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]

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)

[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.