Secukinumab for Moderate-to-Severe Hidradenitis Suppurativa [ID4039]

Produced by Aberdeen HTA Group

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Mari Imamura and Moira Cruickshank reviewed and critiqued the clinical effectiveness evidence presented in the company submission and drafted the background section; Neil Scott and Sachin Kumar checked and critiqued all statistical analyses presented in the company's submission as well as the network meta-analysis results provided at clarification, Dwayne Boyers and Mekazin Tsehaye reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission and conducted scenario analyses; Paul Manson checked and critiqued the search strategies presented in the company's submission; Tony Ormerod provided clinical guidance during the course of this appraisal and comments on the draft version of this report. Miriam Brazzelli and Dwayne Boyers coordinated all aspects of this appraisal and are the guarantors of this report. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

Abbreviation	Definition
ADA	Adalimumab
AE	Adverse event
AESI	Adverse events of special interest
AMEA	Asia, Middle East and Africa
AN	Abscesses and inflammatory nodule
BAD	The British Association of Dermatologists
BIA	Budget impact analysis
BMI	Body mass index
BNF	British national formulary
BSC	Best supportive care
BSL	Baseline
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CSR	Clinical study report
CUA	Cost-utility analysis
CVD	Cardiovascular disease
CXCL1	C-X-C motif ligand 1
DAMPs	Danger-associated molecular patterns
DLQI	Dermatology Life Quality Index
DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EOT	End of treatment
EQ-5D	EuroQol Five Dimensions
ESR	Erythrocyte sedimentation rate
FDLQI	Family Dermatology Life Quality Index

HISCR	Hidradenitis Suppurativa Clinical Response
HRQoL	Health-related quality of life
HRU	Health resource use
HS	Hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa Physician's Global Assessment
HSUV	Health state utility value
HTA	Health technology assessment
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
IFNγ	Interferon-γ
IL	Interleukin
IRT	Interactive response technology
ITT	Intention-to-treat
LYG	Life years gained
MAR	Missing at random
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measures
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NRS	Numerical Rating Scale
ONS	Office for National Statistics
OR	Odds ratio
OTC	Over-the-counter
PAS	Patient access scheme
PGI-c	Patient Global Impression of change
PGI-s	Patient Global Impression of severity
PSA	Probabilistic sensitivity analysis
PSQI	Pittsburgh sleep quality index
PSS	Personal social services
PSSRU	Personal Social Services Research Unit

QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF-36	36-item short form health survey
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SpA	Spondyloarthropathy
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TLR	Toll-like receptor
TNF	Tumour necrosis factor
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
WP-NRS	Worst pain numeric rating scale
WTP	Willingness-to-pay

1. Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail and section 1.6 summarises the EAG's preferred base case assumptions and results. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The focus of the submission received from Novartis is secukinumab for the treatment of moderate-to-severe hidradenitis suppurativa (HS) in adults. Given the availability of biosimilar adalimumab in the UK, the submission focuses on adults with active moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment.

The clinical evidence submitted by the company consists of two identically designed studies: SUNRISE and SUNSHINE. These are multicentre, randomised, double-blind, placebo-controlled, parallel group studies with two secukinumab 300 mg dose regimens, Q2W (every 2 weeks) and Q4W (every 4 weeks). The primary efficacy endpoint was the proportion of participants achieving HiSCR50 (at least a 50% reduction in total abscess and inflammatory nodule (AN) count, with no increase in abscess count, and no increase in draining fistula count relative to baseline)) after 16 weeks of treatment.

In both SUNRISE and SUNSHINE, treatment with secukinumab 300 mg Q4W was associated with a numerically higher proportion of participants achieving HiSCR50 at week 16, compared to those receiving placebo. In SUNRISE only, the difference between the groups was statistically significant. Treatment with secukinumab 300 mg Q2W was associated with statistically significant improvement in terms of HiSCR50 at Week 16 compared with placebo in both SUNRISE and SUNSHINE. The EAG's key issues for this assessment are summarised in Table 1.

Table 1 Overview of EAG's key issues

Issue number	Summary of issue	Report sections
1	The company preferred model structure for the BSC arm applies restrictions that do not reflect UK clinical practice	4.2.2 and 4.2.6
2	It is currently unclear whether treatment specific or treatment pooled health state utility values should be used in the economic model.	4.2.7
3	The rates and costs of hospital resource use for HS are highly uncertain and may be over-estimated in the company's economic model.	4.2.8
4	The company economic model includes costs of BSC and surgery but does not include any quality-of-life benefits from these treatments.	4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers modelling assumptions that allow patients treated with BSC to obtain improvements in their condition through surgery and other treatments, whereas the company does not.
- The EAG prefers not to model up-titration of secukinumab dosage because the treatment effectiveness of increasing dosage in a group who failed to respond to lower dose treatment are unknown.
- The EAG prefers an assumption that the quality of life in each model health state (utilities) is independent of treatment received unless the company can provide further reassurance and evidence to support treatment specific health state utilities.

- The EAG prefers to align the modelled BSC costs with the treatments available in the placebo arms of the SUNRISE/SUNSHINE (SUNNY) trials and to use drug prices based on prescription in secondary care.

- The EAG prefers estimates of the frequency of hospital attendance that are weighted by the severity of disease in the SUNNY trials and avoid double counting outpatient visits.

- The EAG prefers the use of hospital costs that include day-case as well as elective overnight admissions.

- The EAG prefers to use lower estimates of resource use and costs for surgery health sates Re-weighting resource use estimates for the proportion of patients with moderate and severe HS from the SUNNY trials.

- Reducing outpatient resource use estimates to avoid the potential of double counting surgical related, non-surgical related and wound related attendances.

- Re-weighting hospital inpatient stay costs to include day-case admissions, aligned with clinical expert opinion and committee preferred costing from TA392.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

For this assessment QALY gains are accrued through improvements in quality of life only, as the company base modelling assumes there are no life year gains associated with secukinumab. The company's base case analysis model predicts that the technology generates QALY gains compared to BSC, by:

- Allowing transition probabilities to higher HiSCR response states for secukinumab, compared to BSC (placebo) based on data from the SUNNY trials.

- Extrapolating secukinumab health state transition probabilities observed from the SUNNY trials up to week 52 over the full model time horizon but retaining BSC treated patients in

the same health state as observed at their 16-week assessment unless they lose a response and enter the lowest response state (HiSCR <25).

- Allowing secukinumab but not BSC treated patients to regain a response (i.e., an improvement from the HiSCR<25 state) once it is lost.

- Applying treatment specific health state utility values.

Overall, the technology is modelled to lead to higher costs compared to BSC, by:

- Including lifetime treatment acquisition costs for secukinumab, which are substantially higher than BSC costs, particularly when biologics are excluded from BSC.

- Offsetting additional treatment acquisition costs through lower health state costs, driven by improved treatment effectiveness for secukinumab, leading to less time in more severe health states compared to BSC.

- Offsetting additional treatment acquisition costs through restrictive structural modelling assumptions which ensure a greater proportion of the secukinumab treated cohort achieve higher HiSCR response rates, maintained for longer than BSC.

- Reducing health state costs for secukinumab associated with higher rates of costly hospitalisations (surgical and non-surgical).

The modelling assumptions that have the greatest effect on the ICER are:

- Model structural restrictions applied to the BSC arm of the model, but not the secukinumab arm. Less restrictive model structures for BSC increase the ICER substantially.

- The decision to apply treatment specific or treatment pooled health state utility values. Treatment specific health state utility values substantially reduce the ICER.

- The rates and unit costs of hospitalisations (including both surgical and non-surgical procedures) assumed for each model health state. Higher rates and unit costs increase the ICER. The magnitude of increase in the ICER is substantially greater when model structure restrictions are imposed on the BSC arm compared to when they are not.

1.3 The decision problem: summary of the EAG's key issues

The company's decision problem defined secukinumab in a narrower scope than that proposed by NICE. The company has positioned secukinumab as a second-line treatment in the situation where adalimumab is contraindicated or otherwise unsuitable, such as for those who fail to respond to prior adalimumab treatment. The company also maintain that, as there are no current recommended therapies for this second-line position, best supportive care should be considered the only comparator to secukinumab.

The EAG, in consultation with their clinical advisor, considers the company's positioning of secukinumab in the treatment pathway to be reasonable and in line with current clinical practice in the UK. However, the ERG notes that the available evidence submitted by the company (the SUNSHINE and SUNRISE studies) comes from a population that differs from that considered for the company's positioning. Only around 23.8% and 23.2% of participants in SUNSHINE and SUNRISE, respectively, had received prior biologic treatment, such as adalimumab.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence from the two trials presented in the CS (SUNSHINE and SUNRISE) and identified no key issues for consideration by the committee, assuming that the Committee is satisfied with the company's positioning of secukinumab as a second-line therapy. The EAG also obtained a report of a network meta-analysis (NMA) conducted by the company, which also included adalimumab, the comparator listed in NICE's final scope.

[redacted]

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

There are several remaining key issues of uncertainty regarding the cost-effectiveness evidence for secukinumab compared to BSC for adults with moderate to severe HS. These include differences of opinion between the EAG and the company regarding the most appropriate model structure for BSC, the appropriateness of treatment specific or treatment pooled health state utility values, the costs, and benefits of BSC and surgery and the estimates of hospital resource use applied in the company's economic model. All these issues would

benefit from further engagement, literature reviewing and clinical expert opinion. The key issues are summarised in the following tables.

Issue 1 The company preferred model structure for the BSC arm applies restrictions that do not reflect the effectiveness of BSC and surgery treatments.

Report section	4.2.2 and 4.2.6
Description of issue and why the EAG has identified it as important	The company's economic model assumes that long-term transitions between different response health states are not possible for BSC beyond week 16, and patients can only lose a response after which it can never be regained. This is despite inclusion of surgery and BSC treatments. By contrast, similar restrictions are not applied to the secukinumab arm of the model, where long term transition probabilities are extrapolated from trial data. This issue is important because removing the semi-absorbing non-response state (and applying transition probabilities from the BSC arm of the trials) has a substantial upward impact on the ICER.
What alternative approach has the EAG suggested?	The EAG prefers to apply similar methodologies to the secukinumab and BSC arms of the model, extrapolating 52 weeks of data (secukinumab) and 16 weeks of data (BSC) over the full model time horizon. This approach ensures that both arms follow a similar model structure removing potential for bias, aligns with clinical expert opinion that symptoms may improve spontaneously, with BSC treatment or with surgery and removes the implausible assumption that BSC / surgery cannot be effective.
What is the expected effect on the cost-effectiveness estimates?	The EAG preferred approach increases the company's base case deterministic ICER (post clarification queries) from £28,165 to £61,844 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further evidence, including a systematic literature review of any trials or real-world evidence describing the clinical effectiveness of surgery or other treatments for patients with moderate to severe HS would help to reduce uncertainty, and support or refute the EAG's position that it is implausible to assume these treatments deliver no clinical benefit.

Issue 2 It is currently unclear whether treatment specific or treatment pooled health state utility values should be used in the economic model.

Report section	4.2.7
Description of issue and why the EAG has identified it as important	The company base case applies treatment specific health state utility values, on the grounds that there is a treatment effect of secukinumab compared to BSC in each model health state. This decision was supported by the company during clarification responses by providing a repeated measures regression analysis of EQ-5D utilities on treatment, baseline utility, and health state. However, the EAG is not yet satisfied that sufficient information has been provided to support the use of treatment specific HSUVs in each model health state. This issue is important because applying treatment pooled utilities from the SUNNY trials leads to a substantial upward impact on the ICER.
What alternative approach has the EAG suggested?	The EAG currently prefers the use of treatment pooled utility values unless the company provides further reassurance and evidence that treatment specific HSUVs can be applied in each model health state.
What is the expected effect on the cost-effectiveness estimates?	The EAG preferred approach increases the company's base case deterministic ICER (post clarification queries) from £28,165 to £44,245 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	To support the use of treatment specific health state utility values, the EAG would like to see evidence of each component of the HiSCR response derivation by treatment, for each health state to support treatment differences in clinical outcomes within state. The EAG would also like to see a repeated measures regression model of utilities, but with interaction terms between treatment and health state.

Issue 3 The rates and costs of hospital resource use for HS are highly uncertain and may be over-estimated in the company's economic model.

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Estimates of hospital resource use applied to each model health state in the company submission are obtained from a survey of N=41 clinical experts, conducted for a previous NICE appraisal of adalimumab (TA392). The EAG are concerned that the company base case model predictions that BSC and secukinumab patients will have [redacted] and [redacted] surgeries for HS respectively over their lifetime may be substantially higher than would be expected in UK clinical practice. Uncertainty in estimates from clinical experts has not been described, it is unknown how questions were framed, the estimates may be out of date and do not appear to have been validated by the company. This issue is important because reducing hospital resource use frequencies (surgery and non-surgery related admissions) increases the ICER substantially.
What alternative approach has the EAG suggested?	The EAG presents the results of a range of exploratory analyses reducing resource use estimates by 15%, 50%, 75% and 100% to explore the impact on the ICER.
What is the expected effect on the cost-effectiveness estimates?	The EAG exploratory analyses demonstrate that resource use estimates are an important driver of the ICER and any over-estimates of resource use frequency led to a substantial bias in favour of secukinumab.
What additional evidence or analyses might help to resolve this key issue?	A literature review to identify existing published resource use estimates would help reduce uncertainty. In the absence published data, the EAG request that the company conducts its own elicitation exercise with clinical experts, presenting variability in expert opinion and incorporating this within the probabilistic analyses.

Issue 4 The company economic model includes costs of BSC and surgery but does not include any quality-of-life benefits from these treatments.

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Despite including the costs of multiple surgical procedures and BSC treatments (anti-biotics, retinoids, dapsone, ciclosporin and anti-androgens), the benefits of these treatments are excluded from the model. There are several related areas of concern: 1) including the costs but not the benefit of treatment under-estimates the ICER; 2) it is unclear what constitutes BSC treatments in UK clinical practice; and 3) the costs of BSC are not aligned with the placebo arms of the SUNNY trials. These issues are important because including the effectiveness of BSC / surgery or removing the costs to align costs and benefits would increase the ICER substantially.
What alternative approach has the EAG suggested?	Given the current evidence provided by the company, the EAG is unable to suggest an alternative approach for estimating treatment benefit of surgery and BSC but prefers to remove restrictive structural assumptions for BSC (See issue 1) and prefers application of BSC treatments available in the trials to algin modelled benefits and costs.
What is the expected effect on the cost-effectiveness estimates?	Aligning BSC costs with treatments provided in the placebo arms of the SUNNY trials increases the ICER from £28,165 to £30,938 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The EAG would appreciate engagement with clinical experts to understand the treatments that comprise BSC in UK clinical practice. The EAG also request the company to provide a summary of evidence from the literature regarding the outcomes of surgery, and a range of scenario analyses to capture the potential benefits of surgery within the model. An alternative approach to align benefits and costs would be to remove the costs of surgery from the model.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAGs preferred base case analysis implements the following amendments to the company base case model:

- Updating the BSC model structure to allow transitions between response states and transitions out of the non-response state (HiSCR<25). The amendment aligns the modelling approach for secukinumab and BSC and allows for the potential for BSC treatments and surgery to provide improvements in clinical response.
- Removing up-titration of secukinumab dosing. It is inappropriate to apply Q2W effectiveness parameters from the full trial cohort to the subgroup of patients who fail to achieve a response to the Q4W dose. The selection bias likely over-estimates the effectiveness of the Q2W dose in a group of patients who are more difficult to treat.
- Applying treatment pooled health state utility values unless the company provides further reassurances and clinical outcome evidence to support treatment specific health state utility values for each of the model health states.
- Including the costs and treatment utilities of adverse events.
- Aligning modelled BSC costs with the treatments available in the placebo arms of the SUNNY trials to ensure consistency between modelled costs and outcomes.
- Updating BSC costs in the model using eMIT prices because most treatments will be provided in secondary care.
- Re-weighting resource use estimates for the proportion of patients with moderate and severe HS from the SUNNY trials.
- Reducing outpatient resource use estimates to avoid the potential of double counting surgical related, non-surgical related and wound related attendances.
- Re-weighting hospital inpatient stay costs to include day-case admissions, aligned with clinical expert opinion and committee preferred costing from TA392.

The impact of each individual change on the ICER is detailed in Table 2.

Table 2 Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER	Change in ICER from base case
Company's base case (unchanged post clarification queries)	[redacted]	[redacted]	£28,165	--
Allow BSC non-responders to transition out of the HiSCR<25 health state, according to transition probabilities from the placebo arm of the SUNNY trials	[redacted]	[redacted]	£61,844	+£33,678
Remove up-titration of secukinumab dosing	[redacted]	[redacted]	£28,554	+£389
HSUVs pooled across treatment arms	[redacted]	[redacted]	£42,245	+£14,080
Include costs and disutilities of AEs	[redacted]	[redacted]	£28,153	-£12
Align the costs of BSC with the treatments provided within the placebo arms of the SUNNY trials	[redacted]	[redacted]	£30,938	+£2,773
Apply eMIT pricing for BSC treatments	[redacted]	[redacted]	£29,177	+£1,012
Apply severity weighting of disease as per SUNNY trials	[redacted]	[redacted]	£27,905	-£260
Remove outpatient wound care appointments to avoid double counting	[redacted]	[redacted]	£29,037	+£872
Allow day case admissions for hospital inpatient procedures, weighted according to FCEs reported in NHS reference cost data 2020/21	[redacted]	[redacted]	£37,470	+£9,305
Scenarios 1-9 combined (EAG preferred base case analysis, with treatment pooled HSUVs	[redacted]	[redacted]	£143,584	+£115,419
Scenarios 1-2 & 4-9 combined (EAG preferred base case analysis, with treatment specific HSUVs)	[redacted]	[redacted]	£72,030	+£43,865

Abbreviations: BSC: best supportive care; EAG: external assessment group; FCE: finished consultant episodes; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years

The EAG has not identified any modelling errors in the submission. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2 of the report.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Novartis is moderate-to-severe hidradenitis suppurative (HS). The company's description of the condition appears generally accurate in terms of prevalence, symptoms, and complications and in line with the decision problem. The relevant intervention for this submission is secukinumab (Cosentyx®).

2.2 Background

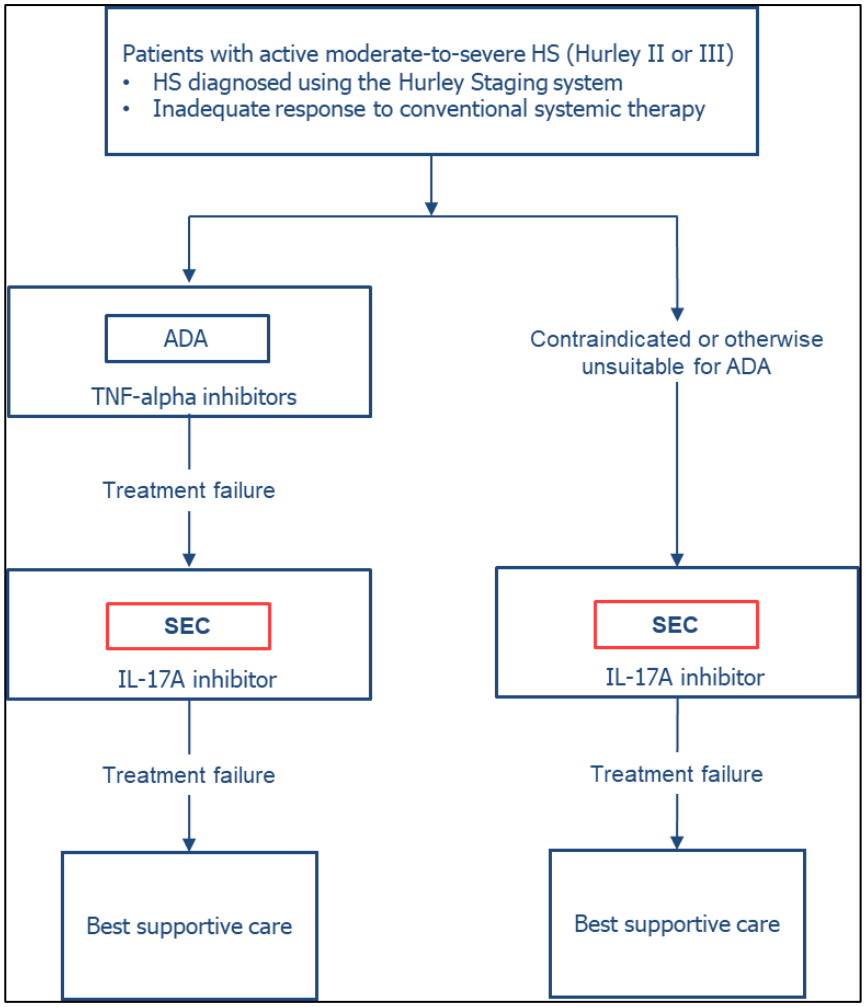
The company submission (CS) describes HS as a debilitating, chronic skin condition characterised by recurrent, painful, deep-seated, inflammatory lesions mainly affecting skin folds, in particular, the groin and armpits.[1-4] The focus of the CS is moderate-to-severe HS.

Disease onset of HS is typically soon after puberty and commonly in early adulthood.[5, 6] Early symptoms include isolated, painful nodules sometimes present and unchanging for months or with intermittent occurrences of inflammation. These solitary lesions are not typical of HS and may be passed off as boils or common abscesses leading to delayed diagnosis,[6] with mean time from onset of symptoms to diagnosis being 7.2 years (compared to 1.6 years for people with psoriasis).[7] Progression of disease is characterised by development of sinus tracts (pus-discharging tunnels), fistulas and/or abscesses.[5, 6, 8] People with HS commonly present with moderate-to severe disease,[9-12] possibly due to misdiagnoses as well as diagnostic delays.[7, 13] Prevalence of self-reported HS in Western Europe is 1%,[14-16] in line with estimates of prevalence of clinically detected HS, which range from 0.05%[17] to 4.1%.[18] However, some people are never formally diagnosed with HS, presenting challenges for its epidemiology, which remains uncertain.[19] In general, in North America and Europe, HS is most prevalent in working age women.[4] Hospital Episode Statistics for England for the year 2021-22 show 2645 finished consultant episodes (1648 females, 997 males, mean age 39 years) for hidradenitis suppurative (code L73.2), with 2478 admissions.[20] HS is associated with smoking and obesity[4] and can cause substantial morbidity if left untreated.[7] In addition, the impact of HS on patients' quality of life and psychosocial wellbeing can be devastating,[21] including increased rates of anxiety, depression and risk of completed suicide.[22]

There is no biological or pathological test to diagnose HS. Instead, diagnosis is based on the presence of three criteria, all of which are required for the diagnosis to be established: typical lesions, typical topography and chronicity and recurrences.[2] Extent and severity of disease are assessed by examination of the total body skin,[1] often by use of the Hurley[23] staging system that classifies people with HS into three stages: mild disease (stage I), moderate disease (stage II) and severe disease (stage III).

Current treatment of HS in the UK is based on guidelines issued by the British Association of Dermatologists.[24] In brief, recommendations include offering oral tetracyclines for at least 12 weeks followed by oral clindamycin and rifampicin for those unresponsive to oral tetracyclines. Consideration should be given for acitretin or dapsone in people unresponsive to antibiotic therapies. Adalimumab should be offered to people who are unresponsive to conventional systemic therapy and infliximab (off label) should be considered for those unresponsive to adalimumab. Adalimumab is licensed for treating moderate-to-severe HS in adults whose disease has not responded to conventional systemic therapy (TA392).[25]

The company presents the proposed positioning of secukinumab in the clinical care pathway in Document B, Figure 2 of the CS, reproduced as Figure 1. The EAG's clinical expert agrees with the company's positioning of secukinumab in the clinical care pathway.



*The red square indicates the anticipated position of secukinumab in the treatment pathway.

Abbreviations: ADA: adalimumab; HS: hidradenitis suppurativa; IL-17: interleukin-17; SEC: secukinumab; TNF: tumour necrosis factor.

Figure 1 Anticipated treatment pathway including the proposed positioning of secukinumab for people with active moderate-to-severe HS who have responded inadequately to conventional systemic therapy [reproduced from Figure 2, Document B of the CS]

2.3 Critique of the company's definition of the decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with moderate-to-severe HS	Adults with active moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment	Secukinumab is not anticipated to be cost-effective in the full population, given the availability of biosimilar adalimumab	The EAG is satisfied that the population addressed in the company submission is appropriate
Intervention	Secukinumab	Secukinumab 300 mg Q4W, with the possibility to up-titrate to Q2W	In line with the final NICE scope	The intervention described in the CS matches the NICE final scope. Secukinumab has existing marketing authorisation for other indications (TA350, TA407, TA445, TA719, TA734).[26-30] The company anticipates that the indication specified by the license extension will be for the treatment of active moderate-to-severe HS in adults with an inadequate response to conventional HS therapy and that it will be granted by the MHRA in [redacted]
Comparator(s)	• Adalimumab • Best supportive care	Best supportive care	Given the recommendation by NICE for the use of adalimumab in HS (TA392)[25] and the availability of	The EAG has some concerns about the company's justification for the omission of adalimumab as a comparator for this appraisal. Although not included in the CS, a report of network meta-analyses including secukinumab and adalimumab as comparators was received by the EAG during the clarification process. The company has positioned secukinumab as a second-line treatment following biologics such as adalimumab.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			biosimilar adalimumab, secukinumab is anticipated to be positioned in the UK for people with HS in whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. Therefore, adalimumab does not represent a relevant comparator given the anticipated UK positioning for secukinumab.	The EAG's clinical expert is of the opinion that off-label infliximab may still provide an alternative treatment option for people with HS in the UK if there is a lack of response from adalimumab and could be part of the treatment pathway, which is reflected in the BAD guidelines.[24] At clarification, the company presented the following rationale for the exclusion of infliximab from the treatment pathway: • "*As noted during the draft scope consultation and Section B.1.3.3 (page 23) of Document B, it was highlighted by the British Association of Dermatologists (BAD) that infliximab no longer represents established clinical practice in the NHS and is now rarely used for treating HS.*[31] • *The NHS England Clinical Commissioning Policy cited a lack of evidence for the use of infliximab in treating HS, and stated that it should not be routinely commissioned.*[32] • *Infliximab was not included in the Final Scope published by NICE for the appraisal of secukinumab in HS.*[33] *As such, infliximab is not a relevant comparator in this appraisal.* *In conclusion, based on the anticipated positioning for secukinumab in the treatment pathway for HS (see Figure 2 in Section B.1.2 of Document B), patients are*

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				expected to be receiving no active therapy. As such, best supportive care (BSC) is anticipated to represent the sole relevant comparator to secukinumab." The EAG accepts the company's position that infliximab is not established clinical practice, despite its recommendation in the BAD guidelines
Outcomes	The outcome measures to be considered include: • Disease severity • Disease progression • Clinical response • Inflammation and fibrosis • Discomfort and pain • Adverse effects of treatment • HRQoL	Key outcome measures reported in the SUNSHINE and SUNRISE trials include: • Disease severity, disease progression, clinical response, inflammation and fibrosis, and discomfort and pain, as assessed by HiSCR, HS flares, AN count, Patient's Global Assessment of Skin Pain, HS-PGA, mHSS, PGI-c and PGI-s. • HRQoL as assessed by DLQI, EQ-5D-3L, PGI-c, PGI-s, WPAI-SHP and HS Symptom Diary • Safety and tolerability, including AEs of treatment	In line with the final NICE scope	The EAG clinical expert considers the outcomes to be appropriate for addressing the topic of this appraisal. The following outcomes specified in Document B, Table 5 of the CS are not explicitly reported in the CS: HS-PGA, mHSS, PGI-s, PGI-c, WPAI-SHP, HS symptom diary, CRP and ESR. The EAG notes that these outcomes are reported in the respective CSRs and that none are used to inform the cost-effectiveness model. The EAG, thus, has no concerns about the outcomes considered by the company
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in	The economic analysis has been conducted in line with the NICE reference case	In line with the final NICE scope	The EAG is generally satisfied that the company submission is in line with the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	terms of incremental cost per 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 PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account			For a full assessment against reference case criteria, see Section 4.2.1.
Subgroups	People who have failed to respond to prior adalimumab treatment	In line with final NICE scope	In line with final NICE scope	The EAG has no issues.
Special considerations including issues related to equity or equality	None specified	N/A	N/A	The company highlighted (Document B, p25) that "the incidence of HS is higher in people of African-Caribbean family background as compared with people of European family background". The EAG notes that most participants in SUNSHINE and SUNRISE were white (79.5% and 76.4%, respectively). Thus, the generalisability of the company's findings to the minority population is limited

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The EAG's appraisal of the company's systematic review methods is shown in Table 4 below.

Table 4 EAG's appraisal of the systematic review methods presented in the CS

Review process EAG	EAG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, and Cochrane Database of Systematic Reviews and HTA databases for secondary research. Relevant conference proceedings and trial registers were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, Section D.1.2: *"Titles and abstracts of studies identified from the search strategy, where available, were reviewed independently by two separate reviewers in accordance with the pre-specified PICOS selection criteria above. Articles, which were identified as potentially*

Review process EAG	EAG response	Comments
		relevant on the basis of titles and abstracts, were then further reviewed by two separate reviewers in full text and selected in accordance with the list of pre-specified inclusion/exclusion criteria. Any discrepancy at either title/abstract or full-text review stage was resolved by discussion with a third reviewer."
Was data extraction conducted by two or more reviewers independently?	Yes	Appendix D, Section D.1.2: *"Data extraction was performed by two independent reviewers in a pre-specified data extraction grid. […] A third independent reviewer undertook a quality check of the data extraction for accuracy and completeness by reviewing 100% of the extracted articles.*"
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	Appendix C, section D.4: *"Risk of bias assessments were performed in line with NICE's quality assessment for clinical trials and guidance from the Centre for Reviews and Dissemination at the University of York."*[34]
Was the risk of bias assessment conducted by two or more reviewers independently?	Yes	From clarification response: *'The risk of bias assessments for the SUNSHINE and SUNRISE trials (as well as the other included randomised controlled trials) were carried out by two separate reviewers for both the original and updated systemic literature review (SLR). These reviewers worked independently.*'
Was identified evidence synthesised using appropriate methods?	Yes	Two randomised controlled trials (RCTs) were identified that met the criteria for the company's modified decision problem. Pooled data were used in the cost-effectiveness analyses as they had identical design. The EAG is happy with this decision.

The EAG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5. *The EAG considers the methods used by the company for the systematic review of clinical effectiveness evidence adequate.*

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Document B, Section B.2 of the CS. The main source of evidence for the clinical effectiveness and safety of secukinumab consist of two identically designed studies sponsored by the company, SUNRISE and SUNSHINE. These are multicentre, randomised, double-blind, placebo-controlled, parallel group studies with two secukinumab dose regimens in the population with moderate to severe HS. *The EAG has no major concerns about the design and conduct of these trials.*

The participant flow in the SUNRISE and SUNSHINE studies is presented in Tables 10 to 12, Appendix D.2 of the CS. An overview of the two studies is presented in Document B, Table 5 of the CS and reproduced as Table 6.

Table 6 Clinical effectiveness evidence [reproduced from Table 5, Document B of the CS]

Study	SUNSHINE (NCT03713619)	SUNRISE (NCT03713632)
Study design	Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre trials	
Population	Adults (≥18 years old) with moderate-to-severe HS	
Intervention(s)	• Secukinumab 300 mg SC injection Q2W (N=181) or • Secukinumab 300 mg SC injection Q4W (N=180)	• Secukinumab 300 mg SC injection Q2W (N=180) or • Secukinumab 300 mg SC injection Q4W (N=180)
Comparator(s)	Placebo SC injection Q2W or Q4W (N=180)	Placebo SC injection Q2W or Q4W (N=183)
Indicate if study supports application for marketing authorisation	Yes – marketing authorisation for secukinumab in HS will be informed by the Q4W dosing regimen arm of each trial, with the possibility to up-titrate to the Q2W dosing regimen	
Indicate if study used in the economic model	Yes – the SUNSHINE and SUNRISE trials represent the primary source of efficacy and safety data for secukinumab in this indication. Data reported from these trials are relevant to the decision problem and have been used in the economic model	
Rationale if study not used in model	N/A	
Reported outcomes specified in the decision problem[a]	Measures of clinical response and disease severity: • **HiSCR50** • NRS30 • AN count • HS flares • HS-PGA • mHSS • PGI-s • PGI-c • WPAI-SHP • HS Symptom Diary • CRP and ESR HRQoL: • DLQI • **EQ-5D-3L** Safety and tolerability • **AEs**	
All other reported outcomes	N/A	

[a] Endpoints in bold are those that are used to inform the cost-effectiveness model.
Abbreviations: AEs: adverse events; AN: abscess and inflammatory nodule; CRP: C-reactive protein, DLQI: Dermatology Life Quality Index; EQ-5D-3L: EuroQoL 5 dimensions 3 level version; ESR:

erythrocyte sedimentation rate; HiSCR: Hidradenitis Suppurativa clinical response; HRQoL: health-related quality of life; HS: hidradenitis suppurativa; HS-PGA: HS-Physician's Global Assessment; mHSS: Modified Hidradenitis Suppurative Score; NRS: Numerical Rating Scale; PGI-c: Patient Global Impression of change; PGI-s: Patient Global Impression of severity; Q2W: every two weeks; Q4W: every four weeks; SC: subcutaneous; WPAI-SHP: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
Source: Novartis SUNSHINE and SUNRISE Protocol.[35, 36]

The methods used by the two studies are reported in Document B, Section 2.3 of the CS and summarised in Document B, Table 6 of the CS. The primary objective of SUNRISE and SUNSHINE was to evaluate the efficacy of secukinumab compared to placebo with respect to HiSCR (hidradenitis suppurativa clinical response) after 16 weeks of treatment. The CS states that '*the 16 weeks timepoint was chosen because 16 weeks was considered to represent the maximal acceptable duration of treatment exposure to placebo in this indication*' (Section B.2.6, page. 45 of the CS). At this time point participants in the control group underwent re-randomisation to receive secukinumab with doses either every two or four weeks. Although the trial continued to 52 weeks, this limits the direct comparison of secukinumab versus best supportive care to the first 16 weeks and we do not have direct evidence of the effectiveness of secukinumab versus control beyond this point. Considering ethical implications for patient care, the EAG clinical expert agrees that 16 weeks is a reasonable timepoint.

The studies' secukinumab dosing regimens are in line with the anticipated licensed posology for secukinumab in moderate-to-severe HS, which is 300 mg Q4W (every 4 weeks), with the possibility to up-titrate to Q2W (every 2 weeks).

The studies consisted of three periods: Screening (up to 4 weeks), placebo-controlled Treatment Period 1 (baseline to Week 16 pre-dose) and Treatment Period 2 (Week 16 post-dose to Week 52). In Treatment Period 1, participants were randomised in a 1:1:1 ratio to one of the three treatment arms:

- Secukinumab 300 mg Q2W (SUNSHINE: N=181; SUNRISE: N=180)
- Secukinumab 300 mg Q4W (SUNSHINE: N=180; SUNRISE: N=180)
- Placebo group to secukinumab 300 mg Q2W or Q4W (SUNSHINE: N=180; SUNRISE: N=183)

Those who completed Treatment Period 1 were allowed to enter the second period (36 weeks) where either of the secukinumab groups (Q2W or Q4W) maintained the same

dosing regimens, while those in the placebo groups were re-randomised in a 1:1 ratio to receive secukinumab Q2W or Q4W.

The studies were conducted in 132 sites in five geographic regions (Asia, Middle East and Africa; Region Europe; Latin America and Canada; United States and Japan), including 12 sites in the UK.

The company performed a quality appraisal of the SUNSHINE and SUNRISE trials in Table 13, Section B.2.5 of the CS. *Overall, the EAG generally agrees with the company's assertion that risk of bias was low across both studies*.

Details of the baseline characteristics of SUNSHINE and SUNRISE are reported as Document B, Tables 7, 8, 9 and 10 of the CS and reproduced as Table 7 and Table 8, below. The study populations were wider than those specified in the company's decision problem and the NICE final scope. Both SUNRISE (n=25, 4.6%) and SUNSHINE (n=15, 2.8%) included participants classified as Hurley stage I disease, indicating mild disease severity. *The EAG's clinical advisor notes that, while the percentage may be too small to make much difference, people with Hurley stage I HS are likely to respond to treatment more favourably than those with more severe forms of this condition.*

Around three-quarters of participants across both studies had not previously received systemic biologic therapy prior to receiving secukinumab. This group is relevant to the final scope issued by NICE but would not be eligible for treatment under the proposed care pathway by the company. Of those who did receive prior systemic biologic therapy (129/541 [23.8%] and 126/543 [23.2%] for SUNSHINE and SUNRISE, respectively), the vast majority were treated with adalimumab (122/129 [95%], and 116/126 [92%], respectively). *The EAG's clinical advisor notes that, since adalimumab and secukinumab use a different mechanism of action, non-response to adalimumab would not systematically impair the response to secukinumab. However, perhaps most importantly, if patients first get adalimumab under the proposed pathway, the better responders are no longer eligible for secukinumab until they lose response to adalimumab, leaving more of the severe and difficult-to-treat cases, which are possibly under-represented in the SUNSHINE and SUNRISE study participants.*

Thus, the inclusion of the adalimumab-naïve population (which differs to that considered for the company's positioning) may have increased the effect size in the included trials in favour of secukinumab.

Overall, slightly more than half of participants were female. Around three-quarters were White, with 37/541 (6.8%) participants in SUNSHINE and 49/543 (9%) participants in SUNRISE classified as Black or African American. The mean BMI was higher than 30 (in the obesity range), with the majority of participants weighing ≥90 kg. More than half of participants were current smokers. The mean age was 36.1 years in SUNSHINE and 36.3 years in SUNRISE, with around two-thirds aged from 30 to 65 years.

The demographic and disease characteristics were generally comparable between the secukinumab Q2W and Q4W dose groups, although the secukinumab Q2W group in the SUNRISE trial was slightly older, with a higher proportion of participants aged from 40 to <65 years (42.8%) compared with the Q4W and placebo groups (31.7% and 32.2%, respectively). The treatment groups in SUNSHINE were balanced for baseline age.

The secukinumab Q2W group across both studies also had more severe HS with a higher proportion of participants with Hurley stage III disease (38.7% and 45.6% for SUNSHINE and SUNRISE, respectively) compared with the secukinumab Q4W and the placebo groups (35.0% and 28.3% for SUNSHINE; 37.8% and 38.3% for SUNRISE). Correspondingly, draining and total fistulae and abscess count, and the proportion of participants classified as HS-PGA 5 (very severe), as well as a mean DLQI (Dermatology Life Quality Index) total score, were also slightly higher in the secukinumab Q2W group than in the other treatment groups. The EAG's clinical expert suggests that the presence of more severe disease in the higher dose (Q2W) group might result in more unfavourable outcomes, despite a general assumption that those patients on higher dose might be expected to do better.

In general, the EAG's clinical advisor is satisfied that the baseline characteristics of SUNSHINE and SUNRISE are representative of patients with moderate-to-severe HS who would be eligible for this treatment in the UK.

Table 7 Demographics and baseline characteristics of patients in SUNSHINE and SUNRISE (randomised analysis set) [reproduced from Tables 7 and 8, Document B of the CS]

Characteristics	SUNSHINE				SUNRISE			
	Secukinumab Q2W (N=181)	Secukinumab Q4W (N=180)	Placebo (N=180)	Total (N=541)	Secukinumab Q2W (N=180)	Secukinumab Q4W (N=180)	Placebo (N=183)	Total (N=543)
Age groups in years, n (%)								
<30	58 (32.0)	69 (38.3)	51 (28.3)	178 (32.9)	52 (28.9)	60 (33.3)	57 (31.1)	169 (31.1)
30–<40	56 (30.9)	45 (25.0)	70 (38.9)	171 (31.6)	48 (26.7)	61 (33.9)	65 (35.5)	174 (32.0)
40–<65	64 (35.4)	63 (35.0)	58 (32.2)	185 (34.2)	77 (42.8)	57 (31.7)	59 (32.2)	193 (35.5)
≥65	3 (1.7)	3 (1.7)	1 (0.6)	7 (1.3)	3 (1.7)	2 (1.1)	2 (1.1)	7 (1.3)
Age, years								
Mean (SD)	37.1 (12.5)	35.7 (11.7)	35.5 (10.8)	36.1 (11.7)	37.3 (11.5)	35.5 (11.4)	36.2 (11.3)	36.3 (11.4)
Median	35.0	34.0	33.5	34.0	37.0	33.5	34.0	35.0
Min–Max	18–73	18–67	19–65	18–73	18–67	18–71	18–71	18–71
Gender, n (%)								
Male	79 (43.6)	80 (44.4)	78 (43.3)	237 (43.8)	82 (45.6)	77 (42.8)	78 (42.6)	237 (43.6)
Female	102 (56.4)	100 (55.6)	102 (56.7)	304 (56.2)	98 (54.4)	103 (57.2)	105 (57.4)	306 (56.4)
Race, n (%)								

White	145 (80.1)	146 (81.1)	139 (77.2)	430 (79.5)	133 (73.9)	139 (77.2)	143 (78.1)	415 (76.4)
Black or African American	15 (8.3)	10 (5.6)	12 (6.7)	37 (6.8)	18 (10.0)	19 (10.6)	12 (6.6)	49 (9.0)
Asian	19 (10.5)	23 (12.8)	24 (13.3)	66 (12.2)	16 (8.9)	16 (8.9)	19 (10.4)	51 (9.4)
Native Hawaiian or Other Pacific Islander	--	--	--	--	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
American Indian or Alaska Native	1 (0.6)	1 (0.6)	2 (1.1)	4 (0.7)	7 (3.9)	5 (2.8)	8 (4.4)	20 (3.7)
Multiple[a]	1 (0.6)	0 (0.0)	3 (1.7)	4 (0.7)	4 (2.2)	1 (0.6)	1 (0.5)	6 (1.1)
Ethnicity, n (%)								
Hispanic or Latino	18 (9.9)	21 (11.7)	22 (12.2)	61 (11.3)	35 (19.4)	30 (16.7)	33 (18.0)	98 (18.0)
Not Hispanic or Latino	157 (86.7)	152 (84.4)	157 (87.2)	466 (86.1)	136 (75.6)	144 (80.0)	143 (78.1)	423 (77.9)
Not Reported	4 (2.2)	6 (3.3)	0 (0.0)	10 (1.8)	8 (4.4)	6 (3.3)	7 (3.8)	21 (3.9)
Unknown	2 (1.1)	1 (0.6)	1 (0.6)	4 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Weight, kg[b]								
Mean (SD)	95.9 (25.0)	95.43 (25.9)	92.88 (22.1)	94.73 (24.4)	92.6 (24.3)	93.1 (22.3)	91.0 (22.0)	92.2 (22.9)
Median	92	92.35	92	92	90	90	89.4	90
Min–Max	51–205	43–201.6	47.4–159.2	43–205	50–181.9	50–152	49.8–157	49.8–181.9

Weight groups in kg, n (%)[b]								
<90	82 (45.3)	80 (44.4)	83 (46.1)	245 (45.3)	86 (47.8)	89 (49.4)	92 (50.3)	267 (49.2)
≥90	99 (54.7)	100 (55.6)	97 (53.9)	296 (54.7)	94 (52.2)	91 (50.6)	91 (49.7)	276 (50.8)
BMI, kg/m^2 [b]								
n	181	179	180	540	NR	NR	NR	NR
Mean (SD)	32.6 (7.9)	32.8 (7.9)	32.0 (7.1)	32.5 (7.6)	31.9 (7.8)	32.0 (7.5)	31.4 (7.4)	31.8 (7.5)
Median	31.8	31.8	31.3	31.6	31.8	31.1	30.4	31.1
Min–Max	14.7–59.0	18.3–61.8	16.8–51.3	14.7–61.8	16.9–64.3	19.3–56.9	18.2–52.2	16.9–64.3
Smoking status, n (%)								
Never	60 (33.1)	56 (31.1)	49 (27.2)	165 (30.5)	51 (28.3)	65 (36.1)	53 (29.0)	169 (31.1)
Current	95 (52.5)	96 (53.3)	101 (56.1)	292 (54.0)	97 (53.9)	90 (50.0)	106 (57.9)	293 (54.0)
Former	26 (14.4)	28 (15.6)	30 (16.7)	84 (15.5)	32 (17.8)	25 (13.9)	24 (13.1)	81 (14.9)

[a] Race 'Multiple' means multiple entries are selected in the eCRF. [b] Weight and height are taken from baseline visit.

Abbreviations: BMI: body mass index; eCRF: electronic case report form; kg: kilogram; m: metres; Max: maximum; Min: minimum; SD: standard deviation; Q2W: every two weeks; Q4W: every four weeks. **Source:** Novartis SUNSHINE CSR (1st October 2021 data cut-off).[37] **Source:** Novartis SUNRISE CSR (23rd September 2021 data cut-off).[38]

Table 8 Baseline patient disease characteristics in SUNSHINE and SUNRISE (randomised analysis set) [reproduced from Tables 9 and 10, Document B of the CS]

Characteristics	SUNSHINE				SUNRISE			
	Secukinumab Q2W (N=181)	Secukinumab Q4W (N=180)	Placebo (N=180)	Total (N=541)	Secukinumab Q2W (N=180)	Secukinumab Q4W (N=180)	Placebo (N=183)	Total (N=543)
Baseline Hurley stage, n (%)								
I	7 (3.9)	10 (5.6)	8 (4.4)	25 (4.6)	6 (3.3)	6 (3.3)	3 (1.6)	15 (2.8)
II	104 (57.5)	107 (59.4)	121 (67.2)	332 (61.4)	92 (51.1)	106 (58.9)	110 (60.1)	308 (56.7)
III	70 (38.7)	63 (35.0)	51 (28.3)	184 (34.0)	82 (45.6)	68 (37.8)	70 (38.3)	220 (40.5)
Time since HS symptom(s) onset (years)								
Mean (SD)	13.4 (9.92)	13.1 (9.2)	12.6 (9.55)	13.0 (9.55)	13.3 (10.3)	13.7 (9.9)	13.0 (9.5)	13.3 (9.9)
Time since diagnosis of HS (years)								
n	--	--	--	--	180	180	182	542
Mean (SD)	7.4 (8.0)	6.6 (6.7)	7.5 (7.0)	7.1 (7.3)	7.1 (7.0)	8.2 (8.4)	7.0 (6.7)	7.4 (7.4)
Baseline AN count								
Mean (SD)	12.9 (9.6)	12.6 (8.4)	12.8 (8.2)	12.8 (8.7)	13.9 (9.9)	13.3 (8.8)	12.8 (8.5)	13.3 (9.1)
Baseline inflammatory nodule count								
Mean (SD)	10.1 (7.8)	9.9 (7.6)	10.1 (7.0)	10.0 (7.5)	10.0 (7.7)	10.4 (7.6)	9.6 (6.8)	10.0 (7.4)
Baseline abscess count								

Mean (SD)	2.9 (4.3)	2.7 (4.0)	2.7 (3.8)	2.7 (4.0)	3.9 (5.4)	2.9 (4.1)	3.2 (5.0)	3.3 (4.9)
Baseline draining fistulae count								
Mean (SD)	2.9 (3.4)	2.5 (3.5)	2.4 (3.2)	2.6 (3.4)	3.0 (3.6)	2.5 (3.5)	2.6 (3.2)	2.7 (3.5)
Baseline total fistulae count								
Mean (SD)	5.3 (5.6)	4.4 (5.2)	4.7 (5.3)	4.8 (5.4)	5.1 (5.0)	4.7 (5.3)	4.6 (4.9)	4.8 (5.1)
Baseline NRS								
n	163	163	162	488	166	163	166	495
Mean (SD)	4.5 (2.5)	4.2 (2.5)	4.3 (2.5)	4.3 (2.5)	4.8 (2.4)	4.6 (2.5)	4.7 (2.4)	4.7 (2.4)
Baseline HS-PGA, n (%)								
0=Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1=Minimal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2=Mild	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
3=Moderate	90 (49.7)	96 (53.3)	91 (50.6)	277 (51.2)	74 (41.1)	85 (47.2)	91 (49.7)	250 (46.0)
4=Severe	27 (14.9)	28 (15.6)	34 (18.9)	89 (16.5)	39 (21.7)	37 (20.6)	33 (18.0)	109 (20.1)
5=Very severe	63 (34.8)	55 (30.6)	54 (30.0)	172 (31.8)	67 (37.2)	58 (32.2)	58 (31.7)	183 (33.7)
Baseline DLQI total score								
n	164	151	163	478	161	168	175	504
Mean (SD)	14.2 (6.7)	13.4 (6.2)	13.8 (7.2)	13.8 (6.7)	15.7 (7.1)	14.6 (7.2)	14.5 (6.9)	14.9 (7.1)
Prior surgery for HS, n (%)								
Yes	71 (39.2)	73 (40.6)	72 (40.0)	216 (39.9)	78 (43.3)	70 (38.9)	78 (42.6)	226 (41.6)

No	110 (60.8)	107 (59.4)	108 (60.0)	325 (60.1)	102 (56.7)	110 (61.1)	105 (57.4)	317 (58.4)
Previous exposure to systemic biologic therapy, n (%)								
Yes	44 (24.3)	39 (21.7)	46 (25.6)	129 (23.8)	36 (20.0)	42 (23.3)	48 (26.2)	126 (23.2)
No	137 (75.7)	141 (78.3)	134 (74.4)	412 (76.2)	144 (80.0)	138 (76.7)	135 (73.8)	417 (76.8)
Previous exposure to adalimumab, n (%)								
Yes	41 (22.7)	38 (21.1)	43 (23.9)	122 (22.6)	34 (18.9)	38 (21.1)	44 (24.0)	116 (21.4)
No	140 (77.3)	142 (78.9)	137 (76.1)	419 (77.4)	146 (81.1)	142 (78.9)	139 (76.0)	427 (78.6)
Previous exposure to systemic antibiotics, n (%)								
Yes	146 (80.7)	149 (82.8)	150 (83.3)	445 (82.3)	151 (83.9)	152 (84.4)	151 (82.5)	454 (83.6)
No	35 (19.3)	31 (17.2)	30 (16.7)	96 (17.7)	29 (16.1)	28 (15.6)	32 (17.5)	89 (16.4)

Abbreviations: AN: abscess and inflammatory nodule; DLQI: Dermatology Life Quality Index; HS: hidradenitis suppurativa; HS-PGA: HS-Physician's Global Assessment; NRS: Numerical Rating Scale; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation. **Source:** Novartis SUNSHINE CSR (1st October 2021 data cut-off).[37] **Source:** Novartis SUNRISE CSR (23rd September 2021 data cut-off). [38]

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: disease severity, disease progression, clinical response, inflammation and fibrosis, discomfort and pain, adverse effects of treatment and health-related quality of life (HRQoL).

Primary analysis was based on a data cut-off date of 1 October 2021 for SUNSHINE and 23 September 2021 for SUNRISE. Of the 541 randomised patients in SUNSHINE, 509 patients completed the 16-week treatment period. Of the 543 randomised patients in SUNRISE, 506 patients completed the 16-week treatment period. At the primary endpoint analysis data cut-off, 315 (59.1%) and 311 (59.0%) patients had completed the entire treatment period (Week 52), respectively.

Primary and secondary outcomes are presented below. In most cases results from SUNSHINE and SUNRISE were provided separately in the CS, except for the NRS30 skin pain outcome which was presented using pooled data from SUNSHINE/SUNRISE combined. It is not clear to the EAG why most analyses were presented separately except for this one outcome. The subgroup analyses for the primary outcome were also presented using data from the two trials combined.

Primary endpoints: SUNSHINE and SUNRISE

The primary endpoints of SUNSHINE and SUNRISE was achieving HiSCR50 (hidradenitis suppurativa clinical response score of 50) at Week 16, defined as a ≥50% decrease in AN (abscesses and inflammatory nodule) count with no increase in the number of abscesses and/or in the number of draining fistulae. The CS reports these outcomes in terms of "n*/m", defined as a "*rounded average number of patients with response in 100 imputations divided by the number of patients evaluable*", as opposed to actual observed counts of participants achieving the respective outcomes. A summary of the primary outcome is presented in Table 9.

At Week 16, the odds ratio estimate (95% CI) in SUNSHINE for the secukinumab Q2W dose vs placebo comparison was 1.75 (1.12, 2.73) and for the secukinumab Q4W dose vs placebo comparison was 1.48 (0.95, 2.32). This difference was statistically significant in favour of secukinumab for the Q2W group (p = 0.0070) but not for the Q4W group (one-sided p = 0.0418). For SUNRISE, the odds ratio

estimates (95% CI) for the comparison with placebo of both secukinumab treatment regimens were statistically significant (1.64 (1.05, 2.55), p = 0.0149 for the Q2W group; 1.90 (1.22, 2.96), p = 0.0022, for the Q4W group).

The proportion of participants with HiSCR50 by week up to Week 16 is presented in Figures 5 and 6 of the CS. In the SUNSHINE study, greater response rates for both secukinumab treatment groups compared with placebo were achieved by Week 4 (31.4% for Q2W, 34.0% for Q4W and 20.4% for placebo) and sustained over time until Week 16 (45.0% for Q2W, 41.8% for Q4W and 33.7% for placebo). Similar results were observed for the SUNRISE study with greater response for secukinumab compared with placebo achieved by Week 2 (17.4% for Q2W, 22.1% for Q4W and 11.3% for placebo) and sustained until Week 16 (42.3% for Q2W, 46.1% for Q4W and 31.2% for placebo).

Available observed long-term data beyond Week 16 up to Week 52 at the time of the primary analysis of SUNSHINE and SUNRISE show that clinical response in terms of HiSCR50 was sustained throughout this period in the secukinumab Q2W and Q4W groups (Figures 7 and 8, Section 2.6.1 of the CS). However, a comparison with placebo was not available for this period.

Secondary endpoints: SUNSHINE and SUNRISE

The company also assessed abscesses and inflammatory nodule (AN) count, HS flares, and skin pain (Numerical Rating Scale score of 30 or NRS30). A summary of these secondary outcomes is presented in Table 9.

- **AN count:** The mean percentage change from baseline in AN count at Week 16 in SUNSHINE shows a greater decrease in AN count for both secukinumab Q2W and Q4W regimens (-46.8 and -42.4, respectively) compared with placebo (-24.3). Similar results were found in SUNRISE with a greater decrease for both secukinumab dosing regimens (-39.3 and -45.5, respectively) compared with placebo (-22.4). The difference from placebo was statistically significant for both secukinumab Q2W groups in SUNSHINE and SUNRISE (one-sided p <0.0001 and p = 0.0051 respectively) but only for secukinumab Q4W in SUNRISE (p = 0.0001). The percentage change from baseline in AN count by week shows that the treatment effect with secukinumab compared

with placebo was seen consistently from Week 2 to Week 16 (Figures 9 and 10, Section B.2.6.2 of the CS).

- **HS flares:** Flare was defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline. At Week 16, fewer participants experienced HS flares in both secukinumab Q2W and Q4W groups compared with the placebo group in SUNSHINE (15.4% and 23.2% vs. 29.0%) and SUNRISE (20.1% and 15.6% vs. 27.0%). The estimated odds ratio was statistically significant only for the secukinumab Q2W group in SUNSHINE (one-sided p = 0.0010; SUNRISE: p = 0.0732) and the secukinumab Q4W group in SUNRISE (one-sided p = 0.0049; SUNSHINE: p = 0.0926). The proportion of participants with HS flares by visit up to Week 16 in SUNSHINE and SUNRISE shows a consistently slower increase in the flare rates compared with placebo for both secukinumab dosing regimens from Week 2 until Week 16 (Figures 13 and 14, Section B.2.6.3 of the CS).
- **NRS30 (skin pain):** NRS30 was defined as a ≥30% reduction and ≥1 unit reduction from baseline in the Patient's Global Assessment of Skin Pain (range 0-10; where 0 represents no skin pain and 10 represents the worse skin pain imaginable). NRS30 was analysed based on the combined data from the two studies (SUNSHINE and SUNRISE) and consisted of participants with NRS≥3 at baseline. At Week 16, NRS30 was achieved in a higher proportion in the secukinumab Q2W and Q4W groups than in the placebo groups (38.9% and 35.8% vs. 26.9%), although results were statistically significant only for the Q2W group (one-sided p = 0.0031; Q4W: p = 0.0249). The proportion of participants achieving NRS30 by week up to Week 16 shows that a larger NRS30 response was achieved with the secukinumab Q2W dosing regimen than with the secukinumab Q4W dosing regimen and placebo, from Week 4 through to Week 16 (Figure 15, Section B.2.6.4 of the CS).

Table 9 Summary of primary and secondary outcomes (multiple imputation; full analysis set) [adapted from Tables 14, 15, 17, 18, 19, 20, 22, Document B of the CS]

Endpoint	Unit	Study	Placebo (SUNSHINE: n=180; SUNRISE: n=183)	Secukinumab 300 mg Q2W (SUNSHINE: n=181; SUNRISE: n=180)	Secukinumab 300 mg Q4W (SUNSHINE: n=180; SUNRISE: n=180)	Q2W effect vs. placebo (95% CI); one-sided p-value	Q4W effect vs. placebo (95% CI); one-sided p-value
HiSCR50 at Week 16	Response, n*/m (%)	SUNSHINE	60.7/180 (33.7)	81.5/181 (45.0)	75.2/180 (41.8)	OR 1.75 (1.12, 2.73), p=0.0070**	OR 1.48 (0.95, 2.32), p=0.0418
		SUNRISE	57.1/183 (31.2)	76.2/180 (42.3)	83.1/180 (46.1)	OR 1.64 (1.05, 2.55), p=0.0149**	OR 1.90 (1.22, 2.96), p=0.0022**
AN count at Week 16	Percentage change from baseline, mean (SE)***	SUNSHINE	-24.3 (4.33)	-46.8 (3.33)	-42.4 (4.01)	LSMD -23.05 (-33.90, -12.21), p<0.0001**	LSMD -18.46 (-29.32, -7.60), p=0.0004
		SUNRISE	-22.4 (4.84)	-39.3 (4.43)	-45.5 (4.08)	LSMD -16.33 (-28.79, -3.88), p=0.0051**	LSMD -22.94 (-35.24, -10.63), p=0.0001**
HS flare at Week 16	Response, n*/m (%)	SUNSHINE	52.2/180 (29.0)	27.8/181 (15.4)	41.7/180 (23.2)	0.42 (0.25, 0.73), p=0.0010**	0.71 (0.43, 1.17), p=0.0926
		SUNRISE	49.5/183 (27.0)	36.1/180 (20.1)	28.0/180 (15.6)	0.68 (0.41, 1.14), p=0.0732	0.49 (0.29, 0.84), p=0.0049**
NRS30 (skin pain) at Week 16****	Response, n*/m (%)	Combined SUNSHINE and SUNRISE	61.9/230 (26.9)	90.8/233 (38.9)	79.4/222 (35.8)	1.80 (1.18, 2.74), p=0.0031**	1.54 (1.00, 2.38), p=0.0249

n* = rounded average number of patients with response in 100 imputations. m = number of patients evaluable.
** Statistically significant based on the pre-defined testing hierarchy
*** The mean is the pooled mean over 100 imputations. SE is the pooled standard error over 100 imputations.
**** Only patients with a baseline NRS≥3 are included.
Covariates included in the model for HiSCR, AN count and HS flare: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight; Covariates included in the model for NRS30: treatment group, Hurley stage, baseline NRS, geographical region, use of antibiotic, baseline body weight, study.
Abbreviations: AN: abscess and inflammatory nodule; CI: confidence interval; HiSCR: Hidradenitis Suppurativa clinical response; LSMD: least squares mean difference; NRS: numeric rating scale of the Patient's Global Assessment of Skin Pain - at worst (averaged over the last 7 days); OR: odds ratio; Q2W: every two weeks; Q4W: every four weeks; SE: standard error.

Health-related quality of life (HRQoL): SUNSHINE and SUNRISE

- **Dermatology Life Quality Index (DLQI):** Mean DLQI total score had a greater decrease from baseline to Week 16 in both secukinumab Q2W and Q4W groups compared with the placebo group in both studies (SUNSHINE: -4.3 in Q2W and -3.5 in Q4W vs. -1.2 in placebo; SUNRISE: -4.3 in Q2W and -3.7 in Q4W vs. -1.5 in placebo). When looking at DLQI response (a decrease greater than 5.0 points from baseline), favourable results for both secukinumab dosing regimens over placebo were observed consistently from Week 2 in SUNSHINE and Week 4 in SUNRISE up to Week 16 in both studies (SUNSHINE at Week 16: 47.8% in Q2W and 48.4% in Q4W vs. 28.9% in placebo; SUNRISE at Week 16: 37.5% in Q2W and 47.2% in Q4W vs. 31.7% in placebo).
- **EQ-5D-3L:** There was a slight imbalance in the mean EQ-5D-3L health visual analogue scale (VAS) score at baseline. In particular, the secukinumab Q2W group in SUNRISE had a lower EQ-5D-3L VAS score (59.7) compared with the Q4W (64.7) and placebo (63.0) groups. By Week 2, EQ-5D-3L VAS score increased sharply and was sustained up to Week 16. The change (increase) from baseline in EQ-5D-3L VAS score at Week 16 was higher in the Q2W group compared with the Q4W and the placebo groups in both studies (SUNSHINE: 4.5 in Q2W vs. 2.8 in Q4W and 0.8 in placebo; SUNRISE: 9.9 in Q2W vs. 3.3 in Q4W and 0.3 in placebo).

3.2.3 Subgroup analyses

Details of subgroup analyses of the primary efficacy outcome, HiSCR, at Week 16 are presented in Figures 29 to Figure 32, Section B.2.7 of the CS. Details of subgroup analyses of the secondary efficacy outcomes at Week 16 are presented in Appendix E of the CS. The only subgroup listed in the NICE final scope for this appraisal was people who have failed to respond to prior adalimumab treatment. The company pre-specified additional subgroups including age, gender and race, as well as baseline CRP levels, ESR levels, Hurley stage, AN count and disease duration.

Pre-specified subgroup analyses were based on the pooled SUNSHINE and SUNRISE studies and carried out at the primary analysis data cut-off (i.e., when all patients completed the visit at Week 16) of SUNSHINE (23rd September 2021) and SUNRISE (1st October 2021).

Results from the subgroup analyses show that achievement of HiSCR was broadly consistent across most specified sub-groups in the secukinumab Q2W and Q4W groups, including previous exposure to biologics and concomitant use of antibiotics.

Focusing on biologic-experienced subgroup as compared with biologic-naïve subgroup (Figure 31 of the CS), efficacy with respect to HiSCR compared with placebo was generally consistent with the estimated OR 1.60 (95% CI: 0.83, 3.08) and OR 1.64 (95% CI: 1.15, 2.33), respectively, for the secukinumab Q2W group and OR 1.67 (95% CI: 0.86, 3.22) and OR 1.61 (1.13, 2.29), respectively, for the secukinumab Q4W group. Nominal significance was not met in the biologic-experienced subgroups ([redacted] in Q2W; [redacted] in Q4W), possibly due to small sample size. As noted in Section 3.2.1 of the EAG report, the biologic-experienced subgroup consisted of 23.8% (129/541) and 23.2% (126/543) of the SUNSHINE and SUNRISE study participants, respectively, the vast majority of whom were treated with adalimumab (122/129 [95%], and 116/126 [92%], respectively).

NSR30 for pain relief was numerically under-achieved for the biologic-experienced group compared with the biologic naïve group (NRS30 was achieved by [redacted] and [redacted] of biologic-naïve and biologic-experienced patients at the Q4W dosing level, respectively, and [redacted] and [redacted] of biologic-naïve and biologic-experienced patients in the Q2W treatment group, respectively, with placebos of [redacted] and [redacted], respectively; Appendix E.3 of the CS). There were similar effects on the AN count where the degree of a decrease was smaller for the biologic-experienced group compared with the biologic-naïve group [redacted] for Q2W, [redacted] for Q4W and [redacted] for placebo, in biologic-naïve participants, compared with [redacted] for Q2W, [redacted] for Q4W and [redacted] for placebo in biologic-experienced participants; Appendix E.1 of the CS). The EAG's clinical expert suggests that the AN count is the main driver of the primary outcome and the most sensitive to change with therapy. While the biologic-experienced are experiencing effects superior to placebo, it does give room for doubt as to whether the results from SUNSHINE and SUNRISE would be quite so favourable to secukinumab if the studies had included only the biologic experienced population.

3.2.4 Adverse events

The safety analysis sets of SUNSHINE and SUNRISE included all patients who received at least one dose of study treatment. The methods used to assess safety are reported in

Document B, Sections B.2.10 of the CS and are considered appropriate by the EAG. In general, the EAG clinical expert is of the opinion that the safety profile for secukinumab is as expected for patients with this clinical condition. Median duration of exposure in Treatment Period 1 was 112 days in both SUNRISE and SUNSHINE.

Overviews of safety data in Treatment Period 1 in SUNRISE and SUNSHINE are presented in Document B, Table 27 and 28 of the CS, summarised as Table 10 below.

Table 10 Overview of safety data in SUNRISE and SUNSHINE in Treatment Period 1 [adapted from Tables 27 and 28, Document B of the CS]

n (%)	SUNRISE			SUNSHINE		
	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)
Patients with ≥1 TEAE	116 (63.4)	113 (62.8)	114 (63.3)	120 (66.7)	122 (67.4)	118 (65.6)
SAE	5 (2.7)	6 (3.3)	6 (3.3)	6 (3.3)	3 (1.7)	3 (1.7)
AEs leading to treatment discontinuation	4 (2.2)	1 (0.6)	4 (2.2)	1 (0.6)	5 (2.8)	1 (0.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE: adverse event; Q2W: every two weeks; SAE serious adverse event; TEAE: treatment-emergent adverse event.

In Treatment Period 1, around two-thirds of patients in both SUNRISE and SUNSHINE experienced at least one TEAE but very few were SAEs or led to treatment discontinuation and there were no deaths.

Treatment-emergent adverse events occurring in at least 5% of any treatment group in Treatment Period 1 are summarised in Document B, Table 29 and Table 30 of the CS and presented as Table 11 below.

Table 11 TEAEs by preferred term (≥5% in any treatment group) in Treatment Period 1 of SUNRISE and SUNSHINE (Safety Set) [adapted from Tables 29 and 30, Document B of the CS]

	SUNRISE			SUNSHINE		
Preferred term, n (%)	**Placebo (N=183)**	**Secukinumab 300 mg Q2W (N=180)**	**Secukinumab 300 mg Q4W (N=180)**	**Placebo (N=180)**	**Secukinumab 300 mg Q2W (N=181)**	**Secukinumab 300 mg Q4W (N=180)**
Any preferred term	116 (63.4)	113 (62.8)	114 (63.3)	120 (66.7)	122 (67.4)	118 (65.6)
Headache	15 (8.2)	21 (11.7)	17 (9.4)	14 (7.8)	17 (9.4)	20 (11.1)
Nasopharyngitis	16 (8.7)	13 (7.2)	9 (5.0)	13 (7.2)	20 (11.0)	16 (8.9)
Hidradenitis	14 (7.7)	10 (5.6)	11 (6.1)	24 (13.3)	11 (6.1)	5 (2.8)
Diarrhoea	13 (7.1)	8 (4.4)	7 (3.9)	9 (5.0)	5 (2.8)	13 (7.2)
Upper respiratory tract infection	7 (3.8)	9 (5.0)	3 (1.7)	4 (2.2)	5 (2.8)	6 (3.3)

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Abbreviations: Q2W: every two weeks; Q4W: every four weeks; TEAE: treatment-emergent adverse event.

Rates of TEAEs were generally low across both trials, with headache and nasopharyngitis being the most reported TEAEs in the secukinumab groups. Worsening of hidradenitis tended to be more commonly reported in the placebo groups, albeit still in low numbers of participants. Treatment-emergent adverse events by system organ class (SOC) for Treatment Period 1 are reported in Appendix F, Table 15 and Table 16 of the CS. In both SUNRISE and SUNSHINE, infections and infestations were the most commonly reported AEs, occurring in around one-third of patients. Gastrointestinal disorders were reported in 13-16% of patients and skin and subcutaneous disorders in up to one-fifth of patients.

Treatment-emergent adverse events possibly related to study treatment during Treatment Period 1 are reported in Document B, Table 31 and Table 32 of the CS, and summarised as Table 12 below.

Table 12 TEAEs possibly related to study treatment by primary system organ class (≥5% in any treatment group) in Treatment Period 1 of SUNRISE and SUNSHINE (Safety set) [adapted from Tables 31 and 32, Document B of the CS]

	SUNRISE			SUNSHINE		
Primary system organ class, n (%)	**Placebo (N=183)**	**Secukinumab 300 mg Q2W (N=180)**	**Secukinumab 300 mg Q4W (N=180)**	**Placebo (N=180)**	**Secukinumab 300 mg Q2W (N=181)**	**Secukinumab 300 mg Q4W (N=180)**
Any organ class	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Abbreviations: Q2W: every two weeks; Q4W: every four weeks; TEAE: treatment-emergent adverse event.

Up to one-quarter of participants experienced TEAEs possibly related to treatment in Treatment Period 1, the most common of which was infections and infestations in all groups.

Serious adverse events in Treatment Period 1 in SUNRISE and SUNSHINE are reported in Document B, Table 33 and Table 34 of the CS. Rates of SAEs were low across all groups in both trials, with similar rates between placebo (2.7% in SUNRISE; 3.3% in SUNSHINE) and secukinumab groups (3.3% in both groups in SUNRISE; 1.7% in both groups in SUNSHINE). No particular SAE was higher in frequency across the trials.

Adverse events of special interest (AESI) in Treatment Period 1 as specified in the Risk Management Plan were infections, hypersensitivity, suicidal ideation and behaviour, and malignant or unspecific tumours. Infections were the most frequently reported AESI, affecting around one-third of patients in all groups of the trials. Most were mild-to-moderate in severity and only one patient in each trial (from the placebo group in SUNRISE and the secukinumab Q2W group in SUNSHINE) discontinued the study drug.

Over the Entire Study Period, the incidence and severity of adverse events was generally consistent with those in Treatment Period 1. The most frequent TEAEs by primary system order class were infections and infestations, consistent with Treatment Period 1 but reported in around half of patients, as compared to around one-third in the initial treatment period. Skin and subcutaneous disorders affected around one-third of patients and gastrointestinal disorders, around one-quarter. Considering TEAEs by preferred term, headache, nasopharyngitis hidradenitis and diarrhoea were most reported, again in line with Treatment Period 1. Serious adverse events were rare over the Entire Study Period, although in slightly higher absolute numbers than in Treatment Period 1. There were two deaths over the Entire Study Period, both in SUNRISE and in the any secukinumab Q4W group, and neither were considered to be related to the study treatment.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The only comparators considered by the company were secukinumab and best supportive care and SUNSHINE and SUNRISE were the only trials included in the CS. The EAG has not identified any additional eligible randomised trials involving secukinumab.

No meta-analyses were presented in the original company submission. As SUNSHINE and SUNRISE were considered to have an identical design, naive pooling of the data from these two trials was used in the cost-effectiveness modelling. The EAG agrees that, although formal meta-analysis of SUNSHINE and SUNRISE would be possible, there would not be any advantage in this situation because the two studies have the same population, interventions, comparator, outcomes, and time points. It should also be pointed out that the current cost-effectiveness model uses individual participant data from these two studies and, in its current form, cannot easily incorporate estimates such as odds ratios from a meta-analysis.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

No network meta-analysis (NMA) was presented in the company submission, even though there appeared to be relevant trials of adalimumab, the comparator included in NICE's scope, listed in the Appendix to the CS. As part of the clarification process the company revealed that an NMA had in fact been conducted for a different purpose and the report of this was eventually shared with the EAG.

The company's position is that the NMA is not relevant to the submission because they are positioning secukinumab as a second-line treatment in the situation where adalimumab is contraindicated or otherwise unsuitable, such as for those who fail to respond to prior adalimumab treatment. The company maintain that, as there are no current recommended therapies for this second-line position, best supportive care should be considered the only comparator to secukinumab.

However, NICE's final scope specifies both adalimumab and best supportive care as comparators to secukinumab and makes no mention of using secukinumab as a second-line treatment. Moreover, the available evidence from SUNSHINE/SUNRISE comes from a population that differs to that considered for the company's positioning. Only around 23.8% and 23.2% of participants in SUNSHINE and SUNRISE, respectively, had received a prior biologic treatment, such as adalimumab.

The EAG, therefore, believes that the Committee should be aware of the results of the NMA as the most appropriate analysis for addressing NICE's scope.

A further comparator that could be considered is infliximab, which is an off-label treatment. Infliximab was not listed as a relevant comparator by NICE, but *the EAG's clinical advisor is of the opinion that it may still provide an alternative treatment option when there is a lack of response from adalimumab*. In response to a clarification question, the company gave three reasons why infliximab should not be considered as a comparator: 1) that it was rarely used in NHS clinical practice according to the British Association of Dermatologists (BAD), 2) that there is a lack of evidence for its effectiveness and 3) because it was not considered in the final scope published by NICE. *The EAG accepts the company's position that infliximab is not established clinical practice, albeit one of the recommended treatments in the BAD guidelines.*[24]

3.4.1 Summary of company's NMA report

The original CS did not include any meta-analyses. In response to a clarification question, the company revealed that network meta-analyses (NMA) (also known as in indirect treatment comparisons [ITC]) had in fact been conducted for another purpose and the report of these, 149 pages and dated November 2022, was subsequently shared with the EAG.[39]

The EAG did not consider it appropriate to conduct a formal critique of this document, as it did not form part of the company's submission and was only received relatively late in the clarification process. However, the EAG is of the opinion that the Committee should be aware of the NMA as relevant to the decision problem in NICE's final scope. In this section, the main findings of these analyses are described along with their strengths and limitations. Selected copies of tables and figures from the PDF document have been included.

3.4.2 Systematic literature review and feasibility assessment

[redacted]

Table 13 Description of included studies [reproduced from Table 4, pages 22-23 of the NMA report]

[redacted]

Figure 2 Network diagram used to illustrate the extended network of all comparators [reproduced from Figure S.8, page 99 of NMA report]

[redacted]

[redacted]

3.4.3 Methods of the NMA

[redacted]

[redacted][40][redacted]

[redacted]

3.4.4 Results of the “base case” NMA

[redacted]

Figure 3 Network diagram used for HiSCR50 for the company's "base case" NMA [reproduced from Figure 15, page 46 of NMA report]

Table 14 Summary of the results for the "base case" NMA [reproduced from Table 1, page 12 of the NMA report]

[redacted]

3.4.5 Sensitivity analyses

[redacted]

[redacted]

3.4.6 Strengths and limitations of the NMA

[redacted]

[redacted]

3.4.7 Overall conclusions

[redacted]

[redacted]

3.5 Additional work on clinical effectiveness undertaken by the EAG

None

3.6 Conclusions of the clinical effectiveness section

The EAG is satisfied that SUNRISE and SUNSHINE are relevant well-conducted randomised trials that should be used as the primary evidence to compare secukinumab with best supportive care.

The main consideration of the Committee is whether it agrees with the company that secukinumab should be positioned as a second-line treatment following biologics such as adalimumab. If so, the EAG agrees that pooled data from SUNRISE and SUNSHINE should be used in the cost-effectiveness modelling. Otherwise, the results of the NMA including adalimumab provide relevant information.

There is nothing in the NICE final scope to indicate that secukinumab should be a second-line therapy. In addition, the overall population of SUNSHINE/SUNRISE does not match the company's positioning, as only 23.8% and 23.2% of participants in SUNSHINE and SUNRISE, respectively, received prior biologics. Subgroup analyses using combined data from SUNSHINE and SUNRISE indicated that very similar results were obtained for the primary outcome with respect to prior biologics status.

The EAG also notes that the decision problem addressed in the CS specifically concerns secukinumab 300mg Q4W, with the possibility to up-titrate to Q2W. However, the actual data used in the CS concern roughly equal numbers receiving doses every two (Q2W) and every four (Q4W) weeks.

If the Committee is satisfied with the company's positioning, the EAG agrees that data from SUNSHINE and SUNRISE should be used in the cost-effectiveness modelling.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The CS states that a systematic literature review was performed to find relevant economic evaluations for the treatment of adult patients with moderate-to-severe HS. Full details of the literature review of existing cost-effectiveness studies are provided in Appendix G of the CS. Briefly, the searches were done in June 2021 (no date restrictions applied) and updated in August 2022 (restricted to studies published from 2021 onwards**)**. The searches were restricted to studies published in English. The company identified 10 economic evaluations, from 7 publications, including 5 CUAs and 5 BIAs. Of the 5 CUAs, four assessed the cost-effectiveness of adalimumab (NICE, SMC, CADTH and PBAC), and one assessed a hypothetical new drug compared to adalimumab.[25, 41-43] Most models were structured around HiSCR response states, while one model was structured around Hurley states. Of the identified CUAs, the company deemed the previous assessment by NICE of adalimumab (TA392) to be most relevant for decision making.[25]

The EAG is satisfied that the company's searches are unlikely to have missed any relevant economic evaluation studies. The EAG provides a comparison of key inputs and outputs from the TA392 and current appraisals in Table 15 for the committee's information.

Table 15 Comparison of previous NICE appraisal of adalimumab against the company submission for secukinumab.

Study	NICE TA392, 2015[25]	Current appraisal of Secukinumab
Model method	Markov model	Markov model
Intervention	Adalimumab	Secukinumab
Comparator	Supportive care	Best supportive care
Patient population (weighted mean age in years)	Adults with active moderate to severe hidradenitis suppurativa which had not responded to conventional therapy (36.2 years in the overall PIONEER population)	adults with moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond, or lost a response, to previous adalimumab treatment. full trial population from the SUNNY trials (*56.3%* female, mean age: *36.2)*
QALYs (intervention, comparator)	Adalimumab: 12.58 Supportive care: 11.63	**Company preferred:** Secukinumab: [redacted]; BSC: [redacted] **EAG preferred:** Secukinumab: [redacted]; BSC: [redacted]
Costs (currency) (intervention, comparator)	Adalimumab (with confidential PAS discount): £140,342 Supportive care: £128,647	**Company preferred:** Secukinumab (with confidential PAS discount): £[redacted]; BSC: [redacted] **EAG preferred:** Secukinumab (with confidential PAS discount): [redacted]; BSC: [redacted]
ICER (deterministic)	£12,336/QALY (Company base case) £28,500–£33,200/QALY (Committee conclusion)	£28,165(Company case) £143,584 (EAG preferred base case)

Abbreviations: BSC: best supportive care; EAG: external assessment group; PAS: patient access scheme, QALY: quality-adjusted-life-years

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

The company's model assesses the cost-effectiveness of secukinumab as compared with BSC for the treatment of patients with moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. The CS states that no previous study has used secukinumab for the patient population in question and thus the company developed its own *de novo* Markov cohort model cost-utility analysis.

4.2.1 NICE reference case checklist

The EAG's appraisal of the company submission against the NICE reference case is summarised in Table 16 below.[44]

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Partly.** The company submission includes direct health effects for patients through health state utility values but does not incorporate the health effects of downstream surgery.
Perspective on costs	NHS and PSS	**Yes.** The company submission is aligned with the NICE reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	**Yes.** A cost-utility analysis, with results reported as incremental cost per QALY gained.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	**Yes.** The model time horizon runs for a maximum of 100 years, which captures all relevant cost and outcomes.
Synthesis of evidence on health effects	Based on systematic review	**Yes.** The EAG is satisfied that there are no other secukinumab studies in the moderate to severe HS population. However, the EAG notes that health effects to populate the model are obtained from a naïve pooling of data from the SUNNY trials

Element of health technology assessment	Reference case	EAG comment on company's submission
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Yes.** Health effects are expressed in QALYs, measured using the EQ-5D-3L version.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**Yes.** Health state utility values are based on patient participant responses to EQ-5D from the SUNNY trials.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**Yes.** Valued using UK general population tariffs.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes.**
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	**Yes.** However, the EAG has several concerns that resource usage and costs, particularly for surgery have been over-estimated in the model, whilst the benefits of these treatments have not been considered, particularly in the BSC arm of the model.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Yes.** The CS aligns with the NICE reference case.

Abbreviations: CS: company submission; EAG: EQ-5D: standardised instrument for use as a measure of health outcome; PSS: personal social services; QALYs: quality-adjusted life years.

4.2.2 Model structure

The company developed a *de novo* Markov cohort decision analysis model in Microsoft Excel to assess the cost-effectiveness secukinumab versus best supportive care (BSC) for adults with moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable. Two separate Markov models were developed, one for secukinumab and one for

BSC. Both models included five mutually exclusive health states, including four HiSCR response states, with lower scores describing more severe disease, and a death state:

- Non-response, defined as HiSCR: <25
- Partial response, defined as HiSCR: 25–49
- Response, defined as HiSCR: 50–74
- High response, defined as HiSCR: ≥75
- Death

For secukinumab all patients enter the model in the non-response health state, start treatment with secukinumab Q4W, for an induction phase that lasted 4 model cycles (16 weeks). Whilst response was assessed every 4 weeks, patients remained on treatment during this phase, regardless of their 4-weekly HiSCR outcome. The proportion of the cohort that were in the "non-response" health state (HiSCR<25) at week 16, were up-titrated to the higher Q2W secukinumab dose, where they received treatment in the 12 week "up-titration" phase of the model (from week 16-28). Non-responders to the up-titrated dose at week 28, defined as the proportion of the cohort in the HiSCR <25 state at the 28-week assessment discontinued treatment and transitioned to BSC. The transition to BSC at week 28 was based on a single measurement time point and did not consider whether the assessment represented a transient of consistent loss of response. Once the cohort discontinued secukinumab at this point, it was assumed that a response would not be regained for the remainder of the model time horizon. Responders, defined as HiSCR ≥25 at the 16-week assessment (Q4W dose) or 28-week assessment (Q2W dose) entered the maintenance phase of the model where they continue to receive secukinumab, and were allowed to transition between any of the model response health states for the remainder of the model time horizon. This includes the potential for secukinumab patients to experience a transient loss of response that can be regained through continued treatment usage.

Secukinumab treatment discontinuation rates for any reason, beyond week 28, were assumed to be linear over time and independent of treatment state. Data were obtained from the SUNNY trial data for Q4W or Q2W doses respectively. The proportion of the cohort who discontinued treatment from the response states in the maintenance phase, were assumed to enter the same health state in the BSC arm of the model, where they subsequently received BSC transition probabilities.

The BSC arm of the model also enter in the non-response health state and follow the same model structure as for the induction phase in the secukinumab arm up to week 16. At week 16, they are assessed for response, and non-responders at that point are assumed to enter a semi-absorbing non-response state for the remainder of the model time horizon. Those achieving a response at week 16 enter the maintenance phase of the model where they remain in the state identified at week 16 unless they lose a response. Unlike secukinumab, it is not possible for BSC patients to transition between the response health states, meaning that further improvement or deterioration between response categories (i.e., those states with HiSCR ≥25) is not possible beyond week 16, regardless of the treatments applied in the BSC arm (including surgery). In contrast to secukinumab, patients treated with BSC are assumed to be unable to have a transient loss of response, and all losses of response are assumed to be permanent, with the cohort entering the semi-absorbing non-response state for the remainder of the model time horizon, exiting only to the death state.

Patients can also transition to death from any model health state based on the age matched general population mortality rate. The company's schematic of the model framework, showing health state transitions for the secukinumab and BSC arms of the model are reproduced in Figure 1 and 2, respectively.

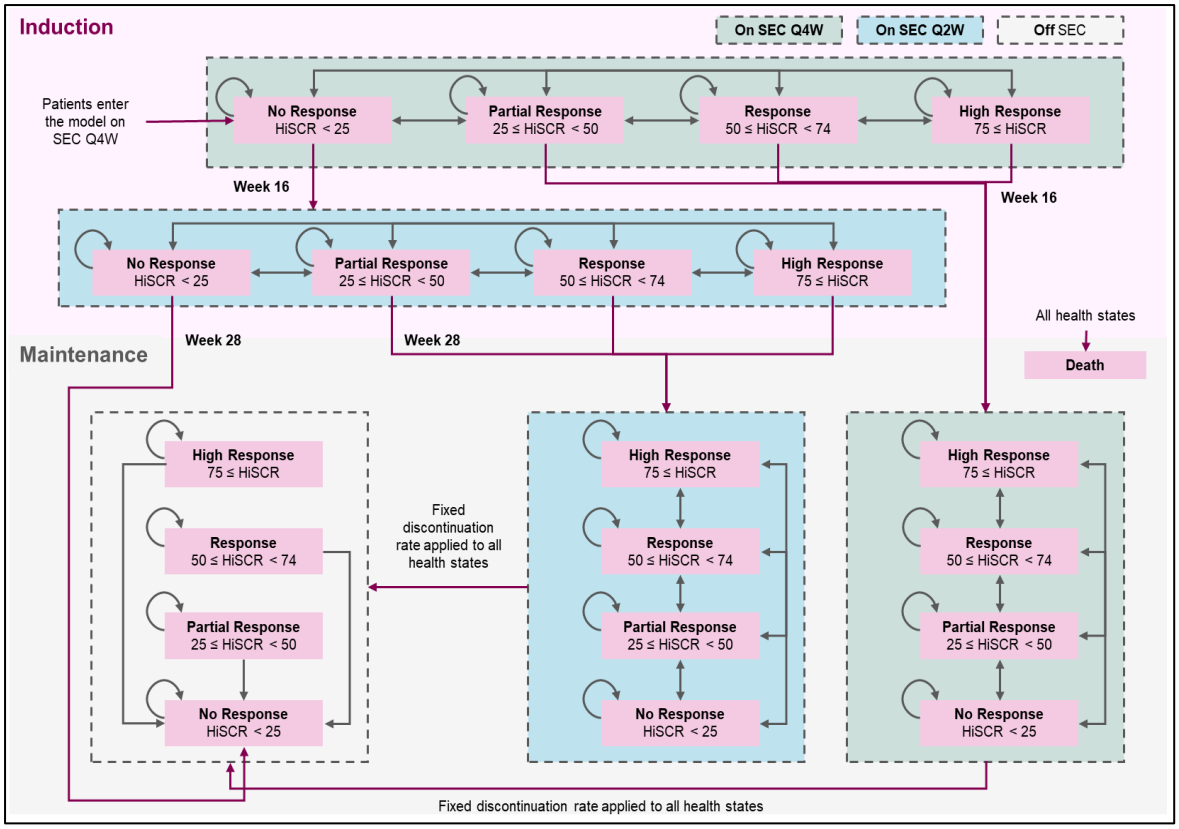


Figure 4 Health state transitions for patients receiving secukinumab [reproduced from Figure 33 of the CS]

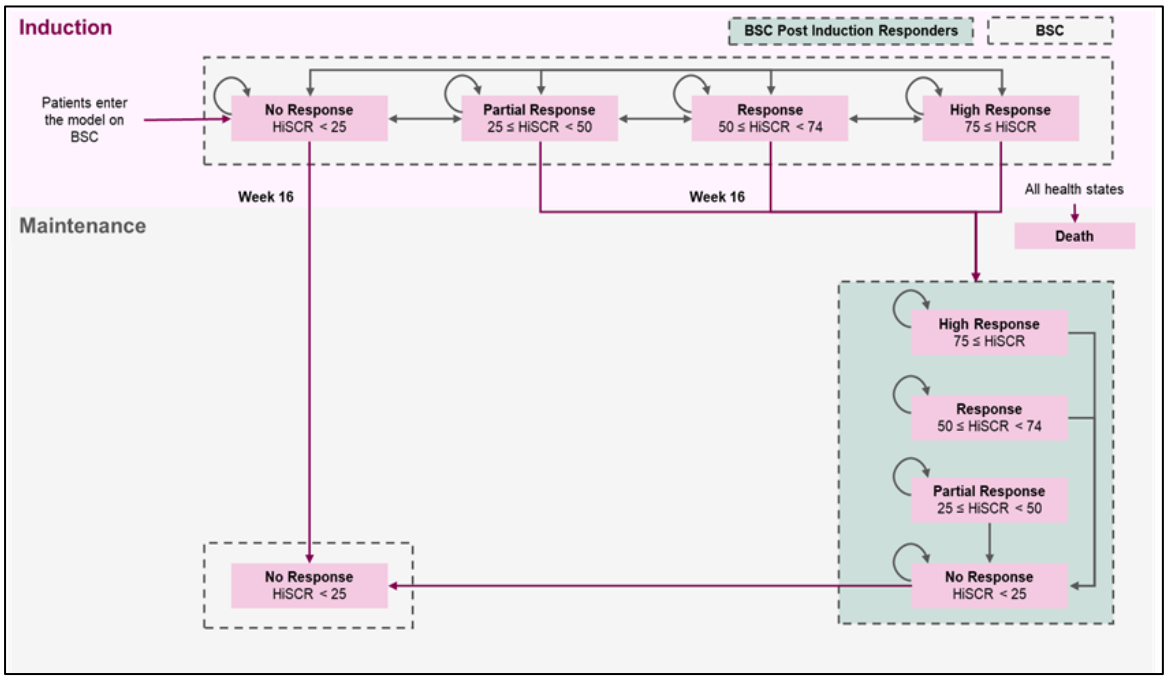


Figure 5 Health state transitions for patients receiving BSC [reproduced from Figure 34 of the CS]

The EAG is satisfied that the company's general model structure, and the decision to model four different levels HiSCR response, rather than a two-state response / non-response model is appropriate. The general model structure is consistent with that applied to model adalimumab for TA392[25] and was confirmed as being clinically plausible by the EAG's expert advisor. The EAG's expert advisor further clarified that there is likely to be substantial variability in terms of resource use and quality of life between patients at the upper and lower ends of the response threshold (HiSCR 50) used as the primary clinical outcome from the SUNNY trials, and so further granularity in the model is appropriate.

The EAG is however concerned that the differences in the company's modelling approach between secukinumab and BSC may introduce a bias in favour of secukinumab. The current secukinumab model structure allows those who lose a response beyond week 28 to continue treatment with the potential to regain that lost response again in future model cycles. However, it is assumed that those on BSC could never regain a response once it is lost. The EAG notes clinical expert opinion that transient improvements and deterioration in condition are plausible as wounds flare up and heal over time. This would be the case, even for a purely placebo comparator, as in the placebo arm of the SUNNY trials. However, because the company base case model assumes people receive multiple surgeries over their lifetime, in addition to BSC treatments including dapsone, retinoids, anti-androgens and ciclosporin, an assumption of no potential to improve health state is likely to be biased in favour of secukinumab. The current model structure implies that BSC and surgery have no impact on the clinical course of HS, do not lead to improvements in HiSCR response and have no impact on patient quality of life. The EAG's clinical expert advisor confirms that surgery and BSC treatments have been the mainstay of treatment for HS up until the recent introduction of biologics into the treatment pathway and do provide some benefits for patients. Whilst the magnitude of benefit is less than would be optimal, it is inaccurate to assume there is no benefit at all. Whilst integrating utility gains of surgery is difficult within the current model structure, the EAG would, as a minimum expect to see an analysis where those with a loss of BSC response have the same potential to have a health state benefit as modelled in the secukinumab arm of the model.

4.2.3 Population

The economic model was developed to assess cost-effectiveness in adults with moderate-to-severe HS for whom adalimumab is contraindicated or otherwise unsuitable, including those

who have failed to respond, or lost a response, to previous adalimumab treatment. However, the starting cohort for the model was obtained from the full trial population from the SUNNY trials (56.3% female, mean age: 36.2), including those who had no previous treatment with adalimumab. Of the participants in the SUNNY trials, only 22.6% and 21.4% of the SUNSHINE and SUNRISE trial participants had previous adalimumab treatment, including those who failed to respond or lost a response to adalimumab. Adalimumab accounted for most of the previous biologic treatment in the studies.

The EAGs full critique of the company's suggested positioning of secukinumab in the treatment pathway is provided in Section 2.3. Except for the starting age and sex characteristics, the modelled cohort (those who have failed to respond to or are contraindicated to adalimumab) is inconsistent with the trial population (which included both biologic experienced and naïve patients) and the scope for the assessment (which included adalimumab as a comparator). The EAG's clinical expert advisor is broadly satisfied that secukinumab and adalimumab have different mechanisms of action, and so it may be feasible that one could be effective when the other is not. This is evident from clinical effectiveness subgroup analyses which do not show any significant differences in treatment effect sizes between adalimumab naïve and experienced patients. However, those who have failed previous adalimumab treatment may be more difficult to treat across both arms of the model and might be expected to have worse outcomes overall compared to the full trial sample. The EAG is concerned that, by applying data from adalimumab naïve patients (approx. 80% of the SUNNY trials) to those who have previously failed or are contraindicated to adalimumab may over-estimate the effectiveness of treatment and health state utility values applied in the model. It is plausible that the magnitude of treatment benefit would be smaller in a more difficult to treat subgroup, who are less likely to respond to treatment. The impact on the ICER of applying transition probability and utility data from the biologic experienced subgroup of patients in the SUNNY trials is explored in Section 4.2.6 and 4.2.7 respectively.

4.2.4 Interventions and comparators

The intervention was secukinumab 300 mg, given weekly over a 5-week induction phase (Week 0-4), followed by a four-weekly dose (Q4W) up until week 16. Responders at week 16 continued treatment at the Q4W dose, whereas non-responders were up titrated to a two-weekly dosage (Q2W) between weeks 16 and 28. Non-responders to the higher Q2W dose at week 28 were discontinued from treatment and transitioned to the BSC arm of the model. This stopping

rule was applied regardless of whether an earlier response had been achieved and subsequently lost. The company provided a scenario analysis removing the possibility of up-titration and applying a stopping rule at week 16 for the Q4W dose.

The EAG is satisfied that the Q4W dosing schedule in the model is consistent with the use of secukinumab Q4W arm of the SUNNY trials. However, the EAG is concerned that the modelling approach of up-titration may be biased, and this is critiqued in Section 4.2.6.

The comparator in the economic model is best supportive care (BSC) as delivered in UK clinical practice. The composition of BSC was derived from clinical expert opinion and included topical and oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens.

The EAG has several concerns with the way in which BSC has been implemented in the model. First, it is unclear how many clinical experts were consulted by the company, what questions they were asked, or how variability in clinical expert opinion was incorporated into the model. Secondly, the EAG note that the composition of BSC used in the economic model includes substantially more active treatments than were allowed in the placebo arms of the SUNNY trials. This generates a bias against BSC because the BSC costs are substantially higher than the costs of treatments allowed within the trials. The EAG therefore prefers to realign the BSC costs with those used in the placebo arm of the SUNNY trials. Further details of the company and EAG preferred BSC costs are provided in Section 4.2.8.

4.2.5 Perspective, time horizon and discounting

The company model applies a lifetime (100 years) horizon and a discount rate of 3.5% was used for costs and effects. The model adopted the perspective of NHS/PSS and had a cycle length of three months.

The EAG is satisfied that the perspective, time horizon and discounting approach applied are appropriate, consistent with the NICE reference case and have been correctly implemented in the economic model file.[46]

4.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness is incorporated into the model through a set of transition probabilities governing the movement of the secukinumab and BSC cohorts through the modelled health states. Transition probability data are primarily sourced from the SUNNY trials, supplemented with data from the control arm of the PIONEER study for long-term risk of response loss for BSC.[45] The following sections describe the modelled transition probabilities for secukinumab and BSC, split into three treatment phases (induction, up-titration, and maintenance). The EAG then provides a critique of the most appropriate data source to inform transition probabilities in the model (biologic experienced or the whole ITT population from the SUNNY trials).

Induction phase (Week 0 – 16)

The effectiveness of secukinumab 300 mg was determined using combined data from the SUNSHINE and SUNRISE trials for the Q4W and Q2W doses respectively. Whilst both doses were evaluated as separate trial arms, the company has chosen to model Q4W first, with up-titration to Q2W after 16 weeks in patients who fail to respond on the lower dosage. The threshold of response for up-titration was HiSCR < 25, considered as a non-response in the model, rather than the HiSCR 50 threshold applied as the primary clinical trial outcome. Treatment effectiveness for BSC up to week 16 was obtained from the placebo control arm of the SUNNY trials. For both BSC and secukinumab, the probability of transitioning between health states up to week 16 was estimated individually for each arm of the trial, using a multinomial model applied to the number of transitions observed in each four-week cycle to calculate the average, treatment specific, four-weekly transition probability up to week 16. Cycle specific transitions were explored in scenario analyses. Table 17 provides a summary of the average transition probabilities for each treatment regimen during the Induction phase (Week 0-16).

Table 17 HiSCR average (four-weekly) transition probabilities up to week 16 [reproduced from Table 39 of the CS]

Treatment	Induction phase (Week 0–16)					Source
	To > From	HiSCR ≥75	HiSCR 50– 74	HiSCR 25–49	HiSCR <25	
SEC Q4W	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from the SUNSHINE and SUNRISE trials
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC: best supportive care; HiSCR: Hidradenitis Suppurativa Clinical Response; SEC: secukinumab; TP: transition probabilities

The EAG is satisfied that the approach to estimating transition probabilities in the induction phase is robust, and the decision to use cycle specific data or average data has little impact on cost-effectiveness results.

Up-titration phase (Week 16–28 for secukinumab Q2W only)

The proportion of patients in the secukinumab arm of the model who fail to achieve a response to the Q4W dose at week 16 are up titrated to the increased Q2W dose, where they receive the week 16-28 transition probabilities from all participants in the Q2W arm of the SUNNY trials. From week 16 onwards, no further transitions are allowed between modelled health states for BSC, unless a response is lost (see maintenance phase below). Table 18 provides a summary of transition probabilities for the secukinumab Q2W treatment regimen during the Up-Titration phase (Week 16–28).

Table 18 Secukinumab Q2W transition probabilities week 16-28 [reproduced from Table 40 of the CS]

Treatment	Up-Titration phase (Week 16–28)					Source
	To > From	HiSCR ≥75	HiSCR 50– 74	HiSCR 25–49	HiSCR <25	
SEC Q2W	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from SUNNY trials
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; SEC: secukinumab.

The EAG note that the SUNNY trials were not designed to assess a strategy of up-titration of treatment dosage. The company base case model assumes that the transition probabilities from the Q2W arm of the study (between week 16-28) are generalisable to the proportion of the Q4W arm who fail to achieve a response at week 16. The EAG are concerned that this approach likely over-estimates the effectiveness of the Q2W secukinumab dose in the up-titrated group of patients. It is likely that there is a positive correlation between those failing Q4W and Q2W dosages and those failing the Q4W are a more difficult to treat subgroup of the full trial population. Due to the selection bias concerns, and a lack of evidence to support improved effectiveness with a Q2W dose, the EAG prefers not to apply up-titration within the economic model. The EAG notes that another option available to the company, but not implemented in the economic model, would have been to start all patients on the Q2W secukinumab dose.

Maintenance phase: long term extrapolation from week 16 (BSC and Secukinumab Q4W) and from week 28 (Secukinumab Q2W)

Secukinumab treatment responders continued to transition between health states, based on follow up data from the SUNNY trials, taking the average of 4-weekly transitions between week 16 and week 52. These data were further extrapolated over the duration of the model time horizon for patients who continued receiving treatment. As detailed in Section 4.2.2, the model structure for the BSC arm was restricted so that the BSC cohort were assumed to remain in the health state assigned at week 16, without any further opportunity to change

health state, unless they lost a response. The long-term risk of a loss of response, and entry to the HiSCR < 25 state is calculated as 9.61% per cycle, based on 36-week follow-up data from the placebo arm of the PIONEER study and extrapolated linearly over the full model time horizon. Table 19 provides a summary of transition probabilities for the secukinumab Q4W and Q2W treatment regimens during the Maintenance phase (Week 16/28–52) and the BSC group (Week 16 onwards).

Table 19 HiSCR average four-weekly transition probabilities for the secukinumab Q4W, Q2W and BSC treatments during the Maintenance phase of the model [reproduced from Table 41 of the CS and company economic model]

Treatment	To > From	HiSCR ≥75	HiSCR 50– 74	HiSCR 25–49	HiSCR <25	Source
SEC Q4W	Maintenance phase (Week 16–52) & long-term extrapolation					Pooled data from the SUNNY trials
	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	
SEC Q2W	Maintenance phase (Week 28–52) & long-term extrapolation					
	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	
	Maintenance phase (Week 16–52) & long-term extrapolation					
BSC (company preferred)	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	Company assumptions
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	
BSC (EAG preferred)	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	Pooled placebo data from the SUNNY trials
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; SEC: secukinumab.

The EAG notes that the approach to long-term extrapolation is highly uncertain, but that the company approach of extrapolation using the available data for the secukinumab arms in the SUNNY trials seems reasonable in the absence of any longer-term data.

The implication of combining a linear loss of response of 9.61% per cycle for patients receiving BSC and the semi-absorbing nature of the non-response (HiSCR<25) health state is that 80% of BSC patients have entered the non-response state 12 months in the model. The EAG view is that the current model effectiveness parameters and structural assumptions over-estimate the proportion of the BSC cohort entering, and remaining in, the non-response health states over the model lifetime horizon. The EAG prefers to extrapolate the available data from the BSC arms of the SUNNY trials over the full model time horizon to maintain consistency of modelling approach with that used for secukinumab. The EAG approach may be considered a conservative estimate of BSC effectiveness given the inconsistency between the treatment intensity of BSC allowed in the trials and included in the economic model (See Section 4.2.8 for a discussion of the BSC treatment costs).

Choice of transition probability data source

The company preferred base case uses secukinumab (and BSC up to week 16) transition probabilities obtained from the intention to treat population pooled across the SUNNY trials. The company seeks reimbursement of secukinumab in a subgroup of the trial population who have previously failed adalimumab treatment or are contra-indicated. The EAG therefore requested additional data from the company, exploring the impact of applying transition probabilities derived from the biologic experienced subgroup of the SUNNY trials. The company provided a full set of transition probability model parameters for the biologic experienced subgroup. Full details are provided in Tables 1-3 of the company response to clarification for transition probabilities, and Table 4 for utilities. The company has provided a scenario analysis using these data, which shows that using adalimumab subgroup data leads to a small increase in the base case ICER.

The EAG would generally prefer the use of model parameters that align the modelled cohort with the underlying trial population. The advantages of doing so are to ensure that costs and benefits are closely aligned. For example, parameters sought through clinical expert opinion (e.g., BSC treatments, surgery rates etc) sought for the model population may be inconsistent

with transition probability or utility data sought from the trial, where disease may be comparatively easier to treat.

However, the economic model is data intensive, particularly for transition probabilities, and the EAG note that using a small subgroup from the trial wastes a large volume of data and increases uncertainty due to small cell sizes. The EAG is also aware that using the subgroup data could lead to concerns over face validity. As pointed out by the company, when using the subgroup data, one of the non-response states BSC utilities is higher than a response state, leading to concerns over face validity. The EAG has further explored the face validity of applying transition probabilities sourced from the biologic experienced and full trial population by inspecting markov cohort traces when applied to the EAG's preferred base case analysis. The EAG notes that the full trial population data provide more sensible long-term projections, where the proportion in higher response states remains higher for secukinumab compared to BSC for the duration of the model time horizon.

On balance, whilst there are concerns that applying data from the full ITT population to a biologic experienced subgroup may over-estimate treatment effectiveness in a more difficult to treat subgroup, the EAG is satisfied that the choice of data source does not have a major impact on the base case ICER. The full ITT population provides greater certainty, larger cell sizes for transition counts and provides results with better face validity. The EAG therefore agrees that, despite limitations, the use of the full ITT population is appropriate for deriving model transition probabilities.

4.2.7 Health related quality of life

There are no mortality differences between model arms, therefore all QALY gains for secukinumab vs. BSC are derived from improvements in health-related quality of life. The company preferred base case analysis applies treatment dependent health state utility values to each model health state.

Health state utility values

Treatment specific health state utility values (HSUVs) are obtained from patient reported EQ-5D-3L data, collected at all time points between weeks 2-16, from the SUNNY trials and valued using UK general population tariffs. Scenario analysis explores the impact of pooling HSUVs across treatment arms. The company conducted a literature review to identify further

utility data and identified 12 publications. Of those, only the utility values from the adalimumab appraisal for HS (TA392) were reported and included as a scenario analysis in the economic model.[25]

The EAG is satisfied that the one identified study is the only available evidence that provides EQ-5D based utilities for the health states modelled in this assessment. Other utility studies as detailed in appendix H, Table 40 of the company submission either use Hurley staging of disease or use other quality of life measurement tools (e.g., the health utility index).

Table 20 summarises the different HSUVs considered in the economic model together with additional information on parameter uncertainty and numbers contributing data to each utility estimate provided in response to clarification queries. Data are provided separately for the biologic experienced subgroup and the overall ITT population from the SUNNY trials.

The utility data show that, as expected, utilities are lower in the adalimumab experienced subgroup, on average [redacted] *across the different treatments and health states. This would support the assumption that patients who have previously been treated with, and failed adalimumab may be a more difficult to treat cohort, with more impactful disease. The company has provided a scenario analysis using this data, which reassuringly shows that using adalimumab subgroup data leads to a small increase in the base case ICER. Given the potential for slightly counter-intuitive utility estimates from the smaller sample subgroup who are biologic experienced (i.e., BSC HSUV for HiSCR >75 is slightly lower than for HiSCR state 50-75), the EAG is satisfied that it is appropriate to source HSUVs from the full ITT population.*

Table 20 Comparison of modelled health state utility values (HSUVs)

Health state	Treatment arm	Company base case utility: Mean (SE); N	Biologic experienced subgroup; Mean (SE); N	Company scenario 1 (Pooled from SUNNY Trials) Mean (SE); N	Company scenario 2 (Pooled from TA392[25]
HiSCR (≥75)	SEC Q4W	[redacted]	[redacted]	[redacted]	0.782
	SEC Q2W	[redacted]	[redacted]		
	BSC	[redacted]	[redacted]		
HiSCR (50-74)	SEC Q4W	[redacted]	[redacted]	[redacted]	0.718
	SEC Q2W	[redacted]	[redacted]		
	BSC	[redacted]	[redacted]		
HiSCR (25-49)	SEC Q4W	[redacted]	[redacted]	[redacted]	0.576
	SEC Q2W	[redacted]	[redacted]		
	BSC	[redacted]	[redacted]		
HiSCR (<25)	SEC Q4W	[redacted]	[redacted]	[redacted]	0.472
	SEC Q2W	[redacted]	[redacted]		
	BSC	[redacted]	[redacted]		

The EAG generally prefers the use of health state utility values pooled across treatments, because pooling provides greater certainty, particularly when sample sizes are small. It also often ensures that health state costs and utilities are aligned. In this case, the company make an argument in favour of treatment specific HSUVs, on the grounds that there are treatment benefits of secukinumab that are not captured by the health state definitions. The EAG appreciates that health state definitions are broad. For example, HiSCR50 is defined as: "a ≥ 50% reduction in inflammatory lesion count (abscesses + inflammatory nodules), and no increase in abscesses or draining fistulas when compared with baseline". It is plausible that secukinumab patients may lie in the upper bound of a particular health state range, with BSC at the lower bound, but the evidence provided in the company submission was not sufficient to support this conclusion. The EAG therefore asked the company to provide further reassurance and evidence to support the use of treatment specific HSUVs in the model. The EAG requested:

A) *the raw clinical data underpinning the HiSCR outcome for each health state, by treatment arm of the SUNNY trials. The company responded that this was not possible, given that HiSCR is not a calculated continuous score, but rather the combination of several aspects of HS disease. The EAG appreciates this, but notes that the company could have provided the percentage reduction in inflammatory lesion count for each health state, by treatment arm. They could also have provided details about the proportional increase in abscesses or draining fistulas, compared to baseline, by treatment arm and health state. Clear evidence that clinical outcomes may differ within different states by treatment arm would help validate the company's base case modelling assumptions.*

B) *Statistical evidence to support an EQ-5D utility treatment effect within the health states. The company response provided details of a repeated measures model with EQ-5D utility regressed on treatment arm, baseline utility and health state. The results are provided in Table 10 of the clarification response, and show a statistically significant treatment effect on utility, controlling for health state. The EAG is satisfied that a repeated measures model is satisfied that significant treatment co-efficients provide some reassurance that the differences in treatment specific utilities are not wholly described by differences in health state. However, this does not provide reassurance that treatment effects within health state are observed across all*

health states in the model. The EAG would consider a revised analysis, where treatment is interacted with health state to provide a stronger rationale in support of treatment specific utilities across all the modelled health states.

Until the EAG receives further reassurance from the company regarding both points, we are unable to support the use of treatment specific HSUVs in all the model health states.

Impact of surgery on quality of life and HSUVs

The company base case assumes that there is no impact of surgery on HS outcomes or utilities. The company submission makes the case that excluding any utility implications of surgery could be considered conservative, because people requiring surgery may be in an even poorer QoL state than attributable to their HiSCR state.

The company has not provided any evidence to support the exclusion of surgery utilities. Whilst the EAG accepts that patients may experience an immediate disutility whilst having surgery, these utility decrements are likely to be transient, and effective surgical procedures would be expected to lead to benefits in QoL that are not currently captured in the model.

The base case model configuration incorporates all the costs associated with high frequencies of hospital resource use and surgery, but none of the utility gains. This modelling approach lacks clinical face validity. The EAG's clinical expert confirms that surgery is used in clinical practice as an effective component of HS treatment, particularly for those with more severe disease. Whilst most patients would prefer to avoid the need for surgery if they can, they do receive benefit. Indeed, it would be unethical to provide surgical treatment to patients if there were no benefits to be achieved. Given that secukinumab surgery rates are lower than BSC, due to higher response health states in the model, any bias of excluding the utility benefits of surgery create a bias in favour of secukinumab.

The company's approach is also inconsistent with findings from the literature, which show that surgery can improve quality of life for patients with for HS.[48] Whilst the EAG is not aware of any studies reporting EQ-5D following surgery for HS, many of these studies do report condition specific quality of life data, which refute the company's assumption. The bias generated from assuming no utility gain following surgery is further magnified by the structural assumptions in the model that prevent the BSC cohort regaining a response

once they've lost it, regardless of the treatments provided. This means that BSC non-responders continue to receive high rates of costly surgery (See Section 4.2.8) for the full model duration but receive no utility benefit or transition to the response health states (See Section 4.2.2). Whilst a surgery utility benefit is not explicitly incorporated in the secukinumab arm of the model, the cohort are allowed to transition out of the non-response state in each cycle, further magnifying the existing bias in favour of secukinumab.

The EAG view is that the current model does not adequately capture the role of surgery in the treatment pathway. The EAG accepts that modelling the costs and outcomes of surgery would be difficult to achieve, and instead provides several further analyses to try and reduce the magnitude of bias in the modelling. Two approaches are considered for the committee's information: 1) removing all the costs of surgery to equalise the treatment of costs and benefits in the model; 2) removing the restriction that precludes patients receiving BSC from transitioning out of the 'non-response' health state (this is the EAG's preferred approach).

Adverse event disutilities

Whilst no adverse events were included for the base case cost-effectiveness analysis, a scenario explored the impact of applying disutilities to all adverse events, assuming a duration of 1 week for all AEs. Disutilities for the company provided scenario analysis were sourced from Sullivan et al.[49] Details of AE rates per cycle and disutilities applied are provided in Tables 44 and 46 of the company submission respectively.

The EAG is satisfied that adverse event rates are low and that most will be resolved quickly with only minor impact on patient quality of life. Nonetheless, the EAG prefers that disutilities associated with AEs are incorporated in the economic model because doing so provides the most complete assessment of the QoL impact of treatment. The EAG therefore prefers the use of the company scenario including AE disutility.

Age adjustment of utilities

All utilities in the model are age adjusted using UK general population norms to account for reducing utility with increasing age in the model.

The EAG has checked the company's approach to age adjustment of utilities and is satisfied that this has been correctly implemented.

4.2.8 Resources use and costs

Secukinumab and BSC treatment acquisition and administration costs

For the Q4W dosing schedule, 4 doses of secukinumab 300mg are required in the first cycle, followed by 1 dose in each cycle thereafter. The treatment acquisition cost of secukinumab is [redacted] per pre-filled syringe, representing a [redacted]% discount on the list price of £1218.78 per dose.

[redacted] In addition to treatment acquisition costs, the model included the costs of the first administration of secukinumab via subcutaneous injection from a community-based nurse at a cost of £54.92. After that, it is assumed that secukinumab is self-administered with no further administration costs incurred by the NHS.

The EAG is satisfied that the treatment acquisition costs of secukinumab have been correctly incorporated in the economic model. During clarification, the EAG queried whether some patients would require more regular visits to healthcare professionals for treatment administration (for example if they were unable or unwilling to self-administer the treatment). The company clarified that secukinumab is provided via homecare providers where patients are supported for up to three nurse visits upon delivery of secukinumab. The company assumed that no further administration costs would be incurred by the NHS, and the EAG is satisfied that this is appropriate for most patients.

The costs of BSC are modelled to include topical and oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens, with the type and distribution of treatment informed by clinical expert opinion sought by the company. Biologic treatment costs were included as a scenario analysis.

The EAG note that the company has not provided details of the number of clinical experts contacted regarding the distribution of BSC, how the proportions were elicited, whether there was uncertainty in opinion across contacted clinical experts, and what magnitude of heterogeneity was observed. Whilst the type and distribution of treatments are highly

uncertain, the EAG's clinical expert considers them to be broadly reflective of non-surgical, non-biologic management of moderate to severe HS in UK clinical practice.
Whilst the composition of BSC may be plausible in UK clinical practice, it is inconsistent with the BSC treatments allowed as concomitant medications in the SUNNY trials. The SUNNY trial protocols restricted concomitant medication (BSC) to simple pain management and restricted use of antibiotics, but excluded retinoids, other biologics, ciclosporin, dapsone or anti-androgens. This creates a bias in favour of secukinumab because the modelled BSC treatment costs are substantially higher than the costs which would be incurred to deliver the treatment effectiveness observed in the control arms of the SUNNY trials (used to inform model transition probabilities). The EAG prefers scenarios where the costs and benefits of treatments are aligned and explore this issue further in scenario analyses.

The unit costs of BSC treatments used in the company's economic model are obtained from prescription cost analysis for England. The EAG's clinical expert notes that most treatments for HS will be prescribed in secondary care. The EAG therefore considers it most appropriate to apply eMIT unit costs for BSC treatments. Company preferred, BNF (assuming primary care prescribing) and eMIT (assuming secondary care prescribing) unit costs per dose are compared for information in Table 21.

Table 21 Comparison of alternative BSC unit costs per dose

	Company base case prices	Primary care (BNF prices)	Secondary care (eMIT prices)
Topical antibiotics:			
Clindamycin 1% solution 30 mL	£6.07	£5.08	£5.08
Oral antibiotics:			
Doxycycline 100 mg	£0.14	£0.10	£0.07
Lymecycline 408 mg	£0.23	£0.18	£0.16
Minocycline 100 mg	£0.50	£0.42	£0.33
Tetracycline 250 mg	£0.20	£0.25	£0.14
Clindamycin 300 mg	£1.27	£1.27	£0.18
Rifampicin 300 mg	£1.26	£1.41	£0.28
Dapsone:			
Dapsone 100 mg	£1.15	£1.08	£0.61
Retinoids:			
Acitretin 10 mg	£0.47	£0.50	£0.16
Isotretinoin 40 mg	£1.30	£1.00	£0.30
Ciclosporin:			
Ciclosporin 100 mg	£2.28	£2.28	£2.28
Anti-androgens:			
Cyproterone 100 mg	£0.86	£1.27	£0.61

Abbreviations: eMIT: electronic Market Information Tool

Health state resource use

Health state specific hospital resource use are included in the model separately for attendances related and unrelated to HS surgery. The hospital resource use includes inpatient admissions, outpatient visits, wound care appointments and emergency care attendances. The annual frequency of resource use in each model health state was obtained from a survey of 40 UK clinical experts conducted for the previous assessment of adalimumab (TA392).[25] It was assumed that resource use was health state specific and independent of treatment received.

The EAG raises several points of concern in relation to the resource use estimates included in the model:

1) *It is unclear how these resource use estimates have been derived, and whether the data reported are based on consensus amongst respondents or a mean estimate across all respondents. The magnitude of uncertainty or heterogeneity in clinical expert opinion has not been reported. Whilst the parameters are included in the probabilistic analysis assuming a standard error of 10% of the mean, it is likely that the true level of heterogeneity is much greater. The implication is that the company's base case results overstate the certainty surrounding the base case ICER.*

2) *In response to clarification queries, the company acknowledged that the resource use estimates were not validated by the company's own clinical experts. As a minimum, the EAG would have expected the company to conduct their own updated expert elicitation exercise. Use of the existing data is of concern for two reasons. First, the survey data used by the company are out of date, being conducted before 2016 (exact date unclear), and may not be reflective of current UK clinical practice and disease management, particularly in a world where other biologic treatment options now exist that may help reduce or prevent the need for large volumes of surgical procedures. The EAG's clinical expert is of the opinion that the average number of surgeries reported by the company is larger than might be expected in current UK clinical practice. For example, the company's base case analysis predicts [redacted] and [redacted] inpatient surgical admissions for HS over the full model time horizon in the BSC and secukinumab arms of the model respectively. The company's base case assumptions would rely on very high repeat surgery rates, which do not appear to be supported by the literature.*[50, 51]

3) *The company were asked at clarification whether they had conducted a literature review to identify surgery resource use in the UK for patients with moderate to severe HS, but a definitive response to this question was not provided. The EAG would have preferred if the company completed a full systematic review of the long-term surgery and inpatient admission rates for use in the model, given the sensitivity of the ICER to these parameters. Any biases from the company's resource use estimates are likely to bias in favour of secukinumab.*

4) *The EAG was concerned that the frequency of total outpatient attendance (summed for surgery related, non-surgery related and wound care) may over-estimate the resource use in clinical practice. The EAG was further concerned that there may be double counting outpatient visits for "any reason", may double count outpatient costs due to HS surgery. However, the company clarified at factual accuracy check stage that this was a typographical error in Table 54 of the CS. Despite the clarification, the EAG remains concerned that outpatient resource use may be over-estimated. As neither the company nor the EAG have access to the survey materials, or insight into how questions were framed in the survey, it is not possible to verify the extent to which any double counting may exist. Given that resource use increases with severity of disease, and that secukinumab is modelled to keep patients in better health states for longer, any double counting of resource use would lead to a bias in favour of secukinumab.*

5) *The EAG noted that the resource use estimates, provided in the clinician survey for TA392 applied weightings to moderate and severe disease as per the breakdown from the PIONEER study. The company provided revised estimates applying weightings observed in the SUNNY trials in response to clarification queries and the EAG considers these weightings to be more appropriate for the base case model.*

6) *Finally, the EAG is concerned that the model structure prevents any benefits from surgery, particularly in the BSC non-response state. These likely over-estimates the costs and under-estimates the benefits. One way to equalize the costs and benefits is to consider a scenario analysis where surgery resource use is removed from the model. Additional EAG scenario analyses explore the impact of reducing the resource use by 25%, 50%, 75% and 100% to illustrate the substantial impact of health state resource use assumptions on the ICER.*

The company and EAG preferred resource use estimates are summarised in Table 22.

Table 22 Company and EAG preferred annual resource use frequency by health state

Resource use	Company preferred base case				EAG preferred base case				EAG justification (where different from company resource use)
	HiSCR ≥ 75	HiSCR 50-74	HiSCR 25-49	HiSCR < 25	HiSCR ≥ 75	HiSCR 50-74	HiSCR 25-49	HiSCR < 25	
Surgery related									
Inpatient stay due to HS surgery	0.13	0.22	0.54	0.80	0.13	0.22	0.54	0.80	--
Outpatient visits due to HS surgery	0.22	0.35	0.67	0.94	0.00	0.00	0.00	0.00	Removes potential double counting of outpatient visits
Visits to wound-care due to HS surgery	0.12	0.17	0.4	0.85	0.00	0.00	0.00	0.00	Removes potential double counting of outpatient visits
Non-Surgery Related									
Non-surgical inpatient visits	0.11	0.23	0.29	0.45	0.11	0.23	0.29	0.45	--
Outpatient visits (due to any reason)	3.1	3.51	4.44	4.68	3.1	3.51	4.44	4.68	--
Visits to wound care not due to HS surgery	0.67	0.47	0.64	0.45	0.00	0.00	0.00	0.00	Removes potential double counting of outpatient visits
Emergency room visits	0.12	0.2	0.47	0.57	0.12	0.2	0.47	0.57	--

Health state unit costs:

Health state unit costs for each item of resource use are provided in Table 53 of the company submission and a comparison to the previous adalimumab assessment is provided in Table 9 of the company response to clarification queries.

The EAG is satisfied that the unit costs of emergency department attendance and outpatient consultations is appropriate. However, there are several uncertainties regarding the costing approach taken by the company for inpatient admissions and surgical procedures:

1) *It is unclear whether the chosen HRG codes are appropriate for HS patients. The EAG requested the company to provide details of the exact procedures they envisaged taking place in UK clinical practice and to provide details of OPCS codes and appropriately mapped HRGs. This information was not provided, and the EAG considers the most appropriate HRG codes for HS surgeries to be a remaining issue of uncertainty.*

2) *The company assumed that all surgical procedures will be conducted as elective inpatient admissions that require overnight admission. The EAG considers this unrealistic and is advised by our clinical expert that many procedures for HS will take place as day case procedures. Including day case procedures also aligns the EAG's preferred assumptions with those preferred by the appraisal committee for TA392.*[25]

3) *HRG costs are assumed to be independent of health state, so for example, the allocated HRGs for a patient receiving surgery in the HiSCR high response state are equal to the unit costs applied in the non-response state. This raises some uncertainty because it could be argued that those with poorer responses may require more intensive surgery (and thus incur a higher unit cost) to complete their surgical procedure. However, the EAG is not aware of robust data describing intensity of surgery by health state for patients with HS, and therefore considers the company's approach to be acceptable given the lack of data available.*

The EAG and company preferred unit costs of resource use are summarised in Table 23.

Table 23 Company and EAG preferred unit costs for health state resource use

Resource use	Company preferred base case			EAG preferred base case		
	Procedure / treatment code	Calculation approach	Unit cost	Procedure / treatment code	Calculation approach	Unit cost
Surgery related						
Inpatient stay due to HS surgery[52]	JC40Z JC41Z JC42C JC43C	Weighted average (elective)	£4,652.57	JC40Z JC41Z JC42C JC43C	Weighted average (elective + day case))	£1,216.68
Outpatient visits due to HS surgery	330	Unit cost	£168.29	330	Unit cost	£168.29
Visits to wound-care due to HS surgery	330	Unit cost	£168.29	330	Unit cost	£168.29
Non-surgery related						
Non-surgical inpatient visits[52]	JD07D JD07K	Weighted average (elective)	£2,964.06	JD07D JD07K	Weighted average (elective)	£2,964.06
Outpatient visits (due to any reason)	330	Unit cost	£168.29	330	Unit cost	£168.29
Visits to wound care not due to HS surgery	330	Unit cost	£168.29	330	Unit cost	£168.29
Emergency room visits	VB01Z-VB09Z	Weighted average	£332.46	VB01Z-VB09Z	Weighted average	£332.46

Abbreviations: HS: hidradenitis suppurativa

5 COST EFFECTIVENESS RESULTS

Section 5.1 provides the company preferred deterministic and probabilistic base case model results, including Markov cohort traces reproduced by the EAG. Section 5.2 summarises the sensitivity and scenario analyses completed by the company in the original submission and in response to clarification queries. Section 5.3 describes the company and ERG model validation and face validity checks.

5.1 Company's base case cost effectiveness results

Markov cohort traces were not provided within the company submission but are available from the economic model file. Given the EAG's concerns regarding the BSC model structure detailed in Section 4.2.2, it is important to consider the plausibility of the longer-term model projections. Figures 6 and 7 therefore reproduce the Markov cohort traces, showing health state occupancy in each HiSCR response state and the death state for secukinumab and BSC arms of the model respectively. EAG preferred Markov cohort traces are provided for comparison in Section 6.2.

Figure 6 Company preferred Markov cohort traces for the secukinumab arm of the model [reproduced from company submitted economic model file]

Figure 7 Company preferred Markov cohort traces for the BSC arm of the model [reproduced from company submitted economic model file]

A comparison of the health state occupancy for each model arm illustrates the concerns raised by the EAG in Section 4.2.2. The restrictions placed on the BSC arm (i.e., no transition between response states after week 16, and setting non-response as a semi-absorbing state beyond week 16) are evident in that [redacted] and [redacted] of the BSC cohort are in the lowest HiSCR<25 non-response state by years 1 and 2 respectively. By comparison only [redacted] and [redacted] of the secukinumab arm have entered the HiSCR<25 state by 1 and 2 years respectively. The magnitude of difference between the arms is inconsistent with the effect sizes observed from the clinical trials, and inconsistent with the EAG clinical experts' opinion that the modelled BSC treatments and surgery can both have a positive impact on patient's HiSCR, both of which are excluded through the restrictions placed on the BSC arm

of the model. By contrast, the EAG preferred base case continues to show a benefit for secukinumab, but of a much lower magnitude (See Section 6.2 for comparison).

Disaggregated QALYs and costs accrued in each model health state, are provided in Tables 48-50, appendix J to the company submission. The company's preferred base case deterministic and probabilistic ICERs are re-produced in Table 24 and remained unchanged following clarification queries.

The EAG noted a minor error on the CODA parameters tab of the economic model, where it appears that the average transitions from the response states are applied to transitions from the non-response state and vice versa. The EAG raised this concern with the company, who subsequently corrected the error. The corrected PSA results are reported in Table 24 below. Figures 8 and 9 illustrate the corrected CEACs and scatter-plots, showing a slight reduction in the probabilistic ICER compared to that included in the company submission.

Table 24 Summary of company provided base case analyses [reproduced from Tables 62 and 65 of the CS]

	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	Incremental (£/QALY)
Company preferred deterministic base case results							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165
Company preferred probabilistic base case results							
BSC	[redacted]	22.754	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.754	[redacted]	[redacted]	0.000	[redacted]	£28,220

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The scatter plot of incremental costs and QALYs and the cost-effectiveness acceptability curve (CEAC) from the company's base case probabilistic analysis are re-produced from the company submission in Figures 8 and 9 respectively.

Figure 8 Cost-effectiveness acceptability curve for the company preferred base case analysis [reproduced from Figure 36 of the company submission]

Figure 9 Scatter plot of incremental costs and QALYs for the company preferred base case analysis [reproduced from Figure 37 of the company submission]

The corrected CEAC illustrates a [redacted] and [redacted] probability that secukinumab is cost-effective at a threshold value of WTP for a QALY of £20,000 and £30,000 respectively.

The EAG has reviewed the company's probabilistic analysis and is mostly satisfied that it has been implemented correctly and that selection of distributions for each parameter is appropriate (e.g., beta distributions for probabilities and utilities, gamma distributions for costs). However, the EAG raises several concerns that suggest the overall magnitude of uncertainty in model parameters may have been underestimated:

- *Standard errors were obtained only for utility parameters and were set to 10% of the mean for all other parameters in the PSA. The company has not provided a justification for selectin a standard error value of 10%, and the EAG is concerned that this may underestimate uncertainty, particularly surrounding parameters with low mean values.*

- *The company does not appear to have made use of all the data available to them to parameterize transition probability distributions. For example, the company could have used count data for transitions in the SUNNY trials to obtain a more accurate estimate of uncertainty.*

- *The EAG is concerned that uncertainty may also be underestimated surrounding other important model parameters, especially the rates of surgical and non-surgical hospital resource use. As detailed in Section 4.2.8, these resource use estimates are obtained from a survey of n=40 clinical experts conducted by the manufacturer of adalimumab to inform TA392. Uncertainty surrounding these resource use rates has not been described, but it is plausible that there may have been substantial variability in clinical expert opinion, which is not adequately accounted for in an assumed standard error of 10% of the mean. The EAG would prefer the company to conduct their own systematic review and expert elicitation exercise, integrating uncertainty surrounding the findings directly in the PSA.*

- *It should be noted that the PSA does not capture uncertainty surrounding differences in EAG and company preferred model structures, use of BSC treatment or preferred HRG unit costs for hospital resource use, which are instead captured in scenario analyses conducted by both the company and EAG.*

5.2 Company's deterministic sensitivity and scenario analyses

Tornado diagrams illustrating the impact on the ICER of increasing / decreasing key model parameters by 10% are provided in Figure 38 of the company submission. The parameters with the greatest impact on the ICER are estimates of health state resource use and utilities.

As with the EAG's critique of the probabilistic sensitivity analysis, the company's deterministic analyses are useful for understanding the key parameters that drive uncertainty, but the magnitude of that uncertainty is likely better captured through scenario analyses.

The company conducted nine scenario analyses in the original company submission and a further two in response to clarification queries. The scenarios explored the impact of removing

up titration, varying the source of health state utility inputs (treatment specific, pooled, and applying utilities from TA392), varying the BSC treatment basket and costs on the ICER. The ICER was most sensitive to the use pooled health state utility values from the SUNNY trials (increased the ICER), applying TA392 utilities (decreased the ICER), removing up-titration (increased the ICER) and removing BSC costs (increased the ICER).

The EAG is satisfied that company scenario analyses have been correctly implemented, and several of the company scenario analyses are included within the EAG preferred base case ICER (described in Section 6.2). Table 68 of the company submission details the results of the nine scenarios conducted as part of the CS, applied probabilistically. Tables 25 and 26 reproduce the full range of scenario analyses conducted in the company submission and response to clarification queries respectively. The EAG's results detailed below are applied deterministically to enable reproducibility and to ensure plausible directional results for changes in parameters with minimal impact on the ICER.

Table 25 Scenario analyses results (deterministic) conducted in the company submission [detailed in Table 67 of the company submission and reproduced deterministically using the company submitted economic model file]

Treatment	Total			Incremental			ICER vs BSC (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Company preferred base case analysis							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165
Apply cycle specific transition probabilities for BSC and secukinumab							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,471
Assume no up-titration of secukinumab dosage							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,554
Apply HSUVs pooled across all treatment arms from the SUNNY trials							
BSC	[redacted]	22.797	[redacted]	-	-	-	
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£42,245
Apply HSUVs from TA392							
BSC	[redacted]	22.797	[redacted]	-	-	-	
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£23,726

Treatment	Total			Incremental			ICER vs BSC (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Apply adverse event costs and utility decrements [A]							
BSC	[redacted]	22.797	[redacted]	-	-	-	
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,153
Apply 2018-2020 mortality risks							
BSC	[redacted]	22.733	[redacted]	-	-	-	
Secukinumab	[redacted]	22.733	[redacted]	[redacted]	0.000	[redacted]	£28,167
Assume 31% of BSC treatments are biologics							
BSC	[redacted]	22.797	[redacted]	-	-	-	
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£21,915
Assume 5% of BSC treatments are biologics							
BSC	[redacted]	22.797	[redacted]	-	-	-	
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£27,157
Assume no BSC costs							
BSC	[redacted]	22.797	[redacted]	-	-	-	
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£31,701

[A] Note that the results for inclusion of AE costs and disutilities may initially appear counter intuitive. However, the EAG is satisfied that the reduction in the ICER is due to a slightly higher proportion on BSC with slightly more costly AE management costs in the model. The impact on the ICER is minimal.

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

Table 26 Scenario analyses results (deterministic) in response to clarification letter [reproduced from Tables 5 and 7 of the company response to clarification queries]

Treatment	Total			Incremental			ICER vs BSC (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Company preferred base case analysis							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165
Transition probabilities and utilities calculated for biologic-experienced patients only instead of for the full ITT cohort							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£29,760
Hospital resource use frequencies re-weighted for moderate / severe disease using data from the SUNNY trials instead of PIONEER							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£27,905

Abbreviations: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; ITT: Intention to treat; LY: life years; QALYs: quality-adjusted life years.

5.3 Model validation and face validity check

Section B.3.14 of the company submission notes that the decision to model multiple health states for HiSCR response aligns with clinical expert opinion and the preferred modelling approach from TA392. The model is therefore stated to reflect clinical management of HS disease.

The EAG's clinical expert advisor agrees that the use of a 4-state markov model, based on increasing degrees of response is appropriate for decision making and is required to allow the model capture different degrees of improvement in HS and the impact on resource use and quality of life. However, the EAG is concerned that the company's base case model QALY gains may be over-estimated. The base case model for TA392 estimated 0.95 QALY gains for adalimumab compared to supportive care, whereas the current company model base case estimates QALY gains of [redacted]. *The EAG considers this to be highly optimistic, particularly given the data provided by the company's NMA, which suggests the clinical response from secukinumab is similar to, or less than adalimumab. The EAG preferred base case QALY gains (see Chapter 6) are lower than those estimated for TA392, which are more consistent with the NMA results and considering that the current indication is for a harder to treat population, who have already failed or are contraindicated to adalimumab treatment.*

The company submission describes a range of technical validity and stress tests conducted by an independent health economist. This included checking all formulae, cell by cell review and applying extreme value tests to model parameters.

The EAG also conducted its own technical validity checks, using the checklist proposed by Tappenden and Chilcott et al (Table 27).[53] *The EAG initially raised a technical validity query with the company at clarification stage, relating to concern that reducing the probability of BSC response loss for year two and beyond leads to a reduction, rather than an increase in the ICER as might be expected. The company clarified that the unanticipated reduction in the ICER was that a higher proportion of the cohort were subjected to a risk of BSC response loss in the secukinumab arm compared to the BSC arm beyond year two, because a higher proportion remained at risk of losing a response. The EAG is satisfied that the model formulae are technically correct but note that removing the semi-absorbing state improves the face validity of the model outputs.*

Table 27 Model validation checklist

Model component	Model test	Unequivocal criterion for verification	Issues identified
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	Not Applicable
	Sum expected health state populations at any model time-point (state transition models)	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None
	Increase intervention cost	ICER is increased*	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None

Model component	Model test	Unequivocal criterion for verification	Issues identified
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x[0, etc.)	None
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	Not possible, given differences in the model structures across arms.
	Amend value of each individual model parameter*	ICER is changed	None
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	Not possible, given differences in the model structures across arms.

Abbreviations: EAG: external assessment group; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life-year

* Note this assumes that the parameter is part of the total cost function and/or total QALY function

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Chapter 4 has identified several issues of remaining uncertainty and differences between EAG, and company preferred assumptions. The additional scenario analyses contributing to the EAG preferred base case are described in Table 28. Where the EAG prefers the use of company conducted scenarios, this is identified in the table. Further exploratory analyses are described in Table 29.

Table 28 EAG justification for model amendments leading to EAG preferred base case assumptions.

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
Model structure					
1.	Transitions out of the BSC and secukinumab non-response (HiSCR <25) health state over the maintenance phase of the model	The company base case assumes that secukinumab treated patients can regain a response (transiting out of the HiSCR <25 state) at any time point in the maintenance phase of the model, whereas the BSC treated cohort enter a semi-absorbing non-response state once HiSCR drops below 25.	**EAG preferred scenario:** Allow the BSC treated cohort to exit the non-response health state according to the transition probabilities available from the placebo arms of the SUNNY and PIONEER trials.	Aligning the model structures removes any biases associated with allowing secukinumab to have transient response, but not BSC. The EAG preferred approach also allows the model structure to allow the potential for patients to benefit from surgery (despite surgery benefits not being explicitly modelled).	4.2.2
Dosing schedule for secukinumab					
2	Up-titration	Allow up-titration to Q2W from Q4W dose for those in the non-response health state at week 16, and assume	**EAG preferred scenario**: remove the option for up-titration from the model [A]	The EAG prefers to remove up-titration because the effectiveness data from the SUNNY trials are applied to a more difficult to treat subgroup. This creates a selection	4.2.6

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
		effectiveness equal Q2W arm of SUNNY Trials		bias, where only the more difficult to treat patients receive the higher dose. It is not appropriate to assume that effectiveness in the 'difficult to treat' subgroup would be equivalent to the full sample randomized to Q2W in the SUNNY trials.	
Utilities					
3	Treatment specific vs. pooled HSUVs	The company prefer to use treatment specific health state utility values on the grounds that there may be benefits of treatment not captured in health state classifications.	**EAG preferred scenario:** The EAG tentatively prefers the use of HSUVs pooled across treatment arms. [A]	The current evidence provided by the company in response to clarification queries is not sufficient to support the use of treatment specific HSUVs. However, the EAG would be willing to reconsider its position if provided with additional supporting evidence as detailed in the report	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
4	Costs and disutilities of adverse events	Excluded	**EAG preferred scenario:** Included [A]	Despite the likely minimal impact on the ICER, due to non-severe, short duration AEs, the EAG nonetheless prefers the inclusion of adverse event costs and disutilities in the model for completeness.	4.2.7 4.2.8
Resource use and costs					
5	Best supportive care	Aligned with UK clinical practice, based on clinical expert opinion	**EAG preferred scenario:** Costs of BSC aligned with the use of BSC in the placebo arms of the SUNNY trials.	Despite not aligning with clinical practice, the EAG prefers to include costs that are aligned with the treatments used to generate the transition probabilities used in the placebo arm of the SUNNY trials. The approach ensures minimal chance of bias in cost-effectiveness results.	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
6	Costs of BSC treatments	Data based on prescription cost analysis	**EAG preferred scenario:** Apply eMIT costs as most treatments are provided within a secondary care setting	The EAG clinical expert's view is that most BSC treatments would be administered within the secondary care setting, and therefore eMIT prices are the most appropriate sources for unit costing.	4.2.8
7	Weighting of moderate and severe disease for estimates of health state resource use	Frequency of resource usage weighed by mod / severe disease from the PIONEER studies	**EAG preferred scenario:** Apply weighting of moderate / severe disease as per SUNNY trials. [B]	EAG amendment maintains consistency with data obtained from SUNNY studies.	4.2.8
8	Surgery outpatient and wound care appointments	Outpatient appointments incorporated for all reasons, and separately for wound care	**EAG preferred scenario:** Remove outpatient appointments for 'wound care'.	Removing outpatient appointments for 'wound care' removes the risk of double counting as these would most likely already be counted in clinicians estimates of resource use under the heading 'all outpatient consultations.	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
9	Surgery inpatient costs	Excludes the costs of day case admissions	**EAG preferred scenario:** re-calculate HRG costs to allow weighting for day case and elective admissions	The EAG's clinical expert is of the opinion that surgeries will often be conducted as day-case procedures, particularly more minor excisions. The weighted average across elective and day-case settings in each HRG code provides a more accurate estimate of HS resource use, whilst ensuring that more complex procedures are unlikely to be conducted as day cases.	4.2.8
10	Combined scenarios 1-9 EAG preferred base case analysis				
11	Combined scenarios 1-2 & 4-9 EAG preferred base case analysis, with treatment specific HSUVs (EAG preferred pending further evidence from company)				

[A] Indicates a scenario contributing to the EAG preferred base case that was provided within the company submission.

[B] Indicates a scenario contributing to the EAG preferred base case that was provided by the company in response to clarification queries.

Abbreviations: EAG: external assessment group, HSUV: health state utility values, Q2W: twice weekly secukinumab dose, Q4W: four weekly secukinumab dose.

Table 29 EAG justification for further exploratory scenario analyses conducted by the EAG

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
12	Model effectiveness and utility parameters	Sourced from full trial population	**EAG exploratory scenario**: EAG explores the use of applying data from the adalimumab treated population. [A]	The EAG's approach aligns the data sources for utilities and transition probabilities with the subgroup of the moderate-to-severe HS population in which the company is seeking approval for secukinumab. Not included as base case due to EAG concerns about face validity of some transitions driven by small sample size.	4.2.6 and 4.2.7
13-16	Surgery related hospital resource use	Based on clinical expert opinion	**EAG exploratory scenario:** Reduce resource use by 25%, 50% and 100%	The EAG scenarios serve to illustrate the impact of uncertainty in estimates of surgery rates on cost-effectiveness outcomes.	4.2.8
17-20	Non-surgery related hospital resource use	Based on clinical expert opinion	**EAG exploratory scenario:** Reduce resource use by 25%, 50% and 100%	The EAG scenarios serve to illustrate the impact of uncertainty in estimates of non-surgical hospital admission rates on cost-effectiveness outcomes.	4.2.8
21	Scenarios 16 and 20 combined (reducing surgery and non-surgery resource use by 100%)				

[A] Indicates a scenario contributing to the EAG preferred base case that was provided by the company in response to clarification queries.

Abbreviations: EAG: external assessment group

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 30 provides full details of the results of additional scenario analyses conducted by the EAG, as applied to the company preferred base case analysis. Scenarios 1-11 describe the changes that contribute to the EAG's preferred base case analyses. Changes are applied one at a time. The scenario analyses show that results are most sensitive to assumptions about model structure, resource use and cost estimates and the decision to include treatment specific or treatment pooled HSUVs.

Table 30 Results of EAG conducted scenario analyses applied to the company preferred deterministic base case.

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY gained)
0	**Company base case analysis.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£28,165
1	**Allow BSC non-responders to transition out of the HiSCR<25 health state, according to transition probabilities from the placebo arm of the SUNNY trials**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£61,844
2	**Remove up-titration of secukinumab dosing**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£28,554
3	**HSUVs pooled across treatment arms**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£42,245
4	**Include costs and disutilities of AEs**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£28,153

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY gained)
5	**Align the costs of BSC with the treatments provided within the placebo arms of the SUNNY trials**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£30,938
6	**Apply eMIT pricing for BSC treatments**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£29,177
7	**Apply severity weighting of disease as per SUNNY trials**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£27,905
8	**Remove outpatient wound care appointments to avoid double counting**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£29,037
9	**Allow day case admissions for hospital inpatient procedures, weighted according to FCEs reported in NHS reference cost data 2020/21**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	-
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£37,470

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY gained)
10A	**Scenarios 1-9 combined (EAG preferred base case deterministic analysis)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£143,584
10B	**Scenarios 1-9 combined (EAG preferred base case Probabilistic analysis)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£144,585
11	**Scenarios 1-2 & 4-9 (EAG alternative base case with treatment specific HSUVs)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£72,030
12	**Use transition probability parameters from the biologic experienced subgroup of the SUNNY trials [A]**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£31,122
13	**Reduce surgery related hospital resource use by 25%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£31,564

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY gained)
14	**Reduce surgery related hospital resource use by 50%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£34,963
15	**Reduce surgery related hospital resource use by 75%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£38,362
16	**Reduce surgery related hospital resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£41,761
17	**Reduce non-surgery related hospital resource use by 25%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£29,356
18	**Reduce non-surgery related hospital resource use by 50%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£30,546

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY gained)
19	**Reduce non-surgery related hospital resource use by 75%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£31,737
20	**Reduce non-surgery related hospital resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£32,928
21	**Reduce surgery and non-surgery related hospital resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£46,523

Abbreviations: BSC: best supportive care; EAG: external assessment group; HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

6.3 EAG's preferred assumptions

The key differences between the company's and ERG's preferred analyses are:

Model structure:

- The company base case analysis extrapolates long-term (beyond 52 weeks) transition probabilities between different HiSCR response health states based on data observed in the secukinumab arms of the SUNNY trials. However, for BSC, it is assumed that the cohort remain in the health state assigned at week 16 (placebo arms of the SUNNY trials), for the remainder of the model time horizon, unless they lose their response and enter the semi-absorbing HiSCR < 25 health state, where they can only exit to the death state. The EAG prefers a model that allows transitions between health states, based on the placebo arm of the SUNNY trials, extrapolated for the full model time horizon, with removal of the semi-absorbing non-response state for BSC. The EAG preferred structure is more clinically plausible as it allows for the potential of BSC and surgery treatments to be effective and improve HiSCR response.

Treatment effectiveness:

- The company base case applies up-titration of secukinumab dosing from Q4W to Q2W for patients who do not achieve a Q4W response at week 16. It is assumed that Q2W has the same effectiveness in those failing Q4W as it does for the broader, unselected trial population. The EAG prefers to remove up-titration because the selection bias is likely to over-estimate treatment effectiveness, in a patient group who are more difficult to treat.

Health state utility values:

- The company preferred base case applies treatment specific health state utility values. Until the EAG receives further reassurance and evidence from the company that a treatment effect is evident in all health states, the EAG retain a base case preference for pooled HSUVs. The EAG is open to reviewing this pending further clarification from the company.

Adverse event costs and utilities:

- Despite only minor implications for the ICER, the EAG prefers the inclusion of adverse event management costs and treatment disutilities for completeness.

Costs of best supportive care:

- The EAG notes that BSC costs were derived from clinical expert opinion, but are inconsistent with the BSC treatments allowed in the SUNNY trials. The EAG prefers to use the BSC costs from the SUNNY trials to ensure consistency of data source when modelling costs and benefits in the model.

- The company generate costs of BSC treatments based on prescription cost analysis for England, utilizing information on total costs of prescribing. The EAG prefers to use the corresponding eMIT prices for BSC treatments as these are most likely to be prescribed in secondary care in the UK.

Hospital resource use and costs:

- When calculating resource use estimates, the company applied the weightings of moderate and severe disease from the PIONEER studies, whereas the EAG prefers to use weightings from the SUNNY trials as they are more relevant to the current assessment.

- The company base case analysis includes resource use estimates for outpatients under 4 different categories (surgical and non-surgical wound care and other outpatient attendances). The EAG considers that the three lowest estimates are likely to be double counted and prefers a scenario where they are set equal to 0, retaining the estimate of outpatient attendance frequency for all reasons in the base case.

- HRG costs for inpatient admissions are all assumed to be overnight elective admissions in the company base case analysis. The EAG prefers to also weight the respective HRG codes including day-case admissions. The EAG approach is more aligned with clinical practice and the decisions taken by the NICE committee for TA392.

The cumulative impact of the ERG's preferred assumptions on the base case ICER is illustrated in Table 31. Results are presented for an EAG preferred ICER with and without treatment specific health state utility values.

Table 31 EAG's preferred model assumptions

Preferred assumption	Section in EAG report	Δ Costs (£)	Δ QALYs	Cumulative ICER £/QALY
Company base-case	*5.1*	[redacted]	[redacted]	£28,165
Allow BSC non-responders to transition out of the HiSCR<25 health state, according to transition probabilities from the placebo arm of the SUNNY trials	*4.2.2*	[redacted]	[redacted]	£61,844
Remove up-titration of secukinumab dosing	*4.2.6*	[redacted]	[redacted]	£59,634
HSUVs pooled across treatment arms	*4.2.7*	[redacted]	[redacted]	£118,860
Include costs and disutilities of AEs	*4.2.7 & 4.2.8*	[redacted]	[redacted]	£118,842
Align the costs of BSC with the treatments provided within the placebo arms of the SUNNY trials	*4.2.8*	[redacted]	[redacted]	£127,404
Apply eMIT pricing for BSC treatments	*4.2.8*	[redacted]	[redacted]	£128,961
Apply severity weighting of disease as per SUNNY trials	*4.2.8*	[redacted]	[redacted]	£128,725
Remove outpatient wound care appointments to avoid double counting	*4.2.8*	[redacted]	[redacted]	£129,892
Allow day case admissions for hospital inpatient procedures, weighted according to FCEs reported in NHS reference cost data 2020/21	*4.2.8*	[redacted]	[redacted]	£143,584

Preferred assumption	Section in EAG report	Δ Costs (£)	Δ QALYs	Cumulative ICER £/QALY
Scenarios 1-9 combined (EAG preferred base case analysis, with treatment pooled HSUVs		[redacted]	[redacted]	£143,584
Scenarios 1-2 & 4-9 combined (EAG preferred base case analysis, with treatment specific HSUVs)		[redacted]	[redacted]	£72,030

Abbreviations: BSC: best supportive care; HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

The results in Table 31 show that the EAG's preferred ICER is substantially higher than the company preferred assumptions. Differences are driven mainly by EAG amendments to the BSC model structure and the decision to include or exclude treatment specific HSUVs. The impact of further uncertainty, surrounding the choice of transition probability data source (biologic experienced of full ITT population from the SUNNY trials) and the estimates of hospital resource use in each model health state are described in Table 32, applied to the EAG's preferred base case analysis (with treatment pooled HSUVs).

Figures 10 and 11 provide the markov cohort traces for secukinumab and BSC respectively generated from the EAG preferred base case model. The figures can be compared to Figures 6 and 7 in Section 5.1 to show the differences in health state occupancy between the company and EAG preferred base case analyses. Differences are driven primarily by the EAGs preferred assumption to remove the semi-absorbing status of the non-response (HiSCR<25) state and allow transitions to other model health states extrapolated over the full model time horizon, according to data available from the placebo arms of the SUNNY trials up to week 16.

Figures 12-15 illustrate the probabilistic results on the cost-effectiveness plane and CEACs for the EAG preferred analyses with and without treatment specific HSUVs. Probabilistic analyses are conducted using the PSA correction detailed in Section 5.1.

Figure 10 Markov cohort traces for the secukinumab arm of the EAG preferred base case analysis [reproduced from company economic model]

Figure 11 Markov cohort traces for the BSC arm of the EAG preferred base case analysis [reproduced from the company economic model]

Figure 12 Scatter plot of the cost-effectiveness plane for the EAG preferred base case analysis [reproduced from the company economic model].

Figure 13 CEAC for the EAG preferred base case analysis [reproduced from the company economic model]

Figure 14 Scatter plot of the cost-effectiveness plane for the EAG alternative base case analysis with treatment specific health state utility values [reproduced from the company economic model].

Figure 15 CEAC for the EAG alternative base case analysis with treatment specific health state utility values [reproduced from the company economic model].

Table 32 Results of additional selected company and EAG conducted scenario analyses applied to the EAG preferred base case.

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY)
BC	**EAG preferred base case analysis**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£143,584
12	**Use transition probability parameters from the biologic experienced subgroup of the SUNNY trials [A]**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£180,462
13	**Reduce surgery related hospital resource use by 25%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£144,796
14	**Reduce surgery related hospital resource use by 50%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£146,008
15	**Reduce surgery related hospital resource use by 75%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£147,220

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY)
16	**Reduce surgery related hospital resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£148,432
17	**Reduce non-surgery related hospital resource use by 25%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£145,497
18	**Reduce non-surgery related hospital resource use by 50%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£147,410
19	**Reduce non-surgery related hospital resource use by 75%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£149,323
20	**Reduce non-surgery related hospital resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£151,236

Sc. No.	Technologies	Costs (£)	Δ Costs (£)	QALYs	Δ QALYs	ICER (£/QALY)
21	**Scenarios 16 and 20 combined**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	£156,085

[A] Indicates scenario analyses provided in the company submission or in response to clarification queries.

Abbreviations: BSC: best supportive care; EAG: external assessment group; HSUV: health state utility values; ICER: incremental cost-effectiveness ratio; LY: life years; QALYs: quality-adjusted life years.

6.4 Conclusions of the cost effectiveness section

The company have developed a transparent and flexible economic model to assess the cost-effectiveness of secukinumab compared to best supportive care for adults with Hidradenitis Suppurative (HS). The EAG is broadly satisfied that the company submission meets the NICE reference case and prefers the use of data from the SUNNY trials to populate the model where possible. Whilst the proposed positioning of secukinumab treatment is inconsistent with the NICE scope and the SUNNY trial population, the EAG is satisfied that the company's positioning post-adalimumab is reasonable. It represents the most likely positioning for secukinumab to demonstrate value, given that adalimumab is available as a biosimilar at reduced cost.

The EAG notes several concerns with company preferred modelling assumptions that are likely to generate biases in favour of secukinumab. The first concern is that up-titration of dosing to Q2W following failure to respond to a lower Q4W dose causes a selection bias that over-estimates treatment effectiveness in a group who are more difficult to treat, The second concern is that the costs of BSC included in the model are much more intense than those allowed in the placebo arms of the SUNNY trials, thereby overestimating the BSC costs required to deliver treatment effectiveness modelled from the trial. Finally, there is a bias in favour of secukinumab because of different model structures in the secukinumab and BSC arms. Assuming that patients receiving BSC beyond week 16 can only lose a response and never regain it, whereas secukinumab patients can continue to experience health state transitions unfairly restricts the potential for other treatments such as BSC and costly surgery to generate treatment benefit.

The ICER is also sensitive to the decision about whether to use health state specific or treatment pooled utilities from the SUNNY trials. Until further confirmation is received by the EAG regarding the treatment specific clinical profile within each health state, and reassurance is provided that treatment specific utilities are observed across all model health states, the EAG retains a preference to assume treatment pooled HSUVs in the model.

7 QALY SEVERITY WEIGHTING CONSIDERATIONS

QALY shortfall calculations are provided in Table 59 of the company submission and the company are not making a case for additional QALY weighting in this assessment.

The EAG has checked the QALY shortfall calculations and reproduced these for a cohort, average age 36, proportion female 56% and is satisfied that neither the company nor EAG preferred base case analyses would qualify for QALY weighting in this assessment.

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