Adalimumab for treating moderate to severe hidradenitis suppurativa: A Single Technology Appraisal. Addendum

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

Authors Paul Tappenden, Reader in Health Economic Modelling, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Christopher Carroll, Reader in Health Technology Assessment, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

John W Stevens, Reader in Decision Science, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Andrew Rawdin, Research Associate, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Sabine Grimm, Research Associate in Health Economics, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Eva Kaltenthaler, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

John R Ingram, Senior Lecturer and Consultant Dermatologist, Institute of Infection and Immunity, Cardiff University, Glamorgan House, University Hospital of Wales, Health Park, Cardiff, CF14 4XN

Fiona Collier, Specialist General Practitioner, Forth Valley Dermatology Centre, Stirling Community Hospital, Livilands, Stirling, FK8 2AU

Mohammad Ghazavi, Consultant Dermatologist, Nottingham NHS Treatment Centre, Lister Road, Nottingham, NG7 2FT

Correspondence to Paul Tappenden, Reader in Health Economic Modelling, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

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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)

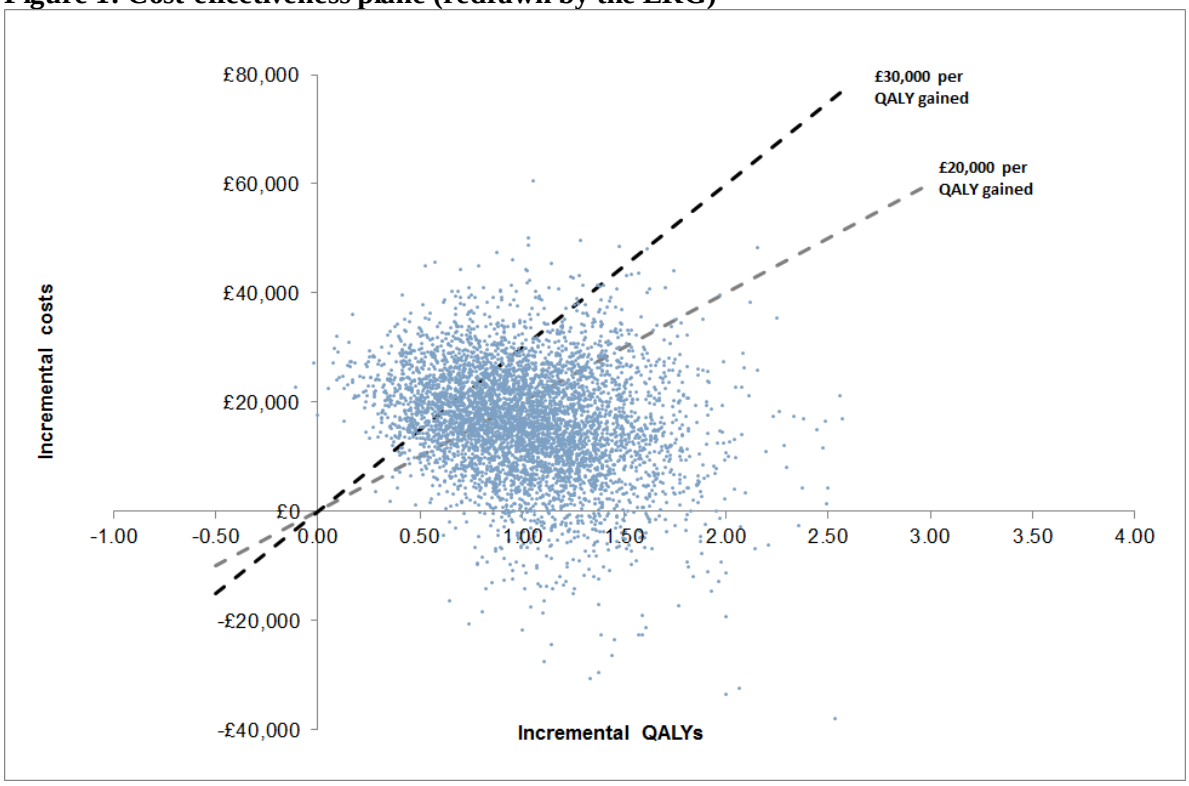
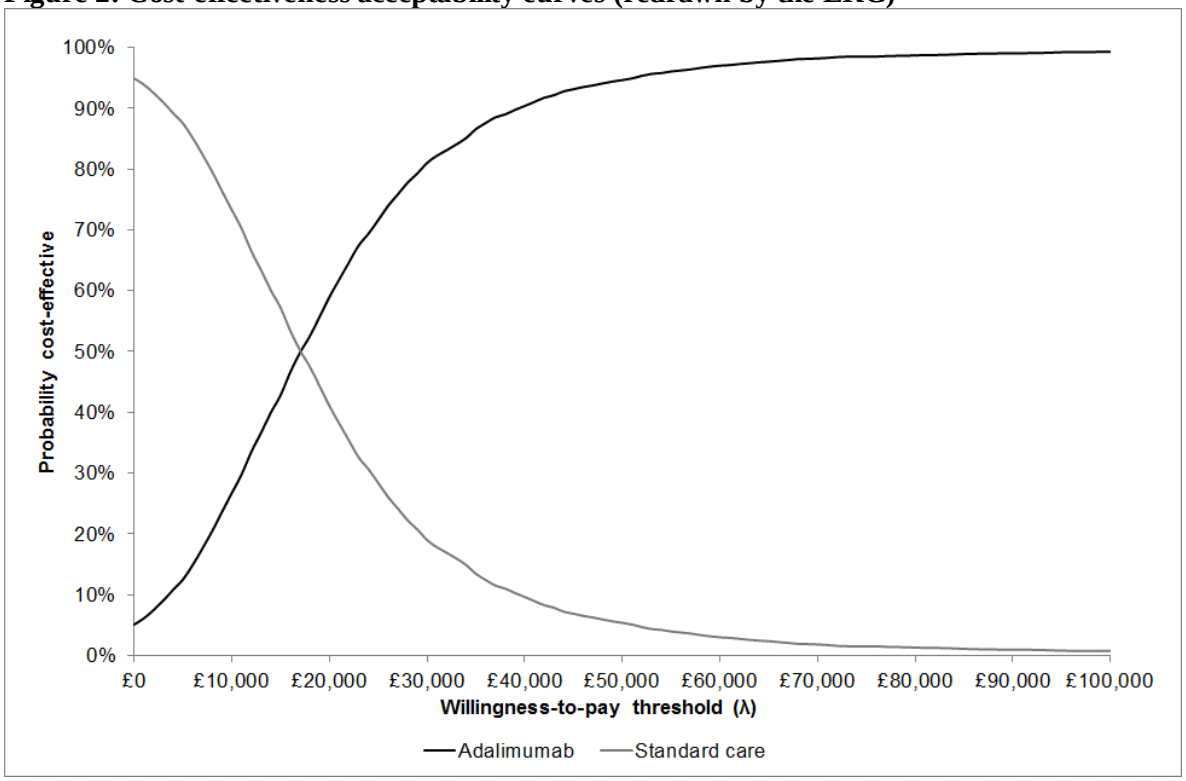


Figure 2: Cost-effectiveness acceptability curves (redrawn by the ERG)



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.