case deterministic ICER for adalimumab versus standard care by applying the price reduction and the additional PAS implementation costs to the company's original submitted version of the model. The ERG was also able to produce similar probabilistic results to those presented in the PAS application,[1] although these are not directly reproducible as the company's model does not use a fixed set of random numbers.

3. Company's base case results including proposed PAS

3.1 Base case cost-effectiveness results

Table 1 presents the company's base case results. Based on a re-run of the probabilistic version of the company's base case model by the ERG, adalimumab is expected to produce an additional 1.02 QALYs at an additional cost of £16,471 compared with standard care; the ICER for adalimumab versus standard care is expected to be £16,162 per QALY gained. The results of the deterministic model are similar, with adalimumab yielding a slightly lower ICER of £15,182 per QALY gained compared with standard care.

Table 1: Company's base case cost-effectiveness results

Probabilistic model*					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Adalimumab	12.63	£145,256	1.02	£16,471	**£16,162**
Standard care	11.61	£128,784	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Adalimumab	12.61	£143,683	1.00	£15,142	**£15,182**
Standard care	11.61	£128,541	-	-	-

** derived from the company's model*

3.2 Probabilistic sensitivity analysis results

Figures 1 and 2 present the cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) for adalimumab versus standard care, respectively. Assuming a willingness-to-pay (WTP) threshold of £20,000 per QALY gained, the company's base case model suggests that the probability that adalimumab produces more net benefit than standard care is approximately 0.58. Assuming a WTP threshold of £30,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately 0.80.

Figure 1: Cost-effectiveness plane (redrawn by the ERG)

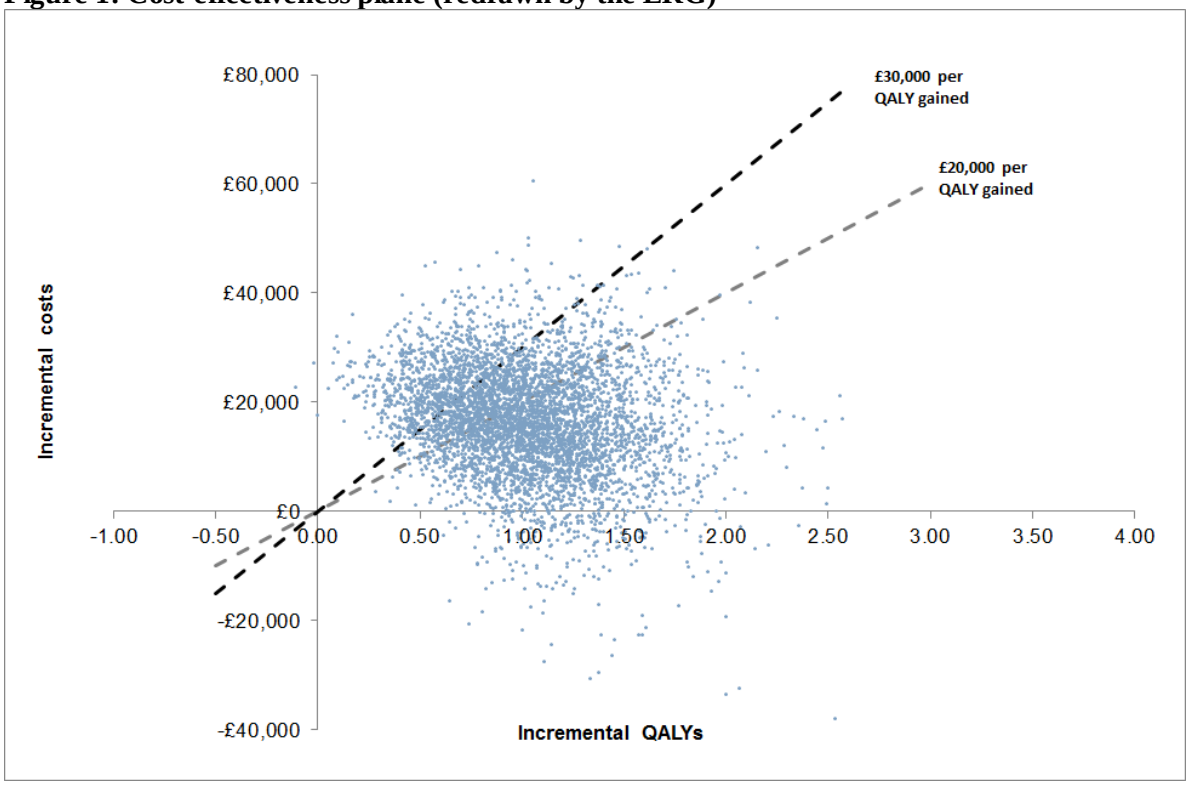
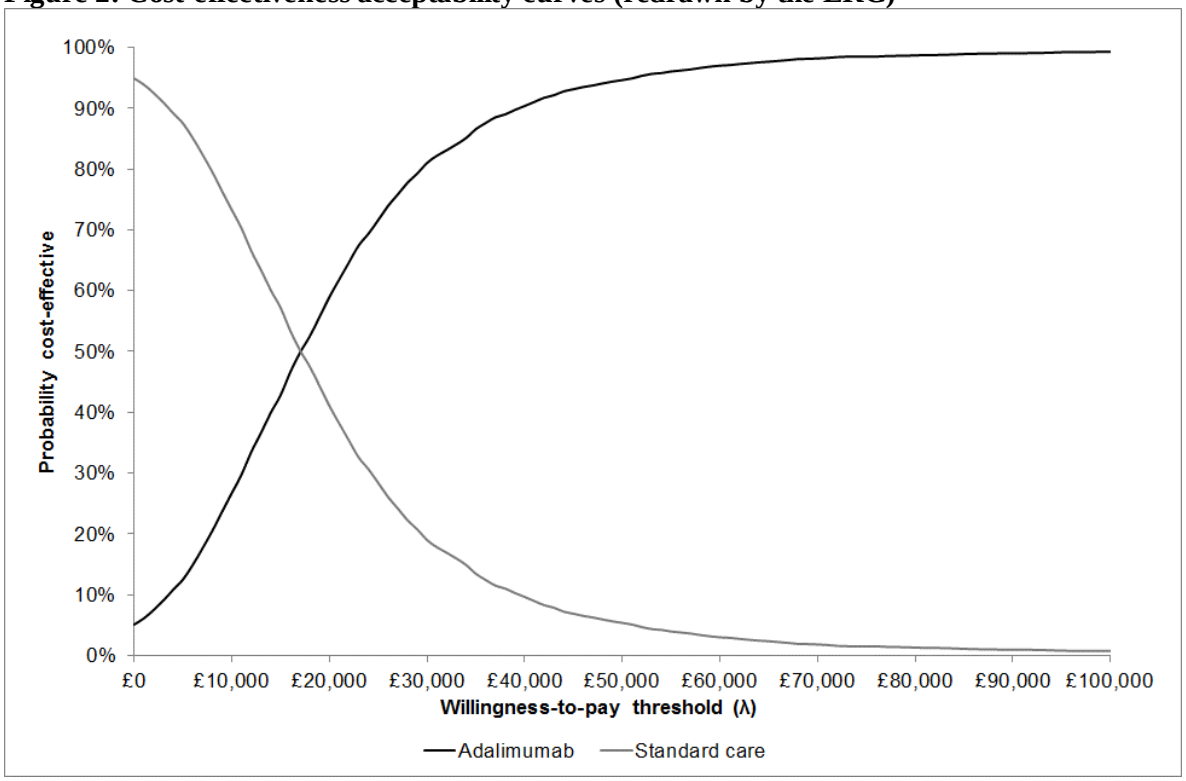


Figure 2: Cost-effectiveness acceptability curves (redrawn by the ERG)



Additional simple sensitivity analyses and scenario analyses including the PAS are presented on pages 21 to 25 of the company's PAS application;[1] for the sake of brevity, these have not been reproduced here.

4. Additional exploratory analyses undertaken by the ERG including the proposed PAS

This section presents the ERG's exploratory analyses including the company's proposed PAS.

ERG Exploratory Analysis 1: Correction of model errors

Table 2 presents the results of ERG Exploratory Analysis 1 which includes only the correction of model errors identified within the ERG report[2] (see critical appraisal point 10 and Appendix 2).

Table 2: ERG Exploratory Analysis 1 – correction of model errors

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.64	£144,369	1.00	£15,939	**£15,941**
Standard care	11.64	£128,430	-	-	-

Based on the corrected version of the company's model, the deterministic ICER for adalimumab is estimated to be £15,941 per QALY gained; this is marginally higher than the company's base case estimate presented within the company's PAS application.[1]

ERG Exploratory Analysis 2: Incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule (including ERG Exploratory Analysis 1)

Table 3 presents the results of the company's model which includes the addition of tunnel states to better reflect the proposed adalimumab non-responder continuation rule during the maintenance phase. The analysis also includes the model corrections presented in ERG Exploratory Analysis 1.

Table 3: ERG Exploratory Analysis 2 – incorporation of tunnel states to reflect the maintenance phase adalimumab non-responder continuation rule

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.72	£149,430	1.07	£21,000	**£19,551**
Standard care	11.64	£128,430	-	-	-

The results presented in Table 3 demonstrate that the incorporation of tunnel states within the company's model increases both the incremental QALY gains and the incremental costs of adalimumab relative to the company's base case estimates. The incorporation of tunnel states for adalimumab non-responders in the corrected version of the model increases the ICER for adalimumab versus standard care to £19,551 per QALY gained.

ERG Exploratory Analysis 3: Revised assumptions regarding costs of HS surgery (including ERG Exploratory Analyses 1 and 2)

Table 4 presents an exploratory analysis in which the cost of surgical inpatient admissions is assumed to be £1,525.74 per procedure (see ERG report,[2] Table 56). This analysis also incorporates the model corrections applied in ERG Exploratory Analysis 1 and the tunnel states applied in ERG Exploratory Analysis 2. This analysis represents the ERG's preferred base case (given the constraints of the company's adopted model structure).

Table 4: ERG Exploratory Analysis 3 – revised assumptions regarding costs of HS surgery (ERG base case)

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Probabilistic model					
Adalimumab	12.72	£96,400	1.09	£32,344	**£29,725**
Standard care	11.63	£64,056	-	-	-
Deterministic model					
Adalimumab	12.72	£94,689	1.07	£30,671	**£28,555**
Standard care	11.64	£64,018	-	-	-

As shown in Table 4, the estimated QALY gains for adalimumab and standard care are the same as those estimated within ERG Analysis 2. However, the total discounted lifetime costs in both treatment groups are reduced considerably. Since the ERG's preferred estimate of the costs of HS surgery are lower than those used in the company's model, and because the company's base case analysis suggests that adalimumab produces cost savings by avoiding HS surgery due to patients spending more time in the better response states, this analysis produces a higher incremental cost for adalimumab versus standard care. Within this analysis, the deterministic ICER for adalimumab versus standard care is estimated to be £28,555 per QALY gained. Based on the probabilistic version of the model, the ICER for adalimumab versus standard care is expected to be £29,725 per QALY gained. Assuming a WTP threshold of £20,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately 0.16. Assuming a WTP threshold of £30,000 per QALY gained, the probability that adalimumab produces more net benefit than standard care is approximately 0.49.

ERG Additional Exploratory Analysis 4: Use of PIONEER II data only (using the ERG-preferred base case)

Table 5 presents an exploratory analysis using only the PIONEER II data. This analysis uses the ERG's base case version of the model (ERG Exploratory Analysis 3).

Table 5: ERG Additional Exploratory Analysis 4 – use of PIONEER II data only

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.63	£99,913	0.99	£35,906	**£36,372**
Standard care	11.64	£64,007	-	-	-

The results presented in Table 5 suggest that deriving the transition matrices and adverse event probabilities only from the PIONEER II trial increases the ICER for adalimumab versus standard care to £36,372 per QALY gained.

ERG Additional Exploratory Analysis 5: Alternative assumptions regarding transition probabilities beyond week 36 (using the ERG-preferred base case)

Table 6 presents the results of two exploratory analyses using alternative long-term transition probabilities.

Table 6: ERG Additional Exploratory Analysis 5 – alternative assumptions regarding transition probabilities beyond week 36

OLE GLM for adalimumab responders (excluding imputation), PIONEER I/II GLMs for adalimumab discontinuers and patients receiving standard care					
Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.68	£93,354	1.04	£29,335	**£28,110**
Standard care	11.64	£64,018	-	-	-
OLE GLM for adalimumab responders (including LOCF), mean of week 12-36 data from PIONEER I/II for adalimumab discontinuers and patients receiving standard care					
Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.58	£95,678	1.17	£30,027	**£25,610**
Standard care	11.41	£65,650	-	-	-

As shown in Table 6, the results of these analyses suggest that the ICER for adalimumab versus standard care is slightly improved when alternative long-term transition matrices are used to project HiSCR outcomes. When LOCF imputation is removed from the GLM for patients receiving adalimumab beyond week 36, the ICER for adalimumab versus standard care is estimated to be £28,110 per QALY gained. When the transition matrices for patients who have discontinued adalimumab and for patients receiving standard care are based on the mean of week 12-36 data from the PIONEER I/II trials (rather than GLMs), the ICER is reduced to £25,610 per QALY gained.

ERG Additional Exploratory Analysis 6: Discontinuation of partial responders and non-responders at 12-weeks (using the ERG-preferred base case)

Table 7 presents the results of an analysis in which only patients achieving response or high response are assumed to continue adalimumab treatment beyond 12 weeks.

Table 7: ERG Additional Exploratory Analysis 6 – discontinuation of partial responders and non-responders at 12 weeks

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	12.62	£86,809	0.98	£22,791	**£23,341**
Standard care	11.64	£64,018	-	-	-

The discontinuation of patients who have achieved only a partial response at 12-weeks results in an estimated ICER for adalimumab versus standard care of £23,341 per QALY gained. This is more favourable than the ERG's base case analysis. The ERG notes however that the impact of discontinuing treatment for partial responders during the maintenance phase is unclear.

ERG Additional Exploratory Analysis 7: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders (using the ERG-preferred base case)

Table 8 presents the results of an analysis in which the model corrections, non-responder tunnel states and lower surgery cost (ERG Exploratory Analyses 1, 2 and 3) are applied to a version of the model in which health utilities, resource use and discontinuation rates are assumed to be the same for partial responders and non-responders, and for high responders and responders, respectively.

Table 8: ERG Additional Exploratory Analysis 7 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.20	£87,344	0.74	£30,278	**£40,923**
Standard care	12.46	£57,065	-	-	-

The results of this analysis suggest a considerably higher ICER than both the ERG's base case and the company's base case. However, it is important to note that whilst partial responders are assumed to continue adalimumab as maintenance therapy, their health utility is assumed to be the same as that for non-responders, hence this analysis assumes that these patients remain on treatment without obtaining further benefit from it. The ERG would have preferred that the company had incorporated adalimumab continuation rules based on the 50% HiSCR AN reduction threshold.

ERG Additional Exploratory Analysis 8: Assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12-weeks (using the ERG-preferred base case)

Table 9 presents the results of the scenario described in ERG Additional Exploratory Analysis 7, combined with an additional assumption that both non-responders and partial responders discontinue adalimumab at 12 weeks.

Table 9: ERG Additional Exploratory Analysis 8 – assumption of no difference in utility, resource use and discontinuation rates for non-responders and partial responders, and for high responders and responders with discontinuation of patients achieving only partial response or no response at 12 weeks

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Incremental cost per QALY gained
Adalimumab	13.13	£80,039	0.67	£22,974	**£34,152**
Standard care	12.46	£57,065	-	-	-

The results presented in Table 9 indicate that assuming no difference in utility, resource use and discontinuation rates for no response and partial response, and for high response and response, together with the discontinuation of partial responders and non-responders at 12-weeks, the ICER for adalimumab versus standard care is estimated to be £34,152 per QALY gained. This is lower than the previous scenario in which only non-responders discontinue at 12-weeks (ERG Additional Exploratory Analysis 7, Table 8). As noted above, due to its structure, it was not possible to apply the company's assumed discontinuation rule to partial responders within the maintenance phase of the model. The ERG does however note that increasing the discontinuation rate for partial responders lowers the ICER for adalimumab. The true impact of applying the discontinuation rules to both adalimumab non-responders and adalimumab partial responders in both the induction and maintenance phases of the model is unclear. This represents an important uncertainty which cannot be fully addressed given the evidence provided by the company.

4. References

1. AbbVie Ltd. Adalimumab for treating moderate to severe hidradenitis suppurativa. Patient Access Scheme application (updated). AbbVie: Berkshire, UK; 2016.

2. Tappenden P, Carroll C, Stevens J, Rawdin A, Grimm S, Clowes M, Kaltenthaler E, Ingram J, Collier F, Ghazavi M. Adalimumab for treating moderate to severe hidradenitis suppurativa: A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2015.