NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Committee Papers

Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Contents:

The **final scope** and **final stakeholder list** are available on the NICE website.

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Please note that the full submission, appendices to the company's submission, and company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

December 2022

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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
BMI	Body mass index
BSC	Best supportive care
BSL	Baseline
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
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
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

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 *Decision problem*

It is anticipated that the indication added by the license extension for secukinumab will be for the treatment of active moderate-to-severe HS in adults. This submission focuses on a sub-population of this licensed population: 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. This proposed positioning is narrower than the marketing authorisation because secukinumab is not anticipated to be cost-effective in the full population, given the availability of biosimilar adalimumab. Therefore, the anticipated positioning of secukinumab is reflected in the decision problem addressed in this submission, as outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with 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
Intervention	Secukinumab	Secukinumab 300 mg Q4W, with the possibility to up-titrate to Q2W	In line with the final NICE scope
Comparator(s)	• Adalimumab • Best supportive care	Best supportive care	Given the recommendation by NICE for the use of adalimumab in HS (TA392)[1] and the availability of 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.

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
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in 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	The economic analysis has been conducted in line with the NICE reference case	In line with the final NICE scope
Subgroups to be considered	People who have failed to respond to prior adalimumab treatment	In line with final NICE scope	In line with final NICE scope

[a]HiSCR is defined as at least a 50% reduction from baseline in abscesses and inflammatory nodules (ANs); no increase in the number of abscesses and/or in the number of draining fistulas.

Abbreviations: AEs: adverse events; DLQI: Dermatology Life Quality Index; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version; 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; NICE: National Institute for Health and Care Excellence; PGI-s: Patient Global Impression of severity; PSS: Personal Social Services; PGI-c: Patient Global Impression of change; QALY: quality-adjusted life year; Q2W: every two weeks; Q4W: every four weeks; TA: technology appraisal; UK: United Kingdom; WPAI-SHP: Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

B.1.2 *Description of the technology being evaluated*

A description of the technology being appraised, secukinumab, is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Secukinumab (Cosentyx®)
Mechanism of action	Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine IL-17A. Upregulation of mRNA for IL-17A and thus high levels of IL-17A or downstream markers in HS lesions, and increased IL-17A serum levels have been implicated in the immunology of HS.[2] Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers.[2]
Marketing authorisation/CE mark status	It is anticipated that the extension of the existing marketing authorisation to add the new indication in hidradenitis suppurativa through the European Commission Decision Reliance Procedure (ECDRP) will be granted by the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted].

Indications and any restriction(s) as described in the SmPC	It is anticipated that the indication added by the license extension will be for the treatment of active moderate-to-severe HS in adults with an inadequate response to conventional systemic HS therapy.
	
	Secukinumab already has marketing authorisation in a number of other indications, all of which have previously been recommended by NICE.[3-7]
	
	Contraindications:[2]
	• Hypersensitivity to the active substance or to any of the excipients listed below:
	  ○ Trehalose dihydrate
	  ○ Histidine
	  ○ Histidine hydrochloride monohydrate
	  ○ Methionine
	  ○ Polysorbate 80
	  ○ Water for injections
	• Clinically important, active infection, e.g., active tuberculosis
	
	Special warning and precaution for use
	• Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)

Method of administration and dosage	Secukinumab 300 mg is to be self-administered by subcutaneous injection using an autoinjector pen, with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by maintenance dosing Q4W with the possibility to up-titrate to Q2W.
Additional tests or investigations	No additional tests or investigations are needed compared with current clinical practice.

List price and average cost of a course of treatment	Each 300 mg is given as one subcutaneous injection. List price for one 300 mg solution for injection in pre-filled pens is £1,218.78. Assuming that patients receive 300 mg Q4W for one year, the annual cost of a secukinumab treatment course is £15,898.55 at the maintenance dose (i.e., excluding the loading dose cost).
Patient access scheme	Novartis has an existing commercial arrangement for secukinumab. This makes secukinumab available to the NHS with a simple confidential discount. The discounted price for 300 mg solution for injection in pre-filled pens is [redacted]

Abbreviations: ECDRP: European Commission Decision Reliance Procedure; HS: hidradenitis suppurativa; IgG1: immunoglobulin G1; IL-17A: interleukin-17A; MHRA: Medicines and Healthcare products Regulatory Agency; mRNA: messenger ribonucleic acid; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; Q2W: every two weeks; Q4W: every four weeks; SmPC: summary of product characteristics.

B.1.3 *Health condition and position of the technology in the treatment pathway*

- Hidradenitis suppurativa (HS) is a debilitating skin condition that is defined by its chronic course and the presence of recurrent, painful, deep-seated, inflammatory lesions[8-10]
- HS has a prevalence in the UK of 770 cases per 100,000 people (95% confidence interval [CI]: 760–780),[11] with onset occurring after puberty and women being three times more likely to develop HS as compared with men (3:1)[12]
- The Hurley system is used to classify disease severity.[13] At the time of diagnosis, most people present with moderate-to-severe HS (defined as Hurley Stage II or III)[14-17]
- A cascade of inflammatory events underlies the pathogenesis of HS, with a growing body of evidence implicating the upregulation of interleukin (IL)-17 in HS inflammation.[18-24] Intrafollicular bacterial growth and immune cell infiltration both lead to rupture of the dilatated hair follicle, manifesting as inflamed nodules and abscesses, eventually leading to the formation of sinus tracts (pus-discharging tunnels) and fistulas, characteristic of moderate-to-severe disease.[8] Sinus tracts may have malodorous discharge, which may persist for months and sometimes years, unless surgically excised[9]
- The mean duration of a single painful nodule has been reported as 6.9 days, and 62% of people with HS reported the persistence of at least one boil that failed to subside[25]
- The most common and burdensome symptoms in HS are pain (reported by 97% of people with HS)[26], malodourous discharge (88%)[27] and pruritus (62%)[26]
- A substantial negative impairment to quality of life (QoL) and daily activities is seen across physical and emotional domains, as well as to sleep, psychological and sexual health,[27-32] with 30% and 57.5% of people with HS reporting depression and anxiety, respectively[31]
- Major drivers of costs in HS include productivity loss, biological treatment, informal care and surgery.[33-35] Within 7.5 years of diagnosis, two-thirds of people with HS (64%, n=254) required surgery[15]
- Real-world studies have demonstrated the far-reaching effects of HS on people's employment and economic status as well as the lives of their family members[31, 36-38]
- Following a formal diagnosis of HS, a stepwise approach to treatment is taken, based on disease severity[39]
- People with milder forms of HS are often managed in primary care and commence treatment with topical antibiotics. For more widespread disease, lack of response to topical antibiotics or people with moderate HS, conventional systemic therapies are offered, such as oral antibiotics or combination antibiotics.[39] Combination antibiotics are considered immediately for severe HS. For moderate-to-severe HS unresponsive to these therapies other conventional systemic therapies maybe offered, such as acitretin, dapsone or ciclosporin

- Adalimumab is licensed for use after a lack of response to conventional systemic therapies in people with moderate-to-severe HS and is initiated in secondary care[39]
- Real-world evidence highlights the clear need for additional licensed therapies in HS with established efficacy and a tolerable safety profile[15, 40, 41]
- A growing body of evidence demonstrates the benefit of anti-IL-17 therapy (e.g., secukinumab) in HS and thus may provide an alternative treatment option for people with HS[18-24]
- Given the availability of biosimilar adalimumab, secukinumab is anticipated to be positioned for people with HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment

B.1.3.1 Disease overview

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a debilitating skin condition that is defined by its chronic course and the presence of recurrent, painful, deep-seated, inflammatory lesions that notably affect the intertriginous regions of the body (skin folds), particularly the groin and axillae.[8-10]

Most people with HS present with moderate-to-severe disease (see the 'Diagnosis and classification' section below for more information on HS classification).[14-17] This is partly explained by misdiagnoses and diagnostic delays experienced by people with HS, whose treatment options become progressively limited.[42] Early lesions in HS manifest as painful nodules or boils that later progress to abscesses and pus-discharging tunnels, known as sinus tracts and fistulas.[43] Owing to the severe pain, movement restrictions and odours caused by sinus tracts and fistulas, HS has a profound negative impact on the lives of people with HS.[8] Real-world studies have demonstrated the far-reaching effects of HS on the employment and economic status of people with HS, as well as the lives of their family members.[31, 36-38]

Genetic predisposition and adverse lifestyle factors may underlie the development of HS.[14] In the latter, smoking and obesity have extensively been linked to the pathogenesis of HS.[1, 44-48] A hospital-based case-control study (people with HS: n=80; age- and sex-matched control: n=100) reported that the prevalence of central obesity (odds ratio [OR]: 5.88; 95% confidence interval [CI]: 2.93–11.91; p<0.001) was higher in people with HS than controls.[46] Most people with HS (nearly 70% or more) were current or former smokers.[45, 47] Additionally, people with HS may also experience a broad range of comorbidities that include depression, inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis) and spondyloarthropathy (SpA).[8] Together with associated comorbidities, HS is associated with a substantially increased mortality compared with controls from the general population (mean incidence ratio of 1.35, 95% CI: 1.15–1.59; after adjustment for age, sex, socioeconomic status, smoking, comorbidity, and medication).[49]

Despite the considerable burden of HS, the number of approved therapies remains limited. As a result, conventional systemic therapies used in the early treatment pathway are prescribed off-label in clinical practice, with adalimumab being the only biologic currently licensed for patients who have an inadequate response to conventional systemic therapies (see Section B.1.3.3).[39]

Epidemiology

HS has an estimated point prevalence of 770 cases per 100,000 people (95% CI: 760–780) in the United Kingdom (UK; estimated in 2013).[11] The same study reported a mean annual incidence rate of 28.3 cases per 100,000 person-years (CI not reported).[11] HS appears, almost

exclusively, after puberty with the average onset in the second or third decades of life, and women are three times more likely to develop HS as compared with men (3:1).[12]

A US epidemiological study of a large database (representing approximately 15% of the US population, across all four census regions) found the age- and sex-adjusted prevalence estimates were three and two times higher in African-Americans and biracial individuals, respectively, as compared with White individuals.[50]

Pathogenesis

While the disease name and distribution of lesions allude to sweat gland involvement, HS is thought to be a result of hair follicle occlusion.[8] Pathogenic events are divided into two broad, consecutive categories based on a cascade of inflammatory events (Figure 1), namely initial pathogenic events and events of advanced disease.[8]

In the initial pathogenic events:[8]

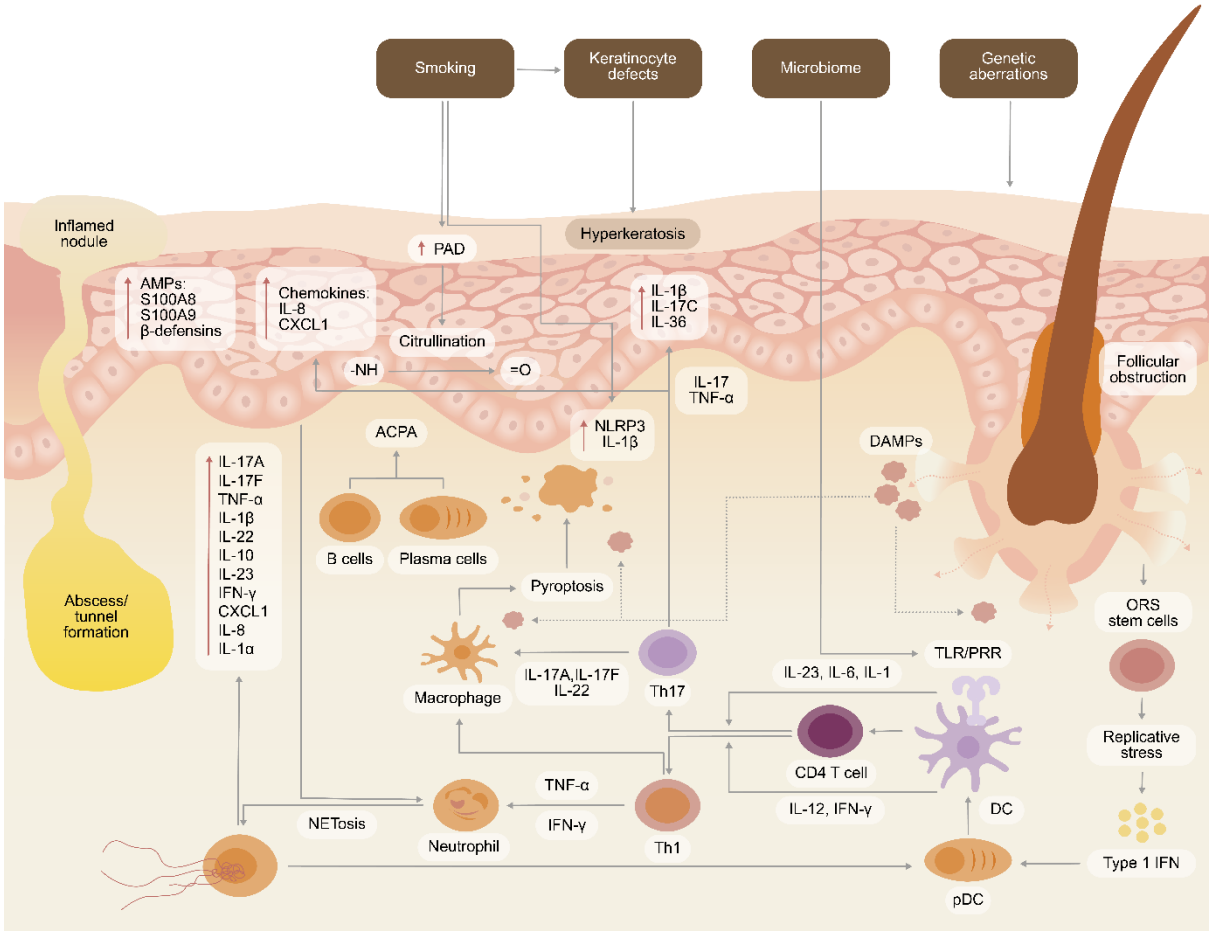
- Histological samples reveal immune cell infiltration in the dermis from surrounding tissue and blood vessels as well as increased thickness and proliferation of the infundibular epithelium (funnel-shaped, uppermost segment of the hair follicle)[51-55]
- Alterations to the infundibular epithelium result in follicular occlusion and subsequently lead to the build-up of follicular content, propagation of resident bacteria and dilatation of hair follicles[8]
- Bacterial propagation and danger-associated molecular patterns (DAMPs) alert resident macrophages to secrete pro-inflammatory cytokines, in particular interleukin (IL)-1 and tumour necrosis factor (TNF)-α.[56, 57] This inflammatory response is further amplified by the increased expression of Toll-like receptor (TLR)-2 in macrophages as well as dendritic cells.[58] Together, the effects of the upregulation of both cytokines lead to the recruitment of an abundance of neutrophils, macrophages, dendritic cells and T cells in HS lesions[8]

In the events of advanced disease:[8]

- The array of immune cells recruited in the earlier stage go on to secrete specific cytokines: the most notable inflammatory mediators are interferon-γ (IFNγ) and IL-17,[56] which are predominantly secreted by T helper (T_H) 1 and T_H17 cells, respectively[59, 60]
- IFNγ acts to recruit more T_H1 cells and other immune cells,[59] while IL-17 stimulates secretion of other pro-inflammatory cytokines (e.g. IL-19) as well as neutrophil-attracting chemokines that include C-X-C motif ligand 1 (CXCL1).[61] IL-17 may also exert its effects synergistically with TNF-α and IFNγ.[60] The significance of IL-17 in the pathogenesis of HS is substantiated by a growing body of scientific evidence that includes real-world evidence from several case reports,[18-21] open-label trials[22, 23], a Phase II randomised controlled trial (RCT)[24] and two identically designed Phase III RCTs[62, 63] demonstrating the benefit of anti-IL-17 therapy in HS
- Consequently, the intrafollicular bacterial growth and immune cell infiltration both lead to rupture of the dilatated hair follicle and the spread of its contents into surrounding tissue, thereby further amplifying skin inflammation. The ruptured hair follicle unit manifests as inflamed nodules (firm swellings of deep skin tissue) or abscess (red, tender, pus-filled cavities, surrounded by inflamed skin).[8] Moreover, the accumulation of pus and seeding of follicular stem cells into the disintegrated tissue facilitates the formation of sinus tracts and fistulas[64, 65]

- Overall, the unrestricted and persistent immune response eventually leads to severe pain, pus formation, irreversible tissue destruction and scar development[8]

Figure 1: Pathogenesis of HS



Abbreviations: ACPA: anti-citrullinated protein antibodies; AMPs: antimicrobial peptides; CD: cluster of differentiation; CXCL: C-X-C motif ligand; DAMPs: damage-associated molecular patterns; DC: dendritic cell; IFN: interferon; NLRP: Nucleotide-binding domain-like receptor protein; ORS: Hair follicle outer root sheath; PAD: peptidylarginine deiminase; pDC: plasmacytoid dendritic cells; PRR: pattern recognition receptors; Th: T helper cell; TLR: Toll-like receptor; TNF: tumour necrosis factor.
Source: Adapted from Fletcher *et al.*, (2020).[66]

Diagnosis and classification

HS is clinically diagnosed based on the presence of typical lesions that affect characteristic sites of the body, with a recurrent or persistent nature. All three typical features must be observed for a formal diagnosis of HS (Table 3).[9]

Table 3: Triad of features in HS

Typical lesions	Inflammatory nodules, abscesses, chronic sinus tracts, cord-like scars, comedones
Typical sites	Most commonly groin and axillae, but other typical sites include breasts, lower abdomen, perineum, and neck

Typical course	Recurrent (at least two lesions occurring or recurring in the last 6 months) or non-resolving (presence for at least 6 months) lesions at the same sites.

Source: Revuz (2009).[9]

There are no specific tests used to diagnose HS, as various serum proteins elevated in HS are not disease-specific.[8] In addition, histological confirmation (skin biopsy) is rarely needed.[39] Accordingly, a total body examination is required to assess the extent and severity of HS.[8] This is often measured using the Hurley staging system: a widely known and useful rapid classification system that approximates disease severity and stratifies people with HS into three groups (Table 4).[13]

Table 4: Hurley staging system for baseline disease severity in each skin region

Stage	Disease severity in skin region	Description
I	Mild	Presence of isolated lesions with no sinus tracts and minimal or no scarring
II	Moderate	Recurrent lesions separated by areas of intervening normal skin with sinus tracts and scarring
III	Severe	Multiple lesions coalescing into inflammatory plaques involving most of the affected region

Source: Hurley (1989).[13]

Across several studies conducted in the UK, Europe, and the United States, the proportion of people diagnosed with moderate-to-severe HS largely varied between 45% and 95%.[14-17, 67, 68] It was also noted that males with HS reported more severe disease (Stage III) than females with HS, for which the risk was twice as high (odds ratio: 2.11; 95% CI: 1.54–2.89; $p<0.001$).[67]

A mean diagnostic delay of 7–10 years has been estimated by several studies.[15, 40, 69] Diagnosis is further complicated by the resemblance of early lesions with other skin dermatoses, such as a simple abscess or a furuncle.[8, 70]

Despite its clinical relevance, the Hurley system is static and therefore insensitive to changes in disease severity; as such, clinicians and clinical trials use other instruments to measure the efficacy of treatment during follow-up.[8, 39] For example, the Hidradenitis Suppurativa Clinical Response (HiSCR) could be used and is based on a count of the number of inflammatory lesions and abscesses, with at least a 50% reduction in baseline score representing treatment success.[71] The Hidradenitis Suppurativa Score (HSS or Sartorius score) is an alternative measure that comprises a dynamic and detailed scoring system that detects changes in disease severity over time and in response to treatment.[72] However, its use in clinical practice is limited by its laborious nature.[8] As such, a modified HSS (mHSS) with minor simplifications has since been developed in the clinical trial setting.[73] The Physician Global Assessment Tool for HS is another instrument frequently used in both clinical trials and daily clinical practice that is validated and quick to use.[73]

Assessment of people with a formal HS diagnosis should also address the common comorbidities associated with HS, such as anxiety, depression and cardiovascular risk factors (see Section B.1.3.2).[39]

Natural history

HS is one of the most debilitating skin disorders owing to its chronicity and recurrent flares of painful lesions. Disease flares are characterised by increased pain and suppuration with a foul-smelling discharge, which stains clothing.[43, 74, 75]

Although current understanding of the natural history of HS is limited, von der Werth and Williams revealed that the average reported age of onset of HS was 21.8 years (standard deviation [SD]: 9.8 years, range 5–54 years),[25] which was in line with reports by Jemec (23 years),[76] and Harrison and Hughes (24.9 years).[77]

Approximately 50% of people with HS tend to experience subjective prodromal symptoms, such as burning stinging, pain, pruritis, warmth or sweating around 48 hours before overt nodules appear.[9] The mean duration of a single painful nodule has been reported as 6.9 days, and 62% of people with HS reported the persistence of at least one boil that failed to subside.[25] Another study reported that 73% of people with HS experienced recurrent flares.[15] The repetition of acute flares and rupture of lesions may lead to the formation of sinus tracts and scarring.[9] Sinus tracts may have malodorous discharge, which may persist for months and sometimes several years, unless surgically excised.[9]

The seriousness and course of the disease is complex, but it has been reported that people with severe HS (Stage III) have a more rapid and aggressive disease course than people with moderate HS (Stage II).[78]

Evidence from real-world studies demonstrate that complete remission from symptoms is unlikely with medical therapy alone and thus people with HS may also require surgery.[14, 15, 40] The UNITE registry revealed that a high percentage of people with HS, particularly those with moderate (67.8%; n=267/394) or severe (75.6%; n=121/160) disease, reported a history of prior surgical procedures despite receiving medical therapy.[14] In the overall cohort of UNITE (n=594), most patients (73.2%) had received prior medication, which mainly comprised conventional therapies, such as antibiotics (68.4%), with retinoids (17.7%), corticosteroids (8.8%), hormonal therapies (4.4%), and immunosuppressants (1.3%) also reported. Only a very small proportion of patients (4.9%) received biologics.

B.1.3.2 Burden on people with HS, carers and society

Symptoms and comorbidities

Due to its chronic nature with recurrent, painful flares, HS has a large negative impact on the lives of people with HS, with progression of disease severity leading to the worsening of their quality of life.

Pain has been reported by most people with HS (97%)[26] and has been found to worsen with increasing HS severity, as measured by the worst pain numeric rating scale (WP-NRS): 2.9 for Stage I, 3.9 for Stage II and 4.9 for Stage III disease ($p<0.001$; possible range: 0–10 with higher scores indicating higher pain intensity).[16] However, evidence from a cross-sectional survey of UK general practitioners revealed that only just under half (n=65/134, 49%) provided analgesia.[79]

Pruritis has also been reported by 62% of people with HS (n=64/103), with this symptom being reported as irritating (62.8%), burdensome (46.5%) or unbearable (16.8%).[26] The intensity of pruritis was rated substantially higher in people with severe HS ($p<0.05$; statistically significant in the study).[26] Additionally, malodorous discharge has been reported by 88% of people with HS (n=51), with the intensity correlating positively with the number of regions affected and disease severity.[27]

Real-world evidence has highlighted associations between HS and cardiovascular disease (CVD),[80] IBD,[81] type 2 diabetes[46] and anxiety and depression.[82] A review of the Danish National Patient Register revealed that HS was associated with a significantly increased risk of adverse cardiovascular outcomes and general population mortality after controlling for confounders (e.g. obesity).[49]

Quality of life (QoL) impairment

Overall, HS substantially impairs QoL and this is seen across a number of instruments, including general health-related QoL (HRQoL) measures (EQ-5D, the 36-item short form health survey [SF-36]) and disease-specific measures (Dermatology Life Quality Index [DLQI], Skindex-29).[16, 17, 27, 29, 31, 83] When compared with a normative sample of the French population (n=3,656), a greater QoL impairment has been observed amongst people with HS (n=61) across all domains, as measured by SF-36 (confounding not reported).[29] Furthermore, a hospital-based study in Denmark that comprised over 75% of patients with moderate HS (Hurley Stage II) reported that patients with HS had a substantially lower EQ-5D utility score (0.71) compared with the general population (0.89), with pain/discomfort having the most adverse effect on overall mean index values.[83] Indeed, the worsening of the QoL of people with HS correlated positively with increasing disease severity, as measured by DLQI (0–30): people with moderate-to-severe HS (Stage II or III) had mean scores between 11 and 20 (categorised as a 'very large effect on patient's life').[83]

Although QoL is shown to be impaired across domains, studies using Skindex-29 have shown that the emotional aspect of the lives of people with HS has been particularly affected, with mean reported scores of 57.4–70.6 (0–100; higher score indicates lower QoL).[27-29] Scores across the symptoms and functions domains were still high (41.6–61.6).[27-29] Accordingly, people with HS experience psychological symptoms as a result of HS. Anxiety, depression and suicidality were more common in people with HS than in the general population.[49, 84, 85] The UNITE registry demonstrated that 30% of people with HS had depression, rising to 36.5% in people with severe disease.[31] Additionally, more than half (57.5%) of people with HS had anxiety.[31] Similarly, the Danish registry revealed that people with HS were prescribed more antidepressant or anxiolytics compared with the general population (OR: 2.02–2.19; adjusted for age and sex).[86] The same study reported a 2.4-times greater risk of completed suicide among people with HS than the general population, which remained elevated even after adjustment for confounding factors such as age, sex, socioeconomic status, smoking, alcohol abuse and healthcare use.[86] A further aspect of the psychological burden for people with HS was an impaired personal body image, which included aspects such as 'self-acceptance' and 'acceptance of one's body by others.[87] In addition, lower self-esteem ($p=0.008$) and higher levels of loneliness ($p<0.001$) than healthy controls have also been noted.[32]

Investigation into the broader impact of HS on family members' QoL, as measured by Family Dermatology Life Quality Index (FDLQI) revealed that cohabitants (n=27) had considerable QoL impairment, with mean FDLQI scores (10.5) directly associated with mean DLQI scores (13.9) of

patients with HS (n=27); scores were measured on a scale of 0–30, where higher scores indicate worse QoL.[36] Another study showed that FDLQI scores for partners of people with HS increased as HS severity increased.[38]

Activity and daily life impairment

In the UNITE study, some degree of activity impairment due to HS was reported by 74.7% of adults, with an average overall activity impairment of 41.1% as measured by the Work Productivity and Activity Impairment (WPAI).[31] Compared with the general population, people with HS reported higher sexual dysfunction, especially in females with HS.[27] A greater proportion of people with HS also reported poorer sleep quality than the general population (70.4% versus 22.0%, respectively), as indicated by a Pittsburgh sleep quality index (PSQI) of ≥5.[30]

Work impairment

HS also negatively affects the professional lives of people with HS, with onset usually occurring during their productive years.[12] In the UNITE study, absenteeism (work time missed) was reported by 27.9% (n=89/319) of adults with HS in employment, of which an average of 33.7% of work time was missed due to HS.[31] Almost two-thirds (63.6%; n=203/319) of people with HS reported presenteeism issues (reduced productivity while at work), of which an average of 43.7% impairment while working was due to HS.[31] Overall work impairment amongst employed adults was 48.9%.[31] In a US claims study, a higher annual total days of work loss was reported for people with HS than controls (18.4 versus 7.7, respectively).[37] Furthermore, people with HS had a greater risk of leaving the workforce than controls (hazard ratio [HR]: 1.6).[37]

Costs and resource use

Major drivers of costs in HS include productivity loss, biological treatment, informal care and surgery.[33-35] Higher medical costs are associated with more severe disease, and coexisting IBD, while worse QoL outcomes predicted higher indirect costs.[33, 34] In a comparative study, people with HS had increased utilisation of high-cost settings when compared with people with psoriasis: the emergency department (7.4% versus 2.6%; p<0.0001) and inpatient care (5.1% versus 1.6%; p<0.0001).[35]

Within 7.5 years of diagnosis, two-thirds of people with HS (64%, n=254) required surgery, a major cost driver, in a cohort study in France.[15] Of these, approximately 80% required multiple surgeries and 61% of people with HS receiving surgical treatment required skin graft or other major surgeries. See the ‘Unmet need despite current treatments’ section below for information on rates of HS recurrence after surgery.

B.1.3.3 Description of the clinical care pathway

Treatment pathway for hidradenitis suppurativa (HS) in the UK

People with HS generally have a high, unmet medical need because of diagnostic delays and the limited range of evidence-based therapies available. In the earlier stages of the treatment pathway in the UK, most therapies are prescribed off-label. When earlier treatments have failed to control the disease, adalimumab is approved and recommended by NICE.[1, 2]

The British Association of Dermatologists (BAD) guideline, published in 2018, remains the main source of recommendations on the management of HS in the UK and is largely based on available low-to-medium quality evidence and expert opinion.[39]

Although no NICE clinical guidelines have been published, NICE have assessed the treatment of HS through the technology appraisal, TA392: Adalimumab for treating moderate to severe hidradenitis suppurativa (2016).[1]

BAD-recommended treatment pathway

The BAD treatment pathway is summarised below and is based on a combination of different therapies:[39]

- In mild-to-moderate HS (Hurley stage I or II), the initial management can be carried out in primary care
- Mild HS is typically managed with topical antibiotics (clindamycin)
- With more extensive disease, scarring or lack of response to topical antibiotics, systemic antibiotics are prescribed (tetracycline or clindamycin and rifampicin)
- Other alternative conventional therapies used after a lack of response to both topical and systemic antibiotics include acitretin, dapsone and ciclosporin
- Potent TNF-α antagonists are often used after a lack of response to conventional systemic therapies, discussed above:
    - Adalimumab is the only licensed treatment recommended by NICE (TA392) for treating moderate-to-severe HS
    - Off-label infliximab is recommended as an alternative by the BAD guideline, if there is a lack of response to adalimumab
        - However, NHS England concluded that evidence for this recommendation was not sufficient for the routine commissioning of infliximab for patients with HS.[88] Supporting this further, feedback received from BAD at the draft scope consultation for secukinumab in HS indicated that infliximab is no longer established clinical practice in the NHS and is rarely used now for treating HS[89]
    - Response to biologic treatment is defined as a reduction of 25% or more in the total abscess and inflammatory nodule (AN) count and no increase in abscesses and draining fistulas[1]

Unmet need despite current treatments

The Global VOICE survey, a real-world, prospective study assessing the unmet needs of people with HS (n=1299) from 14 countries, revealed that 45.9% people with HS (n=596) were dissatisfied or very dissatisfied with their current treatment, which mostly comprised oral antibiotics (85.6% [n=1,112]).[40] Additionally, biologics were prescribed in 20.8% of patients (n=270), with adalimumab being the most frequent (77.0% [n=208]). Among those dissatisfied with their treatment, poor efficacy (n=547; 42.1%) and undesirable adverse effects (n=264; 18.9%) of treatment were the main reasons for dissatisfaction. Additionally, the UNITE registry revealed that inadequate response was the main reason for discontinuation of prior medication

for HS (55.5%; n=594).[31] As noted earlier, a large percentage of people with HS (73%) still experience flares (in this study, 9.6% [n=38/396] of people with HS were treated with biologics).[15]

Although surgical treatment of scars and pus-draining tunnels is typically reserved for patients with moderate-to-severe HS,[42] there is still a high rate of HS recurrence postoperatively: a US study (n=107) reported that 40.2% of people with HS (n=43/107) had recurrence of HS at the same site of operation.[41] Among these, 55.8% reported that HS recurred more than one year postoperatively.[41] Moreover, another study (n=249) revealed that 69% of people with HS (n=173/269) reported the appearance of HS lesions at sites of operation or at any other body site after surgical treatment.[90]

Overall, the real-world evidence noted above highlights the clear need for additional licensed therapies in HS with established efficacy and a tolerable safety profile.

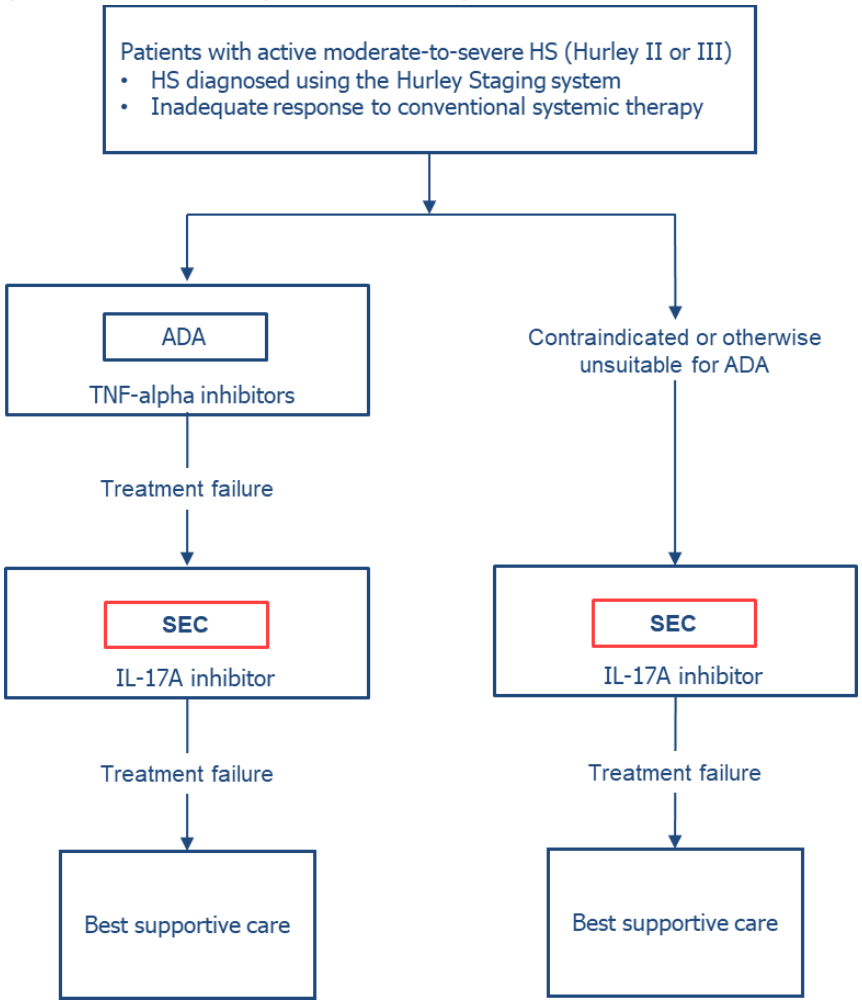
Positioning of secukinumab in the treatment pathway for hidradenitis suppurativa in the UK

TA392[1] recommends offering adalimumab in people with active moderate-to-severe HS who do not respond to conventional systemic therapy. However, not all people with HS respond to adalimumab: results from the pivotal PIONEER I and II trials show that only 41.8% and 58.9% of people with HS respond (HiSCR≥50) after 12 weeks, respectively.[91] This leaves a substantial number of people with HS with inadequate treatment. Based on the BAD guideline, people who do not respond to adalimumab may be treated with another TNF-α inhibitor, such as infliximab; however, there is a lack of robust evidence to support this recommendation.[88] Moreover, not all people with HS are suitable for TNF-α inhibitors, due to intolerance or contraindication. The intravenous mode of administration also makes infliximab less convenient for people with HS than subcutaneous injections, which offers the possibility of home administration.

As noted in B.1.3.1, there is a growing body of evidence that demonstrates the benefit of anti-IL-17 therapy (e.g., secukinumab) in HS and thus may provide an alternative treatment option for people with HS. Moreover, the lack of licensed biologic treatment options with an alternative mechanism of action to TNF-α inhibition means that available treatment options are limited.

Given the availability of biosimilar adalimumab, secukinumab is anticipated to be positioned for people with HS for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment (Figure 2).

Figure 2: 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



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.

B.1.4 *Equality considerations*

As noted in the final NICE scope, the incidence of HS is higher in people of African-Caribbean family background as compared with people of European family background. No equality issues are foreseen if secukinumab were to be recommended for use for all people with active moderate-to-severe HS at the anticipated positioning.

B.2 Clinical effectiveness

Summary of clinical effectiveness evidence

Evidence for secukinumab 300 mg Q4W and secukinumab 300 mg Q2W in HS

- The SUNSHINE and SUNRISE trials represent the primary source of evidence for secukinumab as a treatment for adults with moderate-to-severe HS. SUNSHINE and SUNRISE were two concurrent, identically designed, Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trials, and thus provide robust evidence for the safety and efficacy of secukinumab in moderate-to-severe HS

Efficacy

- The primary endpoint of the two pivotal trials was the proportion of patients achieving HiSCR50 at Week 16
- Across both trials, treatment with secukinumab 300 mg Q4W resulted in a greater proportion of patients achieving HiSCR50 as compared with placebo; however, statistical significance was only met in the SUNRISE trial. Treatment with secukinumab 300 mg Q2W in SUNSHINE and SUNRISE was associated with a statistically significantly higher proportion of patients achieving HiSCR50 at Week 16, as compared with placebo
- Available long-term efficacy data between Weeks 16 and 52 at the primary endpoint analysis of SUNSHINE and SUNRISE demonstrated a consistent and progressive trend of increasing responses over time with respect to HiSCR50 in the secukinumab Q4W and Q2W groups
- Regarding secondary endpoints, data pooled from the SUNSHINE and SUNRISE trials demonstrated a greater reduction in skin pain (NRS30) in the secukinumab Q4W group as compared with placebo, but statistical significance was not met. A significant reduction in skin pain (NRS30) was observed in the secukinumab Q2W group, as compared with placebo.
- A greater decrease in AN count was observed across both Q4W and Q2W groups of SUNSHINE and SUNRISE, as compared with placebo. However, results were significant for the Q4W group in SUNRISE only and the Q2W groups in both trials
- Fewer patients experienced HS flares in the Q4W and Q2W groups of SUNSHINE and SUNRISE. However, results were significant only for the Q4W group of SUNRISE and the Q2W group of SUNSHINE
- Sustained improvements in all secondary endpoints were observed beyond Week 16 through to Week 52 in SUNSHINE and SUNRISE
- Patients in the secukinumab Q4W and Q2W groups also reported better HRQoL compared with placebo, as assessed by DLQI and EQ-5D-3L VAS at Week 16, with sustained improvements seen beyond Week 16 through to Week 52

Safety

- Across both SUNSHINE and SUNRISE trials, no clinically meaningful differences were observed in the incidence of study treatment-related AEs between the secukinumab Q2W, the secukinumab Q4W and placebo groups during Treatment Period 1 (up to Week 16)
- In SUNSHINE, more patients in the placebo group reported SAEs as compared with the secukinumab 300 mg Q2W and Q4W group, while in SUNRISE, SAEs were generally similar across Q2W, Q4W and placebo
- As compared with placebo and secukinumab Q4W, secukinumab Q2W treatment in SUNSHINE was associated with a slightly higher proportion of AEs leading to discontinuation from study treatment. In SUNRISE, fewer patients reported discontinuation due to AEs in secukinumab Q2W group compared with both Q4W and placebo
- No deaths occurred in the secukinumab Q2W, Q4W and placebo groups across both trials during Treatment Period 1

Indirect Treatment Comparisons

- Given that secukinumab is positioned for patients with HS for whom adalimumab is contraindicated, otherwise unsuitable or ineffective, it is anticipated that best supportive care represents the sole comparator of relevance to this submission. As such, it was deemed not necessary to conduct an indirect treatment comparison given the availability of direct evidence from two identically designed, head-to-head comparison trials (SUNSHINE and SUNRISE) of

secukinumab versus placebo

Conclusion

- Secukinumab 300 mg Q4W/Q2W offers an effective and tolerable treatment option for patients with moderate-to-severe HS

B.2.1 *Identification and selection of relevant studies*

A clinical systematic literature review (SLR) of the published literature was conducted to identify relevant clinical evidence on the clinical efficacy and safety of pharmacological and non-pharmacological therapies for adults with moderate-to-severe HS. Given that this SLR was intended for use in health technology assessment (HTA) submissions across multiple countries, a broad approach was taken and therefore included additional therapies not considered relevant to the decision problem addressed in this submission.

The clinical SLR was conducted in April 2021 and updated in August 2022. The original SLR identified 30 unique studies, reported in 71 publications, that met the eligibility criteria for inclusion. Of these, 17 studies were randomised controlled trials (RCTs), two were open-label extension studies and 11 were single-arm trials. After the SLR update in August 2022, a total of 78 publications reporting on 35 unique studies (21 RCTs, two OLE, and 12 single arm trials) were included.

Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

Of the studies identified in the clinical SLR, the trials of direct relevance to the decision problem for this evaluation are the two concurrent, identically designed, parallel-group, Phase III randomised controlled trials (SUNSHINE [NCT03713619] and SUNRISE [NCT03713632]) that have recently been presented at the 31st European Academy of Dermatology and Venereology (EADV) Congress.[92] In addition, Novartis hold further unpublished data on file that are presented in this submission.

The SUNSHINE and SUNRISE trials are the pivotal registration trials presented to the Medicines and Healthcare products Regulatory Agency (MHRA) in support of the marketing authorisation for secukinumab SC injection in adults with moderate-to-severe HS. An overview of each trial (SUNSHINE and SUNRISE) is presented in Table 5, and the methodology and results are presented in Section B.2.3 onwards.

Table 5: Clinical effectiveness evidence

Study	SUNSHINE (NCT03713619)[62]	SUNRISE (NCT03713632)[63]
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.[93, 94]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

The SUNSHINE and SUNRISE trials are two Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre studies, assessing the safety and efficacy of two secukinumab dose regimens (every two weeks [Q2W] and every four weeks [Q4W]) in adults (≥18 years old) with moderate-to-severe HS. Although these are two separate pivotal trials, they

both had an identical study design and methodology and are therefore summarised together below.

At baseline, patients were randomised via an Interactive Response Technology (IRT) in a 1:1:1 ratio to one of three treatment arms:

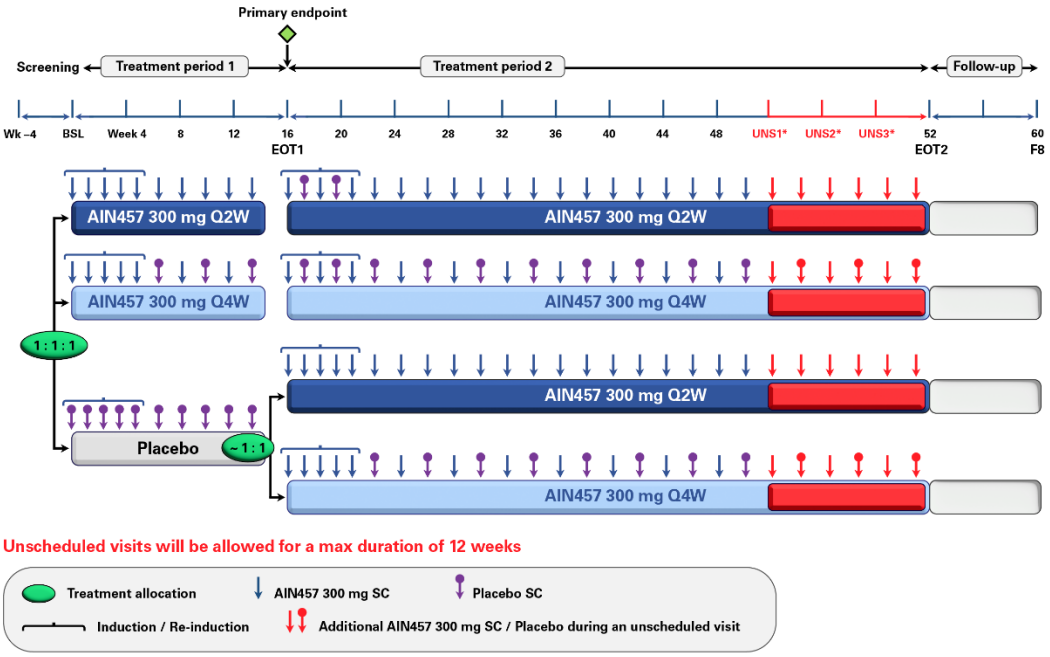
- Secukinumab 300 mg Q2W (SUNSHINE: N=181; SUNRISE: N=180)
- Secukinumab 300 mg Q4W (SUNSHINE: N=180; SUNRISE: N=180)
- Placebo group to secukinumab 300 mg Q2W or Q4W (SUNSHINE: N=180; SUNRISE: N=183)

Randomisation was stratified by geographical region, concomitant antibiotic use and body weight (<90kg or ≥90kg).

The study design of both trials comprised three timepoints: Screening (four weeks prior to baseline), placebo-controlled Treatment Period 1 (baseline to Week 16 pre-dose) and Treatment Period 2 (Week 16 post-dose to Week 52). Patients who completed either of the trials were allowed to enrol in a planned optional Phase III extension study (NCT04179175).[95] Those who prematurely discontinued and those who completed either of the trials but decided not to enrol in the planned optional extension study needed to complete a Post-Treatment Follow-Up period of up to eight weeks. For patients rolling over to the extension study, Week 52 was the end of study visit, while Week 60 was the end of study visit for patients continuing to the Post-Treatment Follow-Up.

A schematic of the design of the SUNSHINE and SUNSHINE trials is present in Figure 3.

Figure 3: Study design of SUNSHINE and SUNRISE (including changes due to COVID-19)



AIN457 is the Novartis internal drug code for secukinumab. In the event that the Week 52 visit could not be performed on-site as scheduled due to a global health disruptive event (e.g., COVID-19 pandemic) or a delay in the approval of the extension study protocol by HAs/ECs, an additional treatment period of up to a maximum of 12 weeks would be considered to ensure treatment continuity until the Week 52 visit could be performed, which is required for rollover to the long-term extension study. A maximum of up to 6 additional unscheduled doses of study treatment could be home administered, with dosing frequency maintained at Q2W to preserve treatment allocation concealment. UNS1, UNS2 and UNS3 correspond to three possible additional IRT calls by investigator staff at which two doses would be dispensed each for home delivery. Treatment allocation for placebo arm switching to secukinumab arms at Week 16 was performed at the randomisation visit in 1:1 ratio and did not account for potential discontinuations during Treatment Period 1. Follow-up: only patients who prematurely discontinued treatment during Treatment Period 1 or 2 or patients who did not enrol in the extension study entered follow-up. Despite the impact that COVID-19 had on the conduct of site study visits as per protocol, special efforts were made to conduct on-site visits for the EOT(s) visits, Week 16 and Week 52.
Abbreviations: BSL: Baseline; EOT1/EOT2: EC: ethics committee; End of treatment 1 or 2; F8: End of Follow-up visit at Week 60; HA: health authority; IRT: Interactive Response Technology; Q2W: every two weeks; Q4W: every four weeks; UNS: Unscheduled; SC: subcutaneous.
Source: Novartis SUNSHINE and SUNRISE Protocol.[93, 94]

During Treatment period 1, which was the period from randomisation (baseline) to Week 16 (pre-dose i.e., before patients received their Week 16 dose), all patients received a SC injection of either secukinumab 300 mg or placebo once every week for five weeks (induction). Thereafter, the injection frequency was reduced to once every two weeks in all treatment groups. Patients in the secukinumab Q4W group received placebo every two weeks in order to conceal treatment allocation. Patients who completed Treatment Period 1 were allowed to enter Treatment Period 2.

Treatment Period 2 was between Weeks 16 (post-dose i.e., after patients receive their Week 16 dose) and Week 52 and comprised only those who had completed Treatment Period 1. In this period of the trial, all patients received secukinumab: patients who were randomised to either of the two secukinumab groups (Q2W or Q4W) at baseline maintained the same dosing regimen, whereas patients randomised to either of the placebo arms at baseline were re-randomised in a 1:1 ratio to receive either secukinumab 300 mg Q2W or secukinumab 300 mg Q4W. At Week 16, consistent with Treatment Period 1, all patients underwent re-induction: those from the placebo group who were re-randomised to either of the two secukinumab groups (Q2W or Q4W) received secukinumab 300 mg once every week for five weeks, whilst patients previously receiving secukinumab received placebo in between doses based on the Q2W or Q4W dosing frequency to conceal treatment allocation. Thereafter, dosing frequency was reduced to once every two weeks in both secukinumab groups (Q2W and Q4W) until Week 50; however, patients in the secukinumab Q4W group received placebo every two weeks to conceal treatment allocation.

In line with guidance released from Health Authorities (EMA and MHRA) to introduce a level of flexibility in drug dispensation, protocol assessments and visit schedule if a major health care event requires it (i.e., COVID-19 pandemic), an additional treatment period of up to a maximum of 12 weeks was also considered to ensure treatment continuity for patients in the event that the Week 52 study visit could not be performed due to a global health disruptive event, such as the COVID-19 pandemic, or a delay in the approval of the extension study protocol by health authorities or ethic committees. In this scenario, patients would be allowed to receive up to six additional unscheduled doses for home administration, where two doses (one dose being placebo for the Q4W group) would be dispensed after three possible additional IRT calls by the investigator staff (UNS1, UNS2 and UNS3). In addition, the dosing frequency would be maintained at Q2W to preserve treatment allocation concealment.

B.2.3.2 Trial methodology

A summary of the study methodology of the SUNSHINE and SUNRISE trials is presented in Table 6.

Table 6: Summary of the methodologies for the SUNSHINE and SUNRISE trials

Trial name	SUNSHINE (NCT03713619) and SUNRISE (NCT03713632)
Location	Worldwide: 132 study sites in five geographical regions: AMEA, RE, LaCAN, US and Japan. This included 12 sites in the UK (six sites for each trial), with each trial and site recruiting patients as follows: SUNSHINE (N=[redacted]) • Chapel Allerton Hospital (n=[redacted]) • University Hospitals Bristol NHS Foundation Trust (n=[redacted]) • Barnsley Hospital NHS Foundation Trust (n=[redacted]) • Salford Royal NHS Foundation Trust (n=[redacted]) • Royal Devon and Exeter NHS Foundation Trust (n=[redacted]) • Norfolk and Norwich University Hospital (n=[redacted]) SUNRISE (N=[redacted]) • Russells Hall Hospital (n=[redacted]) • Queen Elizabeth Hospital (n=[redacted]) • Royal London Hospital (n=[redacted]) • Harrogate and District Foundation Trust (n=[redacted]) • St Luke's Hospital (n=[redacted]) • Guy's Hospital (n=[redacted])
Trial design	Identical, concurrent, Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trials

Eligibility criteria for participants[a]	**Key inclusion criteria:**
	• Written informed consent must be obtained before any assessment is performed
	• Male and female patients ≥18 years of age
	• Diagnosis of HS ≥1 year prior to baseline
	• Patients with moderate-to-severe HS defined as:
	  ○ A total of at least five inflammatory lesions, i.e., abscesses and/or inflammatory nodules
	  ○ AND
	  ○ Inflammatory lesions should affect at least two distinct anatomic areas
	• Patients agree to daily use of topical OTC antiseptics on the areas affected by HS lesions while on study treatment
	
	Key exclusion criteria:
	• Total fistulae count ≥20 at baseline
	• Any other active skin disease or condition that may interfere with assessment of HS
	• Active ongoing inflammatory diseases other than HS that require treatment with prohibited medications or use of or planned use of prohibited treatment (see 'Permitted and disallowed concomitant therapy' row)
	• Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A/F or the IL-17 receptor
	• History of chronic or recurrent systemic infections or active systemic infections during the last two weeks (expect the common cold) prior to randomisation

	• History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years • Pregnant or lactating women or women of childbearing potential For a full list of exclusion criteria, can be found in Appendix M
Settings and locations where the data were collected	Administration of secukinumab or placebo took place during study site visits, except on pre-specified weeks where patients or carers were allowed to administer the medication from home (see below). If neither patients nor carers were able or confident enough to administer the study drug at home, patients were allowed to return to the study site for administration of the medication. **Treatment period 1** • Home administration of study drug was scheduled for Weeks 6, 10 and 14 **Treatment period 2** • Home administration of study drug was scheduled for Weeks 22, 26, 30, 34, 38, 42, 46 and 50. In addition, up to six additional unscheduled doses could be home administered after Week 50 every 2 weeks for a maximum of 12 weeks until the patient is able to perform the Week 52 visit on-site, owing to disruptions due to the COVID-19 pandemic
Study drugs	**All patients** • Induction of either SC secukinumab 300 mg or SC placebo at baseline, with injections once weekly for five weeks (at Weeks 0, 1, 2, 3 and 4). Thereafter, SC injection of secukinumab 300 mg or placebo Q2W (see below for details) • Re-induction of either SC secukinumab 300 mg or SC placebo once weekly commenced at Week 16 and lasted for five weeks (Weeks 16, 17, 18, 19 and 20) Thereafter, a dosing frequency of Q2W was used (see details below) **Secukinumab 300 mg Q2W arm** • SC injection of secukinumab 300 mg Q2W, between Weeks 6 and 50 • Two additional placebo injections at Weeks 17 and 19 to maintain treatment concealment during re-induction **Secukinumab 300 mg Q4W arm** • SC injection of secukinumab 300 mg Q4W, between Weeks 8 and 48 and SC injection of placebo Q4W, between Weeks 6 and 50 • Three additional placebo injections at Weeks 17, 18 and 19 to maintain treatment concealment during re-induction **Placebo group to secukinumab 300 mg Q2W** • SC injection of placebo Q2W, between Weeks 6 and 14 • At Week 16, following re-induction with secukinumab 300mg once weekly, SC injection of secukinumab 300 mg Q2W, between Weeks 22 and 50 **Placebo group to secukinumab 300 mg Q4W** • SC injection of placebo Q2W, between Weeks 6 and 14 • At Week 16, following re-induction with secukinumab 300mg once weekly, SC injection of secukinumab 300 mg Q4W, between Weeks 24 and 48 • Additional placebo injections between Weeks 22 and 50 to maintain treatment concealment
Permitted and disallowed concomitant therapy	**Permitted concomitant therapy** • Patients were instructed to use daily topical OTC antiseptics or wound care dressings on the skin areas affected by HS lesions following the local standard practice **Permitted concomitant therapy requiring caution and/or action**

	• Antibiotics
	  ○ Systemic antibiotics were permitted for treating acute systemic infections related or unrelated to HS
	  ○ Rescue treatment with systemic antibiotics were permitted during Treatment Period 1
	  ○ Patients in the antibiotic strata were permitted to use a stable dose of systemic antibiotics
	• Analgesics
	  ○ A washout period of 14 days prior to baseline was required for ongoing opioid analgesics
	  ○ Ibuprofen and acetaminophen (paracetamol) were permitted for pain due to uncontrolled HS
	Prohibited medication
	• Use of the following treatments were either washed out or completely disallowed prior to randomisation, and were disallowed completely during the study or until Week 16 (see Appendix M for full criteria for each medication) due to the confounding effects on the efficacy outcomes or because they put patients at an additional safety risk:
	  ○ Prior treatment with secukinumab or other agents blocking IL-17 A/F or IL-17 receptor
	  ○ Systemic biological immunomodulating treatment
	  ○ Systemic non-biologic immunomodulating treatment
	  ○ Topical antibiotic therapies for the treatment of HS
	  ○ Antibiotics for the treatment of HS, except for rescue treatment (non-antibiotic strata)
	  ○ Systemic corticosteroids for the treatment of HS
	For a full list of permitted and disallowed therapies can be found in Appendix M

Primary outcome	Proportion of patients with HiSCR50 at Week 16, defined as a ≥50% decrease in AN count with no increase in the number of abscesses and/or in the number of draining fistulae
Secondary outcomes	• Proportion of patients with HS flares at Week 16, defined as patients who experienced at least one flare over 16 weeks. Flare was defined as at least a 25% increase in AN count with a minimum increase of 2 AN relative to baseline • Participants achieving NRS30 at Week 16, among patients with baseline NRS ≥3. 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 worst skin pain imaginable) • Percentage change from baseline in AN count at Week 16
Pre-specified subgroups	Subgroup variables included: • Age • Gender • Race • Previous use of systemic biologics • CRP levels (<5, ≥5 to <10, ≥10 mg/L), • ESR levels (<20 or ≥20 mm/h) • Hurley stage (I, II, III) • Baseline AN count (≤10 or >10) • Baseline disease duration (<2 years, ≥2 to <5 years, ≥5 to <10 years, ≥10 years)

Abbreviations: AMEA: Asia, Middle East and Africa; AN: abscess and inflammatory nodule; BD: twice a day; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HiSCR: Hidradenitis Suppurativa clinical response; HS: hidradenitis suppurativa; IL-17: interleukin-17; LaCAN: Latin America and Canada; NRS: Numerical Rating Scale; OTC: over-the-counter; Q2W: every two weeks; Q4W: every four weeks; RE: Region Europe; SC: subcutaneous; UK: United Kingdom; US: United States.
Source: Novartis SUNSHINE and SUNRISE Protocol.[93, 94]

B.2.3.3 Baseline characteristics

Demographics and baseline characteristics

Summaries of the demographics and baseline characteristics of patients enrolled in SUNSHINE and SUNRISE are presented in Table 7 and Table 8, respectively.

Overall, demographics and baseline characteristics were broadly consistent across both trials and between the treatment arms in each trial. There were slightly more females than males, most patients were White and between the ages of 30 and 65 years. Approximately half of the patients in both SUNSHINE (54.0%) and SUNRISE (54.0%) were current smokers, with 15.5% and 14.9% of patients having a history of smoking, respectively. Additionally, on average, patients enrolled in both trials were obese, as evidenced by the total baseline body mass index.

Slight imbalances in the age of patients between treatment arms were observed in the SUNRISE trial. The secukinumab Q2W group of SUNRISE had a considerably older population with more patients aged 40–<65 years (42.8%), as compared with the secukinumab Q4W (31.7%) and placebo (32.2%) groups. In contrast, the age of patients in all treatment groups in SUNSHINE were balanced.

Table 7: Demographics and baseline characteristics of patients in SUNSHINE (randomised analysis set)

Characteristics	Secukinumab Q2W (N=181)	Secukinumab Q4W (N=180)	Placebo (N=180)	Total (N=541)
Age groups in years, n (%)				
<30	58 (32.0)	69 (38.3)	51 (28.3)	178 (32.9)
30–<40	56 (30.9)	45 (25.0)	70 (38.9)	171 (31.6)
40–<65	64 (35.4)	63 (35.0)	58 (32.2)	185 (34.2)
≥65	3 (1.7)	3 (1.7)	1 (0.6)	7 (1.3)
Age, years				
Mean (SD)	37.1 (12.5)	35.7 (11.7)	35.5 (10.8)	36.1 (11.7)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]
Gender, n (%)				
Male	79 (43.6)	80 (44.4)	78 (43.3)	237 (43.8)
Female	102 (56.4)	100 (55.6)	102 (56.7)	304 (56.2)
Race, n (%)				
White	145 (80.1)	146 (81.1)	139 (77.2)	430 (79.5)
Black or African American	15 (8.3)	10 (5.6)	12 (6.7)	37 (6.8)
Asian	19 (10.5)	23 (12.8)	24 (13.3)	66 (12.2)

American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Multiple[a]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg[b]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]
Weight groups in kg, n (%)[b]				
<90	82 (45.3)	80 (44.4)	83 (46.1)	245 (45.3)
≥90	99 (54.7)	100 (55.6)	97 (53.9)	296 (54.7)
BMI, kg/m^2 [b]				
n	181	179	180	540
Mean (SD)	32.6 (7.9)	32.8 (7.9)	32.0 (7.1)	32.5 (7.6)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)				
Never	[redacted]	[redacted]	[redacted]	[redacted]
Current	95 (52.5)	96 (53.3)	101 (56.1)	292 (54.0)
Former	26 (14.4)	28 (15.6)	30 (16.7)	84 (15.5)

[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).[96]

Table 8: Demographics and baseline characteristics of patients in SUNRISE (randomised analysis set)

Characteristics	Secukinumab Q2W (N=180)	Secukinumab Q4W (N=180)	Placebo (N=183)	Total (N=543)
Age groups in years, n (%)				
<30	52 (28.9)	60 (33.3)	57 (31.1)	169 (31.1)
30–<40	48 (26.7)	61 (33.9)	65 (35.5)	174 (32.0)
40–<65	77 (42.8)	57 (31.7)	59 (32.2)	193 (35.5)
≥65	3 (1.7)	2 (1.1)	2 (1.1)	7 (1.3)
Age, years				
Mean (SD)	37.3 (11.5)	35.5 (11.4)	36.2 (11.3)	36.3 (11.4)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]

Gender, n (%)				
Male	82 (45.6)	77 (42.8)	78 (42.6)	237 (43.6)
Female	98 (54.4)	103 (57.2)	105 (57.4)	306 (56.4)
Race, n (%)				
White	133 (73.9)	139 (77.2)	143 (78.1)	415 (76.4)
Black or African American	18 (10.0)	19 (10.6)	12 (6.6)	49 (9.0)
Asian	16 (8.9)	16 (8.9)	19 (10.4)	51 (9.4)
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Multiple[a]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)				
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg[b]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]
Weight groups in kg, n (%)[b]				
<90	86 (47.8)	89 (49.4)	92 (50.3)	267 (49.2)
≥90	94 (52.2)	91 (50.6)	91 (49.7)	276 (50.8)
BMI, kg/m^2 [b]				
Mean (SD)	31.9 (7.8)	32.0 (7.5)	31.4 (7.4)	31.8 (7.5)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)				
Never	[redacted]	[redacted]	[redacted]	[redacted]
Current	97 (53.9)	90 (50.0)	106 (57.9)	293 (54.0)
Former	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 SUNRISE CSR (23rd September 2021 data cut-off).[97]

Baseline disease characteristics

The baseline disease characteristics for patients in SUNSHINE and SUNRISE are presented in Table 9 and Table 10, respectively.

Overall, baseline disease characteristics between treatment arms and across both trials were representative of patients with moderate-to-severe HS. The mean time since diagnosis of HS was broadly similar across treatments arms in SUNSHINE and SUNRISE, with a total mean time of 7.1 and 7.4 years, respectively. The mean time since onset of symptoms was [redacted] and [redacted] years, respectively. Of the patients previously exposed to systemic biologic therapy (23.8% and 23.2%), approximately [redacted] (n=[redacted]) and [redacted] (n=[redacted]) of patients received adalimumab in SUNSHINE and SUNRISE, respectively. 82.3% and 83.6% of patients had previous exposure to systemic antibiotics, while 39.9% and 41.6% of patients had prior surgery for HS in SUNSHINE and SUNRISE, respectively.

Slight imbalances in treatment arms with respect to baseline disease severity were observed across both trials. Patients in the secukinumab Q2W groups of SUNSHINE and SUNRISE had more severe HS, as evidenced by the higher proportion of patients with Hurley Stage III disease compared with the secukinumab Q4W and placebo groups. This distribution is also reflected in the higher baseline draining and total fistulae count, abscess count, HS-Physician's Global Assessment (HS-PGA) score, and DLQI score, as compared with the secukinumab Q4W and placebo groups.

Table 9: Baseline patient disease characteristics in SUNSHINE (randomised analysis set)

Characteristics	Secukinumab Q2W (N=181)	Secukinumab Q4W (N=180)	Placebo (N=180)	Total (N=541)
Baseline Hurley stage, n (%)				
I	7 (3.9)	10 (5.6)	8 (4.4)	25 (4.6)
II	104 (57.5)	107 (59.4)	121 (67.2)	332 (61.4)
III	70 (38.7)	63 (35.0)	51 (28.3)	184 (34.0)
Time since HS symptom(s) onset (years)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis of HS (years)				
Mean (SD)	7.4 (8.0)	6.6 (6.7)	7.5 (7.0)	7.1 (7.3)
Baseline AN count				
Mean (SD)	12.9 (9.6)	12.6 (8.4)	12.8 (8.2)	12.8 (8.7)
Baseline inflammatory nodule count				
Mean (SD)	10.1 (7.8)	9.9 (7.6)	10.1 (7.0)	10.0 (7.5)
Baseline abscess count				
Mean (SD)	2.9 (4.3)	2.7 (4.0)	2.7 (3.8)	2.7 (4.0)
Baseline draining fistulae count				
Mean (SD)	2.9 (3.4)	2.5 (3.5)	2.4 (3.2)	2.6 (3.4)
Baseline total fistulae count				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline NRS				
n	163	163	162	488
Mean (SD)	4.5 (2.5)	4.2 (2.5)	4.3 (2.5)	4.3 (2.5)
Baseline HS-PGA, n (%)				
0=Clear	[redacted]	[redacted]	[redacted]	[redacted]

1=Minimal	[redacted]	[redacted]	[redacted]	[redacted]
2=Mild	[redacted]	[redacted]	[redacted]	[redacted]
3=Moderate	[redacted]	[redacted]	[redacted]	[redacted]
4=Severe	[redacted]	[redacted]	[redacted]	[redacted]
5=Very severe	[redacted]	[redacted]	[redacted]	[redacted]
Baseline DLQI total score				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Prior surgery for HS, n (%)				
Yes	71 (39.2)	73 (40.6)	72 (40.0)	216 (39.9)
No	110 (60.8)	107 (59.4)	108 (60.0)	325 (60.1)
Previous exposure to systemic biologic therapy, n (%)				
Yes	44 (24.3)	39 (21.7)	46 (25.6)	129 (23.8)
No	137 (75.7)	141 (78.3)	134 (74.4)	412 (76.2)
Previous exposure to adalimumab, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Previous exposure to systemic antibiotics, n (%)				
Yes	146 (80.7)	149 (82.8)	150 (83.3)	445 (82.3)
No	35 (19.3)	31 (17.2)	30 (16.7)	96 (17.7)

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).[96]

Table 10: Baseline patient disease characteristics in SUNRISE (randomised analysis set)

Characteristics	Secukinumab Q2W (N=180)	Secukinumab Q4W (N=180)	Placebo (N=183)	Total (N=543)
Baseline Hurley stage, n (%)				
I	6 (3.3)	6 (3.3)	3 (1.6)	15 (2.8)
II	92 (51.1)	106 (58.9)	110 (60.1)	308 (56.7)
III	82 (45.6)	68 (37.8)	70 (38.3)	220 (40.5)
Time since HS symptom(s) onset (years)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis of HS (years)				
n	180	180	182	542
Mean (SD)	7.1 (7.0)	8.2 (8.4)	7.0 (6.7)	7.4 (7.4)
Baseline AN count				
Mean (SD)	13.9 (9.9)	13.3 (8.8)	12.8 (8.5)	13.3 (9.1)
Baseline inflammatory nodule count				
Mean (SD)	10.0 (7.7)	10.4 (7.6)	9.6 (6.8)	10.0 (7.4)
Baseline abscess count				
Mean (SD)	3.9 (5.4)	2.9 (4.1)	3.2 (5.0)	3.3 (4.9)

Baseline draining fistulae count				
Mean (SD)	3.0 (3.6)	2.5 (3.5)	2.6 (3.2)	2.7 (3.5)
Baseline total fistulae count				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline NRS				
n	166	163	166	495
Mean (SD)	4.8 (2.4)	4.6 (2.5)	4.7 (2.4)	4.7 (2.4)
Baseline HS-PGA, n (%)				
0=Clear	[redacted]	[redacted]	[redacted]	[redacted]
1=Minimal	[redacted]	[redacted]	[redacted]	[redacted]
2=Mild	[redacted]	[redacted]	[redacted]	[redacted]
3=Moderate	[redacted]	[redacted]	[redacted]	[redacted]
4=Severe	[redacted]	[redacted]	[redacted]	[redacted]
5=Very severe	[redacted]	[redacted]	[redacted]	[redacted]
Baseline DLQI total score				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Prior surgery for HS, n (%)				
Yes	78 (43.3)	70 (38.9)	78 (42.6)	226 (41.6)
No	102 (56.7)	110 (61.1)	105 (57.4)	317 (58.4)
Previous exposure to systemic biologic therapy, n (%)				
Yes	36 (20.0)	42 (23.3)	48 (26.2)	126 (23.2)
No	144 (80.0)	138 (76.7)	135 (73.8)	417 (76.8)
Previous exposure to adalimumab, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Previous exposure to systemic antibiotics, n (%)				
Yes	151 (83.9)	152 (84.4)	151 (82.5)	454 (83.6)
No	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 SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Trial populations

The definitions of the study populations in the SUNSHINE and SUNRISE trials are presented in Table 11.

All randomised patients in the SUNSHINE (N=541) and SUNRISE (N=543) trials in Treatment Period 1 were included in the Randomised, Full and Safety analysis sets, with no differences in

patient numbers in each analysis set. During the Entire study period, patients in the placebo groups who discontinued in Treatment Period 1 and did not receive secukinumab were excluded from the patient numbers in the Randomised, Full and Safety analysis sets of the SUNSHINE ([redacted]) and SUNRISE ([redacted]) trials, with no differences in patient numbers in each analysis set.

The number of patients in each analysis set in Treatment Period 1 and the Entire study period of the SUNHINE and SUNRISE trials stratified by treatment arm are presented in Appendix M.

Table 11: Trial populations used for the analysis of endpoints of the SUNSHINE and SUNRISE trials

Analysis set	Definition
Randomised analysis set	Included all randomised patients. Patients were analysed according to the treatment they were assigned to at randomisation.
Full analysis set	Included all patients to whom study treatment had been assigned. Patients were analysed according to the treatment they were assigned to at randomisation.
Safety analysis set	Included all patients who received ≥1 dose of study treatment. Patients were analysed according to the study treatment received.

Source: Novartis SUNSHINE and SUNRISE Protocol.[93, 94]

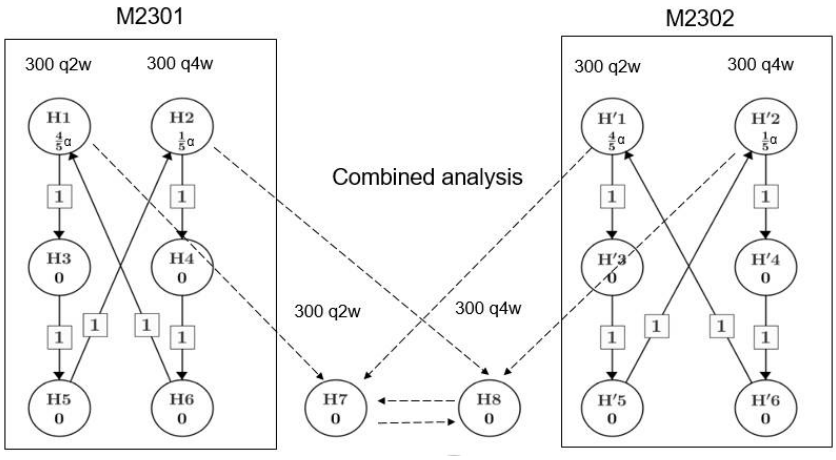
B.2.4.2 Statistical methods

The statistical analyses used to analyse the primary endpoint (HiSCR50 response at Week 16), alongside sample size calculations and methods for handling missing data, are presented in Table 14.

Table 12: Statistical methods for the primary analysis of the SUNSHINE and SUNRISE trials

Hypothesis objective	**Primary endpoint** • Null hypothesis 1 (H_1): secukinumab 300 mg Q2W SC is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment • Null hypothesis 2 (H_2): secukinumab 300 mg Q4W SC is not different to placebo regimen with respect to HiSCR after 16 weeks of treatment **Secondary endpoints** • Null hypothesis 3 (H_3): secukinumab 300 mg Q2W SC is not different to placebo regimen with respect to percentage change from baseline in AN count at Week 16 • Null hypothesis 4 (H_4): secukinumab 300 mg Q4W SC is not different to placebo regimen with respect to percentage change from baseline in AN count at Week 16 • Null hypothesis 5 (H_5): secukinumab 300 mg Q2W SC is not different to placebo regimen with respect to flare over 16 weeks of treatment • Null hypothesis 6 (H_6): secukinumab 300 mg Q4W SC is not different to placebo regimen with respect to flare over 16 weeks of treatment • Null hypothesis 7 (H_7): secukinumab 300 mg Q2W SC is not different to placebo regimen with respect to NRS30 at Week 16 • Null hypothesis 8 (H_8): secukinumab 300 mg Q4W SC is not different to placebo regimen with respect to NRS30 at Week 16

	As outlined below, H_1 to H_6 were analysed by trial, whereas the pooling of data for H_7 and H_8 across the SUNSHINE and SUNRISE trials for analysis was pre-planned.
Statistical analysis	• The SUNSHINE and SUNRISE trials were of identical design and conducted in parallel with the same sample sizes. The studies were independently powered to address the primary endpoint (HiSCR50 response) and secondary endpoint on percentage change in AN count and flare. The secondary endpoint of Pain/NRS30 at Week 16 was tested using combined data from the two studies in a pre-planned pooled analysis • The primary analysis method was logistic regression with treatment group, geographical region, Hurley stage, use of antibiotic, baseline body weight and baseline AN count as explanatory variables. Odds ratios were computed for comparisons of secukinumab dose regimens versus placebo utilising the logistic regression model fitted • In order to control for the type-I error rate ("false positive rate") at the level of the individual studies, and at the level of the combined dataset of both studies, a hierarchical testing strategy was implemented as presented in Figure 4 ○ The efficacy of the two secukinumab regimens compared with placebo with respect to HiSCR after 16 weeks of treatment could be demonstrated if H_1 and/or H_2 was/were rejected, and the treatment effect was in favour of secukinumab ○ The efficacy of the two secukinumab regimens compared with placebo with respect to percentage change from baseline in AN count at Week 16 could be demonstrated if H_3 and/or H_4 was/were rejected, and the treatment effect was in favour of secukinumab ○ The efficacy of the two secukinumab regimens compared with placebo with respect to flare over 16 weeks could be demonstrated if H_5 and/or H_6 was/were rejected, and the treatment effect was in favour of secukinumab ○ The efficacy of the two secukinumab regimens compared with placebo with respect to Pain/NSR30 at Week 16 could be demonstrated if H_7 and/or H_8 was/were rejected, and the treatment effect was in favour of secukinumab • Using this testing procedure and under the global null hypothesis (that there is no difference between secukinumab and placebo), type I error rate (one-sided) was controlled at the study-level to <0.025, and at the submission level to <0.000625 ($=0.025^2$). Considering all possible configurations of true and false null hypotheses, the type I error control at the level of the submission was <0.000625 for the primary objectives, and <0.025 for all hypotheses

	Figure 4: Hierarchical testing strategy of the SUNSHINE (M2301) and SUNRISE (M2302) studies  Hypotheses were tested only in the order indicated by the arrows.

Sample size, power calculation	• The sample size requirements for this study were primarily driven by HiSCR at the Week 16 timepoint
	• A 5% two-sided type I error rate was used. Two secukinumab doses were tested versus placebo with respect to the primary endpoint (HiSCR50 at Week 16). The type I error was split to 4% and 1% two-sided for secukinumab 300 mg Q2W versus placebo and secukinumab 300 mg Q4W versus placebo, respectively. Sample sizes were based on this type I error assumption
	• Each trial originally aimed to randomise approximately 471 patients to study drug or placebo in a 1:1:1 ratio. However, to account for disruptions due to the COVID-19 pandemic on the conduct of the study, an amendment to the protocol permitted an increase to approximately 541 patients (a 15% increase compared with the original trial population). This was done in order to ensure the originally planned power in the statistical test procedure was maintained
	  ○ The original total sample size of 471 patients per trial was sufficient to achieve 93% power for the demonstration of 20% difference of secukinumab 300 mg Q2W over placebo based on the primary endpoint (HiSCR) when assuming a secukinumab response rate to be 50%. The placebo response rate of 30% was assumed based on the Phase III placebo-controlled trials of adalimumab, PIONEER I and PIONEER II[91]
	  ○ For the comparison of secukinumab 300 mg Q4W to placebo, the original total sample size was sufficient to achieve 83% power for demonstration of superiority

Data management, patient withdrawals	**Patient withdrawals**
	• Patients were withdrawn from the study for any of the following reasons:
	  ○ Withdrawal of informed consent
	  ○ Lost to follow-up
	  ○ Sponsor terminates the study
	• A patient was not considered lost to follow-up until the investigator had shown due diligence in trying to contact them, such as via telephone calls or letters, with all measures taken to follow-up with the patient documented

	• When a patient withdrew before completing the study, the investigator had to make a reasonable effort, such as telephone calls and letters, to understand and record the primary reason for the patient's decision to withdraw consent • The study treatment assigned to a withdrawn patient was discontinued and the data that would have been collected at subsequent visits was considered missing **Missing data** • Missing data for primary and secondary endpoints were addressed using multiple imputation based on the estimand strategy related to intercurrent events or missing at random assumption for all missing values not related to intercurrent events. The intercurrent events considered were: 1. **Intake of prohibited medication or treatment** (medication/treatment with possible confounding effect defined as biologics if taken more than once, antibiotics in the nonantibiotic stratum if taken over a period of more than 14 days, or any major HS-related surgery for HS other than allowed as a rescue therapy). Such events were ignored, all observed values were considered, and missing data were multiply imputed using a reference-based approach for the secukinumab groups and based on missing at random assumption for the placebo arm. 2. **Intake of rescue medication.** A composite strategy was applied; if such an event (intake of rescue antibiotics) occurred, the subject was considered as a non-responder. 3. **Permanent discontinuation of study treatment due to adverse events or lack of efficacy.** A composite strategy was applied in the same way as described under 'intake of rescue medication'. 4. **Permanent discontinuation of study treatment due to reasons other than adverse events or lack of efficacy.** A hypothetical strategy was applied; any observation after such an event was discarded and imputed via multiple imputation under the MAR assumption. 5. **COVID-19 related intercurrent events** (missed at least one dose prior to Week 16 due to COVID-19 *or* discontinued treatment prior to Week 16 due to COVID-19). A treatment policy strategy was applied in the same way as described under 'Intake of prohibited medication or treatment'. • As the primary endpoint was a binary outcome derived from underlying continuous variables, the imputations were performed on those continuous variables. In this analysis, the number of abscesses, inflammatory nodules, and draining fistulae were imputed and the response variable were derived based on the imputed values.

Abbreviations: HiSCR: Hidradenitis Suppurativa clinical response; MAR: missing at random; NRS: Numerical Rating Scale; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE and SUNRISE Protocols and CSRs.[93, 94, 96, 97]

B.2.4.3 Participant flow in the relevant randomised controlled trials

Summaries of patient flow in the SUNSHINE and SUNRISE trials are presented in Appendix D.

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

RCTs captured in the clinical SLR were assessed for quality using the NICE clinical effectiveness quality assessment checklist. The results of these quality assessments are presented in Appendix D, and a summary of the quality assessments for the SUNSHINE and SUNRISE trials is presented in Table 13.

Table 13: Quality assessment of the two identically designed Phase III SUNSHINE and SUNRISE trial

	SUNSHINE and SUNRISE	
	Response	**Risk of bias**
Was randomisation carried out appropriately?	Yes. Following confirmation that a patient met the selection criteria, the IRT was contacted to assign a randomisation number to the patient, which was used to link the patient to a treatment arm. A patient randomisation list was produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomisation numbers.	Low
Was the concealment of treatment allocation adequate?	Yes. The randomisation numbers were generated using the IRT to ensure that treatment assignment was unbiased and concealed from patients and investigator staff.	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographics (age, gender, race, weight, BMI, smoking status) and baseline characteristics (Hurley stage, HS duration, severity, lesion counts, prior surgery, antibiotics and biologics) of randomised patients were broadly consistent across the secukinumab Q2W, secukinumab Q4W and placebo groups.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes. Patients, investigator staff, persons performing the assessments, and the Novartis clinical trial team remained blinded to the identity of the treatment from the time of randomisation until database lock with the exception of Drug Supply Management and specific vendors whose roles required unblinding (e.g., IRT).	Low
Were there any unexpected imbalances in drop-outs between groups?	No. 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.	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All prespecified efficacy and safety outcomes were measured and reported.	Low

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Outcomes were analysed using the randomised analysis set which consisted of all randomised patients. Patients were analysed according to the treatment they were assigned to at randomisation. Unless otherwise specified, mis-randomised subjects (mis-randomised in IRT) were excluded from the randomised analysis set. Missing data for primary and secondary endpoints were addressed using the multiple imputation method.	Low

Abbreviations: BMI: body mass index; HS: hidradenitis suppurativa; IRT: interactive response technology; Q2W: every two weeks; Q4W: every four weeks.

B.2.6 *Clinical effectiveness results of the relevant studies*

Summary of clinical effectiveness results

- Treatment with secukinumab 300 mg Q4W resulted in a greater proportion of patients achieving HiSCR50 as compared with placebo in both SUNSHINE and SUNRISE; however, statistical significance was only met in the SUNRISE trial. Treatment with secukinumab 300 mg Q2W was associated with a statistically significantly higher proportion of patients achieving HiSCR50 at Week 16, as compared with placebo in both trials
- Available long-term efficacy data between Weeks 16 and 52 at the primary endpoint analysis of SUNSHINE and SUNRISE demonstrated a consistent and progressive trend of increasing responses over time with respect to HiSCR50 in the secukinumab Q4W and Q2W groups
- Regarding secondary endpoints, data pooled from the SUNSHINE and SUNRISE trials demonstrated a greater reduction in skin pain (NRS30) in the secukinumab Q4W group as compared with placebo, but statistical significance was not met. A significant reduction in skin pain (NRS30) was observed in the secukinumab Q2W group, as compared with placebo.
- A greater decrease in AN count was observed across both Q4W and Q2W groups of SUNSHINE and SUNRISE, as compared with placebo. However, results were significant for the Q4W group in SUNRISE only and the Q2W groups in both trials
- Fewer patients experienced HS flares in the Q4W and Q2W groups of SUNSHINE and SUNRISE. However, results were significant only for the Q4W group of SUNRISE and the Q2W group of SUNSHINE
- Sustained improvements in all secondary endpoints were observed beyond Week 16 through to Week 52 in SUNSHINE and SUNRISE
- Patients in the secukinumab Q4W and Q2W groups also reported better HRQoL compared with placebo, as assessed by DLQI and EQ-5D-3L VAS at Week 16, with sustained improvements seen beyond Week 16 through to Week 52

The anticipated licensed posology based on EMA feedback for secukinumab in moderate-to-severe HS is 300 mg Q4W, with the possibility to up-titrate to Q2W. As such, results for the secukinumab 300 mg Q4W and the 300 mg Q2W dosing regimens in SUNSHINE and SUNRISE are presented below.[96, 97]

The primary and secondary endpoints were evaluated at Week 16 before patients in the placebo group were re-randomised to either of the secukinumab treatment arms (see Section B.2.3.1). This timepoint was chosen because 16 weeks was considered to represent the maximal acceptable duration of treatment exposure to placebo in this indication.

B.2.6.1 HiSCR50 response

HiSCR50 at Week 16

The primary efficacy endpoint, Hidradenitis Suppurativa Clinical Response (HiSCR), was developed and validated in the context of the development program of adalimumab in HS. HiSCR is considered to be adequately described and validated for use as the primary efficacy endpoint in pivotal studies and has already been the basis for the European Medicines Agency (EMA) approval of adalimumab for treating moderate-to-severe HS.[2]

At Week 16, the primary efficacy endpoint was met for the secukinumab Q2W group in both trials, and by the Q4W group in the SUNRISE trial, as presented in Table 14 and Table 15, respectively. A HiSCR50 response was achieved by more patients in the secukinumab Q2W and secukinumab Q4W groups than in the placebo groups in the SUNSHINE (45.0% and 41.8% versus 33.7%, respectively) and SUNRISE trials (42.3% and 46.1% versus 31.2%, respectively). This difference was statistically significant for the secukinumab 300 mg Q2W group in SUNSHINE (OR: 1.75; CI 95%: 1.12, 2.73; p=0.0070) and both the Q2W and Q4W groups in SUNRISE (Q2W: OR: 1.64; 95% CI: 1.05, 2.55; p=0.0149; Q4W: OR: 1.90; 95% CI: 1.22, 2.96; p=0.0022).

Table 14: Proportion of patients in SUNSHINE achieving HiSCR50 at Week 16 (Full analysis set)

HiSCR50 at Week 16	Placebo	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W
Response, n*/m (%)	60.7/180 (33.7)	81.5/181 (45.0)	75.2/180 (41.8)
Odds ratio vs placebo (95% CI)		1.75 (1.12, 2.73)	1.48 (0.95, 2.32)
One-sided p-value		0.0070**	0.0418

n* = rounded average number of patients with response in 100 imputations. m = number of patients evaluable. Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.
** Statistically significant based on the pre-defined testing hierarchy.
Abbreviations: CI: confidence interval; HiSCR: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; vs: versus.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

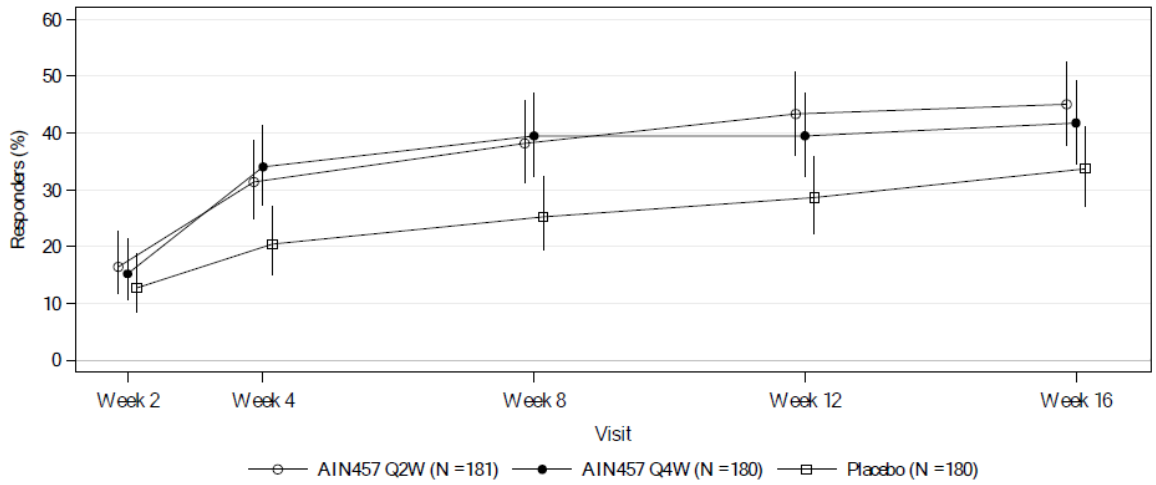
Table 15: Proportion of patients in SUNRISE achieving HiSCR50 at Week 16 (Full analysis set)

HiSCR50 at Week 16	Placebo	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W
Response, n*/m (%)	57.1/183 (31.2)	76.2/180 (42.3)	83.1/180 (46.1)
Odds ratio vs placebo (95% CI)		1.64 (1.05, 2.55)	1.90 (1.22, 2.96)
One-sided p-value		0.0149**	0.0022**

n* = rounded average number of patients with response in 100 imputations. m = number of patients evaluable. Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.
** Statistically significant based on the pre-defined testing hierarchy.
Abbreviations: CI: confidence interval; HiSCR: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; vs: versus.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

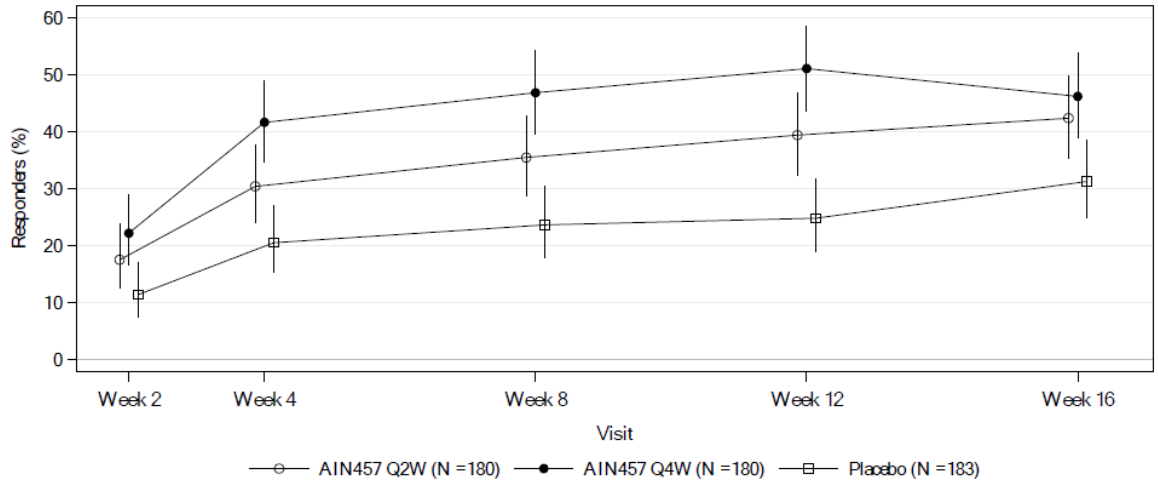
The proportion of patients achieving a HiSCR50 response each week up to Week 16 in SUNSHINE and SUNRISE is presented in Figure 5 and Figure 6, respectively. In both trials, the onset of response was rapid for both secukinumab Q2W groups, with a clear differentiation from the placebo groups observed as early as Week 4 for SUNSHINE (31.4% versus 20.4%) and Week 2 for SUNRISE (17.4% versus 11.3%). Similarly, in the secukinumab Q4W groups, the onset of response was rapid across both trials, with differentiation also observed at Week 4 for SUNSHINE (34.0% versus 20.4%) and Week 2 for SUNRISE (22.1% versus 11.3%). Response rates were sustained at all timepoints from Week 4 up to Week 16 in SUNSHINE, while greater response rates were observed in SUNRISE from Week 2 to Week 16.

Figure 5: HiSCR50 responders up to Week 16 in SUNSHINE (mean response rate with 95 CI%; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: HiSCR: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 6: HiSCR responders up to Week 16 in SUNRISE (mean response rate with 95 CI%; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: HiSCR: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

HiSCR up to Week 52 (primary endpoint analysis data cut-off: SUNSHINE: 1st October 2021; SUNRISE: 23rd September 2021)

At the primary endpoint analysis data cut-off, [redacted] ([redacted]) and [redacted] ([redacted]) patients had completed the entire treatment period (Week 52), respectively. With respect to the secukinumab Q2W group, [redacted] ([redacted] and [redacted] ([redacted]) of patients had completed the entire treatment period in SUNSHINE and SUNRISE, respectively. Regarding the secukinumab Q4W group, [redacted] ([redacted]) of patients in SUNSHINE and [redacted] ([redacted]) of patients in SUNRISE completed the entire treatment period.

Available observed long-term data up to Week 52 in SUNSHINE and SUNRISE at the time of the primary analysis are presented in Table 16, Figure 7 and Figure 8. Results from both trials show a consistent and progressive trend of increasing responses over time with respect to HiSCR50 in the secukinumab Q2W and Q4W groups.

Table 16: HiSCR50 responders to secukinumab 300 mg Q2W and to secukinumab 300 mg Q4W up to Week 52 by visit in SUNSHINE and SUNRISE at the time of the primary endpoint analysis (observed data; full analysis set)

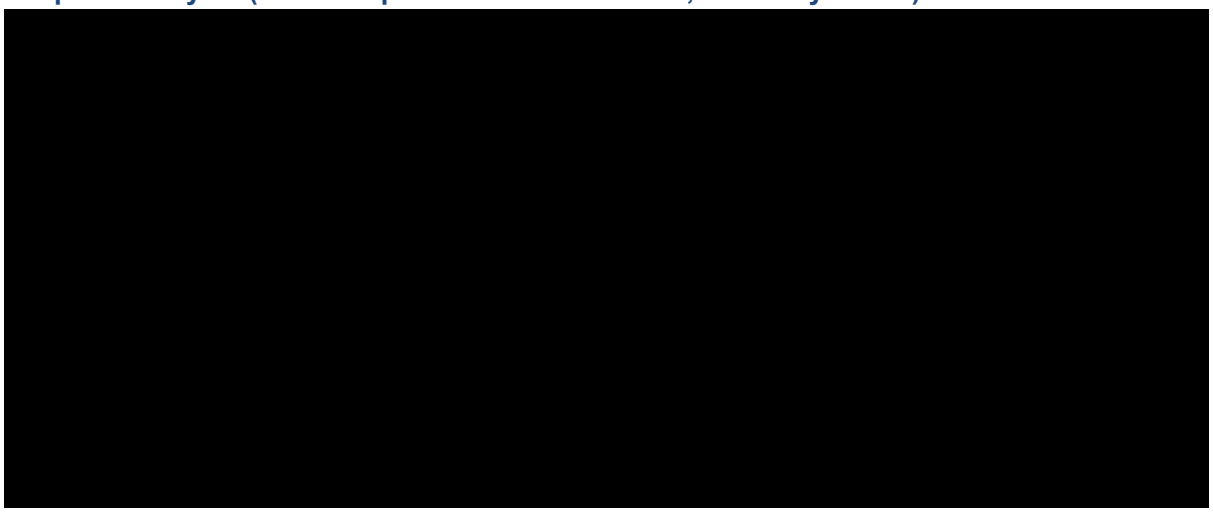
Visit	HiSCR50 response, %			
	SUNSHINE		SUNRISE	
	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (n=180)	Secukinumab 300 mg Q2W (n=180)	Secukinumab 300 mg Q4W (n=180)
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HiSCR50: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

Figure 7: HiSCR50 responders up to Week 52 in SUNSHINE at the time of the primary endpoint analysis (mean response rate with 95% CI; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: HiSCR: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 8: HiSCR50 responders up to Week 52 in SUNRISE at the time of the primary endpoint analysis (mean response rate with 95% CI; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: HiSCR: Hidradenitis Suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.6.2 AN count

AN count, number of flares (Section B.2.6.3) and reduction in skin pain (Section B.2.6.4) were selected as secondary endpoints due to their impact on patient's QoL. These endpoints provided complementary clinically relevant information not fully evaluated by HiSCR.

Percentage change from baseline in AN count at Week 16

At Week 16, only the secukinumab Q2W group was superior to placebo with respect to change from baseline in AN count in SUNSHINE (Table 17). However, both secukinumab Q4W and Q2W groups were superior to placebo in SUNRISE (Table 18).

The mean percentage change from baseline in AN count was clinically relevant and numerically higher in the secukinumab Q2W groups compared with the placebo groups (−46.8 and −39.3 versus −24.3 and −22.4) in SUNSHINE and SUNRISE, respectively. Similar results were observed in the secukinumab Q4W groups compared with placebo (−42.4 and −45.5 versus −24.3 and −22.4) in SUNSHINE and SUNRISE respectively. Statistical significance based on the pre-defined testing hierarchy was only achieved for secukinumab Q2W in SUNSHINE (Least Squares [LS] Mean difference versus placebo of −23.05 and −18.46, one-sided p<0.0001), but was in favour of both secukinumab Q2W and Q4W groups in SUNRISE (Least Squares [LS] Mean difference versus placebo of −16.33 and −22.94, one-sided p=0.0051 and p=0.0001, respectively).

Table 17: Percentage change from baseline in AN count at Week 16 in SUNSHINE (multiple imputation; full analysis set)

Percentage change in AN count at Week 16	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)
Mean (SE)	−24.3 (4.33)	−46.8 (3.33)	−42.4 (4.01)
LS Mean difference estimate (95% CI)		−23.05 (−33.90, −12.21)	−18.46 (−29.32, −7.60)
One-sided p-value		<0.0001**	0.0004

The Mean is the pooled mean over 100 imputations. SE is the pooled standard error over 100 imputations. Covariates included in the model: treatment group, geographical region, Hurley stage, use of antibiotic, baseline body weight and baseline AN count.
**Statistically significant based on the pre-defined testing hierarchy
Abbreviations: AN: abscess and inflammatory nodule; CI: confidence interval; Q2W: every two weeks; Q4W: every four weeks; SE: standard error.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Table 18: Percentage change from baseline in AN count at Week 16 in SUNRISE (multiple imputation; full analysis set)

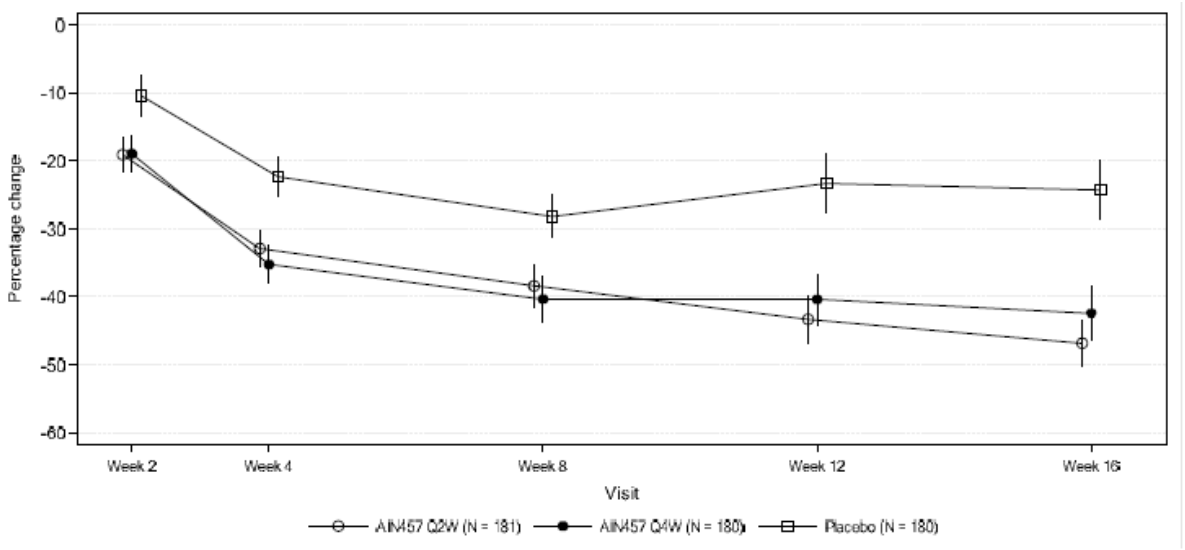
Percentage change in AN count at Week 16	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Mean (SE)	−22.4 (4.84)	−39.3 (4.43)	−45.5 (4.08)
LS Mean difference estimate (95% CI)		−16.33 (−28.79, −3.88)	−22.94 (−35.24, −10.63)
One-sided p-value		0.0051**	0.0001**

The Mean is the pooled mean over 100 imputations. SE is the pooled standard error over 100 imputations. Covariates included in the model: treatment group, geographical region, Hurley stage, use of antibiotic, baseline body weight and baseline AN count.
**Statistically significant based on the pre-defined testing hierarchy
Abbreviations: AN: abscess and inflammatory nodule; CI: confidence interval; Q2W: every two weeks; Q4W: every four weeks; SE: standard error.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

The percentage change from baseline in AN count by week and treatment groups is presented in Figure 9 and Figure 10. In SUNSHINE and SUNRISE, decrease from baseline in AN count was rapid in both secukinumab Q2W groups, with clear differentiation from the placebo groups as early as Week 2 (−19.1 [SE: [redacted]] and −19.1 [SE: [redacted]] versus −10.4 [SE: [redacted]] and −12.2 [SE: [redacted]], respectively). A greater decrease in AN count was observed for both secukinumab Q2W

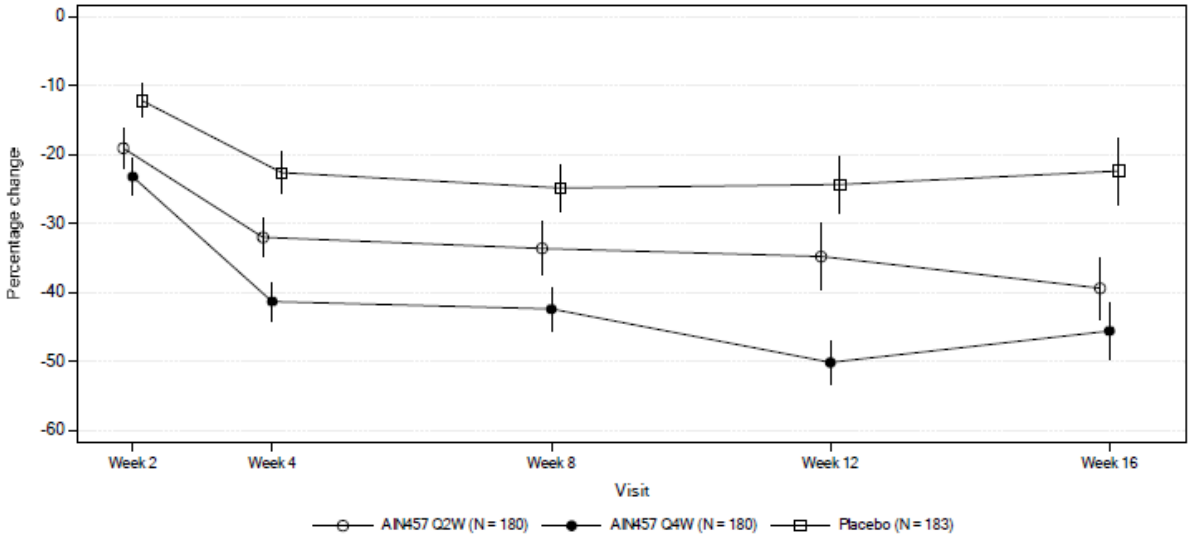
groups compared with the placebo groups from Week 2 to Week 16. Similar results were also observed as early as Week 2 for both secukinumab Q4W groups compared with placebo in the SUNSHINE and SUNRISE trials (−19.0 [SE: [redacted]] and −23.2 [SE: [redacted]], versus −10.4 [SE: [redacted]] and −12.2 [SE: [redacted]], respectively).

Figure 9: Percentage change from baseline in AN count at Week 16 in SUNSHINE (mean ± SE) (multiple imputation; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: AN: abscess and inflammatory nodule; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 10: Percentage change from baseline in AN count at Week 16 in SUNRISE (mean ± SE) (multiple imputation; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: AN: abscess and inflammatory nodule; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

Percentage change from baseline in AN count up to Week 52 (primary endpoint analysis data cut-off: SUNSHINE: 1st October 2021; SUNRISE: 23rd September 2021)

Available observed long-term data up to Week 52 in SUNSHINE and SUNRISE are presented in Figure 11 and Figure 12. Results from both trials show a consistent and progressive trend of

increasing responses over time with respect to AN count in both the secukinumab Q2W and Q4W groups.

Figure 11: Percentage change from baseline in AN count up to Week 52 in SUNSHINE at the time of the primary endpoint analysis (mean ± SE) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: AN: abscess and inflammatory nodule; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 12: Percentage change from baseline in AN count up to Week 52 in SUNRISE at the time of the primary endpoint analysis (mean ± SE) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: AN: abscess and inflammatory nodule; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.6.3 HS flares

Proportion of patients with HS flares at Week 16

At Week 16, the proportion of patients with flares in secukinumab Q2W groups was lower than the placebo groups in SUNSHINE and SUNRISE (15.4% and 20.1% versus 29.0% and 27.0%, respectively). However, the estimated odds ratio was only statistically significant for the secukinumab Q2W group in SUNSHINE (one-sided p=0.0010; SUNRISE: p=0.0732). Similarly, at Week 16, the proportion of patients with flares in secukinumab Q4W groups was lower than the placebo groups in SUNSHINE and SUNRISE (23.2% and 15.6% versus 29.0% and 27.0%, respectively). The estimated odds ratio at this dosing regimen was statistically significant only for

the secukinumab Q4W group in SUNRISE (one sided p=0.0049; SUNSHINE: p=0.0926). These results are presented in Table 19 and Table 20 below.

Table 19: Proportion of patients with HS flares at Week 16 in SUNSHINE (multiple imputation; full analysis set)

HS flares at Week 16	Placebo	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W
Response, n*/m (%)	52.2/180 (29.0)	27.8/181 (15.4)	41.7/180 (23.2)
Odds ratio estimate (95% CI)		0.42 (0.25, 0.73)	0.71 (0.43, 1.17)
One-sided p-value		0.0010**	0.0926

n* = rounded average number of patients with response in 100 imputations. m = number of patients evaluable. Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.
**Statistically significant based on the pre-defined testing hierarchy.
Abbreviations: CI: confidence interval; HS: Hidradenitis Suppurativa; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

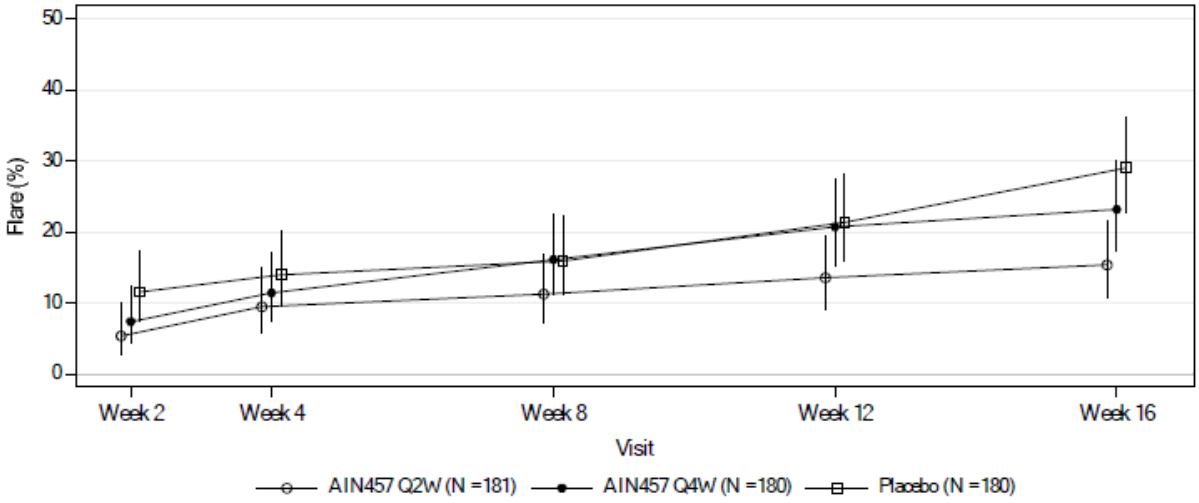
Table 20: Proportion of patients with HS flares at Week 16 in SUNRISE (multiple imputation; full analysis set)

HS flares at Week 16	Placebo	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W
Response, n*/m (%)	49.5/183 (27.0)	36.1/180 (20.1)	28.0/180 (15.6)
Odds ratio estimate (95% CI)		0.68 (0.41, 1.14)	0.49 (0.29, 0.84)
One-sided p-value		0.0732	0.0049**

n* = rounded average number of patients with response in 100 imputations. m = number of patients evaluable. Covariates included in the model: treatment group, Hurley stage, baseline AN count, geographical region, use of antibiotic, baseline body weight.
**Statistically significant based on the pre-defined testing hierarchy.
Abbreviations: CI: confidence interval; HS: Hidradenitis Suppurativa; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

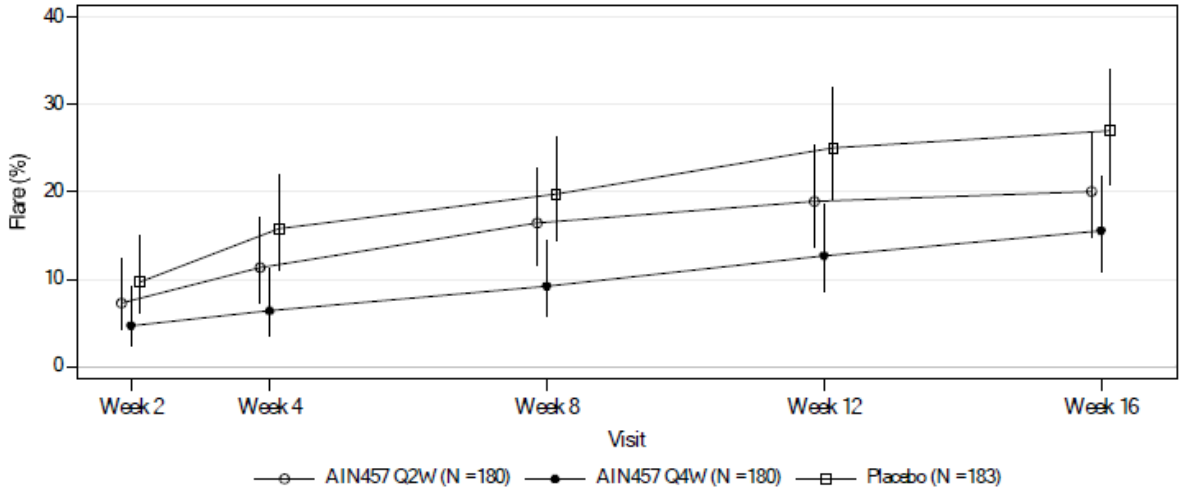
The proportion of patients with flares by visit up to Week 16 in SUNSHINE and SUNRISE is presented in Figure 13 and Figure 14. Greater treatment effects were observed in both secukinumab dosing groups compared with the placebo groups in SUNSHINE and SUNRISE at all timepoints beginning at Week 2 (Q2W: 5.4% and 7.3% versus 11.6% and 9.7%, respectively; Q4W: 7.4% and 4.7% versus 11.6% and 9.7%, respectively) until Week 16.

Figure 13: Proportion of patients with HS flares up to Week 16 in SUNSHINE (mean response rate with 95% CI) (multiple Imputation; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: HS: Hidradenitis Suppurativa; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 14: Proportion of patients with HS flares up to Week 16 in SUNRISE (mean response rate with 95% CI) (multiple Imputation; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: HS: Hidradenitis Suppurativa; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

HS flares up to Week 52 (primary endpoint analysis data cut-off: SUNSHINE: 1st October 2021; SUNRISE: 23rd September 2021)

Available observed long-term data up to Week 52 in SUNSHINE and SUNRISE at the primary analysis data cut-off are presented in Table 21. Results from both trials show a consistently lower percentage of patients experiencing flares in the secukinumab Q2W and Q4W groups.

Table 21: Proportion of patients with HS flares in the secukinumab 300 mg Q2W group and the secukinumab 300 mg Q4W group up to Week 52 by visit in SUNSHINE and SUNRISE at the time of the primary endpoint analysis (observed data; full analysis set)

Visit	HS flares, (%)			
	SUNSHINE		SUNRISE	
	Secukinumab Q2W 300 mg (N=181)	Secukinumab Q4W 300 mg (N=180)	Secukinumab Q2W 300 mg (N=180)	Secukinumab Q4W 300 mg (N=180)
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HS: Hidradenitis Suppurativa; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

B.2.6.4 NRS30

Patients achieving NRS30 (skin pain) at Week 16

The primary analysis of Numerical Rating Scale score of 30 (NRS30; skin pain) at Week 16 based on the pooled data from SUNSHINE and SUNRISE, which consisted of patients with NRS≥3 at baseline, is presented in Table 22.

The secukinumab Q2W dosing regimen was superior to placebo with respect to NRS30 response at Week 16 (38.9% versus 26.9%; one-sided p=0.0031), based on the pre-defined testing hierarchy. The NRS30 response in the secukinumab Q4W group at Week 16 was numerically higher than placebo, but statistical significance was not met (35.8% versus 26.9%; one-sided p=0.0249).

Table 22: NRS30 responders at Week 16 in pooled data from SUNSHINE and SUNRISE (multiple imputation; full analysis set)

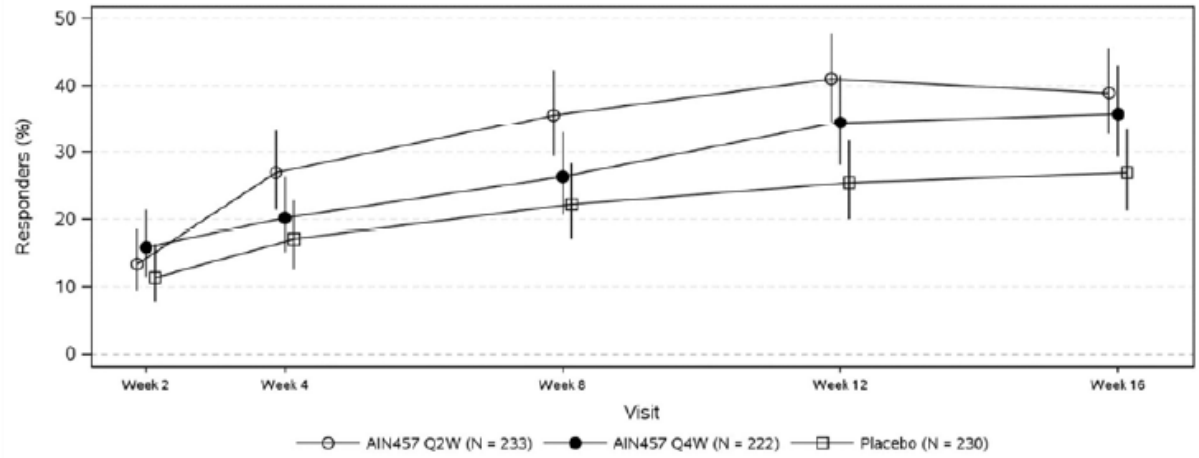
NRS30 (skin pain) at Week 16	Placebo	Secukinumab 300 mg Q2W	Secukinumab 300 mg Q4W
Response, n*/m (%)	61.9/230 (26.9)	90.8/233 (38.9)	79.4/222 (35.8)

Odds ratio estimate (95% CI)		1.80 (1.18, 2.74)	1.54 (1.00, 2.38)
One-sided p-value		0.0031**	0.0249

n* = rounded average number of patients with response in 100 imputations. m = number of patients evaluable. Covariates included in the model: treatment group, Hurley stage, baseline NRS, geographical region, use of antibiotic, baseline body weight, study. NRS is the numeric rating scale of the Patient's Global Assessment of Skin Pain - at worst (averaged over the last 7 days). Only patients with a baseline NRS≥3 are included. NRS30 is defined as at least 30% reduction and at least 2-unit reduction from baseline NRS.
**Statistically significant based on the pre-defined testing hierarchy.
Abbreviations: CI: confidence interval; NRS: Numerical Rating Scale; Q2W: every two weeks; Q4W: every four weeks
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).

The proportion of patients achieving NRS30 by week up to Week 16 is presented in Figure 15. A greater treatment effect was achieved with the secukinumab Q2W regimen compared with both the Q4W dosing regimen and the placebo, beginning as early as Week 4 and was sustained up to Week 16.

Figure 15: NRS30 responders up to Week 16 in pooled data from SUNSHINE and SUNRISE (multiple imputation; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: NRS: Numerical Rating Scale; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).

NRS30 up to Week 52 (primary endpoint analysis data cut-off: SUNSHINE: 1st October 2021; SUNRISE: 23rd September 2021)

Available observed long-term data up to Week 52 in pooled data from SUNSHINE and SUNRISE at the primary analysis are presented in Table 23 and Figure 16. Results from pooled analysis show a consistent and progressive trend of increasing responses over time with respect to NRS30 in both the secukinumab Q2W and Q4W groups.

Table 23: NRS30 responders up to Week 52 by visit in pooled data from SUNSHINE and SUNRISE at the time of the primary endpoint analysis (observed data; full analysis set)

Visit	NRS30 responders, (%)	
	Secukinumab 300 mg Q2W (N=[redacted])	Secukinumab 300 mg Q4W (N=[redacted])
Week 2	[redacted]	[redacted]

Week 4	[redacted]	[redacted]
Week 8	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 18	[redacted]	[redacted]
Week 20	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 28	[redacted]	[redacted]
Week 32	[redacted]	[redacted]
Week 36	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Week 44	[redacted]	[redacted]
Week 48	[redacted]	[redacted]
Week 52	[redacted]	[redacted]

Abbreviations: NRS: Numerical Rating Scale; Q2W: every two weeks.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

Figure 16: NRS responders up to Week 52 in pooled data from SUNSHINE and SUNSHINE at the time of the primary endpoint analysis (mean response rate with 95% CI) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: NRS: Numerical Rating Scale; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

B.2.6.5 DLQI

DLQI at Week 16

Mean DLQI total score decreased at Week 2 and Week 4 and then remained relatively stable up to Week 16 in both secukinumab dose regimens (Figure 17 and Figure 18). A greater and clinically meaningful decrease from baseline in DLQI total score was observed for secukinumab Q2W at all timepoints up to Week 16 compared with placebo (Q2W: [redacted] and [redacted] versus [redacted] and [redacted], respectively; Q4W: [redacted] and [redacted] versus [redacted] and [redacted], respectively).

Figure 17: DLQI (total score) up to Week 16 in SUNSHINE (mean ± SE) (observed data; full analysis set)

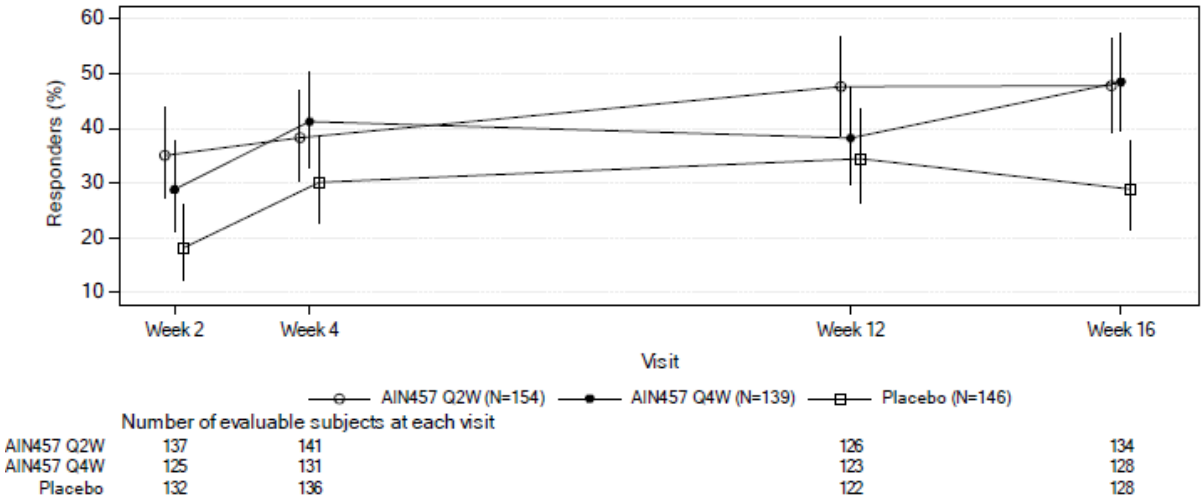
AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 18: DLQI (total score) up to Week 16 in SUNRISE (mean ± SE) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

The treatment effect with secukinumab with respect to DLQI responder rate (a decrease greater than 5.0 points from baseline) was evident as early as Week 2 in SUNSHINE and Week 4 in SUNRISE (Figure 19 and Figure 20). These effects were sustained up to Week 16 in both trials. Greater response rates were observed in both secukinumab Q2W and Q4W groups compared with the placebo groups in SUNSHINE and SUNRISE (Q2W: 47.8% and 37.5% versus 28.9% and 31.7%, respectively; Q4W: 48.4% and 47.2% versus 28.9% and 31.7%, respectively).

Figure 19: DLQI responders up to Week 16 in SUNSHINE (mean response rate with 95% CI) (observed data; full analysis set)

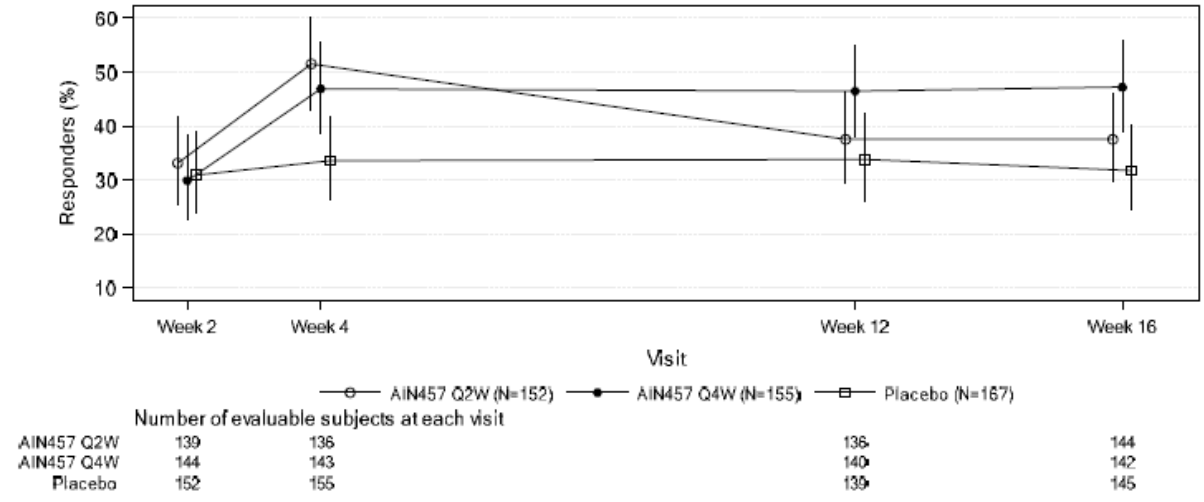


Number of evaluable subjects at each visit

AIN457 Q2W	137	141	126	134
AIN457 Q4W	125	131	123	128
Placebo	132	136	122	128

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 20: DLQI responders up to Week 16 in SUNRISE (mean response rate with 95% CI) (observed data; full analysis set)



Number of evaluable subjects at each visit

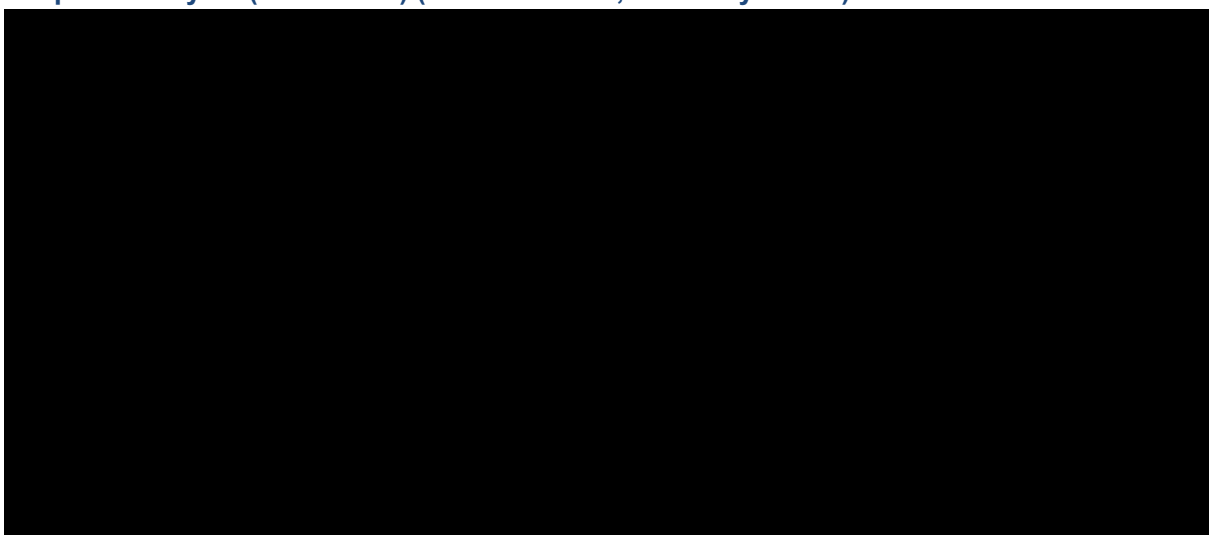
AIN457 Q2W	139	136	136	144
AIN457 Q4W	144	143	140	142
Placebo	152	155	139	145

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

DLQI up to Week 52 (primary endpoint analysis data cut-off: SUNSHINE: 1st October 2021; SUNRISE: 23rd September 2021)

Long-term data up to Week 52 showed that the DLQI total score was also sustained beyond Week 16 up to Week 52 in SUNSHINE and SUNRISE at the time of the primary analysis (Figure 21 and Figure 22). The mean change from baseline in DLQI total score at Week 52 was clinically meaningful in both dose regimens (Q2W: [redacted] and [redacted]; Q4W: [redacted] and [redacted], in SUNSHINE and SUNRISE respectively).

Figure 21: DLQI (total score) up to Week 52 in SUNSHINE at the time of the primary endpoint analysis (mean ± SE) (observed data; full analysis set)



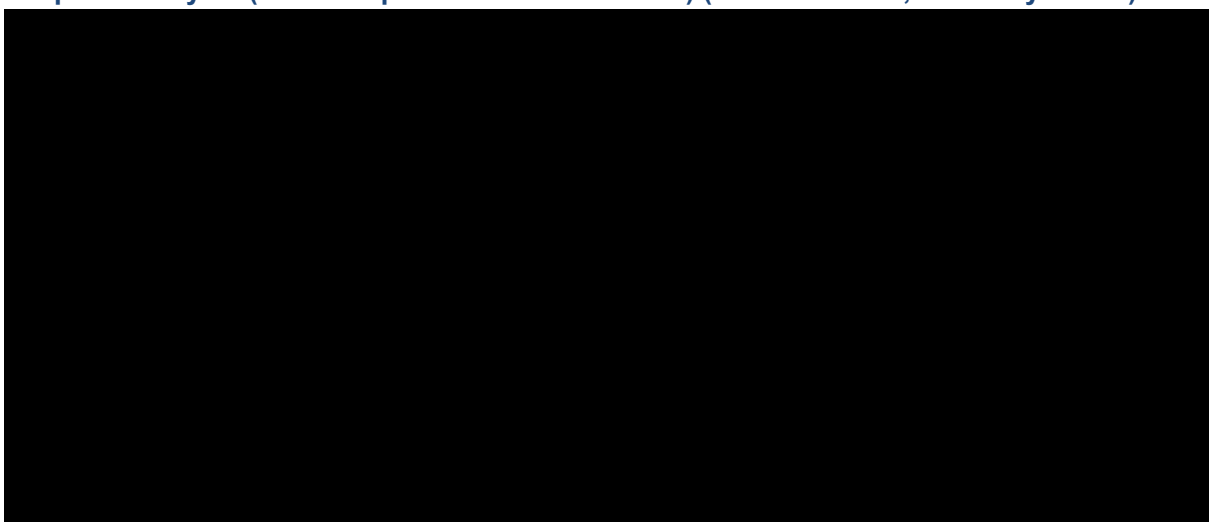
AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 22: DLQI (total score) up to Week 52 in SUNRISE at the time of the primary endpoint analysis (mean ± SE) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

The DLQI response rates also remained relatively stable beyond Week 16 in SUNSHINE and SUNRISE (Figure 23 and Figure 24). The DLQI response rate at Week 52 was higher in the Q2W group ( ) than the Q4W group ( ) of SUNSHINE. Similar results were also observed in SUNRISE for the Q2W (and Q4W ( ) groups.

Figure 23: DLQI responders up to Week 52 in SUNSHINE at the time of the primary endpoint analysis (mean response rate with 95% CI) (observed data; full analysis set)



AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 24: DLQI responders up to Week 52 in SUNRISE at the time of the primary endpoint analysis (mean response rate with 95% CI) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: DLQI: Dermatology Life Quality Index; Q2W: every two weeks; Q4W: every four weeks.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

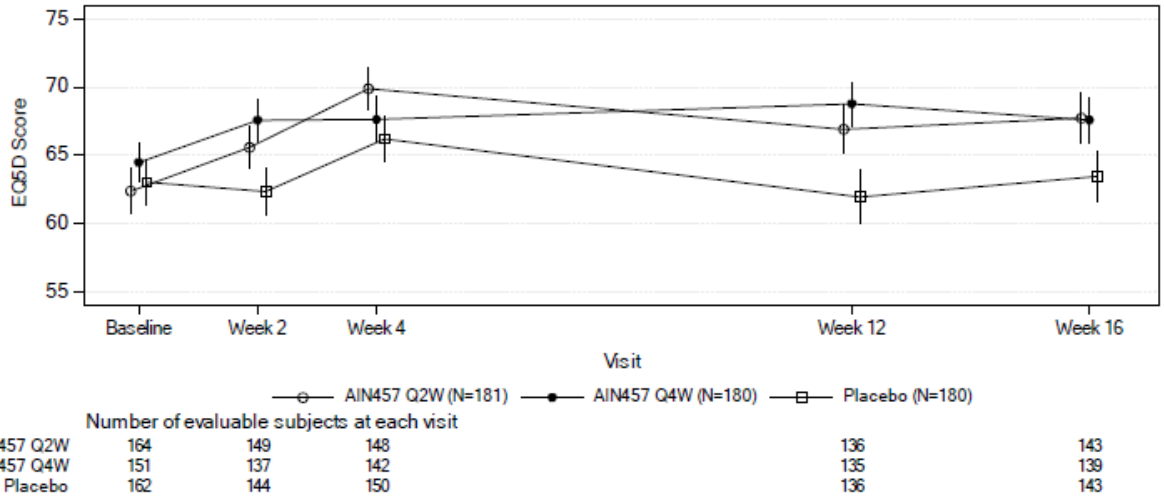
B.2.6.6 EQ-5D-3L

EQ-5D-3L at Week 16

At the primary analysis in SUNSHINE and SUNRISE, there was a sharp increase in the mean EQ-5D-3L health visual analogue scale (VAS) score early in the study (Week 2) particularly in the secukinumab Q2W group in comparison with the Q4W and placebo groups. These results further improved and were sustained up to Week 16 in SUNSHINE and SUNRISE (Figure 25 and Figure 26, respectively). The change (increase) from baseline in the EQ-5D-3L VAS score at Week 16 was higher in the secukinumab Q2W and Q4W groups compared with the placebo groups in SUNSHINE and SUNRISE (Q2W: 4.5 and 9.9 versus 0.8 and 0.3; Q4W: 2.8 and 3.3 versus 0.8 and 0.3 respectively).

Slight differences in ED-5D-3L VAS scores at baseline were observed in both trials, particularly in SUNRISE. The secukinumab Q2W group in SUNRISE had a lower EQ-5D-3L VAS score (59.7) compared with the Q4W (64.7) and placebo groups (63.0), which is aligned with this group being more severe, as noted in Section B.2.3.3.

Figure 25: EQ-5D-3L health state assessment (VAS score) up to Week 16 in SUNSHINE (mean ± SE) (observed data; full analysis set)

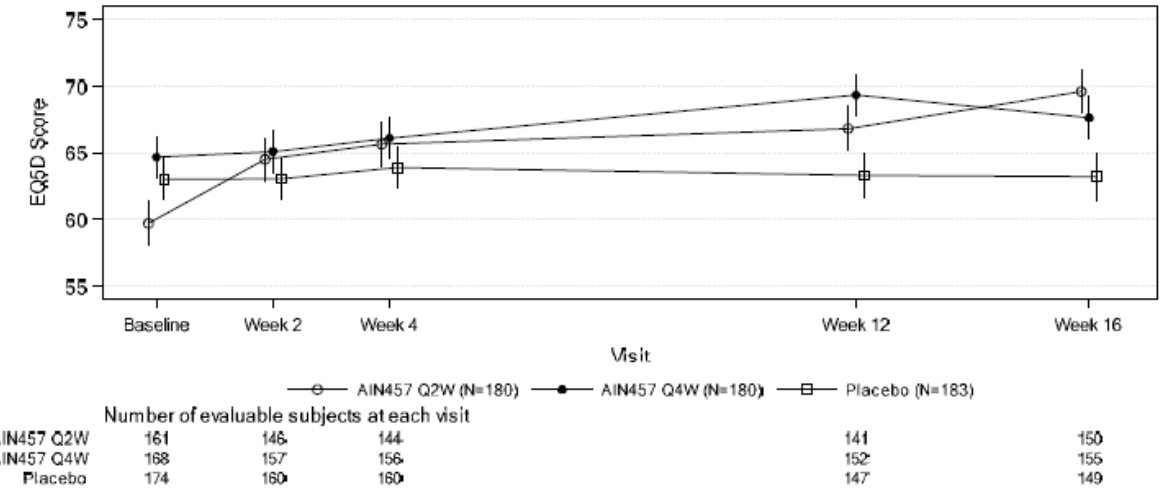


Number of evaluable subjects at each visit

AIN457 Q2W	164	149	148	136	143
AIN457 Q4W	151	137	142	135	139
Placebo	162	144	150	136	143

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: EQ-5D-3L: EuroQoL 5 dimensions 3 level version; Q2W: every two weeks; Q4W: every four weeks; VAS: visual analogue scale.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 26: EQ-5D-3L health state assessment (VAS score) up to Week 16 in SUNRISE (mean ± SE) (observed data; full analysis set)



Number of evaluable subjects at each visit

AIN457 Q2W	161	146	144	141	150
AIN457 Q4W	168	157	156	152	155
Placebo	174	160	160	147	149

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: EQ-5D-3L: EuroQoL 5 dimensions 3 level version; Q2W: every two weeks; Q4W: every four weeks; VAS: visual analogue scale.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

EQ-5D-3L up to Week 52 (primary endpoint analysis data cut-off: SUNSHINE: 1st October 2021; SUNRISE: 23rd September 2021)

The change (increase) from baseline in EQ-5D score improved beyond Week 16 up to Week 52 in SUNSHINE and SUNRISE ([redacted] and [redacted] in the Q2W groups, and [redacted] and [redacted] in the Q4W groups, respectively) (Figure 27 and Figure 28).

Figure 27: EQ-5D-3L health state assessment (VAS score) up to Week 52 in SUNSHINE at the time of the primary endpoint analysis (mean ± SE) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: EQ-5D-3L: EuroQoL 5 dimensions 3 level version; Q2W: every two weeks; Q4W: every four weeks; VAS: visual analogue scale.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Figure 28: EQ-5D-3L health state assessment (VAS score) up to Week 52 IN SUNRISE at the time of the primary endpoint analysis (mean ± SE) (observed data; full analysis set)

AIN457 is the Novartis internal drug code for secukinumab.
Abbreviations: EQ-5D-3L: EuroQoL 5 dimensions 3 level version; Q2W: every two weeks; Q4W: every four weeks; VAS: visual analogue scale.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.7 *Subgroup analysis*

Results from subgroup analyses of the primary efficacy outcome, HiSCR, at Week 16 in the pooled SUNSHINE and SUNRISE trials are presented in Figure 29–Figure 32 below. Covariates included in these analyses were treatment group, baseline AN count, weight (excluded in the analysis of the weight subgroup) and study. Presented p-values are one-sided.

Achievement of HiSCR was broadly consistent across clinically relevant subgroups in the secukinumab Q2W and Q4W groups. When stratified by whether patients had previously been exposed to biologics or not (Figure 31), the relative benefit of secukinumab 300 mg Q2W (OR:

[redacted] [95% CI: [redacted], [redacted]] and OR: [redacted] [95% CI: [redacted], [redacted]]) and Q4W (OR: [redacted] [95% CI: [redacted], [redacted]] and OR: [redacted] [95% CI: [redacted], [redacted]]) as compared with placebo remained consistent, although nominal significance was not achieved in the biologic-experienced subgroup due to the smaller sample size as compared with biologic-naïve patients. As noted in Section B.2.3.3, the bio-experienced subgroup comprised 23.8% and 23.2% of the entire enrolled cohort of the SUNSHINE and SUNRISE trials. Similar results were also demonstrated in patients who were allowed concomitant antibiotics (antibiotics stratum) and those who were not (non-antibiotic stratum), as shown in Figure 31.

As compared with the ITT analyses (see Section B.2.6.1), these subgroup results were broadly aligned: as per the analyses in the ITT population, secukinumab 300 mg Q2W and Q4W dose regimens were favourable versus placebo across almost all subgroups. Therefore, interaction in these subgroups is broadly quantitative rather than qualitative; the size of the effect varies but the direction typically does not.

Figure 29: Forest plot of subgroup analysis of HiSCR at Week 16; pooled analysis (part 1 of 4)

AIN457 is the Novartis internal drug code for secukinumab. One-sided p-value. n* = rounded average number of patients with response in 100 imputations. m=number of subjects evaluable. Covariates included in the model: treatment group, baseline AN count, weight (excluded in the analysis of the weight subgroup), and study.
Abbreviations: CI: confidence interval; F: female; kg: kilogram; M: male; OR: Odds ratio; Q2W: every two weeks; Q4W: every four weeks; vs: versus.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

Figure 30: Forest plot of subgroup analysis of HiSCR at Week 16; pooled analysis (part 2 of 4)

AIN457 is the Novartis internal drug code for secukinumab. One-sided p-value. n* = rounded average number of patients with response in 100 imputations. m=number of subjects evaluable. Covariates included in the model: treatment group, baseline AN count, weight (excluded in the analysis of the weight subgroup), and study.
Abbreviations: AMEA: Asia, Middle East and Africa; CI: confidence interval; LaCAN: Latin America and Canada; NE: not estimable; OR: Odds ratio; Q2W: every two weeks; Q4W: every four weeks; RE: Region Europe; US: United States; vs: versus.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

Figure 31: Forest plot of subgroup analysis of HiSCR at Week 16; pooled analysis (part 3 of 4)

AIN457 is the Novartis internal drug code for secukinumab. One-sided p-value. n* = rounded average number of patients with response in 100 imputations. m=number of subjects evaluable. Covariates included in the model: treatment group, baseline AN count, weight (excluded in the analysis of the weight subgroup), and study.
Abbreviations: CI: confidence interval; N: no; OR: Odds ratio; Q2W: every two weeks; Q4W: every four weeks; vs: versus; Y: yes.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

Figure 32: Forest plot of subgroup analysis of HiSCR at Week 16; pooled analysis (part 4 of 4)

AIN457 is the Novartis internal drug code for secukinumab. One-sided p-value. n* = rounded average number of patients with response in 100 imputations. m=number of subjects evaluable. Covariates included in the model: treatment group, baseline AN count, weight (excluded in the analysis of the weight subgroup), and study.
Abbreviations: AN: abscess and inflammatory nodule; CI: confidence interval; ESR: erythrocyte sedimentation rate; hsCRP: (high sensitivity) C-reactive protein; mg/L: milligrams per litre; mm/hr: millimetres per hour; OR: Odds ratio; Q2W: every two weeks; Q4W: every four weeks; vs: versus.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

B.2.8 *Meta-analysis*

Given the identical trial design and concurrent conduct of the SUNSHINE and SUNRISE trials, a meta-analysis was not deemed necessary.

B.2.9 *Indirect and mixed treatment comparisons*

As discussed in Section B.1.3.3, secukinumab is positioned for use in patients for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. Since there are currently no therapies recommended for use at this second-line position, patients are anticipated to be receiving no active therapy. As such, best supportive care is anticipated to represent the sole comparator relevant for this submission.

Given that direct evidence for secukinumab versus placebo is available from the high quality, Phase III, randomised, double-blind, placebo-controlled, multicentre SUNSHINE and SUNRISE trials, it was not necessary to conduct an indirect comparison comparing the efficacy and safety of secukinumab with that of other treatments in this indication.

B.2.10 *Adverse reactions*

Summary of safety results

- Across both SUNSHINE and SUNRISE trials, no clinically meaningful differences were observed in the incidence of study treatment-related AEs between the secukinumab Q2W, the secukinumab Q4W and placebo groups during Treatment Period 1 (up to Week 16)
- In SUNSHINE, more patients in the placebo group reported SAEs as compared with the secukinumab 300 mg Q2W and Q4W group, while in SUNRISE, SAEs were generally similar across Q2W, Q4W and placebo

- As compared with placebo and secukinumab Q4W, secukinumab Q2W treatment in SUNSHINE was associated with a slightly higher proportion of AEs leading to discontinuation from study treatment. In SUNRISE, fewer patients reported discontinuation due to AEs in secukinumab Q2W group compared with both Q4W and placebo
- No deaths occurred in the secukinumab Q2W, Q4W and placebo groups across both trials during Treatment Period 1

Safety data up to Week 16 of the SUNSHINE and SUNRISE trials are presented in the submission below. Available long-term safety data in both trials at the time of the primary endpoint analysis are presented in Appendix F.

B.2.10.1 Exposure to study treatment

Treatment Period 1

The duration of exposure for Treatment Period 1 of SUNSHINE and SUNRISE was analysed according to the last study visit during this time period. Patients who visited earlier than Week 16 (112 days) had a shorter treatment period and were not included in the '≥16 weeks' rows in Table 24 and Table 25. These patients were included in the ≥16 weeks row for the Entire study period analysis, if they continued treatment after Week 16 (Table 26).

Median duration of exposure in Treatment period 1 was the same across both SUNSHINE and SUNRISE and across all treatment groups ([redacted]). In SUNSHINE, [redacted] of patients in secukinumab Q2W, [redacted] of patients in Q4W and [redacted] of patients in the placebo group received the study treatment for ≥16 weeks. In SUNRISE, [redacted] of patients in secukinumab Q2W, [redacted] of patients in Q4W and [redacted] in the placebo group received treatment for 16 weeks or more.

The cumulative exposure (patient-years) in SUNSHINE was [redacted] patient-years in the secukinumab Q2W, [redacted] patient-years in Q4W and [redacted] patient years in the placebo group, while in SUNRISE, values reported were [redacted] patient-years in secukinumab Q2W, [redacted] patient-years in Q4W and [redacted] patient-years in the placebo group.

Median (range) number of secukinumab injections received by patients during Treatment Period 1 of SUNSHINE and SUNRISE was [redacted] ([redacted]) each in the secukinumab Q2W groups. In Q4W, the median (range) was [redacted] ([redacted]) in SUNSHINE and [redacted] ([redacted]) in SUNRISE.

Entire study period (at the time of the primary endpoint analysis)

A summary of exposure for the Entire study period in SUNSHINE and SUNRISE at the time of the primary analysis is presented in Table 26. Results are only presented for patients who were randomised to the secukinumab Q2W and Q4W groups at baseline. Results of the entire secukinumab population, including patients switching from placebo to secukinumab at Week 16 can be found in the CSR for each trial.[96, 97]

Median duration of exposure for the Entire study period in SUNSHINE and SUNRISE was the same ([redacted]) across either secukinumab Q2W or Q4W groups. More than half of the patients in the Q2W ([redacted] and [redacted]) and Q4W ([redacted] and [redacted]) groups of SUNSHINE and SUNRISE, respectively, had received ≥52 weeks of secukinumab treatment. The cumulative exposure of the Q2W groups was [redacted] and [redacted] patient-years in SUNSHINE and SUNRISE, respectively, while the Q4W group was [redacted] and [redacted] patient-years, respectively.

Median (range) number of secukinumab injections received by patients during the Entire study period of SUNSHINE and SUNRISE in the Q2W groups were [redacted] ([redacted]) and [redacted] ([redacted]), respectively, and [redacted] ([redacted]) and [redacted] ([redacted]) in the Q4W group, respectively.

Table 24: Duration of exposure to study treatment for Treatment Period 1 in SUNSHINE (Safety set)

Duration of exposure	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)
Any exposure, n (%)	[redacted]	[redacted]	[redacted]
≥ 1 week	[redacted]	[redacted]	[redacted]
≥ 2 weeks	[redacted]	[redacted]	[redacted]
≥ 3 weeks	[redacted]	[redacted]	[redacted]
≥ 4 weeks	[redacted]	[redacted]	[redacted]
≥ 8 weeks	[redacted]	[redacted]	[redacted]
≥ 12 weeks	[redacted]	[redacted]	[redacted]
≥ 16 weeks	[redacted]	[redacted]	[redacted]
Days			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]
Patient-time (patient-years)	[redacted]	[redacted]	[redacted]

Duration of exposure to study treatment was defined as min (end date of Treatment Period 1, last dose date + 84 days) − start date of study treatment + 1. Patient-time in patient-years was calculated as a sum of individual patient durations in days divided by 365.25.
Abbreviations: Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Table 25: Duration of exposure to study treatment for Treatment Period 1 in SUNRISE (Safety set)

Duration of exposure	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Any exposure, n (%)	[redacted]	[redacted]	[redacted]
≥ 1 week	[redacted]	[redacted]	[redacted]
≥ 2 weeks	[redacted]	[redacted]	[redacted]
≥ 3 weeks	[redacted]	[redacted]	[redacted]
≥ 4 weeks	[redacted]	[redacted]	[redacted]
≥ 8 weeks	[redacted]	[redacted]	[redacted]
≥ 12 weeks	[redacted]	[redacted]	[redacted]
≥ 16 weeks	[redacted]	[redacted]	[redacted]
Days			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Min–Max	[redacted]	[redacted]	[redacted]
Patient-time (patient-years)	[redacted]	[redacted]	[redacted]

Duration of exposure to study treatment was defined as min (end date of Treatment Period 1, last dose date + 84 days) − start date of study treatment + 1. Patient-time in patient-years was calculated as a sum of individual patient durations in days divided by 365.25.
Abbreviations: Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

Table 26: Duration of exposure to secukinumab 300 mg Q2W and secukinumab 300 mg Q4W for the Entire study period in SUNSHINE and SUNRISE at the time of the primary endpoint analysis (Safety set)

Duration of exposure	SUNSHINE		SUNRISE	
	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Any exposure, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1 week	[redacted]	[redacted]	[redacted]	[redacted]
≥ 2 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 8 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 24 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 32 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥ 52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Days				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]
Patient-time (patient-years)	[redacted]	[redacted]	[redacted]	[redacted]

Duration of exposure to study treatment was defined as min (date of the last study visit, last dose date + 84 days) − start date of study treatment + 1. Patient-time in patient-years was calculated as a sum of individual patient durations in days divided by 365.25. For patients switching from placebo to secukinumab, exposure after the first intake of secukinumab is considered into any secukinumab groups.
Abbreviations: Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: Novartis SUNSHINE (1st October 2021 data cut-off) and SUNRISE CSRs (23rd September 2021 data cut-off).[96, 97]

B.2.10.2 Summary of adverse events

The safety of secukinumab 300 mg Q2W or Q4W versus placebo was evaluated in the Treatment Period 1 (Weeks 0–16) of the SUNSHINE and SUNRISE trials. In line with the anticipated licensed posology for secukinumab in moderate-to-severe HS, safety data for Treatment Period 1 for secukinumab 300 mg Q2W, Q4W and placebo are presented below.

Results for the Entire study period at the time of the primary endpoint analysis are presented in Appendix F.

A summary of safety data from the SUNSHINE and SUNRISE trials is presented in Table 27 and Table 28. In both trials, the proportion of patients who experienced at least one TEAE was similar across the secukinumab 300 mg Q2W, Q4W and placebo groups, with nasopharyngitis and headache representing the most common TEAEs in the SUNSHINE and SUNRISE trials, respectively (Table 29 and Table 30). Despite more patients in the secukinumab 300 mg Q2W group of SUNSHINE reporting AEs which led to treatment discontinuation than Q4W and placebo groups, more patients in the placebo group reported serious adverse events (SAEs) as compared with the secukinumab 300 mg Q2W and Q4W group. In SUNRISE, SAE were generally similar across the Q2W, Q4W and placebo groups. AEs leading to discontinuation were higher in the secukinumab Q4W and placebo groups than the Q2W group. 0% of patients receiving secukinumab or placebo died during Treatment Period 1 in any of the trials.

Table 27: Summary of safety data in the SUNSHINE trial

n (%)	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)
Patients with ≥1 TEAE	120 (66.7)	122 (67.4)	118 (65.6)
SAE	6 (3.3)	3 (1.7)	3 (1.7)
AEs leading to treatment discontinuation	1 (0.6)	5 (2.8)	1 (0.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE: adverse event; AESI: adverse events of special interest; Q2W: every two weeks; SAE serious adverse event; TEAE: treatment-emergent adverse event.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Table 28: Summary of safety data in the SUNRISE trial

n (%)	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Patients with ≥1 TEAE	116 (63.4)	113 (62.8)	114 (63.3)
SAE	5 (2.7)	6 (3.3)	6 (3.3)
AEs leading to treatment discontinuation	4 (2.2)	1 (0.6)	4 (2.2)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE: adverse event; AESI: adverse events of special interest; Q2W: every two weeks; SAE serious adverse event; TEAE: treatment-emergent adverse event.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.10.3 Treatment-emergent adverse events

Summaries of the most frequently reported TEAEs (≥5% in any treatment group) by preferred term for the secukinumab 300 mg Q2W, 300 mg Q4W and placebo groups in the SUNSHINE and SUNRISE trials are presented in Table 29 and Table 30. In SUNSHINE, headache, nasopharyngitis and diarrhoea were the most commonly reported TEAE in the secukinumab treatment groups, while headache, nasopharyngitis and worsening of hidradenitis were the most commonly reported in SUNRISE. Overall, the incidence of TEAEs across arms was very low and

was similar between both secukinumab groups (Q2W and Q4W) and the placebo group of both trials, with no meaningful difference in incidence of any other preferred terms between secukinumab groups and placebo.

Table 29: TEAEs by preferred term (≥5% in any treatment group) for the secukinumab 300 mg Q2W, secukinumab 300 mg Q4W and placebo groups in Treatment Period 1 of the SUNSHINE trial (Safety set)

Preferred term, n (%)	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)
Any preferred term	120 (66.7)	122 (67.4)	118 (65.6)
Headache	14 (7.8)	17 (9.4)	20 (11.1)
Nasopharyngitis	13 (7.2)	20 (11.0)	16 (8.9)
Diarrhoea	9 (5.0)	5 (2.8)	13 (7.2)
Hidradenitis	24 (13.3)	11 (6.1)	5 (2.8)

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.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Table 30: TEAEs by preferred term (≥5% in any treatment group) for the secukinumab 300 mg Q2W, secukinumab 300 mg Q4W and placebo groups in Treatment Period 1 of the SUNRISE trial (Safety set)

Preferred term, n (%)	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Any preferred term	116 (63.4)	113 (62.8)	114 (63.3)
Headache	15 (8.2)	21 (11.7)	17 (9.4)
Nasopharyngitis	16 (8.7)	13 (7.2)	9 (5.0)
Hidradenitis	14 (7.7)	10 (5.6)	11 (6.1)
Diarrhoea	13 (7.1)	8 (4.4)	7 (3.9)
Upper respiratory tract infection	7 (3.8)	9 (5.0)	3 (1.7)

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.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.10.4 Adverse events possibly related to study treatment

TEAEs possibly related to study treatment in the secukinumab 300 mg Q2W, secukinumab 300 mg Q4W and placebo groups of the SUNSHINE and SUNRISE trial are summarised in Table 31 and Table 32. Infections and infestations were the most commonly reported system organ class for study treatment-related AEs in all treatment groups in SUNSHINE and SUNRISE: [redacted] and [redacted] in the secukinumab Q2W groups, [redacted] and [redacted] in the Q4W groups and [redacted] and [redacted] in the placebo groups, respectively. Overall, no clinically meaningful differences were observed in the incidence of study treatment-related AEs between both secukinumab dose regimens and placebo groups in SUNSHINE and SUNRISE during Treatment Period 1.

Table 31: TEAEs possibly related to study treatment by primary system organ class (≥5% in any treatment group) for the secukinumab 300 mg Q2W, 300 mg Q4W and placebo groups in Treatment Period 1 of the SUNSHINE trial (Safety set)

Primary system organ class, n (%)	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)

Any organ class	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Investigations	[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.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Table 32: TEAEs possibly related to study treatment by primary system organ class (≥5% in any treatment group) for the secukinumab 300 mg Q2W, 300 mg Q4W and placebo groups in Treatment Period 1 of the SUNRISE trial (Safety set)

Primary system organ class, n (%)	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Any organ class	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Investigations	[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.
Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.10.5 Adverse events by maximum severity

Most AEs reported during Treatment Period 1 of the SUNSHINE and SUNRISE trials were mild ([redacted] and [redacted] of patients in secukinumab Q2W; [redacted] and [redacted] of secukinumab Q4W patients, [redacted] and [redacted] in the placebo group, respectively) and moderate in severity ([redacted] and [redacted] of patients in secukinumab Q2W; [redacted] and [redacted] of patients in Q4W, [redacted] and [redacted] of patients in the placebo group, respectively).

The severe AEs (SAEs) reported in the secukinumab 300 mg Q2W, secukinumab 300 mg Q4W and placebo groups of the SUNSHINE and SUNRISE trials in Treatment Period 1 are presented in Table 33 and Table 34, respectively. In SUNSHINE, SAEs were reported in 3 (1.7%) patients in secukinumab Q2W and Q4W groups each as compared with 6 (3.3%) patients in the placebo group. In SUNRISE, SAEs were reported in 6 (3.3%) patients in secukinumab Q2W and Q4W groups each, compared to 5 (2.7%) patients in the placebo group. All severe AEs (preferred terms) were single events with no specific trends except for the placebo group in SUNSHINE, where worsening of hidradenitis was reported in 2 (1.1%) patients. These events were mostly not suspected to be related to the study treatment and resolved upon treatment.

Table 33: SAEs by preferred term for the secukinumab 300 mg Q2W, secukinumab 300 mg Q4W and placebo groups in Treatment Period 1 in SUNSHINE (Safety set)

Preferred term	Placebo (N=180)	Secukinumab 300 mg Q2W (N=181)	Secukinumab 300 mg Q4W (N=180)
Any preferred term	6 (3.3)	3 (1.7)	3 (1.7)
Appendicitis	0 (0.0)	0 (0.0)	1 (0.6)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.6)
Hidradenitis	2 (1.1)	1 (0.6)	0 (0.0)
Inguinal hernia	0 (0.0)	1 (0.6)	0 (0.0)
Suicide attempt	0 (0.0)	1 (0.6)	0 (0.0)
Sweat gland infection	0 (0.0)	0 (0.0)	1 (0.6)
Clostridium difficile colitis	1 (0.6)	0 (0.0)	0 (0.0)
Diarrhoea haemorrhagic	1 (0.6)	0 (0.0)	0 (0.0)
Foot fracture	1 (0.6)	0 (0.0)	0 (0.0)
Lung cancer metastatic	1 (0.6)	0 (0.0)	0 (0.0)
Ureterolithiasis	1 (0.6)	0 (0.0)	0 (0.0)

Preferred terms are sorted in descending frequency of AEs in the Any secukinumab group. A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Abbreviations: Q2W: every two weeks; SAEs: serious adverse events.
Source: Novartis SUNSHINE CSR (1st October 2021 data cut-off).[96]

Table 34: SAEs by preferred term for the secukinumab 300 mg Q2W, secukinumab 300 mg Q4W and placebo groups in Treatment Period 1 in SUNRISE (Safety set)

Preferred term	Placebo (N=183)	Secukinumab 300 mg Q2W (N=180)	Secukinumab 300 mg Q4W (N=180)
Any preferred term	5 (2.7)	6 (3.3)	6 (3.3)
Amyloidosis	0 (0.0)	0 (0.0)	1 (0.6)
Arrhythmia	0 (0.0)	1 (0.6)	0 (0.0)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (0.6)
Cholecystitis	0 (0.0)	1 (0.6)	0 (0.0)
Colitis ulcerative	0 (0.0)	1 (0.6)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	1 (0.6)
Hidradenitis	0 (0.0)	1 (0.6)	0 (0.0)
Inflammatory bowel disease	0 (0.0)	0 (0.0)	1 (0.6)
Intentional overdose	0 (0.0)	0 (0.0)	1 (0.6)
Osteoarthritis	0 (0.0)	1 (0.6)	0 (0.0)
Otitis externa	0 (0.0)	0 (0.0)	1 (0.6)
Pelvi-ureteric obstruction	0 (0.0)	1 (0.6)	0 (0.0)
Urinary tract infection	1 (0.5)	1 (0.6)	0 (0.0)
Asthma	1 (0.5)	0 (0.0)	0 (0.0)
COVID-19 pneumonia	1 (0.5)	0 (0.0)	0 (0.0)
Glomerular vascular disorder	1 (0.5)	0 (0.0)	0 (0.0)
Pyrexia	1 (0.5)	0 (0.0)	0 (0.0)

Preferred terms are sorted in descending frequency of AEs in the Any secukinumab group. A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Abbreviations: Q2W: every two weeks; SAEs: serious adverse events.

Source: Novartis SUNRISE CSR (23rd September 2021 data cut-off).[97]

B.2.10.6 Adverse events of special interest (AESI)

Across both trials in Treatment Period 1, infections, hypersensitivity, suicidal ideation and behaviour, and malignant or unspecific tumours were AESI. Of these, infections and infestations were the most common AESI. Overall, most Infections and infestations that occurred during Treatment Period 1 were non-serious and mild to moderate in severity.

[redacted] of the AESI led to treatment discontinuation in both trials during Treatment Period 1, with the exception of [redacted] patient in the secukinumab Q2W group in SUNSHINE, and [redacted] patient in the placebo group in SUNRISE for whom discontinuation of the study treatment was due to sinusitis and upper respiratory tract infection, respectively.

B.2.10.7 Safety-related immunogenicity

At baseline in SUNSHINE and SUNRISE, a total of [redacted] ([redacted]) and [redacted] ([redacted]) patients were anti-drug antibody (ADA) positive in the secukinumab Q2W groups, respectively. TE ADAs (i.e. negative at baseline, positive after start of secukinumab) were only detected in [redacted] ([redacted]) patients in the secukinumab Q2W group of SUNRISE. In the secukinumab Q4W groups, [redacted] ([redacted]) patients in SUNSHINE were ADA positive at baseline and [redacted] ([redacted]) patients were ADA positive at baseline in SUNRISE. TE ADAs were only detected in [redacted] ([redacted]) patient in SUNSHINE and were not found in any patients in SUNRISE.

B.2.11 *Ongoing studies*

The SUNSHINE and SUNRISE trials are ongoing. As described in B.2.3.1, patients who completed the Week 52 study visit were allowed to continue treatment in a planned four-year multicentre, double blind, Phase III, randomised withdrawal extension study (NCT04179175).[95]

This extension study is intended to collect further safety and efficacy data on secukinumab, provide continuous access to treatment for patients and evaluate the sustainability of the treatment effect after study drug discontinuation (in the randomised withdrawal part of this study).

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings from the clinical evidence base

The efficacy and safety of secukinumab 300 mg Q2W and Q4W have been demonstrated in two identically designed Phase III trials (SUNSHINE and SUNRISE). The primary and secondary endpoints assessed across both trials reflect the core outcomes in HS identified as being of most importance to patients: pain, physical signs, HS-specific QoL, global assessment of HS (patient and physician-reported outcomes), progression of HS and symptoms.[98] These core outcomes were proposed by an international multi-perspective Delphi panel, comprising a total of 41 patients and 52 healthcare professionals (HCPs) from 19 countries, including the UK (11 patients and 3 HCPs), the HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC).[98] In line with this, the guidance development group responsible for developing the UK BAD guidelines in HS echoed similar outcome measures, mainly pain, QoL and SAEs.[39]

The results from SUNSHINE and SUNRISE demonstrate that secukinumab 300 mg Q2W, and secukinumab 300 mg Q4W (SUNRISE only), met the primary endpoint at Week 16, with a rapid

and sustained HiSCR50 response between Weeks 16 and 52. Secukinumab showed superiority despite slightly more patients in the Q2W and Q4W groups having severe HS than in the placebo groups at baseline across both trials. Additionally, secondary endpoints across both trials demonstrated that secukinumab was effective at improving skin pain (NRS30). With respect to patient's QoL, secukinumab 300 mg Q2W and Q4W were shown to improve HRQoL as measured by EQ-5D-3L VAS and DLQI, as compared with placebo. These trials also found secukinumab 300 mg Q2W and Q4W to have a tolerable safety profile comparable to placebo. Consistent with the well-established tolerability profile of secukinumab, TEAE were predominantly non-serious and of mild-to-moderate severity.

Strengths and limitations of the clinical evidence base

The SUNSHINE and SUNRISE trials represent the primary source of evidence for secukinumab as a treatment for adults with moderate-to-severe HS. SUNSHINE and SUNRISE were identically designed, Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trials, and thus provide robust evidence for the safety and efficacy of secukinumab in moderate-to-severe HS. Both trials were also considered to be of good quality in Section B.2.5.

Given the anticipated positioning in UK clinical practice, secukinumab is expected to be used in patients with active moderate-to-severe HS. This is consistent with the HS population enrolled in the two pivotal trials. Subgroup analysis indicated that patients with HS achieving HiSCR50 was generally consistent across the bio-exposed and bio-naïve subgroups. Similar results were also demonstrated in patients who were allowed concomitant antibiotics (antibiotics stratum) and those who were not (non-antibiotic stratum). Given that feedback by BAD during the draft scope consultation indicated that long-term antibiotics are being used to maintain disease control in the absence of other treatments in adalimumab primary or secondary failure, this consistent demonstration of effect provide reassurance that the SUNSHINE and SUNRISE ITT results are robustly generalisable to the target population. Patients in both SUNSHINE and SUNRISE were also enrolled from the UK across 12 sites (six sites each). Furthermore, given that HS is more common in people of African origin, both trials enrolled this subpopulation of patients.

A potential limitation was the slight imbalance in the age of patients in the secukinumab Q2W group in SUNRISE, which reflects an older population as compared with placebo. However, as evidenced by the subgroup analysis stratified by age group, no clear trend in the effect of age on outcome was apparent, providing reassurance that the overall trial outcome remains robust.

Summary

Overall, the results from the SUNSHINE and SUNRISE trials demonstrate that secukinumab 300 mg Q2W and secukinumab 300 mg Q4W are effective and tolerable treatment options as compared with the current standard of care (no active treatment) in patients with moderate-to-severe HS. As compared with placebo, a higher proportion of patients in the secukinumab Q2W and Q4W group achieved a HiSCR50 response at Week 16 (though this difference was not significant for SUNSHINE Q4W) and sustained these benefits up to Week 52. These benefits are expected to translate to improved QoL in patients achieving HiSCR50 (i.e., complete response) compared with patients with scores below this threshold. Improved QoL has been identified as an outcome of key importance to patients in current UK guidelines and thus represents a clinically meaningful outcome for assessing efficacy. The use of secukinumab in HS would represent a step-change in treatment of patients in this line of therapy, where there is a lack of robust, licensed and evidenced-based treatments for HS.

B.3 Cost effectiveness

Summary of cost-effectiveness analysis

De novo cost-effectiveness model

- A *de novo* cost-utility analysis was developed to assess the cost-effectiveness of secukinumab versus BSC in 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 model used a Markov structure to capture the key features of HS and to reflect the current clinical pathway of care for the patient population of interest in the UK. The model consisted of an Induction phase (16 weeks), an Up-Titration phase (12 weeks), and a long-term Maintenance phase. The model structure comprises five health states:
    - High Responders (HR) having HiSCR≥75
    - Responders (R) having HiSCR50–74
    - Partial Responders (PR) having HiSCR25–49
    - Non-Responders (NR) having HiSCR<25
    - Death (absorbing state)
- Upon entering the model at the Induction phase, all patients were modelled to receive treatment with secukinumab Q4W or BSC. This phase lasted for a duration of 16 weeks, in line with the primary efficacy endpoint analysis of the SUNSHINE and SUNRISE trials. Treatment response (HiSCR) was assessed at the end of every four-week cycle during induction; treatment was continued irrespective of their response category during this phase
- At the end of the Induction phase (Week 16), patients' HiSCR category determined the treatment received when entering the Maintenance phase. Treatment responders and non-responders were defined as any patients with a HiSCR≥25 and a HiSCR<25, respectively, regardless of treatment received.
- In the Maintenance phase in the base case:
    - Treatment responders were modelled to continue to receive the treatment they received during the Induction phase
    - Treatment responders on secukinumab Q4W could transition between HiSCR categories (HR, R, PR and NR) while no transitions between response categories (HR, R and PR) were modelled for treatment responders on BSC, given the lack of BSC data beyond Week 16 in the SUNSHINE and SUNRISE trials (the trial design reflects the ethical implications of keeping patients on placebo for >16 weeks). However, based on best available data from the literature, transitions from any response category to the NR health state for treatment responders on BSC were modelled based on risk of loss of response estimates from the PIONEER trials
    - In line with the proposed licensing for secukinumab in HS, treatment non-responders at Week 16 who had been receiving secukinumab Q4W were modelled to up-titrate to Q2W dosing for a further 12 weeks (Up-Titration phase). At the end of the Up-Titration phase (Week 28), treatment responders were modelled to continue to receive secukinumab Q2W and these patients could transition between HiSCR categories (HR, R, PR and NR).
    - Treatment non-responders who had been receiving secukinumab Q2W at the end of the Up-Titration phase (Week 28) discontinue treatment with secukinumab and remain in the NR health state. In the NR health state, patients remain on BSC until death or the end of the model
    - All-cause discontinuation rates pooled from the SUNSHINE and SUNRISE trials were applied to treatment responders on secukinumab Q4W or Q2W during the Maintenance phase to capture treatment discontinuation to BSC
    - Treatment non-responders at Week 16 who had been receiving BSC in the Induction phase remain in the NR health state at the start of the Maintenance phase for the remainder of the model
- For patients receiving secukinumab, HiSCR transition probabilities in both the Induction and Maintenance phase were derived from pooled data from the SUNSHINE and SUNRISE trials.

Transition probabilities for the Up-Titration phase were also derived from pooled data from the SUNSHINE and SUNRISE trials
- For those receiving BSC, HiSCR transition probabilities during the Induction phase were derived from pooled data from the SUNSHINE and SUNRISE trials
- Health state utility values were derived from EQ-5D-3L data collected in the SUNSHINE and SUNRISE trials
- Costs included in the model were based on appropriate published sources such as the National Schedule of NHS Costs (2020/21), and Personal Social Services Research Unit (PSSRU 2021)

Base case cost-effectiveness results

- At the confidential PAS price, the probabilistic ICER for secukinumab versus BSC was £29,129 and fell within the £20,000–£30,000 range considered to be cost-effective.
- Overall, the results indicate that secukinumab to be a cost-effective option for the treatment of moderate-to-severe HS versus BSC at the anticipated positioning within the NHS i.e., 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

Sensitivity and scenario analyses

- Results of the sensitivity analyses demonstrated that the base case cost-effectiveness results exhibited little variation when the combined distributional uncertainty across model parameters was taken into account.
- As demonstrated by the deterministic sensitivity analysis results, only three variables crossed the point indifference (i.e., when incremental NHB is zero) for either their upper bound or lower bound value: the BSC NR health state utility, resource use for the number of hospitalisations for HS surgeries and cost of inpatient stay due to surgery.
- The probabilistic scenario analyses results showed that secukinumab was within the £20,000–£30,000 range considered cost-effective, except for scenarios 3 and 9.

Conclusions

- For 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 introduction of secukinumab as an alternative treatment option would represent a step-change in the management of HS, given that these patients are currently receiving BSC, which is insufficient to control HS
- This analysis demonstrates that secukinumab would represent a cost-effective treatment option that would offer value for money to the NHS

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify any relevant economic evaluations for the treatment of adult patients with moderate-to-severe HS. The original SLR searches were performed in June 2021 and updated in August 2022.

In total, 10 economic evaluations were identified for moderate-to-severe HS, of which there were five cost-utility analyses and five budget impact models. Nine of these included adult patients, while one study included adolescent patients. Of these, the NICE TA392 was selected as the most appropriate economic evaluation to inform the model. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

Table 35: Summary of most relevant published cost-effectiveness study, NICE TA392[1]

Study	**NICE TA392, 2015[1]**
Model method	Markov model

Intervention	Adalimumab
Comparator	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)
QALYs (intervention, comparator)	Adalimumab: 12.58 Supportive care: 11.63
Costs (currency) (intervention, comparator)	Adalimumab (with confidential PAS discount): £140,342 Supportive care: £128,647
ICER (deterministic)	£12,336/QALY (Company base case) £28,500–£33,200/QALY (Committee conclusion)

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme QALYs: quality-adjusted life years.

B.3.2 *Economic analysis*

In line with the decision problem for this submission, the objective of this economic analysis was to assess 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. This is consistent with the anticipated positioning of secukinumab in the current clinical care pathway described in Section B.1.3.3.

Of the 10 economic evaluations identified in the economic SLR, none addressed the cost-effectiveness of secukinumab in the patient population relevant to the decision problem. As such, a *de novo* cost-utility analysis (CUA) was developed for the purpose of this submission.

A Markov structure was used for the CUA given that it adequately captures the key features of HS and the current clinical pathway of care for the patient population of interest in the UK. Additionally, the model structure was adapted from the model structure accepted by the NICE Committee in TA392, which provides a useful framework for the economic evaluation of secukinumab in HS.[1]

The model was aligned to the NICE reference case: the perspective on costs was NHS and PSS and the perspective on outcomes was all relevant health effects.

B.3.2.1 Patient population

The economic analysis evaluates the cost-effectiveness of secukinumab in adult 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, in line with the decision problem for this submission. The model uses data from two identically designed Phase III trials, SUNSHINE and SUNRISE.

B.3.2.2 Model structure

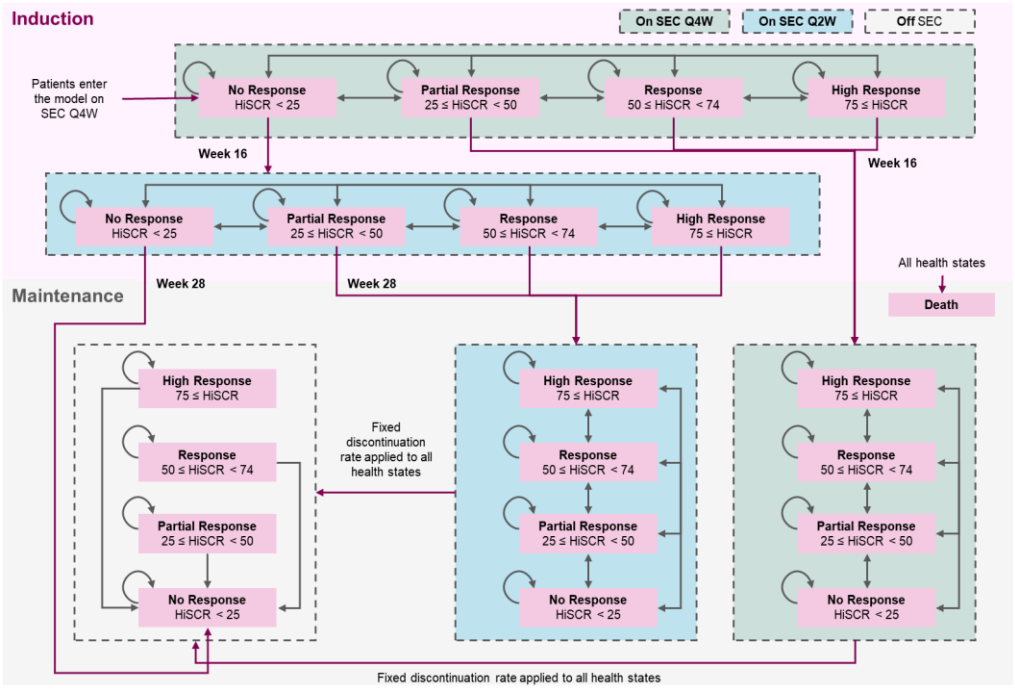
The model consisted of an Induction phase (16 weeks), an Up-Titration phase (12 weeks) and a long-term Maintenance phase. Five health states were modelled, four of which were defined by HiSCR response:

- High Responders (HR) having HiSCR≥75
- Responders (R) having HiSCR50–74
- Partial Responders (PR) having HiSCR25–49
- Non-Responders (NR) having HiSCR<25
- Death (absorbing state)

The use of a granular, four response health state model rather than the dichotomous primary endpoint (HiSCR50 response) in the SUNSHINE and SUNRISE trials was aligned with the Committee's preference in TA392.[1]

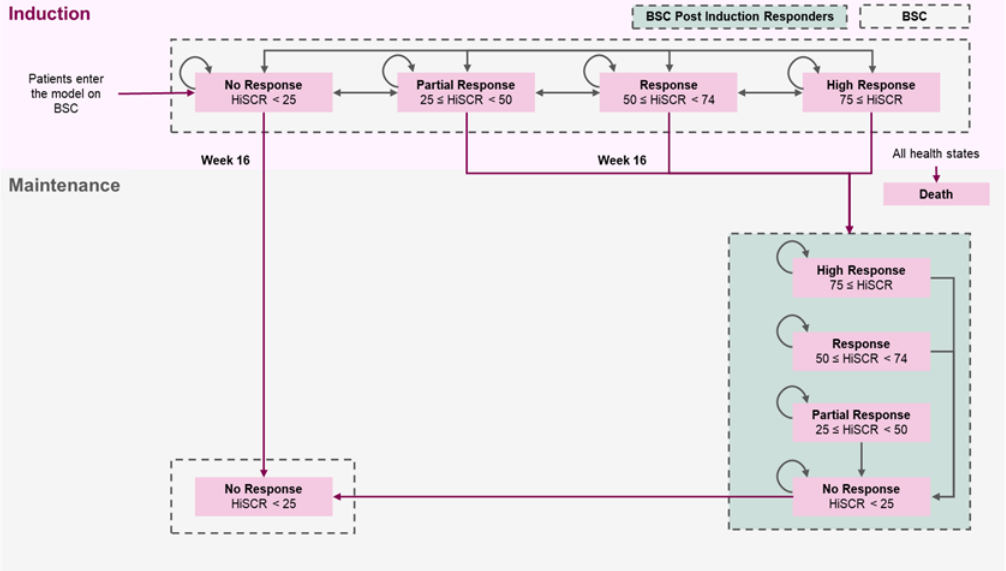
Health state transition diagrams for patients receiving secukinumab and BSC in the base case model are presented in Figure 33 and Figure 34, respectively. In some scenario analyses, the source of efficacy data can be changed to one which includes additional transitions that do not occur in the base case.

Figure 33: Health state transitions for patients receiving secukinumab (base case)



Death can be reached from any other health state at any time during the simulation.
Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; Q4W: every four weeks; SEC: secukinumab.

Figure 34: Health state transitions for patients receiving BSC (base case)



Death can be reached from any other health state at any time during the simulation.
Abbreviations: BSC: best supportive care; HiSCR: Hidradenitis Suppurativa Clinical Response.

Upon entering the model at the Induction phase, all patients received either secukinumab Q4W or BSC. This phase lasted for a duration of 16 weeks, in line with the primary efficacy endpoint analysis of the SUNSHINE and SUNRISE trials. Treatment response (HiSCR) was assessed at the end of every four-week cycle during this phase. Patients continued to receive their assigned treatment irrespective of their HiSCR category during this phase.

At the end of the Induction phase (Week 16), patients' HiSCR category determined the treatment received when entering the Maintenance phase. Treatment responders and non-responders were defined as any patients with a HiSCR≥25 and a HiSCR<25, respectively, regardless of treatment received.

In the Maintenance phase, treatment responders were modelled to continue to receive the treatment they received during the Induction phase, and treatment response was assessed at the end of every four-week cycle during the Maintenance phase.

Treatment responders on secukinumab Q4W could transition between HiSCR health states (HR, R, PR and NR) while no transitions between response health states (HR, R and PR) were modelled for treatment responders on BSC, given the lack of data beyond Week 16 in the SUNSHINE and SUNRISE trials (the trial design reflects the ethical implications of keeping patients on placebo for >16 weeks). However, based on best available data from the literature, transitions from any response health state to the NR health state for treatment responders on BSC were modelled based on risk of loss of response estimates observed from the PIONEER trials.[99]

In line with the proposed licensing for secukinumab in HS, treatment non-responders at Week 16 who had been receiving secukinumab Q4W were modelled to up-titrate to Q2W dosing for a further 12 weeks (Up-Titration phase). At the end of the Up-Titration phase (Week 28), treatment responders were modelled to continue to receive secukinumab Q2W and these patients could transition between HiSCR categories (HR, R, PR and NR). A scenario analysis is provided which omits the Up-Titration phase, where non-responders to secukinumab Q4W discontinue treatment to receive BSC for the remainder of the model.

All-cause discontinuation rates pooled from the SUNSHINE and SUNRISE trials were applied to treatment responders on secukinumab Q4W or Q2W to capture transitions to BSC after Week 16.

Treatment non-responders at Week 16 who had been receiving BSC in the Induction phase remain in the NR health state at the start of the Maintenance phase. Treatment non-responders who had been receiving secukinumab Q2W at the end of the Up-Titration phase (Week 28) discontinued secukinumab and transitioned to the Maintenance phase NR health state. In the NR health state, patients remain on BSC until death or the end of the model.

For patients receiving secukinumab, HiSCR transition probabilities in both the Induction and Maintenance phase were derived from pooled data from the SUNSHINE and SUNRISE trials. Transition probabilities for the Up-Titration phase were also derived from pooled data from the SUNSHINE and SUNRISE trials. For those receiving BSC, HiSCR transition probabilities during the Induction phase were derived from pooled data from the SUNSHINE and SUNRISE trials, while transitions in the Maintenance phase were based on risk of loss of response estimates from the PIONEER trials.[99]

In the model, death was represented by an absorbing health state, accumulating patient flows from all other health states, and patients were at risk of death at any time during the simulation, as modelled by general population mortality.[49, 100] Although the peer-reviewed literature reports an increased risk of mortality in patients with HS as compared with the general population, this was conservatively not modelled as the data were not considered sufficient to appropriately inform the model.[49, 101]

The model also considered resource use due to surgery and resource use that was non-surgery related in patients with HS. Patients who underwent surgery remained in their current health state and incurred the associated cost. However, the disutility of surgery was not modelled, given the absence of data to adequately inform the model and the use of health state specific utilities, as inclusion of surgery disutility values may result in double counting. Additionally, treatment-specific effects on the number of surgeries received in patients on secukinumab or BSC were not modelled.

Features of the economic analysis

The key features of the economic analysis and their justifications are presented in Table 36.

Effectiveness measures include life years (LYs) and quality-adjusted life years (QALYs). The incremental cost-effectiveness ratio (ICER) of secukinumab versus BSC was evaluated in terms of the incremental cost per QALY gained. An annual discount of 3.5% was applied for both costs and QALYs. The cost perspective was of the NHS and PSS, and the outcomes perspective was all relevant health effects over a lifetime horizon. A lifetime horizon was considered appropriate given the chronicity of HS and in order to adequately capture all the differences in costs and outcomes between secukinumab and BSC. Maximal lifetime for patients was set to 100 years, reflecting that the Office for National Statistics (ONS) life tables for mortality end at 100.[100]

Health state utility values were derived based on EQ-5D-3L data sourced directly from the SUNSHINE and SUNRISE trials, in line with the NICE reference case. Treatment-specific utility were used to reflect differences in utility between patients on secukinumab and BSC, as described in Section B.3.4.1.

Costs considered within the model include treatment acquisition costs, associated administration costs and disease management costs including costs associated with surgery.

Table 36: Features of the economic analysis

Factor	Previous evaluations: TA392[1]	Current evaluation	
		Chosen values	Justification
Model structure	Markov model with five health states, including death. The four response health states were based on HiSCR (<25; 25–49; 50–74; ≥75)	Markov model with five health states, including death. The four response health states were based on HiSCR (<25; 25–49; 50–74; ≥75)	A Markov structure was used because it captures the key features of HS and the current clinical pathway of care for the patient population addressed in the decision problem for this submission. Additionally, the model structure used aligns with the Committee's preference in TA392[1]
Time horizon	Lifetime	Lifetime	A lifetime horizon is considered appropriate because it reflects the chronicity of HS and ensures the model captures all costs and benefits of secukinumab versus BSC in line with NICE reference case
Treatment waning effect?	N/A	N/A	Loss of treatment response in patients with HS is clinically measurable and will therefore lead to treatment discontinuation. As such, discontinuation is a suitable proxy for treatment waning
Source of utilities	Based on EQ-5D index scores of adult patients enrolled in Phase III PIONEER II RCT independent of treatments received (Week 12 and Week 36 data)	Health state utility values were derived based on EQ-5D-3L data sourced from the SUNSHINE and SUNRISE trials; treatment-specific utility values are applied	In line with NICE reference case
Source of costs	• NHS Reference cost 2013–14 • PSSRU 2014	• National Schedule of NHS costs 2020/21 • PSSRU 2021	In line with NICE reference case
Health effects measure	QALYs	QALYs	In line with NICE reference case
Half cycle correction	Yes	Yes	A half-cycle correction was applied to the calculation of LYs, QALYs and costs to account for events that occur part way through a cycle

Abbreviations: EQ-5D-3L: EuroQoL 5 dimensions 3 level version; HiSCR: Hidradenitis Suppurativa Clinical Response; HS: hidradenitis suppurativa; LYs: life years; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; QALYs, quality-adjusted life years; RCT: randomised controlled trial; TA: technology appraisal; UK: United Kingdom.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention assessed in the base case model was secukinumab 300 mg Q4W, with up-titration to Q2W for non-responders at Week 16. This is in line with the decision problem and the anticipated licensed posology for secukinumab in moderate-to-severe HS. The base case model reflects the Q4W dosing regimen used in the pivotal SUNSHINE and SUNRISE trials that provide the main source of efficacy data for this intervention arm.[62, 63]

The dosing schedule for secukinumab included in the model is consistent with the SUNSHINE and SUNRISE trials. All patients treated with secukinumab Q4W had an Induction phase in which they received secukinumab 300 mg once weekly for five weeks (Weeks 0, 1, 2, 3 and 4), thereafter the dosing frequency was decreased to Q4W. Given that each cycle in the model is a four-week cycle, the first four induction doses occur in Cycle 1 whilst the fifth dose occurs in the next cycle i.e., Cycle 2.

Within the base case economic model, a stopping rule was applied for patients who failed to respond to secukinumab Q2W at Week 28 (end of the Up-Titration phase); this is described in Section B.3.3.3 below. A scenario analysis omitting the possibility of up-titration is also provided, in this scenario the stopping rule was applied for patients who failed to respond to secukinumab Q4W at Week 16 (end of the Induction phase).

Comparator

As described in Section B.1.3.3, BSC is the sole comparator considered in this economic analysis and reflects the current standard of care for patients in whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment. This is in line with the decision problem addressed in this submission.

In line with feedback received from BAD during draft scope consultation for secukinumab in HS, BSC is difficult to define in UK clinical practice.[89] As such, clinical validation was sought by Novartis to inform the BSC arm of the model, the composition of which is presented in Table 37.

Based on clinical expert opinion, BSC was defined as biologics, topical antibiotics, oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens. In the base case, biologics were excluded as a component of BSC, given that patients are expected to stop treatment with adalimumab due to lack or loss of response in line with recommendations in NICE TA392.[1] This is likely to be a conservative approach given that clinical experts noted that, despite patients failing adalimumab, some patients may remain on adalimumab without deriving any benefits, due to the lack of alternative treatments. A scenario analysis is also presented that includes the cost associated with biologics for patients who failed biologics but who remain on biologics due to the lack of alternative treatment options to capture the impact of this on the economic analysis.

Table 37: BSC treatment composition and percentage use

Treatment	Percentage (%) of use[a]	
	Base case	Scenario analysis
Other biologics	-	[redacted]
Topical antibiotics	[redacted]	[redacted]
Oral antibiotics	[redacted]	[redacted]
Dapsone	[redacted]	[redacted]
Retinoids	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]
Anti-androgens	[redacted]	[redacted]

[a]The proportions of patients receiving treatment for each BSC components may not sum up to 100% because a patient can receive more than one BSC components concurrently.
Abbreviations: BSC: best supportive care.
Source: Novartis Market Research 2022[102]

B.3.3 *Clinical parameters and variables*

The model used clinical data derived from patient-level analyses of the SUNHSINE and SUNRISE trials.

B.3.3.1 Baseline characteristics

The baseline characteristics of the modelled cohort and the source of the data are presented in Table 38.

Baseline characteristics were derived from pooled data from the SUNSHINE and SUNRISE trials. Mortality calculations were based on the proportion of male, female, and age inputs.

Table 38: Baseline characteristics of patients with HS

Parameter	HS population	Source
Mean age (years)	36.2 years	Weighted average of the total estimates from all trial arms of the SUNSHINE (N=541) and SUNRISE (N=543) trials
Female (%)	56.3%	
Weight (kg)	93.47	

Abbreviations: HS: hidradenitis suppurativa; kg: kilogram.

B.3.3.2 Efficacy

Induction phase (Week 0–16 for secukinumab Q4W and BSC)

The efficacy estimates for secukinumab 300 mg Q4W were based on pooled data from the SUNSHINE and SUNRISE trials. As noted in Section B.2.7 and Section B.2.12, subgroup analysis indicated that the primary endpoint, HiSCR50 at Week 16, remained consistent between bio-experienced and bio-naïve patients and was therefore deemed appropriate to use the full trial arm data to inform the efficacy estimates rather than the bio-experienced/-naïve subgroup data, given the larger sample size and thus statistical power. Across both trials, secukinumab was compared with placebo, which provides the efficacy data for BSC up to Week 16.

The four-weekly transition probabilities between HiSCR health states for the first 16 weeks of treatment were estimated using the distribution of people across the four HiSCR health states in the SUNSHINE and SUNRISE trials at four-weekly intervals. The transition probabilities were estimated separately for each arm; in the base case a multinomial model was fitted to the transition counts observed in each four-week cycle of the trials to generate average four-week transition probabilities for patients transitioning between health states.

A summary of the average transition probabilities for each treatment regimen during the Induction phase (Week 0–16) is presented in Table 39.

Table 39: HiSCR average (four-weekly) transition probabilities up to Week 16

Treatment	Induction phase (Week 0–16)					Source
	To > From v	HiSCR≥75	HiSCR50 – 74	HiSCR25 –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.

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

In the absence of trial data to directly inform the Up-titration phase, given that the SUNSHINE and SUNRISE trials were not designed to directly capture the possibility of up-titration, it was considered that transitions for patients in the trial arm which had received 16 weeks of secukinumab Q2W and were continuing to receive secukinumab Q2W would best reflect the modelled population who receive 16 weeks of Q4W followed by 12 weeks of Q2W. As such, the modelling of up-titration to Q2W required the assumptions that: (1) trial data (Week 16–52) for the trial Q2W patients are suitable to be applied for the up-titration period (Week 16–28) to patients who failed to respond to 16 weeks on the Q4W dosing regimen; and (2) trial data (Week 16–52) for the trial Q2W patients are suitable to be applied to patients who have responded to up-titration to Q2W (at week 28) having initially failed to respond to the Q4W dosing regimen.

A summary of transition probabilities for the secukinumab Q2W treatment regimen during the Up-Titration phase (Week 16–28) are presented in Table 40.

Table 40: HiSCR average (four-weekly) transition probabilities for the secukinumab Q2W treatment regimen during the Up-Titration phase (Week 16–28)

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

	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	SUNSHINE and SUNRISE trials
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; SEC: secukinumab; TP: transition probabilities.

Maintenance phase (Week 16–52 for secukinumab Q4W and BSC; Week 28–52 for secukinumab Q2W)*

*for Week 52+ see below

Secukinumab

Treatment responders on secukinumab Q4W or Q2W could transition between HiSCR health states (HR, R, PR and NR). The four-weekly transition probabilities between HiSCR health states for Week 16–52 were estimated using the distribution of people across the four HiSCR health states in the SUNSHINE and SUNRISE trials at four-weekly intervals. The transition probabilities were estimated separately for each secukinumab arm; in the base case a multinomial model was fitted to the transition counts observed in each four-week cycle of the trials to generate average four-week transition probabilities for patients transitioning between health states.

Patients on the Q4W dosing regimen in the Maintenance phase transitioned according to four-weekly transition probabilities reflecting the average Week 16–52 transitions for Q4W patients who had responded at Week 16 in the pooled trials. Patients on the Q2W dosing regimen in the Maintenance phase transitioned according to four-weekly transition probabilities reflecting the average Week 16–52 transitions for Q2W patients who had responded at Week 16 in the pooled trials.

All-cause discontinuation rates pooled from the SUNSHINE and SUNRISE trials were applied to treatment responders on secukinumab Q4W or Q2W during the Maintenance phase to capture treatment discontinuation to BSC (see Section B.3.3.3).

A summary of transition probabilities for the secukinumab Q4W and Q2W treatment regimens during the Maintenance phase (Week 16/28–52) are presented in Table 41.

Table 41: HiSCR average (four-weekly) transition probabilities for the secukinumab Q4W and Q2W treatment regimens during the Maintenance phase (Week 16/28–52)

Treatment	To > From v	HiSCR≥75	HiSCR50 – 74	HiSCR25 –49	HiSCR<25	Source
SEC Q4W	Maintenance phase (Week 16–52)					Pooled data from the SUNSHINE and SUNRISE 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)					
	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: HiSCR: Hidradenitis Suppurativa Clinical Response; SEC: secukinumab; TP: transition probabilities.

BSC

No patients received placebo beyond Week 16 in the SUNRISE and SUNSHINE trials. As such, no data were available from both trials to inform HiSCR transition probabilities for BSC patients beyond Week 16 of the model. Transitions between response categories (HR, R and PR) for BSC treatment responders were not modelled in the Maintenance phase. However, transitions from any response categories to the NR health state were informed based on risk of loss of response estimates from the PIONEER trials, as presented in Table 42. As reported in the trial paper, 44/151 (29.1%) patients on placebo were responders (HiSCR≥50) at Week 12, with 24/151 (15.9%) patients maintaining response at Week 36. Accordingly, 20/44 (45.5%) patients on placebo lost response in the 24-week period from Week 12 to 36, converting the 24-week probability into a 4-week probability resulted in a value of 9.61%.

Patients who discontinued secukinumab Q4W or Q2W in the Maintenance phase were modelled to switch to treatment with BSC, with transitions as described above.

Table 42: Risk of loss of response for BSC

Treatment	Risk of loss of response post response assessment (per cycle)		Source
	First year (Week 16+)	Year 2+	
BSC	9.61%	9.61%	Jemec *et al.,* (2019)[99]

Abbreviations: BSC: best supportive care.

Maintenance phase (Week 52+)

Limited trial data are available for secukinumab beyond Week 52. In the absence of data, it was assumed that the Maintenance phase data for Week 16/28–52 would continue to be applied in Week 52+ for all treatments. The same approach was equally applied for BSC patients in the model.

B.3.3.3 Long-term treatment discontinuation

As noted in Section B.3.2.2, all-cause discontinuation rates pooled from the SUNSHINE and SUNRISE trials were applied to all secukinumab-treated patients regardless of their HiSCR health state in the model during the Maintenance phase to capture long-term discontinuation in the model.

A summary of all-cause discontinuation rates applied in the model for secukinumab is presented in Table 43. The risk of discontinuation for secukinumab in Year 1 was derived from pooled SUNSHINE/SUNRISE trial data which reported that [redacted] and [redacted] patients discontinued secukinumab during the Entire study period (Week 52). The risk of discontinuation in Year 2 onwards was 6.0% based on 52-week data reported in the literature, which was then converted to a four-week cycle estimate. The same discontinuation rate was applied to all on-treatment patients receiving secukinumab, regardless of their dosing regimen or response state once they had passed the response assessment (Week 16 for Q4W patients and Week 28 for Q2W patients).

Table 43: Risk of all-cause treatment discontinuation for secukinumab Week 16/28 onwards (per cycle; 4 weeks)

Treatment	Discontinuation rate Maintenance phase (per cycle)		Source
	First year (Week 16/28+)	Year 2+	
Secukinumab Q4W	[redacted]	0.47%	Year 1: SUNSHINE/SUNRISE trial Year 2+: Corbett *et al.,* (2016)[103]
Secukinumab Q2W			

Abbreviations: Q2W: every two weeks; Q4W: every four weeks.

B.3.3.4 Safety

As reported in Section B.2.10.5, no SAE by preferred term occurred in more than one patient in either secukinumab arm during Treatment Period 1 (Weeks 0–16). Additionally, longer-term data presented in Appendix F showed that safety results in Treatment Period 1 were maintained during the Entire study period (Week 52). The only exception was exacerbation of HS in both trials and sweat gland infection in Q4W of SUNSHINE; however, the incidence rates were still ≤5%. Given these data, no AEs were included in the base case economic analysis. However, a scenario analysis that included all-grade AE was also provided. Risk of AEs per cycle for secukinumab and BSC is presented in Table 44. 16-week AE probabilities from the pooled SUNSHINE and SUNRISE trials were converted to 4-week probabilities based on the assumption that AE rates were constant over time, and these AE probabilities were applied over the full duration of the model.

Table 44: Adverse event probabilities per four-week cycle (scenario analysis)

AE (risk per cycle)	SEC	BSC	Source
Headache	2.71%	2.06%	Pooled all-grade AEs data from the SUNSHINE and SUNRISE trials. Converted from 16-week to 4-week probability
Nasopharyngitis	2.07%	2.06%	
Upper Respiratory tract infection	0.81%	0.77%	
Diarrhoea	1.16%	1.55%	
Gastroenteritis	0.31%	0.14%	
Influenza	0.07%	0.28%	
Toothache	0.38%	0.28%	
Bronchitis	0.24%	0.35%	
Viral gastroenteritis	0.00%	0.00%	

Abbreviations: AE: adverse event; BSC: best supportive care; SEC: secukinumab.

B.3.3.5 Mortality

As discussed in Section B.3.2.2, patients were at risk of general population mortality at every time point in the model, irrespective of whether they received secukinumab or BSC. Although the peer-reviewed literature reports an increased risk of mortality in patients with HS as compared with the general population, this was conservatively not modelled as the data were not considered sufficient to appropriately inform the model.[49, 101] Patients were therefore assumed to have the same mortality rate as for the general population.

Age specific mortality rates were derived from the National UK life tables for 2019 (published by the ONS) weighted by the male-female ratio observed in the SUNNY trials (see Table 38).[100] A scenario analysis using the most recent life tables (2020) is also provided.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

Arithmetic mean utility values for patients with HS stratified by HiSCR response and treatment arm were derived using all available EQ-5D-3L based utility values collected directly from patients from Weeks 2–16 of the SUNSHINE and SUNRISE trials. This is consistent with the NICE reference case. The trial utilities used in the base case and scenario analyses are presented in Section B.3.4.5 below.

B.3.4.2 Mapping

No mapping was performed in the economic analysis because EQ-5D-3L data were directly available from the SUNSHINE and SUNRISE trials.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted in June 2021 to identify any relevant utility data for people with moderate-to-severe HS and updated in August 2022.

In total, 12 publications were identified with utility estimate data for patients with moderate-to-severe HS. Of these, the NICE TA392 was selected as the most appropriate source of utility data to inform scenario analysis in the economic model, given that it represents the most recent and relevant NICE appraisal in HS. A summary of health state utility values used in NICE TA392 is provided in Table 45.

Full details of the SLR search strategy, study selection process and results are reported in Appendix H.

Table 45: Summary of health state utility values used in NICE TA392

Health state	Utility value
High response HiSCR≥75	0.782
Response (HiSCR50–74)	0.718
Partial response (HiSCR25–49)	0.576
Non-response (HiSCR<25)	0.472

Abbreviations: HiSCR: hidradenitis suppurativa clinical response; TA: technology appraisal.
Source: TA392, 2015.[1]

B.3.4.4 Adverse reactions

As noted in Section B.3.3.4, no AEs were included in the model base case. It may also be noted that use of treatment-specific utility data implicitly captures the full treatment effects, regardless of whether they are related to the health states. However, to explicitly capture the impact of AEs on patient quality of life, a scenario analysis that included all-grade AE disutility (Table 46) was provided. Disutility values associated with AEs in patients with HS were not identified in the HRQoL SLR. Therefore, a published literature source was used to inform each AE utility

decrement. It was assumed that utility decrements associated with AEs would last a duration of 1 week for all AEs.

The model did not consider disutility for surgery (the incidence of which was associated with health state, not treatment) given the lack of data identified in the economic SLR to adequately inform the model and the use of health state specific utilities, as inclusion of surgery disutility values may result in double counting. This was a simplifying assumption, given feedback received by the NICE Committee in TA392 indicated biologic treatment in combination with surgery may reduce the need for some types of surgical procedure.[1]

Table 46: Adverse event utility decrements and durations (scenario analysis)

AE	Disutility	Duration of AE, weeks	Per event QALY decrement due to AEs	Weighted average QALY decrement per cycle due to AEs		Source of utility decrement
				SEC	BSC	
Headache	0.027	1	0.00051	0.000032	0.000031	Decrement: Sullivan *et al*., (2011)[104] Duration: Assumption
Nasopharyngitis	0.001	1	0.00002			
Upper Respiratory tract infection	0.001	1	0.00002			
Diarrhoea	0.051	1	0.00098			
Gastroenteritis	0.073	1	0.00139			
Influenza	0.001	1	0.00002			
Toothache	0.001	1	0.00002			
Bronchitis	0.044	1	0.00085			
Viral gastroenteritis	0.073	1	0.00139			

Abbreviations: AE: adverse event; BSC: best supportive care; QALY: quality-adjusted life years; SEC: secukinumab.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the base case utility values by HiSCR response used in the cost-effectiveness analysis is presented in Table 47. Utility values were used in the model to calculate QALYs to reflect the improvement in HRQoL experienced by patients who achieve the various levels of HiSCR response.

Table 47: Utilities by health state (base case)

Health state	Utility			Source
	SEC Q4W	SEC Q2W	BSC	
HiSCR≥75	[redacted]	[redacted]	[redacted]	SUNSHINE and SUNRISE trials (ITT population)
HiSCR50–74	[redacted]	[redacted]	[redacted]	
HiSCR25–49	[redacted]	[redacted]	[redacted]	
HiSCR<25	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC: best supportive care; HiSCR: Hidradenitis Suppurativa Clinical Response; ITT: intention-to-treat; SEC: secukinumab.

In addition, scenario analyses were undertaken to test the effect of pooling the utility values for all trial arms (i.e., treatment-independent utilities) (Table 48) and using health state utility values in NICE TA392 (Table 45).

Table 48: Utilities by health state (scenario analyses)

Health state	All arms (pooled)	Source
HiSCR≥75	[redacted]	SUNSHINE and SUNRISE trials (ITT population)
HiSCR50–74	[redacted]	
HiSCR25–49	[redacted]	
HiSCR<25	[redacted]	

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; ITT: intention-to-treat.

Utility age adjustment

Given the base case analysis is modelled over a lifetime horizon in line with the NICE reference case, the model applies an age-dependent annual adjustment factor to account for the expected decline in health utility with increasing age, using UK data from Hernandez-Alava *et al*., (2022).[105]

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

An SLR was conducted to identify any relevant cost or resource use data for adult patients with moderate-to-severe HS. The original SLR searches were performed in June 2021 and were updated in August 2022.

In total, 23 publications were identified with cost and healthcare resource use (HRU) data for patients with moderate-to-severe HS. Of these, the NICE TA392 was selected as the most appropriate source of resource use data to inform the economic model, given that it represents

the most recent and relevant NICE appraisal in HS. Full details of the SLR search strategy, study selection process and results are reported in Appendix I.

The following cost categories are included in the model base case:

- Drug acquisition costs (Section B.3.5.1)
- Administration costs (Section B.3.5.1)
- Non-surgery and surgery resource use costs across HiSCR states (Section B.3.5.2)

The base case was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS.

B.3.5.1 Intervention and comparators' costs and resource use

Secukinumab acquisition costs

The number of doses in each four-week cycle and the acquisition cost of secukinumab are provided in Table 49. These are consistent with the anticipated marketing authorisation for secukinumab in HS and align with the secukinumab 300 mg Q4W group of the SUNSHINE and SUNRISE trials.

Table 49: Dosing schedule and drug acquisition cost for secukinumab

Dosing regimen	Cycle 1 Doses	Cycle 2+ Doses	Dose per pre-filled pen	Cost per 300 mg pre-filled pen (source)
Secukinumab 300 mg Q4W	4	1	300 mg	List price: £1218.78 (Novartis) PAS price: [redacted] (Novartis)
Secukinumab 300 mg Q2W	N/A	Cycle 5+ only: 2	300 mg	List price: £1218.78 (Novartis) PAS price: [redacted] (Novartis)

[redacted].

Abbreviations: PAS: patient access scheme; Q2W: every two weeks; Q4W: every four weeks.

BSC acquisition costs

Patients in the BSC health state are assumed to receive additional therapy that comprises various BSC treatments. As noted in Section B.3.2.3, the composition of the BSC treatments and the proportion of patients that are assumed to receive such treatments are based on clinical expert opinion (market research) sought by Novartis and are presented in Table 50 (base case) and Table 51 (scenario analysis), respectively.

Table 50: BSC component costs (base case)

Component	Drug regimen	Dose schedule	Units per cycle	Unit cost	Cost per cycle	Average cost per cycle	Source	
							Costs	Dosing schedule
Topical antibiotics	Clindamycin 1% solution 30mL	Twice per day	1	£6.07	£6.07	£6.07	Prescription Cost Analysis – England – 2021/22[106] 1306010F0BBAAAA, 0501030I0AAABAB, 0501030L0AAABAB, 0501030P0AAABAB, 0501030V0AAAFAF, 0501060D0AAAMAM, 0501090R0AAABAB, 0501100H0AAAHAH, 1305020A0AAABAB, 1306020J0AAAEAE, 0802020G0AAADAD and 0803042E0AAABAB	Nesbitt *et al.*, (2020)[107]
Oral antibiotics	Doxycycline 100 mg	100 mg twice per day	56	£0.14	£7.75	£42.47		
	Lymecycline 408 mg	408 mg twice per day	56	£0.23	£12.92			
	Minocycline 100 mg	100 mg twice per day	56	£0.50	£27.94			
	Tetracycline 250 mg	500 mg twice per day	112	£0.20	£21.87			
	Clindamycin 300 mg + Rifampicin 300 mg	Twice per day	56	£1.27	£141.89			Ingram *et al.*, (2018)[39]
		Twice per day	56	£1.26				
Dapsone	Dapsone 100mg	100 mg per day	28	£1.15	£32.33	£32.33		Zouboulis *et al.*, (2014)[108]
Retinoids	Acitretin 10 mg	0.4 mg/kg per day	112	£0.47	£52.65	£62.70		Ingram *et al.*, (2018)
	Isotretinoin 40 mg	0.85 mg/kg per day	56	£1.30	£72.76			Zouboulis *et al.*, (2014)[108]
Ciclosporin	Ciclosporin 100 mg	4 mg/kg per day	112	£2.28	£254.91	£254.91		
Anti-androgens	Cyproterone 100 mg	100 mg per day	28	£0.86	£24.15	£24.15		

Abbreviations: BSC: best supportive care.

Table 51: BSC component costs (scenario analysis)

Component	Drug regimen	Dose schedule	Units per cycle	Unit cost	Cost per cycle	Average cost per cycle	Source	
							Costs	Dosing schedule
Other biologics	Adalimumab	-	-	-	-	£280.75	Based on the annual cost of adalimumab per patient (£3,662.23) provided by NHSE[109]	-
Topical antibiotics	Clindamycin 1% solution 30mL	Twice per day	1	£6.07	£6.07	£6.07	Prescription Cost Analysis – England – 2021/22[106] 1306010F0BBAAAA, 0501030I0AAABAB, 0501030L0AAABAB, 0501030P0AAABAB, 0501030V0AAAFAF, 0501060D0AAAMAM, 0501090R0AAABAB, 0501100H0AAAHAH, 1305020A0AAABAB, 1306020J0AAAEAE, 0802020G0AAADAD and 0803042E0AAABAB	Nesbitt *et al.*, (2020)[107]
Oral antibiotics	Doxycycline 100 mg	100 mg twice per day	56	£0.14	£7.75	£42.47		
	Lymecycline 408 mg	408 mg twice per day	56	£0.23	£12.92			
	Minocycline 100 mg	100 mg twice per day	56	£0.50	£27.94			
	Tetracycline 250 mg	500 mg twice per day	112	£0.20	£21.87			
	Clindamycin 300 mg + Rifampicin 300 mg	Twice per day	56	£1.27	£141.89			Ingram *et al.*, (2018)[39]
		Twice per day	56	£1.26				
Dapsone	Dapsone 100mg	100 mg per day	28	£1.15	£32.33	£32.33		Zouboulis *et al.*, (2014)[108]
Retinoids	Acitretin 10 mg	0.4 mg/kg per day	112	£0.47	£52.65	£62.70		Ingram *et al.*, (2018)
	Isotretinoin 40 mg	0.85 mg/kg per day	56	£1.30	£72.76			Zouboulis *et al.*, (2014)[108]
Ciclosporin	Ciclosporin 100 mg	4 mg/kg per day	112	£2.28	£254.91	£254.91		
Anti-androgens	Cyproterone 100 mg	100 mg per day	28	£0.86	£24.15	£24.15		

Abbreviations: BSC: best supportive care; NHSE: NHS England.

Drug administration costs

The cost of SC administration of secukinumab was considered in the model, as presented in Table 52. This was based on the hourly cost for a community-based Band 6 nurse and was incurred only once on the first use of SC therapy, as patients self-administer thereafter. It was assumed that BSC incurs no administration costs.

Table 52: Administration costs

Administration type	Average cost	Source
SC	£54.92	PSSRU 2021[110]

Abbreviations: PSSRU: Personal Social Services Research Unit; SC: subcutaneous.

B.3.5.2 Health-state unit costs and resource use

The unit costs and associated resource use rates by health state are summarised in Table 53 and Table 54, respectively. The model considered both surgery and non-surgery related disease management costs for the overall resource use cost calculations. In alignment with the approach taken in TA392, resource use rates by health states were informed by input from a survey of physicians (n=40) who actively treat patients with moderate-to-severe HS in the UK.[1, 111] The model assumed resource use rates to be dependent on the response health state and independent of intervention received.

Table 53: List of unit costs by resource type

Resource type	Resource item	Unit cost	Code/Description	Source
Surgery related	Inpatient stay due to HS surgery	£4,652.57	Weighted average, HRG code: JC40Z (elective), JC41Z (elective), JC42C (elective) and JC43C (elective)	National Schedule of NHS costs 20/21[112]
	Outpatient visits due to HS surgery	£168.29	HRG code: 330	
	Visits to wound-care due to HS surgery	£168.29		
Non-surgery related	Non-surgical inpatient visits	£2,964.06	Weighted average, HRG code: JD07D (elective patients) and JD07K (elective patients)	
	Outpatient visits (due to any reasons)	£168.29	HRG code: 330	
	Visits to wound care not due to HS surgery	£168.29	HRG code: 330	
	Emergency room visits	£332.46	Weighted average, HRG code: VB01Z–VB09Z	

Abbreviations: HRG: healthcare resource group; HS: hidradenitis suppurativa; NHS: National Health Service.

Table 54: List of resource use by health state

Resource type	Resource item	Annual resource use frequency				Source
		High Response (HiSCR≥75)	Response (HiSCR50–74)	Partial response (HiSCR25–49)	No response (HiSCR<25)	
Surgery related	Inpatient stay due to HS surgery	0.13	0.22	0.54	0.80	Expert opinion from a survey of UK physicians (n=40)[111]
	Outpatient visits due to HS surgery	0.22	0.35	0.67	0.94	
	Visits to wound-care due to HS surgery	0.12	0.17	0.40	0.85	
Non-surgery related	Non-surgical inpatient visits	0.11	0.23	0.29	0.45	
	Outpatient visits (due to any reasons)	3.10	3.51	4.44	4.68	
	Visits to wound care not due to HS surgery	0.67	0.47	0.64	0.45	
	Emergency room visits	0.12	0.20	0.47	0.57	

Abbreviations: HiSCR: Hidradenitis Suppurativa clinical response; HS: hidradenitis suppurativa.

B.3.5.3 Adverse reaction unit costs

As noted in Section B.3.3.4, no AEs were included in the base case model. However, the impact of all-grade AE management costs (Table 55) were considered in a scenario analysis.

Table 55: AE unit costs

AE	Unit cost	Code/Description	Source
Headache	£0.00	Assumed to have no material implications to costs, given they are mild/moderate AEs	-
Nasopharyngitis	£0.00		
Upper Respiratory tract infection	£199.82	Weighted average, Total Outpatient Attendance, Service codes 340 (Respiratory Medicine) and 341 (Respiratory Physiology)	NHS Reference Costs 2020/2021[112]
Diarrhoea	£39.23	GP consultation lasting 9.22 minutes of patient contact time	PSSRU (2020/2021)[110]
Gastroenteritis	£39.23		
Influenza	£0.00	Assumed to have no material implications to costs, given they are mild/moderate AEs	-
Toothache	£0.00		
Bronchitis	£199.82	Weighted average, HRG code: 340 and 341	NHS Reference Costs 2020/2021[112]
Viral gastroenteritis	£39.23	GP consultation lasting 9.22 minutes of patient contact time	PSSRU (2020/2021)[110]

Abbreviations: AE: adverse event, NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

B.3.5.4 Miscellaneous unit costs and resource use

No additional miscellaneous unit costs and resource use were included in the model.

B.3.6 *Severity*

As noted in Section B.1.3, moderate-to-severe HS is a debilitating skin condition defined by its chronicity, and its recurrent and painful flares that have a considerable negative impact on the QoL of patients with HS. Feedback from BAD during the draft scope consultation indicated that the burden of living with either chronic pain or unpredictable episodic pain associated with HS flares should not be underestimated, noting that quite often patients report pain scores of 10/10 (worst pain imaginable).[89] Without active treatment (i.e., BSC is insufficient), HS is characterised by progressive scarring that can limit function and may require extensive surgery to reverse.[89] It is worth noting that the peer-reviewed literature indicates that the impact of HS on patients' quality of life is comparatively higher than other dermatological diseases, including moderate-to-severe psoriasis, acne and chronic urticaria.[16, 17, 31, 113-115] Additionally, HS is associated with an increased risk of mortality in patients with HS as compared with the general population.[49, 101] However, this was conservatively not modelled as the data were not considered sufficient to appropriately inform the severity analysis. Patients were therefore assumed to have the same mortality rate as for the general population.

Table 56: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission

Sex distribution	56.3% Female (Table 38)	Baseline characteristics Section B.3.3.1
Starting age	36.2 years (Table 38)	Baseline characteristics Section B.3.3.1

Abbreviations: QALY: quality-adjusted life year.
Source: Weighted average of the total estimates from all trial arms of the SUNSHINE (N=541) and SUNRISE (N=543) trials

Table 57: Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
N/A			

Abbreviations: QALY: quality-adjusted life year; TA: technology appraisal

Table 58: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
HiSCR >75	[redacted] ([redacted])	[redacted]
HiSCR 50–74	[redacted] ([redacted])	[redacted]
HiSCR 25–50	[redacted] ([redacted])	[redacted]
HiSCR <25	[redacted] ([redacted])	[redacted]

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; QALY: quality-adjusted life year

Table 59: Summary of QALY shortfall analysis

Expected total QALYs for the general population (discounted)	Total QALYs that people living with a condition would be expected to have with current treatment (discounted)	QALY shortfall	
		Absolute	Proportional
21.583	[redacted]	[redacted]	[redacted]

Abbreviations: QALY: quality-adjusted life year
Source: Hernandez-Alava *et al*., (2022).[105]

B.3.7 *Uncertainty*

As discussed in Section B.3.2.3, the base case was in line with the proposed posology for secukinumab in HS. However, the modelling of up-titration to Q2W required certain assumptions and was based on best available data from the SUNSHINE and SUNRISE trials, even though both trials were not designed to directly account for up-titration.

B.3.8 *Managed access proposal*

Not applicable.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

A summary of the variables applied in the model in the base case analysis is provided in Table 60.

Table 60: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model properties			
Time horizon	Lifetime	N/A	B.3.2.2
Cycle length	4 weeks	N/A	B.3.2.2
Half-cycle correction	Yes	N/A	B.3.2.2
Discount rate, costs	3.5%	N/A	B.3.2.2
Discount rate, benefits	3.5%	N/A	B.3.2.2
Perspective on cost	NHS and PSS	N/A	B.3.2.2
Perspective on outcomes	All relevant health effects	N/A	B.3.2.2
Mortality risk	General population mortality	N/A	B.3.3.5
Age-adjusted utility	Yes	N/A	B.3.4.5
Patient characteristics			
Mean age (years)	36.2	29.1–43.3 (Normal)	B.3.3.1
Female (%)	56.3	45.1–67.1 (Beta)	B.3.3.1
Weight (kg)	93.47	N/A	B.3.3.1
Efficacy			
Response criteria	HiSCR Score	N/A	B.3.2.2
HiSCR threshold	HiSCR≥25	N/A	B.3.3.2
Efficacy assessment point	Week 16	N/A	B.3.2.2
Transition probabilities	Four sets of transition probabilities are used in model: • Induction phase (0–16 weeks) • Maintenance/Up-titration phase (16–28 weeks) • Maintenance phase (28–52 weeks) • Maintenance phase (52+ weeks)	Varied based on CODA parameters generated during the generation of the average probabilities	B.3.2.2
Discontinuation			

Discontinuation rates (per cycle) for secukinumab in Year 1		[redacted]	[redacted]	B.3.3.3
Discontinuation rates (per cycle) for secukinumab in Year 2 and beyond		0.475%	0.004–0.006 (Beta)	B.3.3.3
Utilities				
SEC Q4W	HiSCR≥75	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR25–49	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR50–74	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR<25	[redacted]	[redacted] (Beta)	B.3.4.5
SEC Q2W	HiSCR≥75	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR25–49	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR50–74	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR<25	[redacted]	[redacted] (Beta)	B.3.4.5
BSC	HiSCR≥75	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR25–49	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR50–74	[redacted]	[redacted] (Beta)	B.3.4.5
	HiSCR<25	[redacted]	[redacted] (Beta)	B.3.4.5
Disease management costs				
Acquisition cost: secukinumab 300mg		List price: £1218.78 PAS price: [redacted]	N/A	B.3.5.1
Administration cost: SC		£54.92	£44.59–£66.20 (Gamma)	B.3.5.1
Inpatient stay due to surgery		£4,652.57	£3785.51–£5607.69 (Gamma)	B.3.5.2
Outpatient visits due to HS surgery		£168.29	£136.92–£202.83 (Gamma)	B.3.5.2
Visits to wound care unrelated to HS surgery		£168.29	£136.92–£202.83 (Gamma)	B.3.5.2
Non-surgical inpatient visits		£2,964.06	£2411.68–£3572.55 (Gamma)	B.3.5.2
Outpatient visits (due to any reason)		£168.29	£136.92–£202.83 (Gamma)	B.3.5.2
Visits to wound care not due to HS surgery		£168.29	£136.92–£202.83 (Gamma)	B.3.5.2
Emergency room visits		£332.46	£270.51–£400.72 (Gamma)	B.3.5.2

Abbreviations: BSC: best supportive care; CI: confidence interval; HiSCR: Hidradenitis Suppurativa Clinical Response; HS: hidradenitis suppurativa; N/A: not applicable; NHS: National Health Service; PSS: Personal Social Services; SC: subcutaneous.

B.3.9.2 Assumptions

A list of the assumptions made in the base case analysis and their justifications are provided in Table 61. Where appropriate, the exploration of the potential impact of these assumptions in a scenario analysis is noted.

Table 61: List of assumptions for the base case analysis

Model input	Description of base case assumption	Justification
Up-titration	It was assumed that non-responders to secukinumab Q4W at the end of the 16-week Induction phase would up-titrate to secukinumab Q2W for the 12-week Up-Titration phase	Reflects the anticipated wording in the SmPC
Efficacy	Secukinumab Q4W and BSC patients transition between health states during the Induction phase, informed by average per cycle transition probabilities derived from the secukinumab Q4W and placebo arms of the Week 0–16 data from the SUNSHINE and SUNRISE trials	Reflects available data from the SUNSHINE and SUNRISE trials; use of average transition probabilities across each phase avoids introducing uncertainty from small numbers of patients experiencing some transitions in some 4-week cycles in the trial
	Patients who do not respond to secukinumab Q4W at Week 16 are up-titrated to Q2W and transition between health states over the Up-Titration phase, informed by average per cycle transition probabilities derived from the secukinumab Q2W Week 16–52 data from the SUNSHINE and SUNRISE trials. Following up-titration to Q2W, patients not responding at Week 28 discontinued secukinumab.	In the absence of up-titration in the trial data, it is considered that transitions for patients in the trial arm which had received 16 weeks of secukinumab Q2W and were continuing to receive secukinumab Q2W would best reflect the modelled population who receive 16 weeks of Q4W followed by 12 weeks of Q2W
	It is assumed that secukinumab Q4W responders experiencing loss of response post-Week 16 could not receive up-titration and discontinued directly to BSC	Simplifying assumption taken to avoid adding the significant model complexity that would be required to allow such an analysis, which in the absence of trial data would necessarily be based on strong assumptions.
	In the Maintenance phase, average per cycle transition probabilities for secukinumab-treated patients were derived from the Week 16–52 data from the SUNSHINE and SUNRISE trials for each dosing regimen	Reflects available data from the SUNSHINE and SUNRISE trials; use of average transition probabilities across each phase avoids introducing uncertainty from small numbers of patients experiencing some transitions in some 4-week cycles in the trial
	In the Maintenance phase, no HiSCR transition probabilities were available from the SUNSHINE and SUNRISE trials to inform the BSC-treated patients. As such, risk of loss of response estimates derived from the PIONEER trials were used to model transitions from response categories (HR, R or PR) to the NR health state.	In the absence of data from the SUNSHINE and SUNRISE trials, Maintenance phase transitions for BSC were informed by the PIONEER trials, which were considered the best available data[99]

	In the absence of data, it was assumed that the Maintenance phase data for Week 16–52 would continue to be applied in Week 52+ for all treatments.	Limited trial data are available for secukinumab and BSC beyond Week 52; any treatment waning in the long term is accounted for in discontinuation rate (see below)
Discontinuation rate	For patients responding at the Week 16 response assessment, treatment with secukinumab Q4W was assumed to continue until discontinuation for any reason, death or reaching the end of the model time horizon	Loss of treatment response in patients with HS is clinically measurable and will therefore lead to treatment discontinuation. As such, the discontinuation rate accounts for treatment waning, as well as discontinuation for other reasons
	For patients up-titrated to Q2W who were responding at the Week 28 response assessment, treatment with secukinumab Q2W was assumed to continue until discontinuation for any reason, death or reaching the end of the model time horizon	
	It was assumed that the secukinumab all-cause discontinuation rates do not vary with HiSCR response category or dosing regimen	All-cause discontinuation rate for Year 1 were based on pooled data up to Week 52 from SUNSHINE and SUNRISE trials. As discontinuation data were similar between secukinumab trial arms, separate rates for Q2W and Q4W were not considered necessary. For Year 2 onwards, the estimates were considered from published literature[103]
	It was assumed that patients discontinuing secukinumab in the Maintenance phase initially remain in their current health state but are henceforth subject to the transition probabilities applied to BSC-treated patients in the Maintenance phase, as described under Efficacy above	It was considered a reasonable assumption that all-cause discontinuation did not result in an immediate change of health state
BSC	It was assumed that the patients who commence BSC at any point in the model will continue to receive BSC treatment until end of the model time horizon or death	Reflects that patients who have received BSC have failed or otherwise discontinued all other treatment options or have a contraindication or intolerance to them.
Mortality risk	Patients were assumed to be at risk of death throughout the model time horizon, irrespective of health state or response rate	Age-based mortality risk was derived from the ONS life tables of the general population. Although the peer-reviewed literature reports an increased risk of mortality in patients with HS as compared with the general population, it was conservatively not modelled in the absence of data that could appropriately inform the model
AEs	No AEs were included in the base case analysis	As reported in Section B.2.10.5, no SAE preferred term occurred in more than one patient in either secukinumab arm during Treatment Period 1

		(Weeks 0–16). Longer-term data during the Entire study period (Week 52) presented in Appendix F indicated that SAEs by preferred term had an incidence ≤5% Given these data, no AEs were included in the economic analysis. It may also be noted that use of treatment-specific utility data implicitly captures the impact of variation in disutilities due to treatment related AEs not already captured in the health states.
Surgery	Surgeries due to disease were considered as part of the resource use costs incurred in each cycle (specific to each health state) and not as a separate health state	This approach reflects that surgeries for HS are transient and discrete events, not chronic treatments. They are also heterogeneous in nature. The model considers the management cost associated with these surgeries as part of the disease management cost calculations
Disease management	The model assumed that resource use for surgery related, and non-surgery related disease management activities was only dependent on the health state i.e., different HiSCR response categories, and independent of treatments received	Patients in the same health state are assumed to have a consistent level of health on average. Therefore, patients in the same health state are also assumed to have similar healthcare resource utilisation on average
Secukinumab administration	Administration of secukinumab was associated with a one-off cost for being trained by a community-based Band 6 nurse to self-administer secukinumab	Since patients can self-administer secukinumab after appropriate training, it was assumed that no further administration costs will be incurred
Health state utility values	Utility values were assumed to be treatment-dependent as well as health-state-dependent	HiSCR response rates were assumed as a proxy for change in utility gains. However, analyses of the trial utility data also suggested that utility values varied by assigned treatment arm within each health state.
Disutility due to surgery	Disutility due to surgery was not considered due to lack of data	The model did not consider disutility for surgery due to lack of data identified in the economic SLR. This was a simplifying assumption, given feedback received by the NICE Committee in TA392 indicated biologic treatment in combination with surgery may reduce the need for some types of surgical procedure.[1]

Abbreviations: BSC: best supportive care; CI: confidence interval; HiSCR: Hidradenitis Suppurativa Clinical Response; ONS: Office for National Statistics.

B.3.10 *Base-case results*

B.3.10.1 Base-case incremental cost-effectiveness analysis results

A summary of results in the probabilistic base-case analysis and net health benefits (NHB) are presented in Table 62 and Table 63, respectively.

At the confidential PAS price, the ICER was within the £20,000–£30,000 range considered cost-effective. Incremental NHB indicated that secukinumab was cost-effective at a willingness to pay threshold of £30,000.

The probability of cost-effectiveness at WTP thresholds of £20,000 and £30,000 is presented in Table 64. These results demonstrate secukinumab to be a cost-effective option for the treatment of moderate-to-severe HS versus BSC, the comparator relevant to UK clinical practice.

Disaggregated deterministic results of the base case incremental cost-effectiveness analysis are presented in Appendix J.

Table 62: Probabilistic base-case results

	Total			Incremental			ICER	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Versus baseline (£/QALY)	Incremental (£/QALY)
BSC	[redacted]	22.760	[redacted]	-	-	-	-	
SEC	[redacted]	22.760	[redacted]	[redacted]	0.000	[redacted]	£29,129	

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

Table 63: Incremental net health benefit

	Total		Incremental		Incremental NHB	
	Costs	QALYs	Costs	QALYs	At £20,000	At £30,000
BSC	[redacted]	[redacted]	-	-	-	-
SEC	[redacted]	[redacted]	[redacted]	[redacted]	−0.72	0.06

Abbreviations: BSC, best supportive care; NHB, net health benefit; QALYs: quality-adjusted life years; SEC, secukinumab.

Table 64: Probability of cost-effective

	Probability of cost-effective at £20,000/QALY gained	Probability of cost-effective at £30,000/QALY gained
SEC	0.40%	62.00%
BSC	99.60%	38.00%

Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; SEC, secukinumab.

B.3.11 *Exploring uncertainty*

B.3.11.1 Probabilistic sensitivity analysis

As reflected in the base case results presented in Section B.3.10, probabilistic sensitivity analyses with 1,000 iterations were performed in order to assess the uncertainty associated with model input parameters. Use of 1,000 iterations was deemed appropriate based on the results of an NMB convergence tests, as shown in Figure 35.

Figure 35: Convergence plot for Incremental NHB at £30,000/QALY

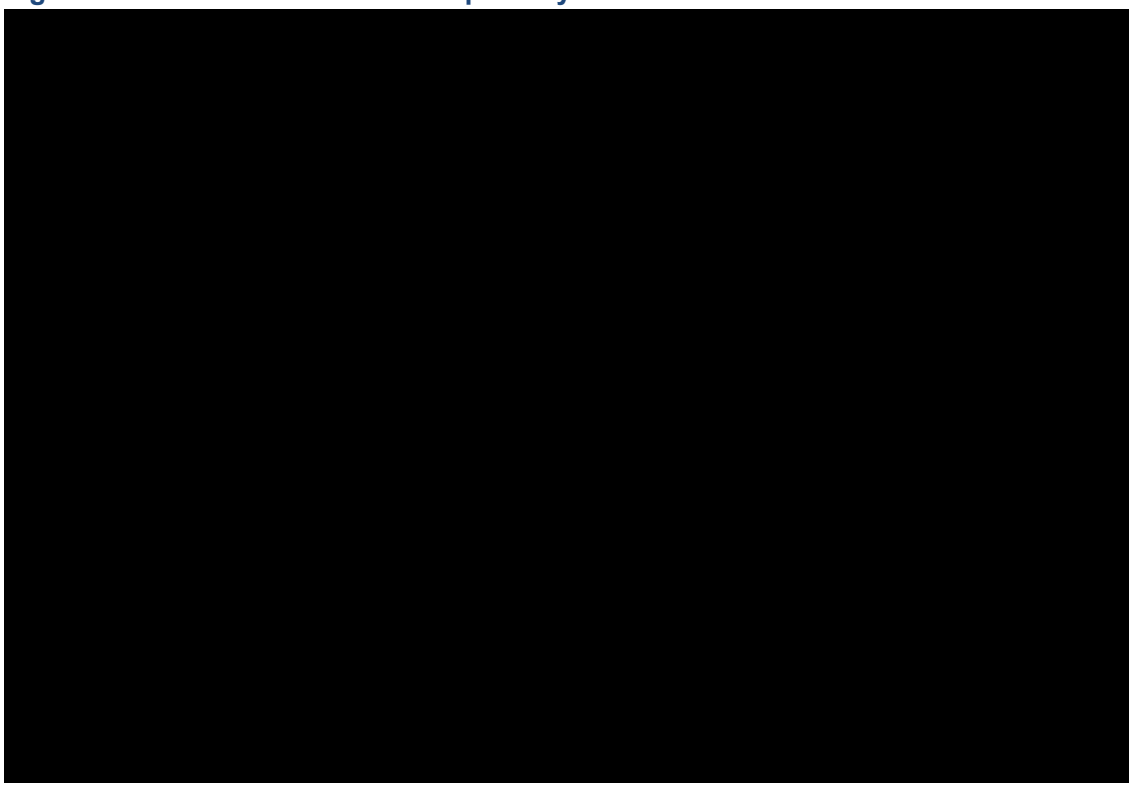
Abbreviations: NHB: net health benefit; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

The probabilistic base case results are presented in Table 62, and the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve in Figure 36 and Figure 37,respectively.

Figure 36: Cost-effectiveness plane scatterplot

Abbreviations: BSC: best supportive care; WTP: willingness to pay; SEC: secukinumab; vs: versus.

Figure 37: Cost-effectiveness acceptability curve



Abbreviations: BSC: best supportive care; CEAC: cost-effectiveness acceptability curve; QALY: quality-adjusted life year; SEC: secukinumab.

B.3.11.2 Deterministic sensitivity analysis

A summary of results in the deterministic base-case analysis and incremental NHB are presented in Table 65 and Table 66, respectively. The deterministic base case results are in close alignment with the probabilistic base case results in Section B.3.10.1.

Table 65: Deterministic base case results

	Total			Incremental			ICER	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Versus baseline (£/QALY)	Incremental (£/QALY)
BSC	[redacted]	22.797	[redacted]	-	-	-	-	
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165	

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

Table 66: Incremental net health benefit

	Total		Incremental		Incremental NHB	
	Costs	QALYs	Costs	QALYs	At £20,000	At £30,000
BSC	[redacted]	[redacted]	-	-	-	-
SEC	[redacted]	[redacted]	[redacted]	[redacted]	−0.65	0.10

Abbreviations: BSC, best supportive care; NHB, net health benefit; QALYs: quality-adjusted life years; SEC, secukinumab.

The ten most influential variables in the deterministic sensitivity analysis (DSA) for the analysis of secukinumab versus BSC are presented as tornado plots in Figure 38. The DSA results indicated that only three variables crossed the point indifference (i.e., when incremental NHB is zero) for either their upper bound or lower bound value: the BSC NR health state utility, resource use for the number of hospitalisations for HS surgeries and cost of inpatient stay due to surgery.

Figure 38: Tornado plot (incremental NHB)

Abbreviations: BSC: best supportive care; HR: high-responders; NR: non-responders; NHB: net health benefit; Q2W: every two weeks; Q4W: every four weeks; QoL: quality of life; R: responders.

B.3.11.3 Scenario analysis

A number of scenario analyses were conducted to explore the impact of certain assumptions and alternative inputs within the base case economic analysis. Each scenario analysis is described in Table 67 and full results of all scenario analyses are presented in Table 68.

Table 67: Summary of scenario analyses

#	Scenario analysis value	Base case value	Rationale
1	Assume per cycle transition probabilities for SEC and BSC	Average 4-week transition probabilities	Use of average transition probabilities across each phase avoids introducing uncertainty from small numbers of patients experiencing some transitions in some 4-week cycles. However, this scenario was provided to quantify this uncertainty.
2	Assume no up-titration	Assume up-titration for secukinumab-treated patients post response assessment at Week 16	This scenario assesses the impact of no up-titration on the model results
3	Assume all treatment pooled utilities for SEC and BSC	Assume treatment-specific utilities for SEC dosing regimens and BSC	This scenario assesses the impact of using treatment-independent utilities from the SUNSHINE and SUNRISE on the overall QALYs and ICER
4	Assume TA392 utilities for SEC and BSC	Assume treatment-specific utilities for SEC dosing regimens and BSC based on pooled utility values from the SUNSHINE and SUNRISE trials	This scenario assesses the impact of using different utility sources on the overall QALYs and ICER
5	Include AE-related QALY decrements and management costs	No AEs included	This scenario assesses the impact of the inclusion of AE-related QALY decrements and management costs on the overall costs and ICER
6	Mortality risk informed by 2018-2020 UK National Life Table	National UK life tables for 2017–2019	This scenario assessed the impact of the latest mortality risk tables on the overall costs and ICER
7	Assume BSC costs include 31% of biologics	Assume BSC costs that include 0% of biologics	This scenario assesses the impact of including biologics as a component of BSC on the overall costs and ICER. Clinical expert opinion indicated that 31% of patients would receive biologics as part of BSC; however, given the lack of data to inform the benefits of biologics as well as costs, it was excluded from the base case
8	Assume BSC costs include 5% of biologics	Assume BSC costs that include 0% of biologics	This scenario assesses the impact of varying the percentage use of biologics on the overall costs and ICER
9	Assume no BSC costs	Assume BSC costs that include 0% of biologics	This scenario assesses the impact of no BSC costs on the overall costs and ICER

Abbreviations: AEs: adverse events; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SEC: secukinumab.

Table 68: Scenario analyses results (probabilistic)

Scenario #	Treatment	Total			Incremental			ICER vs BSC (£/QALY)
		Costs	LYs	QALYs	Costs	LYs	QALYs	
Base case	BSC	[redacted]	22.760	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.760	[redacted]	[redacted]	0.000	[redacted]	£29,129
1	BSC	[redacted]	22.827	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.827	[redacted]	[redacted]	0.000	[redacted]	£28,770
2	BSC	[redacted]	22.817	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.817	[redacted]	[redacted]	0.000	[redacted]	£29,641
3	BSC	[redacted]	22.756	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.756	[redacted]	[redacted]	0.000	[redacted]	£44,143
4	BSC	[redacted]	22.761	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.761	[redacted]	[redacted]	0.000	[redacted]	£27,478
5	BSC	[redacted]	22.770	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.770	[redacted]	[redacted]	0.000	[redacted]	£29,190
6	BSC	[redacted]	22.710	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.710	[redacted]	[redacted]	0.000	[redacted]	£29,279
7	BSC	[redacted]	22.765	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.765	[redacted]	[redacted]	0.000	[redacted]	£22,808
8	BSC	[redacted]	22.731	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.731	[redacted]	[redacted]	0.000	[redacted]	£28,117
9	BSC	[redacted]	22.797	[redacted]	-	-	-	-
	Secukinumab	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£32,599

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

B.3.11.4 Summary of sensitivity analyses results

The scatter plot showed that the base case cost-effectiveness results exhibit little variation when the combined distributional uncertainty across model parameters is taken into account. The probabilistic scenario analyses results showed that secukinumab was within the £20,000–£30,000 range considered cost-effective, with the exception of scenario 3 and 9. As demonstrated by the DSA results, only three variables crossed the point indifference (i.e., when incremental NHB is zero) for either their upper bound or lower bound value: the BSC NR health state utility, resource use for the number of hospitalisations for HS surgeries and cost of inpatient stay due to surgery.

B.3.12 *Subgroup analysis*

No subgroup analyses were conducted.

B.3.13 *Benefits not captured in the QALY calculation*

Systemic comorbidities of HS reported in the peer-reviewed literature include axial spondyloarthritis and psoriatic arthritis.[116-118] Since these are licensed indications for secukinumab with optimised NICE recommendations, the introduction of secukinumab as a treatment for HS could have benefits for patients with these concomitant comorbidities. These benefits will not be captured within the cost per QALY analysis of this appraisal, which captures benefits directly associated with the treatment of HS only. Although the peer-reviewed literature reports an increased risk of mortality in patients with HS as compared with the general population, this was conservatively not modelled as the data were not considered sufficient to appropriately inform the model.[49, 101]

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

Technical validation

In alignment with best practice, validation of the economic model structure was conducted by an independent health economist prior to the submission. These quality-control procedures made use of two checklists similar to that reported in the published literature (for technical and stress test checks) to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.[119] A technical cell by cell verification of formulae, functions and coding was performed as part of this process, as was review of all model calculations, including standalone formulae, equations and Excel macros programmed in Visual Basic for Applications. The correct functioning of the sensitivity and scenario analyses was also reviewed. The stress test ensured that the expected effect is observed when key inputs are varied in the model (e.g., when utilities for all health states and for AEs are set to 0, all QALYs should result equal to 0)

Clinical validity

The model structure was closely aligned with the model used in the adalimumab NICE submission (TA392) for the assessment of the cost-effectiveness of adalimumab in moderate-to-severe HS.[1] The use of a granular Markov model was aligned with clinical expert opinion and the

Committee's preference in TA392, given that it reflected how treatment success is defined in the clinical management of hidradenitis suppurativa.[1]

B.3.15 *Interpretation and conclusions of economic evidence*

Generalisability of the analysis

The economic evaluation is based on the population of patients with moderate-to-severe HS enrolled in the two identically designed Phase III SUNSHINE and SUNRISE trials, which comprised patients with previous biologic exposure, particularly adalimumab, as well as biologic-naïve patients. As noted in Section B.2.7 and Section B.2.12, subgroup analysis indicated that results for HiSCR50 at Week 16 were consistent between bio-experienced and bio-naïve patients, and were consistent in patients who were allowed concomitant antibiotics (antibiotics stratum) and those who were not (non-antibiotic stratum). As such, the trial ITT data were considered the most robust source to inform the efficacy estimates used in the analysis, with the placebo arm up to Week 16 being generalisable to current NHS practice, and the secukinumab arms up to Week 52 being generalisable to future NHS practice should secukinumab be recommended by the Committee.

The patient population informing the analysis remains representative of the population of interest in decision problem for this submission, given that secukinumab is being positioned for 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.

Strengths of the economic evaluation

The model structure appropriately captures the key features of HS and the clinical pathway of care for the patient population addressed in the decision problem for this submission. The use of a granular model given the dichotomous primary end point (HiSCR50 response) in the SUNSHINE and SUNRISE trials was aligned with the Committee's preference in TA392.[1] Treatment pathways included in the model were based on the treatments available in UK clinical practice. As per the NICE reference case, the perspective on cost was NHS and PSS.

Limitations of the economic evaluation

While the longer-term follow up data from the SUNSHINE and SUNRISE trials available at the time of submission demonstrate robust evidence for the sustained benefits of secukinumab, the immaturity of the trial data means that there is uncertainty associated with the extrapolation of lifetime outcomes. In addition, given the lack of trial data for the placebo arms beyond Week 16, data from the PIONEER trials were required to inform the risk of loss of response estimates for BSC in the Maintenance phase. Further, the modelling of up-titration to Q2W required certain assumptions and was based on best available data from the SUNSHINE and SUNRISE trials. Overall, the SUNSHINE and SUNRISE trials are high-quality, robust and blinded RCTs, thus reducing uncertainty in the clinical data that are available.

Summary of economic evidence for secukinumab versus BSC

The cost-effectiveness of secukinumab in HS was evaluated versus BSC, the most clinically relevant comparator for the anticipated positioning of secukinumab. The base case probabilistic ICER was £29,129 per QALY gained and did not differ meaningfully from the deterministic ICER

(£28,165 per QALY gained). The sensitivity results indicated that the base case results exhibited little variation at a cost-effectiveness threshold of £30,000 per QALY gained.

Overall, the results indicate that secukinumab to be a cost-effective option for the treatment of moderate-to-severe HS versus BSC at the anticipated positioning within the NHS.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Summary of Information for Patients (SIP)

December 2022

File name	Version	Contains confidential information	Date
ID4039_Secukinumab_HS_Summary of Information for Patients_[NoACIC]_13Dec2022	N/A	No	13th December 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Secukinumab
Brand name: Cosentyx®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population being considered for this medicine is adults with moderate-to-severe hidradenitis suppurativa (HS). This population is in line with the population expected to be included in the regulatory paperwork for secukinumab in the United Kingdom (UK), known as its marketing authorisation.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The regulatory paperwork for secukinumab in HS is being reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA). This review is currently pending, but more information on the authorisation approval can be found in Document B, Section B.1.2).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

N/A

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is hidradenitis suppurativa?

HS is a painful, long-term inflammatory skin condition.[1, 2] It causes painful bumps and sores (abscesses) to form around hair follicles. Follicles are tiny holes from which hair grows out of the skin. The disease most commonly affects parts of the body where the skin rubs together.[1] This includes the armpits, under the breasts, the groin area, the abdomen folds and the buttocks.

What causes hidradenitis suppurativa?

It is still unclear why some people get this disease and others do not, but evidence suggests that HS is caused by blockage of the hair follicles in the skin.[1] This leads to a build-up of fluid and pus within the hair follicles. The follicles begin to swell and eventually burst, predisposing the skin to inflammation and infection. Pressure or rubbing on the skin can clog the follicles or it can further irritate them.

How many people have HS and what are the risk factors?

HS affects around 1 in 130 people in the UK. This means that around 349,192 people live with the disease in England, making HS a common disease.[3] Although it can occur in anyone, certain risk factors put people at higher risk than others in the general population. The disease tends to run in families with a history of HS.[4] It affects more people of African-Caribbean family origin than people of European family origin.[5] Women are three times more likely to develop the disease than men.[6] It is also more likely to occur in people who are obese or smokers.[7-9] Evidence suggests that hormonal changes play a role. In women, HS may be worse before menstrual periods or improve during pregnancy.[10]

Symptoms and health conditions associated with HS

Although the severity of the disease varies between people, HS usually causes one or more painful red bumps on the skin. These bumps become inflamed and leak pus. They may also itch and burn. In severe cases, sinus tracts may form. These are narrow channels that run under the skin. Blood or a bad-smelling pus may leak from sinus tracts. Scars may also form on the skin.

People with HS often live with other health conditions. They may also have diabetes, heart disease, arthritis, inflammatory bowel disease and depression.[11, 12] As a result, they may present with other symptoms typical of these health conditions.

Disease burden

People with HS often describe the pain, itching and bad-smelling pus as the most burdensome symptoms of the disease.[13] The burden of these symptoms worsen in severe cases of HS. Because of the debilitating nature the disease, it has the greatest burden on the emotional health of people with HS, more than any other skin condition.[14, 15] People

report depression, anxiety and suicidal thoughts.[14] They experience stigmatisation, loneliness and low self-esteem.[16, 17] They also have poor sleep quality and sexual dysfunction.[18, 19] Greater levels of pain are strongly linked to a poorer quality of life, including reduced mental wellbeing.[20] The painful bumps make it very difficult for them to carry out tasks of daily living. For example, they find it difficult even climbing the stairs because of how painful the bumps are.[21] Social interactions and relationships with family and friends are made difficult because people with active disease tend to isolate themselves or avoid others.[21] They also report unemployment, lack of work productivity and absence from work because of their disease.[22, 23]

Living with other health conditions also adds to the disease burden. Research suggests that there is a higher risk of death in people with HS and associated health conditions when they are compared with people without the disease and the associated health conditions.[24]

Burden on carers and society

Family members are also affected by the disease. They report poor mental health and quality of life. This is often the case if their partner with HS has anxiety, depression or sexual dysfunction.[25] The increase in daily spend also negatively affects their quality of life and the household income because of the continuous skin care required in HS.[26]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

There are no specific tests available to diagnose HS. A diagnosis of HS relies on careful examination for the typical signs and symptoms of the disease.[27] Doctors may also perform tests to rule out other conditions that may resemble HS.[28]

Doctors determine the severity of HS using the Hurley staging system.[29] This is a well-known system that groups people into three main stages. Stage I for mild HS, Stage II for moderate and Stage III for severe.

A summary of the Hurley staging system is presented in Table 1.

Table 1: Hurley staging system for HS

Stage	Disease severity	Summary of stage description
I	Mild	Single or multiple bumps present on the area(s) of skin affected. There are no sinus tracts or scars present
II	Moderate	Bumps present are persistent and separated by areas of healthy skin. Sinus tracts and scars are also present
III	Severe	There are multiple, interconnected bumps and sinus tracts present across the entire area(s) of skin affected

Abbreviations: HS: hidradenitis suppurativa
Source: adapted from Hurley (1989).[29]

Because there are no tests to aid diagnosis, people with HS are often misdiagnosed with other conditions or go undiagnosed for many years without treatment.[30] This means that for some people their disease remains uncontrolled. It may also mean that their disease is likely to worsen.

2c) Current treatment options

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

1) Please also consider:
    a. if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    b. are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

How is HS treated in the UK?

The management of HS depends on how severe the disease is. It could involve both medicines and surgical procedures. This is because of how difficult it is to treat the disease with either option alone.

There are published guidelines on the treatment of HS in the UK. The British Association of Dermatologists (BAD) guideline is one set of guidelines that doctors often refer to.[27] They help doctors decide what treatments to give and when to give them. This guideline is informed by evidence-based research and the general understanding in the disease area.

The BAD guideline recommends a stepwise approach to treatment based on disease severity. Medical treatments are split into two categories:

- Conventional therapies
    - Topical antibiotics, such as clindamycin
    - Oral antibiotics, such as tetracycline, or a combination of clindamycin and rifampicin
    - Acitretin
    - Dapsone
    - Ciclosporin
- Biologics
    - Adalimumab
    - Infliximab

The medical treatment ladder starts with conventional therapies, such as topical antibiotics for mild disease. Topical antibiotics are medicines prescribed by a doctor that are applied directly to the skin. An example of a topical antibiotic used in mild HS is clindamycin. If that does not work well enough, or if the bumps or scarring are already widespread, they may give systemic antibiotics, such as tetracycline. This is usually taken by mouth. If that also fails, doctors may give other treatments, such as a combination antibiotic (clindamycin and rifampicin) for moderate disease. For moderate-to-severe HS, unresponsive to these treatments, doctors may consider a number of other medications, including acitretin for men and non-fertile women, dapsone or ciclosporin.

Some people still have uncontrolled, moderate-to-severe disease after receiving all of the conventional therapies described above. For these people, doctors may choose to prescribe another type of medicine called a biologic. Adalimumab is the only biologic currently recommended by NICE for treating these people.[31] Some doctors may choose to give another biologic called infliximab. But because there is not enough evidence to

support its use, the NHS does not recommend doctors prescribing infliximab.[32] For this reason, infliximab is rarely used now in the NHS.[33] If adalimumab does not work well enough, these people no longer have any more biologic options available. They must go back to receiving best supportive care (BSC).

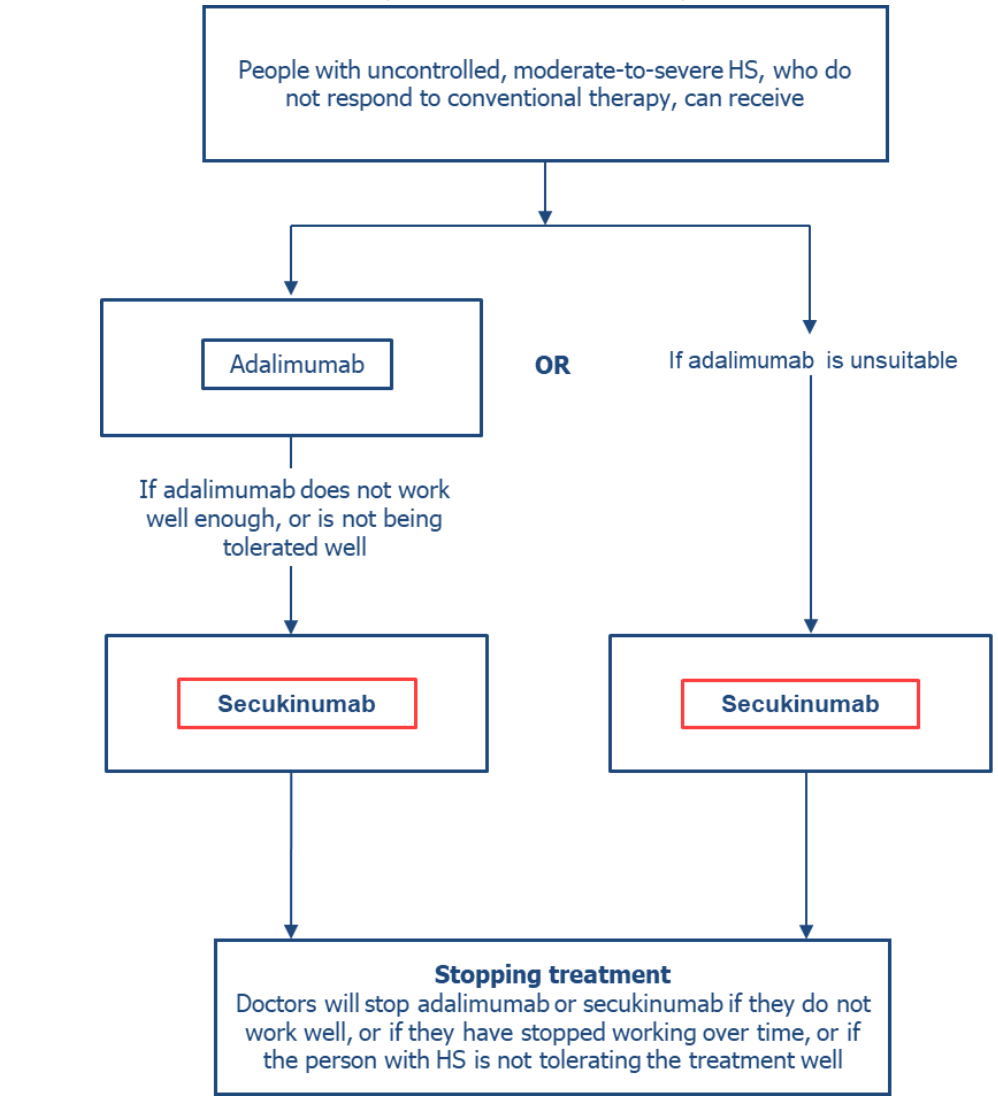
BSC consists of both surgical and non-surgical treatments.[27] Surgical options include steroid injections or simple draining of bumps. Non-surgical options include antiseptic wash, wound care, oral antibiotics, and pain killers. Doctors use both options to treat people with HS when they experience periods of active symptoms called 'flares'. The goal of treatment at this stage is to keep their flares under control rather than to treat the underlying disease. Doctors do this to try and improve the quality of life of people with HS.

Doctors may also perform surgery to treat the underlying disease either as a stand-alone treatment or in combination with medical treatments. Surgery may include extensive removal of an affected area of skin and tissue, or a few affected areas. Less invasive surgery may also be considered, such as deroofing on sinus tracts and narrow margin excision.[27] There is generally less agreement among doctors about the timing of any surgery and type of surgery used.[34] As such, there is variation in how people with HS are treated.

Where does secukinumab fit in the treatment of HS in the UK?

Because there are some people in whom adalimumab does not work well enough in (i.e., they never respond to it or lose their response to it over time) or is unsuitable, there is a need for other alternative treatment options with a different mode of action. The introduction of secukinumab would provide an alternative treatment option for people with HS and doctors who treat them. As shown in Figure 1, patients who would be able to receive secukinumab in the UK are those for whom adalimumab does not work well enough in, those who for whatever reason are unable to use adalimumab or those who do not tolerate adalimumab well enough.

Figure 1: The current treatment pathway for people in the UK with moderate-to-severe HS and where in this pathway secukinumab is likely to be used



The red square shows where in this pathway secukinumab is likely to be used

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

HS from the patients' perspective

Moderate-to-severe HS is a debilitating disease that can place a heavy physical and emotional burden on the lives of patients and carers. This in turn has a negative impact on their quality of life.

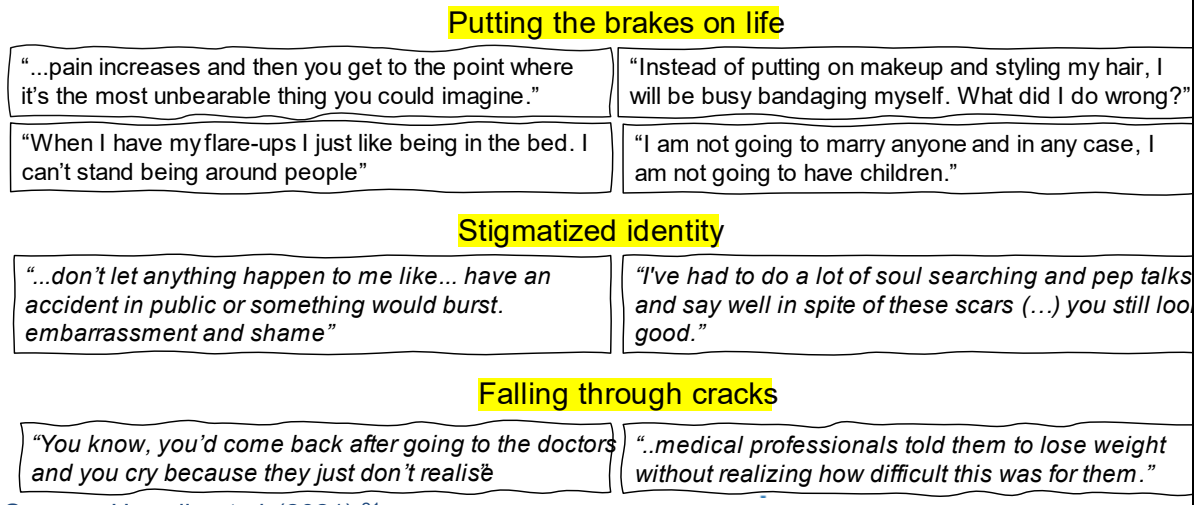
In order to capture the lived experience of people with HS, researchers conducted a systematic literature review.[21] A systematic literature review is a type of review that collects multiple research studies relevant to the topic and summarises them to answer a research question using rigorous methods.

The researchers identified three key themes of the lived experience of people with HS from the literature:

- Putting the brakes on life. The physical, mental and social consequences of HS resulted in people missing out on multiple life events.
- Stigmatized identity: concealed and revealed. People try to conceal their HS, visually and verbally, but this resulted in anticipation and fear of exposure.
- Falling through the cracks. Delayed diagnosis, misdiagnosis and lack of access to care were reported. People felt unheard and misunderstood by healthcare professionals, and healthcare interactions could enhance feelings of shame.

Figure 2 summaries some of the lived experience of people with HS.

Figure 2: How patients perceive the burden of HS



Source: Howells *et al.* (2021).[21]

In summary, evidence confirms there are many physical, mental and social challenges of living with HS and these negatively affect people's lives. Because of shame and embarrassment, people attempt to hide their HS. They are often overlooked by the healthcare system and do not feel supported in managing their condition.

The researchers of this study concluded that there is a need for improved clinical care to allow people with HS to live life more fully. There was need for early access to specialist skin doctors for diagnosis, access to better support networks and improved communication from healthcare professionals.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the

mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Secukinumab is a monoclonal antibody that belongs to a group of medicines called interleukin (IL) inhibitors.[35] Monoclonal antibodies work by recognising and finding specific proteins in the body. Secukinumab works in a similar fashion by blocking the activity of a protein called IL-17A. Evidence suggests that IL-17A plays a role in HS and is found at high levels in people with the disease.[36, 37] By attaching to and blocking the action of IL-17A, secukinumab could be used to treat HS. There are currently no other biologic options recommended by NICE for people with HS for whom adalimumab is unsuitable. These people would experience a step-change in the treatment of their disease if secukinumab was to be recommended by NICE. This is because secukinumab provides an alternative treatment option to these people and works differently to adalimumab. This may mean that their disease may respond to treatment.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Secukinumab 300 mg is given via injection under the skin every week for five doses, then one injection every four weeks (Q4W). The anticipated licence of secukinumab in HS will also allow doctors to increase the frequency of injections to every two weeks (Q2W), if required. Treatment with secukinumab is started by a specialist in hospital. But after proper training by a doctor, nurse or pharmacist, people with HS can do it themselves. Doctors will continue secukinumab and only stop treatment if secukinumab stops working. Doctors judge people's response by comparing the number of bumps they had when they first started secukinumab with the number of bumps they currently have after taking secukinumab for quite some time. This check will be routinely done after 16 weeks of treatment.

Because secukinumab is already being used on the NHS for other diseases (e.g., plaque psoriasis and spondyloarthritis), it is expected that minimal changes will be required with the introduction of secukinumab to UK clinical practice.[35]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Table 2 summarises the ongoing clinical trials for secukinumab in HS.

As of 2022, there are two identically designed Phase III pivotal trials (SUNSHINE and SUNRISE) and one ongoing Phase III extension study assessing the safety and efficacy of secukinumab in moderate-to-severe HS.

Table 2: Clinical trials investigating secukinumab in moderate to severe HS

Phase (clinical trial name and identification number)	Location	Population	Number of enrolled patients	Comparators	Key inclusion and exclusion criteria	Completion date
Phase III (SUNSHINE; NCT03713619)[38]	United Kingdom, Canada, United States, 15 EU countries, and other countries	Moderate-to-severe HS, aged 18 years and older	544	Placebo	Key inclusion • Written informed consent • Male and female patients 18 years and over • Diagnosed with HS 1 year and over to baseline • Patients with moderate-to-severe HS • Patients agree to use antiseptic wash on the areas of skin affected by HS while partaking in the study Key exclusion • Total fistulae count of 20 and over at baseline	August 1, 2022
Phase III (SUNRISE; NCT03713632)[39]	United Kingdom, Canada, United States, 16 EU countries, and other countries	Moderate-to-severe HS, aged 18 years and older	544	Placebo		August 1, 2022

					• Other skin diseases that may interfere with the assessment of HS • Treatment of other inflammatory diseases with disallowed medicines • Use or planned use of disallowed treatment • Previous exposure to secukinumab or other IL inhibitors • History of long term or recurrent infections or active infections in the last two weeks (except common cold) before entering the study • History of cancer within the past 5 years • Pregnant or breastfeeding women or women of childbearing potential	
Phase III extension study (NCT04179175)[40]	United Kingdom, Canada, United States, 16 EU countries, and other countries	Moderate-to-severe HS who have completed the study treatment period (52 weeks) in the core studies (SUNSHINE and SUNRISE), aged 18 years and older	856 (estimated)	N/A	Key inclusion • Written informed consent • Patients must have completed the SUNSHINE and SUNRISE trials Key exclusion • Patients who fail to follow the trial protocol of the SUNSHINE and SUNRISE trials • Patients whose participation	July 28, 2026 (estimated)

					in the extension study will put them at a safety risk • Patients with current severe worsening or uncontrolled disease	

Abbreviations: EU: European Union; HS: hidradenitis suppurativa; IL: interleukin; N/A: not applicable.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Evidence for secukinumab 300 mg Q2W and secukinumab 300 mg Q4W in HS

The SUNSHINE and SUNRISE trials provide the main source of evidence for the efficacy and safety of secukinumab 300 mg Q2W and secukinumab 300 mg Q4W. These were assessed in people with moderate-to-severe HS aged 18 years and over.

In both trials secukinumab 300 mg Q2W and Q4W was compared with placebo up to Week 16. Placebo is also the most relevant comparator for NHS practice. This is because people with HS who will be eligible for secukinumab are those who are not on active treatment with any biologic. They are currently expected to be receiving BSC.

The primary and secondary endpoints assessed across both trials are relevant to clinical practice (see description below). This is because these outcomes are important to people with HS.[41] They include pain, physical signs, quality of life, disease severity, disease progression and symptoms.

Primary endpoint for efficacy: HiSCR50 response

The primary endpoint of the two core trials was the proportion of patients achieving a HiSCR50 response at Week 16.

HiSCR50 was defined as at least a 50% decrease in abscess and inflammatory nodule (AN) count with no increase in the number of abscesses and/or draining fistulae. The Week 16 timepoint was chosen because it was considered unethical to keep people on placebo for longer than 16 weeks.

The results from both trials showed that treatment with secukinumab 300 mg Q2W or Q4W led to a greater number of patients achieving HiSCR50 at Week 16 when compared with placebo (see **section B.2.6.1** of the Company Submission).

Long-term efficacy data between Weeks 16 and 52 showed that patients maintained their response to secukinumab 300 mg Q2W and to secukinumab 300 mg Q4W. The number of HiSCR50 responders also increased over time.

Secondary endpoints for efficacy: AN count, HS flares and skin pain (NRS30)

AN count, number of HS flares, and reduction in skin pain (NRS30) were selected as secondary endpoints because of their potential to impact on patients' quality of life considerably. These endpoints also provide additional information on the efficacy of secukinumab 300 mg Q2W and secukinumab 300 mg Q4W that are not captured by HiSCR50.

Results across both trials showed that secukinumab 300 mg Q2W and Q4W reduced AN count, HS flares and skin pain (NRS30) across both trials at Week 16. These beneficial effects were also maintained beyond Week 16 through to Week 52.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In SUNSHINE and SUNRISE, patients' quality of life was measured using a dermatology-specific scale called Dermatology Life Quality Index (DLQI) as well as a more general scale called EuroQol-5D-3L (EQ-5D-3L) visual analogue scale (VAS). These scales take into account factors such as symptoms, daily activities and feelings in order to capture the impact of HS on patients' quality of life.

Across both trials, patients on secukinumab 300 mg Q2W and secukinumab 300 mg Q4W had better health-related quality of life when compared with placebo using the DLQI and EQ-5D-3L VAS scores at Week 16. These beneficial effects were maintained beyond Week 16 through to Week 52. This means that patients who received secukinumab had a better quality of life than patients receiving placebo and this benefit continued while on treatment, with better DLQI and EQ-5D-3L VAS scores remaining at Week 52.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, secukinumab can cause side effects, although not everybody gets them.

Serious side effects

Stop using secukinumab and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious infection. The signs may include:

- Fever, flu-like symptoms, night sweats
- Feeling tired or short of breath, cough which will not go away
- Warm, red and painful skin, or a painful skin rash with blisters
- Burning sensation when passing urine

Serious allergic reaction. The signs may include:

- Difficulty breathing or swallowing
- Low blood pressure, which can cause dizziness or light-headedness
- Swelling of the face, lips, tongue or throat
- Severe itching of the skin, with a red rash or raised bumps.

Your doctor will decide if and when you may restart the treatment.

Other side effects
Most of the side effects presented in Table 3 are mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse.

Table 3: Commonly reported side effects of secukinumab

Frequency	Side effect
Very common (may affect more than 1 in 10 people)	Upper respiratory tract infections with symptoms, such as: • Sore throat • Stuffy nose
Common (may affect up to 1 in 10 people)	• Cold sores • Diarrhoea • Runny nose • Athlete's foot • Headache • Nausea • Fatigue

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

There is a lack of effective biologic options for treating HS that are recommended by NICE for people in whom adalimumab is unsuitable. Results from the SUNSHINE and SUNRISE trials show that secukinumab 300 mg Q2W and secukinumab 300 mg Q4W offers an effective and tolerable treatment option for people with moderate-to-severe HS.

The way in which secukinumab works is different to adalimumab, so people who are unsuitable for adalimumab may respond to treatment with secukinumab.

After proper training, people with HS can self-inject secukinumab themselves. This means that they can have their treatment closer to home. The ease of use also means that carers can assist them in injecting their medicine.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

In the SUNSHINE and SUNRISE trials, secukinumab Q2W and Q4W was associated with some side effects. But overall, the side effects observed were in line with what is already known about the safety of secukinumab and were similar to the placebo groups in both trials. The most commonly reported side effects were nasopharyngitis and headache. These side effects were mainly non-serious and mild to moderate in severity.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects HS

The economic model was designed to reflect the key features of HS and clinical practice in the UK. The model assigns patients to different treatments (secukinumab or standard of care) and sums up the costs and quality of life over the patients' lifetimes. The goal of the health economic model is to consider the costs and quality of life of patients treated with secukinumab compared with standard of care.

Modelling how much secukinumab improves HiSCR response

The results of the SUNSHINE and SUNRISE trials were used to inform the economic model. The main result from the trials that was used in the model was HiSCR response. People with HS in the model were grouped by their response, with higher scores indicating a better response. There were four response states: 'High Responders' have a HiSCR of 75% or over; 'Responders' have a HiSCR between 50% and 74%; 'Partial Responders' have a HiSCR between 25% and 49%; 'Non-Responders' have a HiSCR less than 25%. This was the main result used in the model because doctors judge the response based on this score. This is also likely to reflect what may happen in clinical practice.

Modelling how much secukinumab improves quality of life

An improvement in quality of life was modelled when a patient achieved a HiSCR response of 25% or over. This reflects the fact that the physical and mental impact of HS would likely be reduced when a patient achieved a HiSCR response. A higher HiSCR response was associated with a higher quality of life in the model than a lower HiSCR response.

The quality-of-life data that was assigned to each response state in each treatment arm came from the SUNSHINE and SUNRISE trials (see **section 3f** for more information on this).

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model for the different HS treatments. These costs include:

- The cost of the medicine itself and its administration
- The cost of managing any side effects that may occur
- Non-surgery and surgery-related resource use costs e.g., surgery, hospitalisation, routine hospital visits

Cost effectiveness results

Overall, secukinumab was associated with higher costs, but also greater benefits (or 'quality-adjusted life years' [QALYs]) than the standard of care for people with moderate-to-severe HS. This resulted in an 'incremental cost-effectiveness ratio' (ICER) of £29,129 per QALY gained, which falls within the range that the NHS usually considers to be cost-effective (£20,000 to £30,000 per QALY gained). The key reasons for this include that:

- Secukinumab may reduce the number of areas of skin affected by HS and so reduce the need for major surgery needed in the long term.
- Current treatment options for HS are associated with higher disease management costs than secukinumab. For example, patients treated with secukinumab experience less HS flare ups and so have less visits to the emergency department.

Uncertainty

There is uncertainty when data from clinical trials are used for long-term estimates. Information about some costs or results are also sometimes not available. Because of these, assumptions are used in the model. There are various assumptions that were used in the model, including the assumption of the up-titration of secukinumab to Q2W for some people. Information on these assumptions can be found in Document B, Section 3.11.

These assumptions were varied in order to see the impact on the cost-effectiveness results. This test is done to measure how sensitive the model is to changes in assumptions. The smaller the difference in the results before and after changing an assumption, the more reassured we are about the robustness of the model. The results of these tests are explained in Document B, Section 3.11.

Conclusion

Overall, the results of the cost effectiveness analysis show that secukinumab is a cost-effective option for the NHS for the treatment of moderate to severe HS compared with the standard of care. Secukinumab treatment was associated with higher costs, but also higher benefits than the standard of care. This resulted in an incremental cost-effectiveness ratio (ICER) of £29,129 per QALY gained, which falls within the range that the NHS usually considers to be cost-effective (£20,000 to £30,000 per QALY gained).

The benefits outlined in **section 3h** and the economic analysis results above suggest that secukinumab represents good value for money and a good use of NHS resources as a new treatment for patients with moderate-to-severe HS.

Benefits of secukinumab not captured in the economic analysis

Evidence suggests that people with HS also have other diseases, such as plaque psoriasis and spondyloarthritis. Because secukinumab is already used in the NHS to treat these conditions, these people are expected to have additional benefits from secukinumab that are not captured in the economic model. This is because the model only captures benefits directly associated with the treatment of HS only. Additionally, although studies report an increased risk of death in patients with HS as compared with the general population (i.e., people without HS), this was not modelled because there were not enough data available to support the model.[42, 43]

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Introduction of a licensed therapy that provides an alternative to adalimumab and that works differently to adalimumab would represent a step-change in the management of HS. Novartis considers that secukinumab will be of significant benefit to people with HS for whom adalimumab is unsuitable, given the lack of biologic options available to these people.

Potential benefits not captured in the modelling are described in **section 3j**.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

As noted in **section B.1.3.1** of the Company Submission, the incidence of HS is higher in people of African-Caribbean family background as compared with people of European family background. No equality issues are foreseen if secukinumab were to be recommended by NICE.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be

useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on HS

- https://www.bad.org.uk/pils/hidradenitis-suppurativa/
- https://www.nhs.uk/conditions/hidradenitis-suppurativa/
- https://www.pcds.org.uk/clinical-guidance/hidradenitis-suppurativa

Further information on secukinumab

- https://www.medicines.org.uk/emc/files/pil.11973.pdf

Further information on the SUNSHINE trial

- https://clinicaltrials.gov/ct2/show/NCT03713619

Further information on the SUNRISE trial

- https://clinicaltrials.gov/ct2/show/NCT03713632

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms in bold in this template. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Abscesses. Red, tender, pus-containing cavities in the skin or any organ, surrounded by inflammation.

Draining fistulae. These are permanent, abnormal tunnels that form between two hollow organs or from a hollow organ to the skin surface.

Economic model. A way to predict the costs and effects of a technology over time or in groups of people not covered in a clinical trial.

Efficacy. The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial.

Inflammation. Refers to a physical condition in which part of the body becomes reddened, swollen, hot, and often painful. In this case, inflammation is caused by the disease.

Inflammatory. Relating to or causing inflammation of a part of the body.

Inflammatory nodule. Firm swellings of the skin, mainly arising from the deeper layers of the skin.

Inflammatory bowel disease. A term for two conditions (Crohn's disease and ulcerative colitis) that are cause long term inflammation of the gut.

Marketing authorisation. The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.

Monoclonal antibody. A type of protein that is made in the laboratory and can bind to certain targets in the body.

Nasopharyngitis. This refers to swelling of the nasal passages and the back of the throat. Your doctor may also refer to this as an upper respiratory infection.

Placebo. A treatment that appears real, but that does not treat the disease. It is used in clinical trials to compare active treatments to.

Primary endpoint. The main result that is measured at the end of a study to see if a given treatment worked. It is usually decided before the study begins.

Protein. These are structures inside all cells of our body that are important for many activities including growth and repair.

Pus. A thick fluid that usually contains white blood cells, dead tissue and germs.

Quality of life. The overall well-being of a person. Many clinical trials assess the effects of the disease of interest and its treatment on the quality of life of patients. These studies measure aspects of a person's sense of well-being and their ability to carry out activities of daily living.

Secondary endpoint. These are additional results measured at the end of a study that complement the results from the primary endpoint. They are not as important as the primary endpoint but are still of interest. Most clinical studies have more than one secondary endpoint.

Sinus tracts. Narrow tunnels that run under the skin and drain to the skin surface through an opening.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Secukinumab for moderate-to-severe hidradenitis suppurativa [ID4039]

Clarification questions

January 2023

File name	Version	Contains confidential information	Date
ID4039_Secukinumab in HS_Clarification Questions [ACIC]_1February2023	Final	Yes	1ST February 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Document B, section B.2.5 and Appendix D.4. These sections of the company submission refer to the quality assessment of the SUNSHINE and SUNRISE studies and other studies included in the SLR. Please clarify how many reviewers carried out the risk of bias assessment of these studies and whether they worked independently.

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.

Treatment pathway for HS

A2. Document B, section B.1.3.3, Figure 2. The anticipated treatment pathway in Figure 2 positions secukinumab with no relevant comparator. 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. Please provide further clarification about the proposed treatment pathway.

The rationale for excluding infliximab in the treatment pathway presented in Figure 2 of Document B is three-fold:

- 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.[1]
- 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.[2]
- Infliximab was not included in the Final Scope published by NICE for the appraisal of secukinumab in HS.[3] 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 expected to be receiving no active therapy. As such, best supportive care (BSC) is anticipated to represent the sole relevant comparator to secukinumab.

Methodology of clinical effectiveness evidence

A3. Document B, section B.2.6, Tables 14, 15, 19, 20 and 22. The following clinical effectiveness outcomes of SUNSHINE and SUNRISE in terms of n*/m, defined as "*rounded average number of participants with response in 100 imputations*" are reported in the company submission: HiSCR50, HS flares, NRS responders. The n* methods are not clear. Please clarify the methods used and, if possible, provide the observed counts of participants achieving these outcomes.

As noted in Table 12 (''Data management, patient withdrawals'' row) of Document B, missing data for the primary and secondary endpoints were addressed using multiple imputation. For the HiSCR50, HS flares and NRS responders outcomes, the number of responders (n) were divided by the total number of observations (m) to obtain the response rate (n/m). Given that these endpoints represent binary outcomes derived from underlying continuous variables, the imputations to account for missing data were performed on those continuous variables. As such, 100 imputations were performed, resulting in 100 imputed data sets for n/m. In order to derive a single value to represent the response rate for each outcome, a rounded average of all of these 100 imputed values of n (denoted as n*) was calculated and subsequently divided by m to obtain a response rate (n*/m).

A4. Document B, section B.2.4.2, Table 12. Please explain the rationale for choosing the significance thresholds mentioned on pages 41-42 of the company submission.

As described in Table 12 (''Statistical analysis'' row) of Document B, the overall alpha (α; type I error rate) at the study level for each trial (SUNSHINE and SUNRISE) was controlled at 0.025 (one-sided) using the hierarchical testing procedure presented in Figure 4 of Document B.

The alpha level across each trial was split (the rationale for this is provided below) into 4α/5 and α/5 to test the secukinumab Q2W dosing regimen versus placebo and Q4W dosing regimen versus placebo, respectively. The primary endpoint of HiSCR50 and secondary endpoints of AN count and HS flare were tested in each trial separately, while the secondary endpoint of NRS30 (skin pain) was tested using the pooled data from both trials. The pooled analysis for NRS30

(skin pain) was tested only if the hypotheses for the primary endpoint of HiSCR50 were rejected in both trials independently (for the respective dosing regimen). The alpha level used in the hypothesis tests for NRS30 was equal to $\alpha-\alpha^2$. The subtraction of α^2 was to account for the maximum possible type I error rate to claim a success for HiSCR50, AN count and HS flare in both trials.[4, 5] Therefore, the submission-level type I error rate was controlled at 0.025 (one-sided) for all hypothesis endpoints.

The use of an unequal alpha split, as described above, for the Q2W dosing regimen versus placebo and Q4W versus placebo was based on final results (September 2020) from the CAIN457A2324 study that evaluated two dosing regimens of secukinumab (300 mg Q2W and 300 mg Q4W) in patients with moderate-to-severe psoriasis weighing ≥90 kg.[6] This study demonstrated superior efficacy of the secukinumab Q2W dosing regimen compared with the secukinumab Q4W dosing regimen in this patient population and triggered an update of the posology for adult plaque psoriasis (EMEA/H/C/003729/II/0076 approved on 20 January 2022).[7] Considering that patients with HS are generally heavier than patients with psoriasis and have a higher inflammatory burden,[8] it was considered reasonable that the same weight-based response seen in psoriasis could apply to patients with HS. This assumption is also supported by the allometric relationship between secukinumab exposure and body weight, with increased clearance and reduced exposure seen with increased body weight.[9]

A5. PRIORITY. Document B, section B.2.9. Please clarify whether a network meta-analysis (NMA) including secukinumab versus adalimumab or any other relevant treatment has been conducted (but not reported). If yes, please provide full details of the NMA.

As described in Section B.1.1 of Document B, the population addressed in the decision problem are “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”.

A network meta-analysis (NMA) was explored in order to allow comparison between secukinumab and other therapies for HS, including adalimumab and infliximab. Following feasibility assessment, only a comparison against adalimumab based on the PIONEER trials was feasible. A comparison with infliximab was not possible based on the outcomes reported in the trials. The PIONEER trials only recruited patients that have never been exposed to biologics (biologic-naïve patients) and therefore the NMA was conducted in this population only.

In summary, details of the NMA for the biologic-naïve population were not included in the Company Submission because:

- For patients that have failed to respond or have lost response to prior adalimumab treatment, the NMA conducted in the biologic-naïve patients is not relevant for decision-making and no network was available for any other HS treatment for the biologic-experienced population relevant to the decision problem;
- For patients for whom adalimumab is contraindicated or otherwise unsuitable, the NMA is not informative as patients are unsuitable to receive adalimumab.

In patients for whom adalimumab is contraindicated or otherwise unsuitable, including those who have failed to respond or have lost response to prior adalimumab treatment, the key comparator is BSC (as described in Question A2). The impact of the NMA not being applicable to the decision problem is mitigated through the availability of direct evidence for secukinumab versus the relevant comparator (BSC) from the high quality, Phase III, randomised, double-blind, placebo-controlled, multicentre SUNSHINE and SUNRISE trials.

While maintaining that an NMA is not relevant to the anticipated positioning of secukinumab, the methods and results of the NMA for the biologic-naïve population are provided as data on file alongside this response for transparency and completeness.

A6. Document B, section B.2.6. The company submission reports the pooling of data from both trials for the purpose of economic modelling. Please explain why, in general, pooled data have not been presented in the clinical effectiveness section of the submission.

The pooling of the SUNSHINE and SUNRISE trial data for the purposes of the economic analysis was considered appropriate given the identical trial designs and in order to make use of the largest dataset available. However, in the interest of transparency, the clinical evidence for secukinumab in HS from the two identically designed and concurrent, Phase III, randomised controlled trials (SUNSHINE and SUNRISE) were presented separately.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY. Document B, section B.3. In the treatment pathway, secukinumab is positioned after adalimumab. Please provide a full set of model parameters, including transition probabilities and health state utility values for the "biologic experienced" subgroup of participants in the SUNSHINE and SUNRISE trials. Please also provide an economic model scenario analysis using these data.

In the original submission, the average four-weekly transition probabilities and utility values from the SUNSHINE and SUNRISE pooled intention-to-treat (ITT) population were used in the base case analysis because the patient numbers in biologic experienced population were considerably lower as compared with the full ITT population: pooled SUNSHINE and SUNRISE patient populations receiving secukinumab Q4W (n=360), secukinumab Q2W (n=361) and placebo (n=363) versus the biologic experienced patients receiving secukinumab Q4W (n=81), secukinumab Q2W (n=80) and placebo (n=94).

As discussed in Section B.2.7 of Document B, when stratified by whether patients had previously been exposed to biologics or not (see Figure 31 of Document B), the relative benefit of secukinumab 300 mg Q2W (odds ratio [OR]: [redacted] [95% CI: [redacted], [redacted]] and OR: [redacted] [95% CI: [redacted], [redacted]) and Q4W (OR: [redacted] [95% CI: [redacted], [redacted]] and OR: [redacted] [95% CI: [redacted], [redacted]) as compared with placebo remained consistent. Therefore, the SUNSHINE and SUNRISE pooled intention-to-treat (ITT) population was deemed appropriate to minimise uncertainties in transition probability and utility estimates of a smaller sample population (biologic-experienced). The issue with the sample size is highlighted by the BSC utility value of the HiSCR50–74 health state being higher than the

BSC utility value of HiSCR≥75 health state, despite HiSCR≥75 representing a better disease state.

For transparency, the average four-weekly transition probabilities and utility values for the biologic experienced subgroup of patients in the SUNSHINE and SUNRISE trials are summarised in Table 1, Table 2, Table 3 and Table 4. Scenario results using these data are presented in Table 5. Despite the concerns with input uncertainty, the scenario results present a deterministic ICER (£29,760), which is in line with the deterministic base case ICER from the original submission (£28,165) (Table 5).

Table 1. HiSCR average (four-weekly) transition probabilities for Week 0–16 for biologic experienced patients

Treatment	Induction phase (Week 0–16)					Source
	To > From v	HiSCR≥75	HiSCR50 – 74	HiSCR25 –49	HiSCR<25	
SEC Q4W	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from the SUNSHINE and SUNRISE trials for biologic experienced patients
	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; Q4W: every four weeks; SEC: secukinumab.

Table 2. HiSCR average (four-weekly) transition probabilities of biologic-experienced patients for the secukinumab Q2W treatment regimen during the Up-Titration phase (Week 16–28)

Treatment	Up-Titration phase (Week 16–28)					Source
	To > From v	HiSCR≥75	HiSCR50 – 74	HiSCR25–49	HiSCR< 25	
SEC Q2W	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	Pooled data from the SUNSHINE and SUNRISE trials for biologic experienced patients
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; SEC: secukinumab.

Table 3: HiSCR average (four-weekly) transition probabilities of biologic-experienced patients for the secukinumab Q4W and Q2W treatment regimens during the Maintenance phase (Week 16/28–52)

Treatment	To > From v	HiSCR≥75	HiSCR50 – 74	HiSCR25 –49	HiSCR<25	Source
SEC Q4W	Maintenance phase (Week 16–52)					Pooled data from the SUNSHINE and SUNRISE trials for
	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	

Treatment	To > From v	HiSCR≥75	HiSCR50 – 74	HiSCR25 –49	HiSCR<25	Source
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	biologic experienced patients
SEC Q2W	Maintenance phase (Week 28–52)					
	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: HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; Q4W: every four weeks; SEC: secukinumab.

Table 4: Mean EQ-5D Utility values by health state for biologic-experienced patients

Health state	Mean EQ-5D Utility (Number of Observations, Standard Error)			Source
	SEC Q4W	SEC Q2W	BSC	
HiSCR≥75	[redacted]	[redacted]	[redacted]	SUNSHINE and SUNRISE trials (biologic experienced population)
HiSCR50–74	[redacted]	[redacted]	[redacted]	
HiSCR25–49	[redacted]	[redacted]	[redacted]	
HiSCR<25	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC: best supportive care; HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; Q4W: every four weeks; SEC: secukinumab.

Table 5: Deterministic results for base case analysis and scenario analysis using transition probabilities and utilities for biologic experienced patients (PAS price)

	Total			Incremental			ICER	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Versus baseline (£/QALY)	Incremental (£/QALY)
Base case results								
BSC	[redacted]	22.797	[redacted]	-	-	-	-	
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165	
Scenario analysis using transition probabilities and utilities for biologic-experienced patients								
BSC	[redacted]	22.797	[redacted]	-	-	-	-	
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£29,760	

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; SEC, secukinumab.

B2. PRIORITY. Document B, section B.3.3.2, Tables 39 and 41 & Model transition matrices. Average four-weekly transition probabilities derived from SUNSHINE and SUNRISE are presented in Tables 39-41 of the CS. Please provide the following additional information:

- The company submission states that average (four-weekly) transition probabilities were estimated by fitting a multinomial model. Please provide further details of the modelling approach used.

- For all transition matrices used in the model, in all phases, and in both treatment arms, please present the count data used (i.e., numerator/denominator).

A Bayesian multinomial model was specified to model transition counts from and to each HiSCR category in each four-week cycle. The probabilities of transition from each HiSCR category were specified with a uniform Dirichlet prior so that the sum of probabilities of being in each health state totalled value one. OpenBUGS code for the model is provided below.

```
model{

for(i in 1:nt){  #Loop over timepoints

r[i, 1:4] ~ dmulti(pi_hr[1:4], n[i, 1:4])             #HR starting

r[i, 5:8] ~ dmulti(pi_r[1:4], n[i, 5:8])                      #R
starting

r[i, 9:12] ~ dmulti(pi_pr[1:4], n[i, 9:12])                #PR
starting

r[i, 13:16] ~ dmulti(pi_nr[1:4], n[i, 13:16])            #NR
starting

}

#Normalise so that all transition probabilities sum to one across
each 'starting' health state

pi_hr[1:4] ~ ddirch(prior[1:4])

pi_r[1:4] ~ ddirch(prior[1:4])

pi_pr[1:4] ~ ddirch(prior[1:4])

pi_nr[1:4] ~ ddirch(prior[1:4])

#Entries of each pi vector correspond to the following 'end'
health states respectively: HR, R, PR, NR

}
```

R code for calling OpenBUGS via R package *R2OpenBUGS* is provided as data on file alongside this response. Count data for all transition matrices used in the model are provided in Appendix – ITT Population patient transition count data.

B3. Economic model, tab "Efficacy and safety", cell "E136". In the model, decreasing the non-response rate for BSC (e.g., setting it to 0%, particularly in year 2+), reduces the ICER for secukinumab versus BSC. We would have expected a reduction in this parameter to increase rather than decrease the ICER. Please

comment on the face validity of this model output and cross-check for any coding errors in the model.

We have investigated this question and can confirm that the model is working as intended.

To clarify, the input in cell E136 on the "Efficacy and Safety" tab refers to the risk of loss of response for BSC in Year 2+. Setting this to 0% implies that patients receiving BSC in response health states (HiSCR≥25) may not transition to the non-response health state (HiSCR<25) in Year 2 or beyond in the model.

It should be noted that BSC may be received in both the comparator arm and as the subsequent treatment in the intervention arm (secukinumab) of the model, meaning that adjustments to parameters for BSC will affect both the comparator and intervention arms in the model. In this case, removing loss of response for patients receiving BSC increases the total QALYs accumulated in both arms as the HiSCR<25 (no response) health state was associated with the lowest utility value among all health states. In the case of BSC risk of loss of response equalling 0%, patients in the secukinumab treatment arm who discontinue treatment whilst in the response health states (HiSCR25–49, HiSCR50–74, HiSCR≥75) move on to BSC in the same response state, where they are then unable to lose response. For example, secukinumab patients in the HiSCR level ≥75 health state, upon discontinuation of secukinumab treatment, would remain in the HiSCR≥75 health state whilst receiving BSC for the remainder of the model (or until death). Therefore, these patients maintain an elevated utility value (relative to HiSCR≤25) for the remainder of the model (or until death) thus significantly increasing the QALYs accumulated in the secukinumab arm. A similar effect occurs in the BSC arm of the model, but due to there being fewer patients in the response health states at the end of induction (or end of Year 1), the increase in QALYs is not as considerable. As such, the overall result is a decrease in the ICER, which is in line with the expected functioning of the model based on the description above, as patients receiving secukinumab maintain their higher initial response rate relative to BSC patients over the duration of the model.

B4. Document B, section B.3.2.2, page 88. Please comment on the comparability of the PIONEER and SUNNY trials to inform long-term transition matrices for the BSC arm in the maintenance phase of the model.

The PIONEER trials represent the only long-term outcome data for placebo beyond the induction period. As presented in Table 6, demographics and baseline characteristics are broadly consistent across the SUNNY and PIONEER trials with some exceptions such as prior surgery. As such, given the lack of available data for long-term transitions beyond Week 16 for BSC in the SUNSHINE and SUNRISE trials, it was considered reasonable to make use of the best available data from the literature, despite the unresolvable uncertainty of using data from another trial.

Table 6: Baseline characteristics from SUNNY and PIONEER trials

Baseline characteristics	SUNSHINE (N=541)	SUNRISE (N=543)	PIONEER I (n=307)[10]	PIONEER II (n=326)[10]
Age, years, mean (SD)	36.1 (11.7)	36.3 (11.4)	37.0 (11.10)	35.5 [11.13]
Gender, female n (%)	304 (56.2)	306 (56.4)	196 (63.8)	221 (67.8)
BMI, kg/m^2, mean (SD)	32.5 (7.6)	31.8 (7.5)	33.8 (7.80)	32.1 (7.71)

			(n=306)	
Baseline Hurley stage, n (%)				
I	25 (4.6)	15 (2.8)	-	-
II	332 (61.4)	308 (56.7)	161 (52.4)	175 (53.7)
III	184 (34.0)	220 (40.5)	146 (46.6)	151 (46.3)
Time since HS symptom(s) onset (years)	[redacted]	[redacted]	11.5 (8.92)	11.5 (9.03)
Baseline AN count	13.3 (9.1)	12.8 (8.7)	14.3 (13.42)	11.3 (9.68)
Baseline NRS skin pain at worst, mean (SD)	4.3 (2.5) (n=488)	4.7 (2.4) (n=495)	5.0 (2.60) (n=297)	4.5 (2.69) (n=314)
Current smokers, n (%)	292 (54.0)	293 (54.0)	173 (56.4)	214 (65.8)
Prior surgery for HS, Yes, n (%)	216 (39.9)	226 (41.6)	34 (11.1)	45 (13.8)
Previous exposure to systemic antibiotics, Yes, n (%)	445 (82.3)	454 (83.6)	-	-
Previous exposure to systemic biologic therapy, Yes, n (%)	129 (23.8)	126 (23.2)	-	-
Previous systemic treatment, n (%)	-	-	134 (43.6)	158 (48.5)

Abbreviations: AN: abscesses and inflammatory nodule; BMI: body mass index; HS: hidradenitis suppurativa; n: number of patients; NRS: Numerical Rating Scale; SD: standard deviation.

B5. <u>PRIORITY.</u> Document B, section B.3.5.2, Table 54, page 98. Estimates of long-term surgery and hospital resource use appear to have been obtained from a survey of n=40 clinical experts conducted by AbbVie for the appraisal of adalimumab. Please provide the following information:

- Please clarify whether you have attempted to validate the resource use estimates with your own clinical experts. If so, please clarify how this was done, and what were the findings.

- Please clarify whether you have attempted to source frequencies of long-term hospital resource use (surgery and non-surgery) from the published literature or real-world data. If so, please provide further details of the methods and the results of any studies identified. If this has not been done, please consider conducting a literature review, summarising the findings, and including alternative estimates in scenario analyses.

- The hospital resource use frequencies appear to have been weighted according to the proportion of patients with moderate/severe disease from the PIONEER trials. Please re-weight these resource use according to the proportions of moderate and severe disease available from the SUNSHINE and SUNRISE studies (relevant data appear to be available from Appendix 6 of the AbbVie's company submission).

Clinical validation was not sought, instead the resource use estimates used in the submitted model were aligned with the resource use estimates that informed the decision-making ICERs used by the Committee in TA392. The company conducted economic SLRs in 2022 in an attempt to identify estimates of resource use for patients with moderate-to-severe HS. NICE TA392 and Willems et al., (2020) were identified as the only two publications relevant to the UK population.[10, 11] For full details of the literature review please see Appendix G of the Company Submission. It is noted that Willems et al., (2020) utilised data from PIONEER II trial and TA392 to inform their model inputs, and therefore TA392 was chosen as the most appropriate evaluation resource use frequencies to inform the model.

Table 7 presents the deterministic results of a scenario analysis with the hospital resource use frequencies collected in the clinician survey in TA392 re-weighted by the proportion of patients with moderate or severe disease (as per the HS-PGA classification) from the SUNSHINE and SUNRISE trials.[10] The resource use frequencies used in this scenario are presented in Table 8

Table 7: Deterministic results for base case analysis and scenario analysis using reweighted hospital resource use frequencies (PAS price)

	Total			Incremental			ICER	
	Costs	LYG	QALYs	Costs	LYG	QALYs	Versus baseline (£/QALY)	Incremental (£/QALY)
Base case results								
BSC	[redacted]	22.797	[redacted]	-	-	-	-	
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165	
Scenario analysis using reweighted hospital resource use frequencies								
BSC	[redacted]	22.797	[redacted]	-	-	-	-	
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£27,905	

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS: patient access scheme; QALYs, quality-adjusted life years; SEC, secukinumab.

Table 8: Resource use frequency per year per patient

	Resource use frequencies, weighted average of moderate and severe patients			
	HiSCR≥75	HiSCR50–74	HiSCR25–49	HiSCR<25
Routine outpatient visits	3.10	3.51	4.42	4.68
Number of hospitalisation non-surgery related	0.11	0.22	0.28	0.46

Visits to wound-care NOT due to HS surgery	0.70	0.49	0.65	0.45
Emergency room visits	0.11	0.20	0.46	0.57
Number of hospitalisations for HS surgeries	0.12	0.22	0.53	0.80
Outpatient visits due to HS surgery	0.22	0.35	0.66	0.93
Visits to wound-care due to HS surgery	0.11	0.17	0.39	0.82

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; HS: Hidradenitis Suppurativa.

B6. <u>PRIORITY.</u> Document B, section B.3.5.2, Table 53, page 98. Please provide the following information and clarification regarding the most appropriate unit costs used for hospital resource use (surgical and non-surgical) in the model.

- Please provide further details of the types of surgical procedures that are intended to be captured in the model (specifically OPCS codes) and provide details of how these procedures map to the HRG codes used for the costing of hospital resource use in the model.

- Please provide details of any clinical expert advice sought regarding the different settings of care for each HRG included in the model (e.g., day case, elective etc.). For example, explain why non-surgical visits do not include day-case data.

- Please clarify why patients would require non-surgical inpatient admission, the type of events included in these admissions, and whether these have been validated by the company's clinical experts.

- Please provide further scenario analyses exploring the impact of uncertainty surrounding hospital resource use on the results of the economic model

The hospital resource use costs have not been through additional clinical validation process for this submission. Where possible, resource unit costs were aligned with the TA392 ERG's preferred assumptions, with updates to the most recent NHS Reference Costs for 2020/2021. Table 9 summarises the HRG codes and costs used in TA392 and the submission model. It is noted that the approach to emergency room visits costs was refined to better reflect the HS-related services in emergency room visits and excluded the following from the weighted average of the emergency room visits: Emergency Medicine, Dental Care; Emergency, No Investigation with No Significant Treatment and Emergency Medicine, Patient Dead on Arrival. The costs for inpatient stay due to HS surgery were assumed to include only elective procedures, as non-elective procedures would be included as emergency room visits and day case procedures would

be considered as outpatient visits due to HS surgery. The HRG codes for inpatient stay due to HS surgery included in the current model aim to capture the variations in length of stay for surgeries at different severity level.

Despite some uncertainty in these resource use inputs, Novartis notes that resource use frequencies and resource use costs are tested in the deterministic sensitivity analyses and their effect on model results may be assessed through this. Scenario analysis using reweighted hospital resource use frequencies based on data from the SUNSHINE and SUNRISE trials are summarised in Table 7.

Table 9. Summary of hospital resource use costs in TA392 and Company submission

Resource use	AbbVie's submitted base case (TA392)[a]	TA392 ERG's preferred base case[a]	Current submission base case[b]
Outpatient visits (due to any reason)	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£168.29** - Total Outpatient Attendance: Dermatology 330
Non-surgical inpatient visits	**£2,202.14** - Weighted average of: • JD07D – elective, (Skin Disorders with Interventions, with CC Score 0-3) - £2,517.37 • JD07K – elective (Skin Disorders without Interventions, with CC Score 0-1) - £1,187.85	**£2,202.14** - Weighted average of: • JD07D – elective, (Skin Disorders with Interventions, with CC Score 0-3) - £2,517.37 • JD07K – elective, (Skin Disorders without Interventions, with CC Score 0-1) - £1,187.85	**£2,964.06** - Weighted average of: • JD07D – elective, (Skin Disorders with Interventions, with CC Score 0–3) - £4,153.07 • JD07K (Skin Disorders without Interventions, with CC Score 0–1) - £1,339.68
Visits to wound-care NOT due to HS surgery	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£168.29** - Total Outpatient Attendance: Dermatology 330
Emergency room visits	**£123.67 -** Total HRGs: Emergency Medicine	**£123.67** - Total HRGs: Emergency Medicine	**£332.46** - Total HRGs: Emergency Medicine, weighted average of VB01Z-VB09Z (Emergency Medicine: Any Investigation with Category 5 Treatment, Category 1–3 Investigation with Category 1–4)[c]
Inpatient stay due to HS surgery	**£5,488.32** - JC40Z – elective, (Major Skin Procedures)	**£1,525.74** - Weighted average of:[d] • JC42A – day case, (Intermediate Skin Procedures, 13 years and over) - £943.17, • Average of JC42A – elective, (Intermediate Skin Procedures, 13 years and over) and JC42A - non-elective, (Intermediate Skin Procedures, 13 years and over),	**£4,652.57** - Weighted average of: • JC40Z – elective, (Multiple Major Skin Procedures) - £21,567.02 • JC41Z – elective, (Major Skin Procedures (elective) - £10,016.33 • JC42C – elective, (Intermediate Skin Procedures, 19 years and over) - £3,795.58

Resource use	AbbVie's submitted base case (TA392)[a]	TA392 ERG's preferred base case[a]	Current submission base case[b]
		assuming length of stay is 2 days - £2,102.73 • JC41Z – inpatient, (Intermediate Skin Procedures, 13 years and over) - £5,488.32	• JC43C – elective, (Minor Skin Procedures, 19 years and over) - £1,894.33
Outpatient visits due to HS surgery	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£168.29** - Total Outpatient Attendance: Dermatology 330
Visits to wound-care due to HS surgery	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£97.63** - Total Outpatient Attendance: Dermatology 330	**£168.29** - Total Outpatient Attendance: Dermatology 330

[a]Based on NHS Reference Costs 2013/2014. [b]Based on NHS Reference Costs 2020/2021. [c]Includes all emergency medicine as per the EAG's preferred base case in TA392, however, Emergency Medicine, Dental Care; Emergency, No Investigation with No Significant Treatment and Emergency Medicine, Patient Dead on Arrival were excluded from the weighted average. [d]It is noted that the exact weightings used in the EAG's preferred base case are not publicly available.
Abbreviations: EAG, External Assessment Group; HRG, Healthcare Resource Group; HS, Hidradenitis Suppurativa; TA, technology assessment.

B7. Document B, section B.3.5.1, Table 52, page 97.

Please comment on the appropriateness of assuming that all patients will proceed to self-administer secukinumab. Please clarify whether there are any real-world data to support the assumption that administration costs will be incurred only once for all patients. Please consider a scenario where a proportion of patients may require administration costs for the duration of time for which they remain on treatment.

Secukinumab is provided via Homecare providers in which patients are supported for up to three nurse visits upon delivery of secukinumab. The training program is sponsored by Novartis and patients will receive education on correct injection technique, device storage and disposal. A nurse will complete a competency assessment regarding the patient's ability to self-administer and this will be shared with the healthcare professional. As such, it was not deemed necessary that any SC administration costs be included. However, conservatively a one-off cost for self-administration training was assumed in the Company Submission in line with previously accepted appraisals for secukinumab in other indications, including psoriasis.[12-15] In TA350, the committee concluded that assuming patients would be able to self-administer after 1–3 hours of training was clinically plausible based on feedback from clinical experts.[12]

B8. <u>PRIORITY</u>. Document B, section B.3.4.5; Table 47, page 93. Please provide further justification (as much detail as possible) to support the use of treatment-specific health state utility values in the model. Please provide statistical evidence to support a treatment effect within health state. For each health state, please also provide a table with the mean clinical response score by treatment arm. This will help to assess the validity of treatment-specific health state utility values used in the company's base case model.

To support the use of treatment-specific health state utility values, a regression model was conducted based on EQ-5D derived utility values data from Weeks 2–16. A mixed model repeated measures (MMRM) approach was taken, with response variable as EQ-5D utility (continuous variable), with fixed effect covariates as: treatment (categorical variable with three levels [placebo, secukinumab Q2W and secukinumab Q4W]), baseline EQ-5D utility (continuous), and HiSCR (categorical variable with four levels [HiSCR<25, HiSCR25–49, HiSCR50–74, HiSCR≥75]). An unstructured covariance matrix was specified with patient ID as the cluster variable. As shown in

Table 10, the fixed effect estimates showed a statistically significant effect for treatment while accounting for HiSCR category, supporting the use of treatment-specific health state utility values.

The mean clinical response score by treatment arm cannot be provided as per definition the endpoint is determined by a continuous and binary outcome. For example, if a patient has a reduction of more than 50% in abscesses and inflammatory nodules, but has an increase in the

number of abscesses or the number of draining fistulae from baseline, they would be considered a non-responder.

The clinical response to treatment (HiSCR achievement) is:

- at least a 50% reduction in abscesses and inflammatory nodules (AN),
- no increase in the number of abscesses, and
- no increase in the number of draining fistulae from baseline.

Thus, it is not possible to provide a mean clinical response score.

Table 10: Regression coefficients, with EQ-5D utility as the response variable

	Fixed Effect	Estimate	Standard Error	P value
	Intercept	[redacted]	[redacted]	[redacted]
Treatment arm	Placebo (reference category)	[redacted]	[redacted]	[redacted]
	SEC Q2W	[redacted]	[redacted]	[redacted]
	SEC Q4W	[redacted]	[redacted]	[redacted]
Baseline EQ-5D	BASELINE EQ-5D	[redacted]	[redacted]	[redacted]
Health state	HiSCR<25 (reference category)	[redacted]	[redacted]	[redacted]
	HiSCR25–49	[redacted]	[redacted]	[redacted]
	HiSCR50–74	[redacted]	[redacted]	[redacted]
	HiSCR≥75	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol-5 dimensions; HiSCR, Hidradenitis suppurativa clinical response.

B9. Document B, section B.3.4.5; Tables 47 and 48, page 93.

For all utility values considered in the model, please provide the mean (SD) and N by treatment arm and health state.

For each health state, mean EQ-5D utility values for all patients in pooled SUNRISE and SUNSHINE weeks 2–16, by treatment arm are provided in Table 11, along with the number of observations and standard errors. The equivalent data from the biologic-experienced population in the pooled SUNRISE and SUNSHINE are provided in Table 4.

Table 11: Mean EQ-5D utility values from SUNRISE and SUNSHINE weeks 2–16 pooled, all patients

Treatment Arm	Mean EQ-5D Utility (Number of Observations, Standard Error)			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
SEC Q2W	[redacted]	[redacted]	[redacted]	[redacted]
SEC Q4W	[redacted]	[redacted]	[redacted]	[redacted]
SEC pooled	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
All treatments pooled	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol-5 dimensions; HiSCR, Hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SEC, secukinumab

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Appendix – ITT Population patient transition count data

Table 12: Patient transition count data (numerators)

		Starting Health State (HiSCR)															
		≥ 75				50-74				25-49				< 25			
		Ending Health State (HiSCR)															
Treatment	Timepoint (weeks)	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25
SEC Q4W	0–4	[redacted]															
	4–8	[redacted]															
	8–12	[redacted]															
	12–16	[redacted]															
	16–20	[redacted]															
	20–24	[redacted]															
	24–28	[redacted]															
	28–32	[redacted]															
	32–36	[redacted]															
	36–40	[redacted]															
	40–44	[redacted]															
	44–48	[redacted]															
	48–52	[redacted]															
SEC Q2W	16–20	[redacted]															
	20–24	[redacted]															
	24–28	[redacted]															
	28–32	[redacted]															
	32–36	[redacted]															
	36 –40	[redacted]															
	40–44	[redacted]															

		Starting Health State (HiSCR)															
		≥ 75				50-74				25-49				< 25			
		Ending Health State (HiSCR)															
Treatment	Timepoint (weeks)	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25
	44–48	[redacted]															
	48–52	[redacted]															
Placebo	0–4	[redacted]															
	4–8	[redacted]															
	8–12	[redacted]															
	12–16	[redacted]															

Abbreviations: HiSCR, Hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SEC, secukinumab

Table 13: Patient transition count data (denominators)

		Starting Health State (HiSCR)															
		≥ 75				50–74				25–49				< 25			
		Ending Health State (HiSCR)															
Treatment	Timepoint (weeks)	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25
SEC Q4W	0–4	[redacted]															
	4–8	[redacted]															
	8–12	[redacted]															
	12–16	[redacted]															
	16–20	[redacted]															
	20–24	[redacted]															
	24–28	[redacted]															
	28–32	[redacted]															
	32–36	[redacted]															
	36–40	[redacted]															

		Starting Health State (HiSCR)															
		≥ 75				50–74				25–49				< 25			
		Ending Health State (HiSCR)															
Treatment	Timepoint (weeks)	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25	≥ 75	50–74	25–49	< 25
	40–44	[redacted]															
	44–48	[redacted]															
	48–52	[redacted]															
SEC Q2W	16–20	[redacted]															
	20–24	[redacted]															
	24–28	[redacted]															
	28–32	[redacted]															
	32–36	[redacted]															
	36–40	[redacted]															
	40–44	[redacted]															
	44–48	[redacted]															
	48–52	[redacted]															
Placebo	0–4	[redacted]															
	4–8	[redacted]															
	8–12	[redacted]															
	12–16	[redacted]															

Abbreviations: HiSCR, Hidradenitis suppurativa clinical response; Q2W: every two weeks; Q4W: every four weeks; SEC, secukinumab

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Association of Dermatologists
3. Job title or position	Consultant dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1) To treat skin inflammation in the form of inflammatory nodules, abscesses and skin tunnels which cause severe pain, pus production and odour, resulting in substantial reduction in quality of life. 2) Prevention of disease progression. This is important in hidradenitis suppurativa (HS) because it is a scarring condition. The scarring limits function, which in turn reduces ability to work and study. Reversal of scarring may require extensive surgery, for example axillary surgery healing times are about 3 months for wide excisions and may exceed 6 months for the groin and buttocks.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The current standard treatment response definition is HiSCR50, a trial endpoint defined as a 50% reduction from baseline in the sum of inflammatory nodules and abscesses, with no increase in abscesses or draining skin tunnels. A reduction of 4 points in the dermatology life quality index (DLQI) is also relevant, as well as a reduction in pain numerical rating scale (NRS).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – in the PIONEER studies for adalimumab, the only currently licensed treatment for HS, the HiSCR50 endpoint was reached by only 50% of trial participants. This means that only 50% of participants had a 50% reduction in their inflammatory lesions. As a consequence, many patients on adalimumab therapy still experience substantial morbidity from their active HS. In addition, secondary failure of adalimumab often occurs and so another biologic therapy option is greatly needed. The HS management pathway follows the BAD guidelines 2018 (https://onlinelibrary.wiley.com/doi/10.1111/bjd.17537) and we envisage secukinumab to fit in the pathway immediately after adalimumab.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	As per the management pathway from the BAD guidelines 2018 (https://onlinelibrary.wiley.com/doi/10.1111/bjd.17537)

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	As above.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	As above.
9c. What impact would the technology have on the current pathway of care?	It would provide an alternative treatment option for patients who have not responded adequately to adalimumab, due to primary or secondary failure of adalimumab therapy
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – secukinumab is already used for moderate-to-severe psoriasis in children (aged 8 years and above), young people and adults
10a. How does healthcare resource use differ between the technology and current care?	Provision of secukinumab would be in the same patient population treated by adalimumab, namely moderate to severe HS. Failure of adalimumab therapy results in many patients needing additional therapy, which can include extensive surgery.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
10c. What investment is needed to introduce the technology? (For example,	No additional investment required as secukinumab is already used for psoriasis.

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – at the moment people with HS receiving insufficient benefit from adalimumab have no other treatment option.
11a. Do you expect the technology to increase length of life more than current care?	Difficult to quantify, however HS is associated with reduced life expectancy. A Finnish study showed that people with HS on average live for 60.5 years, compared to 71.1 years for psoriasis and 75.2 years in naevi controls (https://pubmed.ncbi.nlm.nih.gov/30597518/).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – active HS produces substantial decreases in health-related quality of life, which is an issue when adalimumab therapy is frequently insufficient to control HS and other treatment options are currently unavailable.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Adalimumab and other anti-tumour necrosis factor (TNF) alpha drugs are contraindicated in those with a personal or family history of demyelinating diseases such as multiple sclerosis, so secukinumab is a potential option is this HS patient group. Secukinumab should probably be avoided in those with concomitant inflammatory bowel disease (IBD) because there was a signal in a trial for IBD that it could worsen IBD.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	No issues here – the subcutaneous delivery route mirrors adalimumab and the infrastructure in terms of biologic specialist nurses and home delivery services are already in place. There are no additional baseline or monitoring tests required compared with adalimumab.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The current NICE stopping rule for adalimumab in HS could be applied, i.e. if there is less than a 25% reduction in the sum of inflammatory nodules and abscesses then secukinumab should be discontinued.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients report that pain is a key part of living with HS. While some of the functional impact of pain is included in QALY calculations, the burden of living with either chronic pain, or unpredictable episodic pain associated with flares, should not be underestimated. Pain scores of 10/10 (worst pain imaginable) are quite often reported in HS.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the first anti-IL17 for HS and provides a much-needed alternative to adalimumab. Without an alternative treatment beyond adalimumab, clinicians may delay adalimumab therapy to hold it in reserve, which could allow scarring to accumulate while effective therapy is delayed.
16a. Is the technology a 'step-change' in the	Secukinumab will provide a step-change in HS management, as the first anti-IL17 therapy available for HS and a much needed alternative biologic for the quite high proportion of HS patients exhibiting adalimumab primary or secondary failure. Patients' expectations now exceed the 50% improvement in inflammatory lesions denoted by

management of the condition?	the HiSCR trial endpoint and only 50% of HS patients reached even this endpoint in the adalimumab PIONEER studies (Kimball *et al.* 2016, https://pubmed.ncbi.nlm.nih.gov/27518661/).
16b. Does the use of the technology address any particular unmet need of the patient population?	Needed for those with multiple sclerosis in whom anti-TNF therapy is contraindicated and for primary or secondary failure of adalimumab.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are higher rates of candidiasis reported with secukinumab treatment, however, the candidiasis responds to standard oral therapy. Secukinumab should be avoided in the small group of HS patients with concomitant IBD because it could worsen the IBD.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the patient population is moderate-to-severe HS and previous failure of adalimumab treatment was permitted. A recent systematic review highlighted emerging therapies for HS, including secukinumab https://pubmed.ncbi.nlm.nih.gov/35409118/.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC) has defined six core outcome domains to measure in HS trials (Thorlacius *et al.* 2018 https://pubmed.ncbi.nlm.nih.gov/29654696/): • pain • health-related quality of life • physical signs

	• global assessment (patient & physician) • disease progression (flare frequency/time to recurrence) • other symptoms (drainage & fatigue)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The trials used all the standard outcome measure instruments so surrogate outcomes were not needed.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No.
21. How do data on real-world experience compare with the trial data?	There are currently limited real-world data for secukinumab in HS.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Probable higher incidence in people of Afro-Caribbean family background has been correctly identified. Please bear in mind that peak prevalence (2%) is in females of child-bearing age.
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• The first anti-IL-17 agent for treating hidradenitis suppurativa (HS) • **Error! Bookmark not defined.**There are no new safety signals for secukinumab treatment of HS compared to other inflammatory conditions • Secukinumab will allow biologic therapy for people with HS in whom anti-TNF therapy is contraindicated (eg concomitant multiple sclerosis) • •

Thank you for your time.

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

Produced by Aberdeen HTA Group

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The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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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

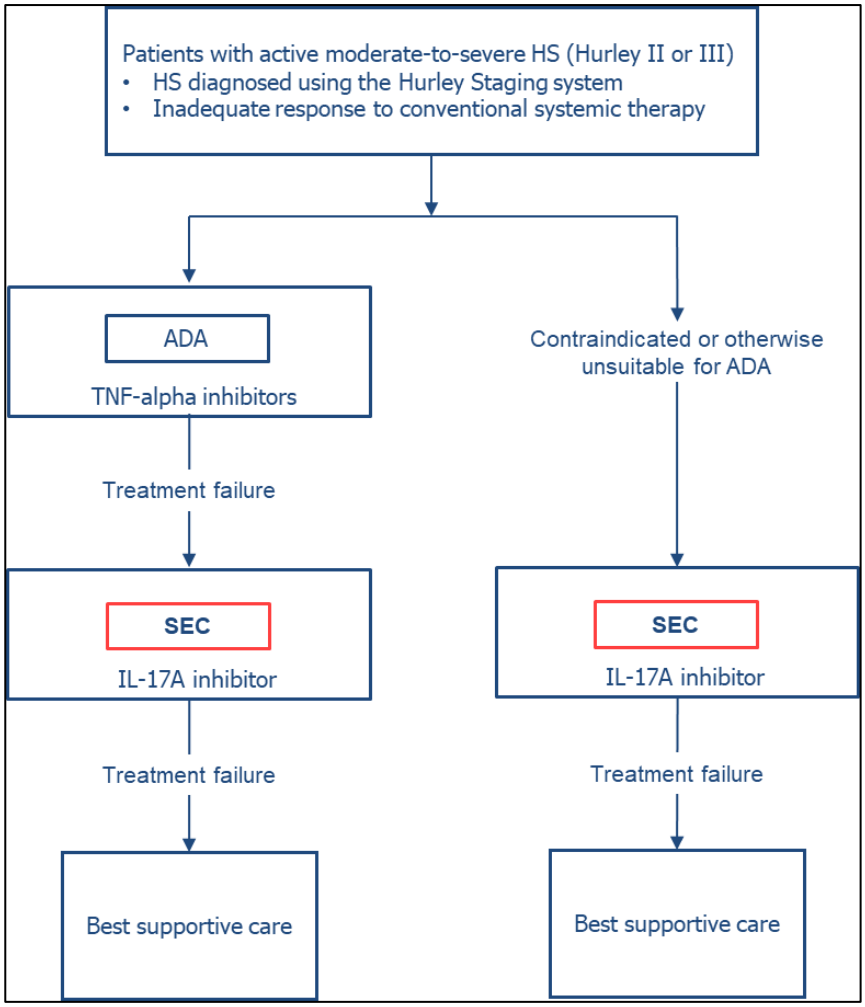
The company submission (CS) describes HS as a debilitating, chronic skin condition characterised by recurrent, painful, deep-seated, inflammatory lesions mainly affecting skin folds, in particular, the groin and armpits.[1-4] The focus of the CS is moderate-to-severe HS.

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]

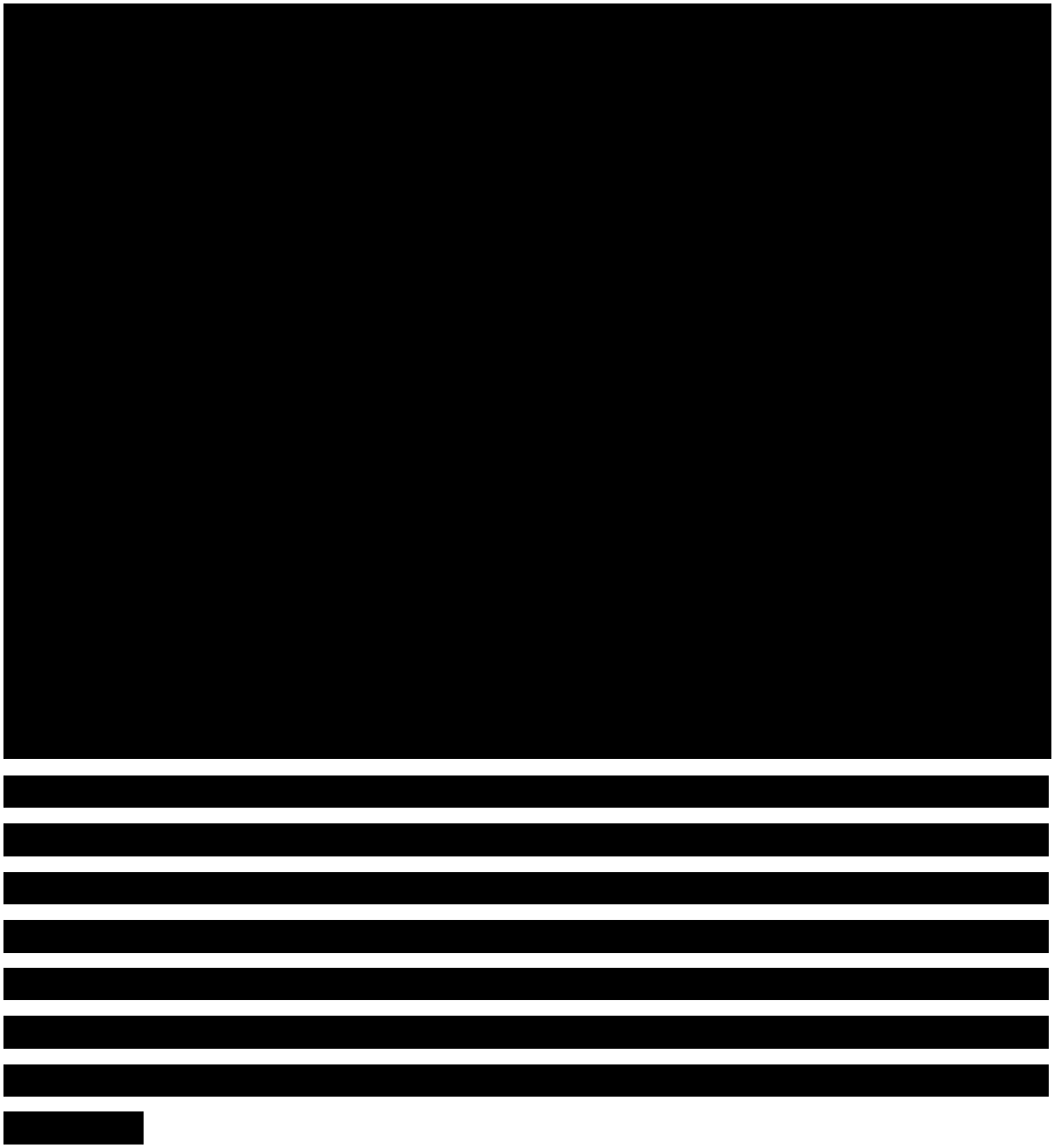


Figure 2 Network diagram used to illustrate the extended network of all comparators [reproduced from Figure S.8, page 99 of NMA report]

[redacted]

3.4.3 Methods of the NMA

[redacted]

[redacted][40]

[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.

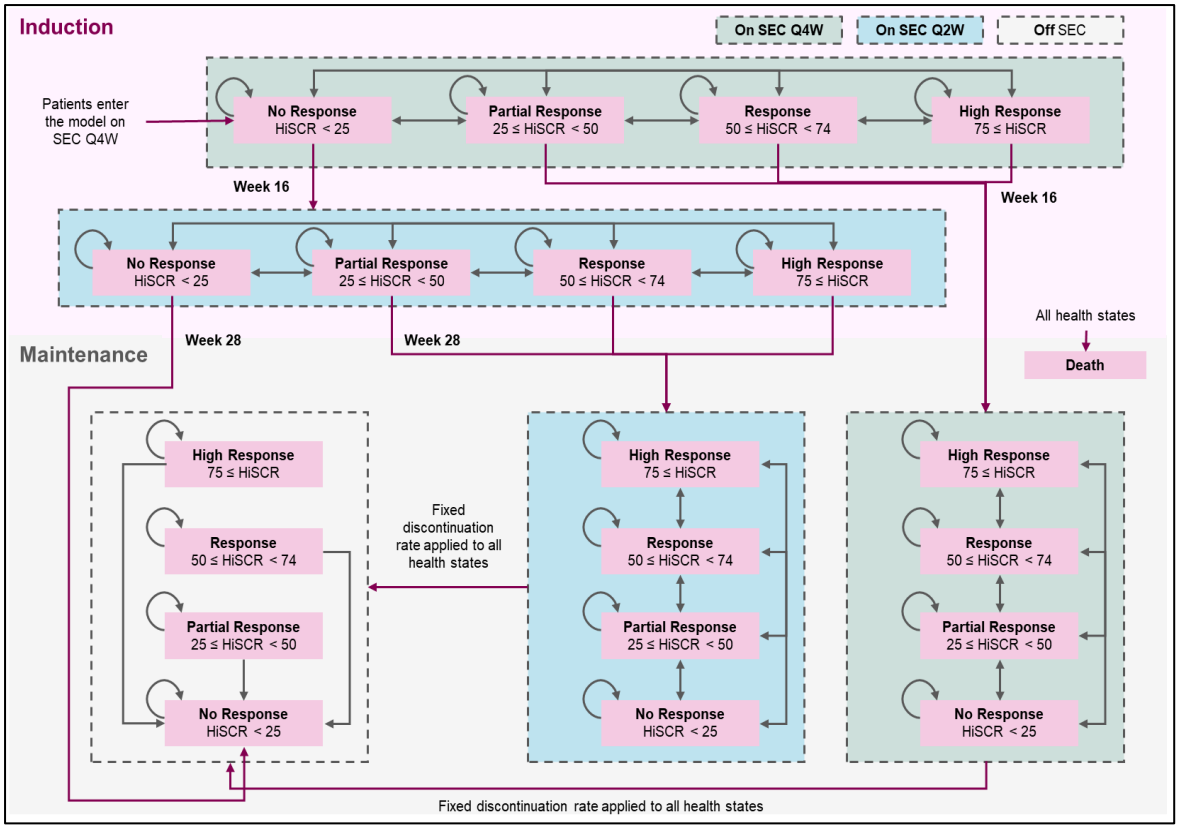


Figure 4 Health state transitions for patients receiving secukinumab [reproduced from Figure 33 of the CS]

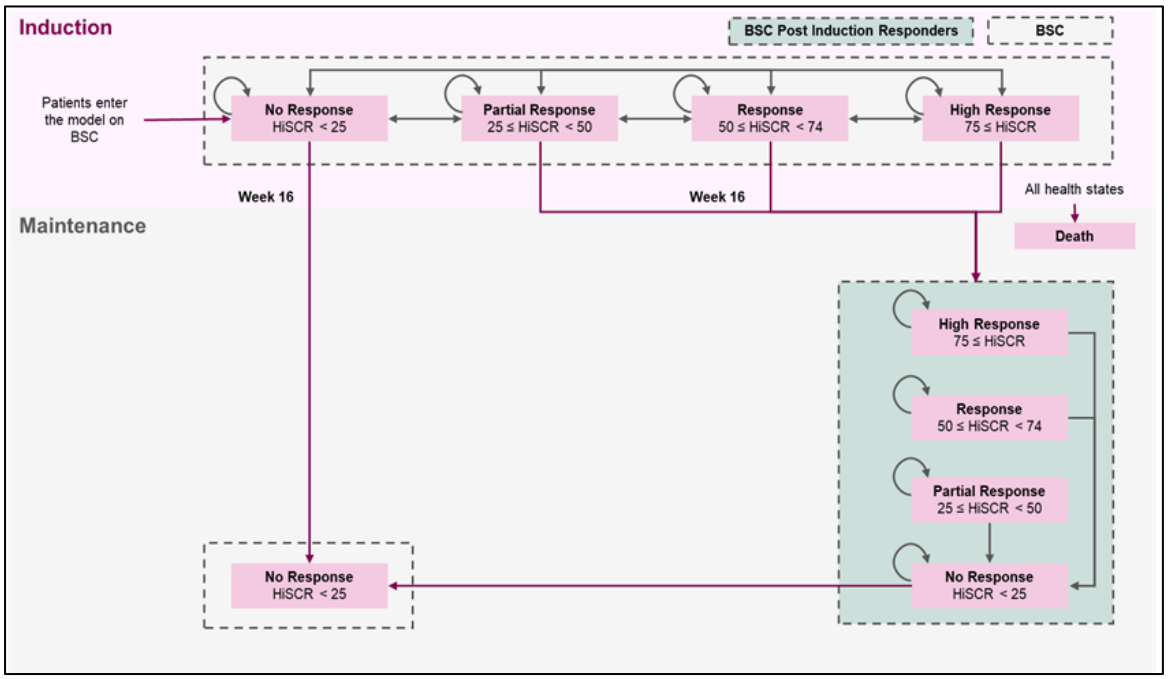


Figure 5 Health state transitions for patients receiving BSC [reproduced from Figure 34 of the CS]

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]		
	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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Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 07 March 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Section 1: Major Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 67 states: "Given the description provided in Table 54 of the company submission, it appears as if outpatient visits for "any reason", may double count outpatient costs due to HS surgery. Furthermore, there is concern that some wound care appointments are already included within the outpatient consultations for 'any reason' as most wound appointments would take place in the outpatient setting (consistent with the costing approach adopted by the company)."	We believe this statement – along with resultant amendments to the EAG base case – is based on a misinterpretation of the approach used in the Company Submission for secukinumab in HS (see justification). Essentially, our approach follows that which was used in TA392. Apologies if the approach taken was unclear. We request this statement is removed, with EAG scenarios incorporating these updates also amended.	As highlighted in Section B.3.5 of Document B, resource use estimates are taken from TA392.[1] "Outpatient visits (due to any reasons)" was labelled incorrectly in Table 54 of Document B. The resource use presented in Table 54 was intended to reflect the "Routine outpatient visits" as labelled in Table 51 (Resource use rates by health states) of the Company Submission in TA392.[1] In addition, "Routine outpatient visits", "Outpatient visits due to HS surgery", "Visits to wound-care due to HS surgery (presumed outpatients)" and "Visits to wound-care NOT due to HS surgery (presumed outpatients)" were also considered as separate	This is not a factual inaccuracy. The EAG appreciates the company clarification, but the remains concerned that the outpatient resource use may be over-estimated from TA392. Without further validation of the resource use frequencies, or new expert elicitation work, the EAG maintain our position. We have however updated the text to reflect the company's clarification.

		resource use from one another in Table 51 of the Company Submission TA392.[1] Apologies for this error, which may have led to the EAG's misinterpretation.	

Section 2: Minor comments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page ix states: "The EAG prefers to apply the **same** methodologies to the secukinumab and BSC arms of the model, thereby extrapolating **short term** data from **both arms** over the full model time horizon"	Please amend to "The EAG prefers to apply the **similar** methodologies to the secukinumab and BSC arms of the model, thereby extrapolating **52 weeks of** data from the **secukinumab arm and 4 weeks of data from the BSC arm (weeks 12–16)** over the full model time horizon"	The EAG stated that the same approach was taken however, 4 weeks of data was used to extrapolate for the BSC arm which is much less than the secukinumab arm.	The EAG intention for this analysis was to extrapolate the average data from the observed period for BSC (i.e., weeks 0-16), to maintain consistency with the approach used for secukinumab. The EAG has now updated the relevant analyses, which lead to a reduced ICER for the EAG preferred base case analysis. Whilst implementing these amendments in the model, the EAG identified an error in the

			company's probabilistic analysis which over-estimated the probabilistic ICER in both the EAG and company preferred base cases. This related to the transitions on the "CODA parameters" tab for BSC week 0-16. This has now been corrected, and the report amended accordingly.
Page 13 states: "…if patients first get adalimumab under the proposed pathway, the better responders are no longer eligible for secukinumab…"	Please amend to: "…if patients first get adalimumab under the proposed pathway, the better responders are no longer eligible for secukinumab **until they lose response to adalimumab**"	While the company acknowledges that responders to adalimumab would not be eligible for secukinumab while maintaining continued response, it is expected that once they lose response to adalimumab, secukinumab will be trialled if accepted by the NICE in the proposed treatment pathway.	Amended as suggested.
Page 21 states: "It is not clear to the EAG why most	Please consider removing the statement as the reason for pooling	The pooling of NRS30/skin pain was	No change. The EAG agrees that this was pre-specified, but

analyses were presented separately except for this one outcome"	the data for this outcome was provided in the Company Submission and CSRs	pre-planned as per Section B.2.4 of Document B and the SUNNY trial protocols.	the rationale for this is still unclear.
Page 42 states: "…the searches were done in June 2021 and updated in August 2022 (start date for searches not reported)."	Please amend to: "…the searches were done in June 2021 **(no date restrictions applied)** and updated in August 2022 **(date restrictions were limited to studies published from 2021 onwards)**."	As noted in Appendix G (Tables 22–28) of the Company Submission, there were no publication timeframe restrictions for the original SLR while the updated SLR was limited to studies published from 2021 onwards.	Amended as suggested.
Page 54 states: "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 (or 28 for Q2W) and week 52."	Please amend to: "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 ~~**(or 28 for Q2W)**~~ and week 52."	The base case model applies average four-weekly transition probabilities based on the corresponding pooled Week 16–52 SUNNY trial data to the Q2W responders at the end of the Up-titration phase.	Amended as suggested.

Page 64 states: “Company preferred, BNF (assuming primary care prescribing) and eMIT (assuming secondary care prescribing) unit costs per dose”	Please amend to: “Company preferred, **Drug Tariff** (assuming primary care prescribing) and eMIT (assuming secondary care prescribing) unit costs per dose”	Minor amendment to specify that prescriptions in primary care are routinely dispensed in community pharmacy and thus drug costs are based on the Drug Tariff prices.	Not a factual inaccuracy. The prices used in the EAG report are correctly described.

Section 3: Minor Typographical and Grammatical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page viii states: “Only around [redacted] of participants in these studies had received prior biologic treatment, such as adalimumab”	Please amend to: “Only around [redacted] and [redacted] of participants in **SUNSHINE and SUNRISE, respectively**, had received prior biologic treatment, such as adalimumab”	Minor amendment to improve accuracy of the report.	Amended as suggested.
Page viii states: “[redacted]”	Dependent on your response to our rationale (see right), please **either**: • If this is a typographical error, amend to “[redacted]”	It is unclear whether this is a minor typographical error or a legitimate construction, given this sentence could be read either way. As such, the company would like	This is a typo (now corrected)

	• Clarify whether the concerns the EAG had in the past were subsequently resolved.	to confirm what the EAG intended here.	
Page 13 states: "…participants classified as Harley 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 Harley stage I HS…"	Please amend to: "…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…"	Minor typographical error.	Amended.
Page 14 states: "The treatment groups in SUNRISE were balanced for baseline age."	Please amend to: "The treatment groups in **SUNSHINE** were balanced for baseline age"	Minor typographical error.	Amended.
Page 14 states: "The secukinumab Q2W group across both studies also had more severe HS with a higher proportion of participants with Harley stage III disease"	Please amend to: "The secukinumab Q2W group across both studies also had more severe HS with a higher proportion of participants with **Hurley** stage III disease"	Minor typographical error.	Amended.

<table>
<tr>
<td>Page 18; Table 8 (Baseline patient disease characteristics in SUNSHINE and SUNRISE [randomised analysis set])</td>
<td>Please amend the mean (SD) values for the “Time since diagnosis of HS (years)” row of the SUNSHINE trial as follows:
<table>
<tr><th colspan="5">Time since diagnosis of HS (years)</th></tr>
<tr><td>n</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Mean (SD)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td>
<td>Minor typographical error.</td>
<td>Amended.</td>
</tr>
<tr>
<td>Page 21 states: “In most cases results from SUNSHINE and SUNRISE were provided separately in the CS, except for the NRSC30 skin pain outcome…”</td>
<td>Please amend to: “In most cases results from SUNSHINE and SUNRISE were provided separately in the CS, except for the NRS30 skin pain outcome…”</td>
<td>Minor typographical error.</td>
<td>Amended.</td>
</tr>
<tr>
<td>Page 21: “The primary endpoints of SUNSHINE and SUNRISE was achieving HiSCR50 (hideradenitis suppurativa clinical response score of 50) at Week 16…”</td>
<td>Please amend to: “The primary endpoints of SUNSHINE and SUNRISE was achieving HiSCR50 (hidradenitis suppurativa clinical response score of 50) at Week 16…”</td>
<td>Minor typographical error.</td>
<td>Amended.</td>
</tr>
</table>

<table>
<tr><td>Page 28 states: “Gastrointestinal disorders were reported in 10-15% of patients…”</td><td>Please amend to “Gastrointestinal disorders were reported in 13-16% of patients…”</td><td>Minor amendment to improve accuracy of the report.</td><td>Amended.</td></tr>
<tr><td>Page 31 states: “Only around [redacted] of participants in these studies had received a prior biologic treatment, such as adalimumab.”</td><td>Please amend to: “Only around [redacted] and [redacted] of participants in SUNSHINE and SUNRISE, respectively, had received prior biologic treatment, such as adalimumab”</td><td>Minor amendment to improve accuracy of the report.</td><td>Amended.</td></tr>
<tr><td>Page 32 states: “The EAG did not consider it appropriate to conduct a formal critique of this document, as it dd not form part of the company’s submission…”</td><td>Please amend to: “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…”</td><td>Minor typographical error.</td><td>Amended.</td></tr>
<tr><td>Page 83; Table 15 (Comparison of previous NICE appraisal of adalimumab against the company submission for secukinumab)</td><td>Please amend “Costs (currency) (intervention, comparator)” row as follows:<table><tr><td>Costs (currency) (intervention, comparator)</td><td>Adalimumab (with confidential PAS discount): £140,342
Supportive care: £128,647</td><td>Company preferred: Secukinumab (with confidential PAS discount): [redacted]; BSC:

EAG preferred:</td></tr></table></td><td>Minor typographical error.</td><td>Text amended and updated in line with response to comments above.</td></tr>
</table>

	Secukinumab (with confidential PAS discount): [redacted]; BSC: [redacted]		
Page 47 states: "…non-responders at that point are assumed to enter an absorbing non-response state for the remainder of the model time horizon"	Please amend to: "…non-responders at that point are assumed to enter a **semi-absorbing** non-response state for the remainder of the model time horizon"	Minor amendments to improve the consistency with the rest of the document.	Amended as suggested
Page 49 states: "…because the company base case model assumes people receive multiple surgeries over their lifetime, in addition to BSC treatments including danazol, retinoids…"	Please amend to: "…because the company base case model assumes people receive multiple surgeries over their lifetime, in addition to BSC treatments including **dapsone**, retinoids…"	Minor typographical error.	Amended as suggested
Page 53 states: "Those achieving a secukinumab response continue to follow the transitions implied by the Q4W arm of the SUNNY trials"	Please amend to: "Those achieving a secukinumab response continue to follow the transitions implied by the **Q2W** arm of the SUNNY trials"	Minor typographical error.	The quoted sentence is not required for this sub-section of the report and has been removed.

Page 59; Table 20 (Comparison of modelled health state utility values [HSUVs])	Please amend the following rows to: HiSCR (**50-74**) and HiSCR (**25-49**)	Minor typographical error	Amended as suggested
Page 63 states: "The company clarified that secukinumab is provided via homecare providers in where patients are supported for up to three nurse visits upon delivery of secukinumab."	Please amend to: "The company clarified that secukinumab is provided via homecare providers ~~in~~ where patients are supported for up to three nurse visits upon delivery of secukinumab."	Minor typographical error.	Amended as suggested

Section 4: Confidentiality Highlighting Amendments due to recently published SUNNY trial results[2]

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page viii	Only around [redacted] of participants in these studies had received prior biologic treatment, such as adalimumab.	Only around 23% of participants in these studies had received prior biologic treatment, such as adalimumab.	AiC highlighting removed. In addition, the percentage (23%) has been amended as per the company's requests in Section 3 of this document (the revised percentages are "23.8% and 23.2% of participants in SUNSHINE and SUNRISE, respectively").

Page 13	Both SUNRISE ([redacted]) and SUNSHINE ([redacted]) included participants classified as Harley stage I disease, indicating mild disease severity.	Both SUNRISE (n=25, 4.6%) and SUNSHINE (n=15, 2.8%) included participants classified as Harley stage I disease, indicating mild disease severity.	Amended.
Page 13	[redacted] across both studies had not previously received systemic biologic therapy prior to receiving secukinumab.	Around three-quarters of participants across both studies had not previously received systemic biologic therapy prior to receiving secukinumab.	Amended.
Page 13	Of those who did receive prior systemic biologic therapy ([redacted] and [redacted] for SUNSHINE and SUNRISE, respectively).	Of those who did receive prior systemic biologic therapy (129/541 [23.8%] and 126/543 [23.2%] for SUNSHINE and SUNRISE, respectively).	Amended.
Page 14	Overall, [redacted] of participants were female. [redacted] were White, with [redacted] participants in SUNSHINE and [redacted] participants in SUNRISE classified as Black or African American. The mean BMI was	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	Amended.

	[redacted] (in the obesity range), with [redacted] of participants weighing ≥90 kg. [redacted] of participants were current smokers. The mean age was [redacted] years in SUNSHINE and [redacted] years in SUNRISE, with [redacted] aged from [redacted] to [redacted] years.	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.	
Page 14	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 [redacted] to [redacted] years ([redacted]) compared with the Q4W and placebo groups ([redacted] and [redacted], respectively). The treatment groups in SUNRISE were balanced for baseline age.	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	Amended.

		groups in SUNRISE were balanced for baseline age.	
Page 14	The secukinumab Q2W group across both studies also had more severe HS with a higher proportion of participants with Harley stage III disease ([redacted] and [redacted] for SUNSHINE and SUNRISE, respectively) compared with the secukinumab Q4W and the placebo groups ([redacted] and [redacted] for SUNSHINE; [redacted] and [redacted] for SUNRISE).	The secukinumab Q2W group across both studies also had more severe HS with a higher proportion of participants with Harley 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).	Amended.
Page 15–17, Table 7	Data points for demographics and baseline characteristics are AiC.	Please remove all AiC highlighting in Table 7, except for the following characteristics or rows: • “Ethnicity” • “Weight” • Median and Min–Max values for “BMI”	Amended.

Page 18–20, Table 8	Data points for baseline patient disease characteristics are AiC.	Please remove all AiC highlighting in Table 8, except for the following disease characteristics: • "Time since HS symptoms(s) onset (years)" • "Baseline HS-PGA" • "Baseline DLQI total score" • "Previous exposure to adalimumab therapy"	Amended.
Page 21	Of the 541 randomised patients in SUNSHINE, [redacted] patients completed the 16-week treatment period. Of the 543 randomised patients in SUNRISE, [redacted] patients completed the 16-week treatment period. At the primary endpoint analysis data cut-off, [redacted] ([redacted] and [redacted] ([redacted] patients had completed the entire treatment period (Week 52), respectively.	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	Amended.

		entire treatment period (Week 52), respectively.	
Page 21–22	At Week 16, the odds ratio estimate (95% CI) in SUNSHINE for the secukinumab Q2W dose vs placebo comparison was [redacted] and for the secukinumab Q4W dose vs placebo comparison was [redacted]. This difference was statistically significant in favour of secukinumab for the Q2W group ([redacted]) but not for the Q4W group (one-sided [redacted]). For SUNRISE, the odds ratio estimates (95% CI) for the comparison with placebo of both secukinumab treatment regimens were statistically significant ([redacted]), [redacted] for the Q2W group; [redacted], [redacted], for the Q4W group).	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).	Amended.

Page 22	**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 ([redacted] respectively) compared with placebo ([redacted]). Similar results were found in SUNRISE with a greater decrease for both secukinumab dosing regimens ([redacted], respectively) compared with placebo ([redacted]). The difference from placebo was statistically significant for both secukinumab Q2W groups in SUNSHINE and SUNRISE (one-sided [redacted] and [redacted] respectively) but only for secukinumab Q4W in SUNRISE ([redacted]). The percentage change from baseline in AN count by week shows that the treatment effect with secukinumab compared	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	Amended.

		treatment effect with secukinumab compared.	
Page 23	**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 ([redacted] and [redacted] vs. [redacted]) and SUNRISE ([redacted] and [redacted] vs. [redacted]). The estimated odds ratio was statistically significant only for the secukinumab Q2W group in SUNSHINE (one-sided [redacted]; SUNRISE: [redacted]) and the secukinumab Q4W group in SUNRISE (one-sided [redacted]; SUNSHINE: [redacted]). 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).	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	Amended.

		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).	
Page 23	**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 ([redacted] and [redacted] vs. [redacted]), although results were statistically significant only for the Q2W group (one-sided [redacted]; Q4W: [redacted]). The proportion of participants achieving NRS30 by week up to Week 16 shows that a larger	**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	Amended.

	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).	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).	
Page 24, Table 9	Data points for primary and secondary outcomes are AiC.	Please remove all AiC highlighting in Table 9.	Amended.
Page 25	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	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	Amended.

	studies (SUNSHINE at Week 16: [redacted] in Q2W and [redacted] in Q4W vs. [redacted] in placebo; SUNRISE at Week 16: [redacted] in Q2W and [redacted] in Q4W vs. [redacted] in placebo).	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).	
Page 25	**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 ([redacted]) compared with the Q4W ([redacted]) and placebo ([redacted]) groups.	**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.	Amended.
Page 27, Table 10	Safety data are AiC	Please remove all AiC highlighting in Table 10.	Amended.
Page 27	In Treatment Period 1, around [redacted] of patients in both SUNRISE and SUNSHINE experienced at least one TEAE but [redacted] were SAEs or	In Treatment Period 1, around two-thirds of patients in both SUNRISE and SUNSHINE	Amended.

	led to treatment discontinuation and there were [redacted] deaths.	experienced at least one TEAE but very few were SAEs or led to treatment discontinuation and there were no deaths.	
Page 28, Table 11	Data points for TEAEs by preferred term are AiC.	Please remove all AiC highlighting from Table 11.	Amended.
Page 29	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 ([redacted] in SUNRISE; [redacted] in SUNSHINE) and secukinumab groups ([redacted] in both groups in SUNRISE; [redacted] in both groups in SUNSHINE). No particular SAE was higher in frequency across the trials.	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.	Amended.
Page 30	There were [redacted] deaths over the Entire Study Period, both in SUNRISE and in the any secukinumab Q4W group, and	There were two deaths over the Entire Study Period, both in SUNRISE and in the	Amended.

	neither were considered to be related to the study treatment.	any secukinumab Q4W group, and neither were considered to be related to the study treatment.	
Page 31	Only around [redacted] of participants in these studies had received a prior biologic treatment, such as adalimumab.	Only around 23% of participants in these studies had received a prior biologic treatment, such as adalimumab.	AiC highlighting removed. In addition, the percentage (23%) has been amended as per the company's requests in Section 3 of this document (the revised percentages are "23.8% and 23.2% of participants in SUNSHINE and SUNRISE, respectively").
Page 41	In addition, the overall population of SUNSHINE/SUNRISE does not match the company's positioning, as only [redacted]% and [redacted]% of participants in SUNSHINE and SUNRISE respectively received prior biologics.	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.	Amended.
Page 50	However, the starting cohort for the model was obtained from the full trial population from the SUNNY trials ([redacted]	However, the starting cohort for the model was obtained from the full trial population	Amended.

	female, mean age: [redacted]), including those who had no previous treatment with adalimumab.	from the SUNNY trials (56.3% female, mean age: 36.2), including those who had no previous treatment with adalimumab.	
Page 107	The EAG has checked the QALY shortfall calculations and reproduced these for a cohort, average age [redacted], proportion female [redacted] and is satisfied that neither the company nor EAG preferred base case analyses would qualify for 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.	Amended.

References

1. National Institute for Health and Care Excellence (NICE). Adalimumab for treating moderate to severe hidradenitis suppurativa (TA392). Available from: https://www.nice.org.uk/guidance/ta392 Accessed: 07 March 2023.
2. Kimball AB, Jemec GBE, Alavi A, Reguiai Z, Gottlieb AB, Bechara FG, et al. Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials. The Lancet. 2023;401(10378):747-61.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

B.1 Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **28 April 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

B.2 About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are composed of, or contain glycopyrronium bromide: · Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for chronic obstructive pulmonary disease [COPD]) · Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD · Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with long-acting beta-agonist (LABA)/ inhaled corticosteroid (ICS) Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc).

B.3 Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The company preferred model structure for the BSC arm applies restrictions that do not reflect UK clinical practice	Yes	The Company's base-case assumed that long-term transitions between the different response health states were not possible for best supportive care (BSC) patients beyond Week 16 of the model, and that patients could only lose a response, after which it could never be regained. This approach was employed due to the lack of available SUNSHINE and SUNRISE trial data to inform long-term transitions beyond Week 16 for BSC in the model and the Company's belief that applying BSC transition probabilities from the 16-week Induction phase of the model to the BSC arm beyond Week 16 lacked face validity. The EAG expressed some concern that the approach taken by the Company for BSC did not align with that used in the secukinumab arm of the model, and that symptoms and quality of life may improve spontaneously, with BSC treatments or with surgery. Therefore, the EAG stated a preference to apply the same structural assumptions to the secukinumab and BSC arms of the model, allowing patients on BSC to transition between the different response health states beyond Week 16 of the model (EAG report, page ix and page 49). However, in the absence of SUNSHINE and SUNRISE trial data to inform transition probabilities for BSC beyond Week 16, the EAG used the transition probabilities for BSC during the Induction phase to model long-term

		transitions between the Hidradenitis Suppurativa Clinical Response (HiSCR) health states beyond Week 16 (Maintenance phase) of the model. This therefore assumes that there are no differences in transitions between the HiSCR health states during the Induction phase (Week 0–16) and Maintenance phase of the model (Week 16–52, Week 52+). It should be noted that transitions for the secukinumab arm beyond Week 16 of the model are informed by pooled SUNSHINE and SUNRISE trial data between Week 16–52, and not transition probabilities derived from the pooled Week 0–16 SUNSHINE and SUNRISE trial data. The EAG recommended that additional evidence is provided to support or refute the EAG's position that it is implausible to assume that BSC and surgery deliver no clinical benefit beyond Week 16 of the model. Therefore, to help reduce the uncertainty and identify the most appropriate approach, evidence was sought that could help validate the predictions for the BSC arm, supplemented by clinical opinion. Firstly, additional rapid literature searches were undertaken using PubMed, seeking to identify any extant observational data for surgery effectiveness (which would not have been captured in the systematic literature review [SLR] of randomised controlled trials [RCTs] in the Company submission [CS]). Given the time constraints of Technical Engagement, the searches could not be performed as part of a formal SLR. The searches yielded no directly usable new evidence. It was notable however that in a UK national survey (Howes et al. 2021) on surgical management that was identified, the authors found that more than half of UK surgeon respondents did not use any well-validated outcome instruments to determine treatment success or failure.[1] Furthermore, the BAD guideline for the management of hidradenitis suppurativa notes that surgical interventions are relatively underrepresented in the management pathway due to the lack of RCT-level evidence to support their use.[2] Based on the limited literature available, TA392 was also reviewed. Section 5.7.2.1 of the committee papers for TA392 reports the Markov trace for BSC (Figure 25, reproduced below in Figure 1).

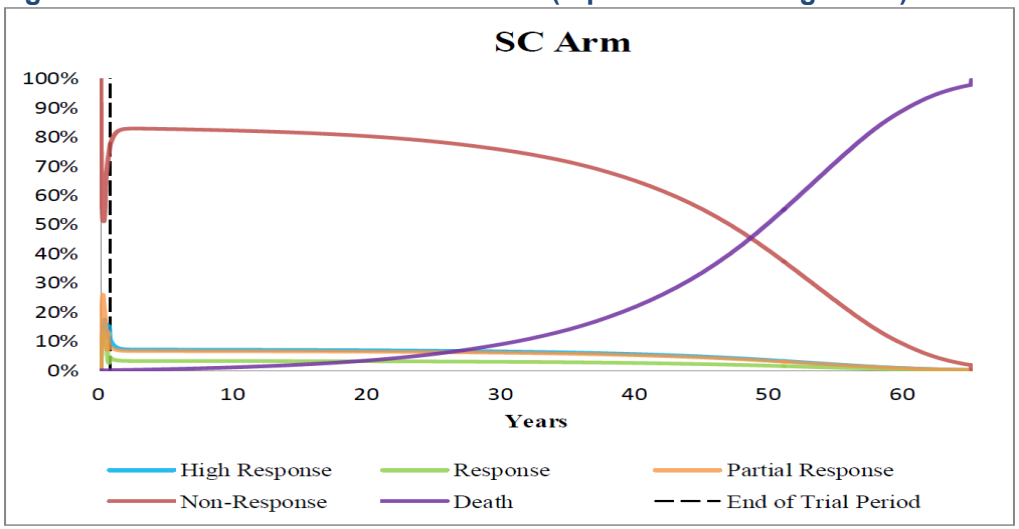
		Figure 1: Markov Trace for BSC in TA392 (reproduction of Figure 25)  BSC represents SC **BSC:** best supportive care; SC: standard of care. The proportion of non-responders predicted for BSC at Week 36, Year 5 and Year 10 in TA392 was 77.20%, 82.71% and 82.19%, respectively. These predictions were used to inform decision-making for adalimumab in biologic-naïve patients. While they can be used to assess the face validity of predictions using the Company's and EAG approach, Novartis notes that the proportion of non-responders in TA392 is likely to be lower compared with the proportion of patients expected for the population addressed in our current decision problem. This is because biologic-naïve patients are more likely to respond to BSC compared with biologic-experienced patients.

Table 1 compares the proportion of non-responders predicted in the BSC arm at Week 36, Year 5 and Year 10 using the EAG's and Company's approach against the proportions reported in TA392.

Table 1: Comparison of the proportion of non-responders in the BSC arm in TA392 and predicted using the EAG's and Company's approach.

Model	Week 36	Year 1	Year 5	Year 10
TA392 – BSC arm	77.20%	-	82.71%	82.19%
EAG's approach	48.70%	48%	47.60%	47.30%
Novartis' approach	70.30%	80%	99.40%	98.70%

Abbreviations: BSC: best supportive care; EAG: evidence assessment group.

It can be seen from Table 1 that the proportion of non-responders over time predicted using the EAG's approach is considerably lower compared with that used in TA392, raising a concern about its face validity – in fact the EAG's approach suggests that more than half of the BSC arm are in one of the response states at Week 36, Year 1, Year 5 and Year 10, respectively. In contrast, the predictions using the Company's approach are more closely aligned with that reported in TA392, albeit higher, with the proportion of non-responders close to 100% by Year 5.

Clinical opinion was sought to determine the proportion of non-responders that would be expected over time on BSC in UK clinical practice, in the population modelled in the decision problem. Four clinical experts were consulted as part of our technical engagement (TE) response and were asked to comment on the face validity of the predictions from the three approaches, as set out in Table 1. Three out of the four clinicians consulted expected the proportion of non-responders to lie in-between predictions using the Company's approach and those reported in TA392. One of the four clinicians consulted found it hard to comment.

Acknowledging the EAG's concerns regarding the potentially over-simplistic approach taken in the manufacturer submission, Novartis proposes to amend its base-case. The amended base-case uses transition probabilities reported in TA392 to inform long-term transitions between response health states in the BSC arm of the model beyond Week 16, thereby addressing the EAG's concerns that patients receiving BSC, and surgery may experience some spontaneous symptom improvement.

The 24-week BSC transition probability matrix reported in TA392 (reproduced in Table 2) following induction is applied once every six model cycles (i.e., 24-week period). This approach avoids the need to convert the 24-week transition probabilities from TA392 to a 4-week basis in line with the model cycle length (converting the 24-week matrix to a 4-week matrix would require assumptions and add uncertainty).

Table 2: HiSCR average (24-week) transition probabilities of patients for BSC during the Maintenance phase (Week 16–52, Week 52+) (Novartis base-case following TE)

Treatment	To > From	HiSCR≥75	HiSCR50–74	HiSCR25–49	HiSCR<25	Source
BSC	Maintenance phase (Week 16–52)					
	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	PIONEER II trial, 12–36 weeks average transition probabilities (NICE TA392)
	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	Maintenance phase (Week 52+)					
	HiSCR≥75	[redacted]	[redacted]	[redacted]	[redacted]	

	HiSCR50–74	[redacted]	[redacted]	[redacted]	[redacted]	PIONEER II trial, 12–36 weeks average transition probabilities (NICE TA392)
	HiSCR25–49	[redacted]	[redacted]	[redacted]	[redacted]	
	HiSCR<25	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: BSC: best supportive care; HiSCR: Hidradenitis Suppurativa Clinical Response.

As transitions are explicitly modelled between health states beyond Week 16, the effects of potential clinical improvement with BSC are accounted for. This approach also addresses the EAG's other concern regarding potential structural bias, by ensuring that both arms follow a similar model structure. Health state occupancy over time for the BSC arm predicted using this alternative approach are shown in Figure 2, for transparency, with the proportion of non-responders predicted compared with that reported in TA392 in Table 3. In summary, the proportion of non-responders predicted in the amended base-case following TE aligns more closely with that reported in TA392 and is consistent with the views expressed by the clinical experts described above.

		Figure 2: Health state occupancy over time for the BSC arm using the average (24-week) transition probabilities from TA392 to inform health state transitions during the Maintenance phase (Week 16–52, Week 52+) (Novartis base-case following TE)  **Abbreviations:** BSC: best supportive care; HiSCR: Hidradenitis Suppurativa Clinical Response. **Table 3: Comparison of the proportion of non-responders in TA392 and in the company's amended base-case following TE.**

Model	Week 36	Year 1	Year 5	Year 10
TA392 – BSC arm	77.20%	-	82.71%	82.19%
Novartis amended base-case following TE	77.65%	84.87%	88.25%	87.25%
EAG's approach	*48.70%*	*48%*	*47.60%*	*47.30%*
Novartis' original base-case	*70.30%*	*80%*	*99.40%*	*98.70%*

Abbreviations: BSC: best supportive care; TE: technical engagement.

Conclusion

In conclusion, there is clear evidence that the EAG's approach of assuming that the majority of BSC patients achieve some level of response lacks face validity. However, Novartis also acknowledges that the original approach of modelling no long-term transitions in the BSC arm beyond Week 16 may have been simplistic. Consequently, to address the EAG's concerns, the company amended its base-case using transitions probabilities for BSC reported in TA392 to allow transitions between the response health states in the Maintenance phase of the model. This addresses both EAG concerns: (1) that transient improvement in symptoms and quality of life associated with BSC treatments and surgery have not been accounted; and (2) the risk of any structural bias between the secukinumab and BSC arms of the model.

The impact on the incremental cost-effectiveness ratios (ICERs) in the CS base-case associated with using data from TA392 (as part of the Company's amended base-case following TE) is shown below in Table 4 for transparency.

Table 4: ICERs for original CS base-case and the original CS base-case amended to incorporate long-term health state transitions informed by Week 12–36 transition probabilities from TA392 for BSC patients.

		<table><tr><th>Treatment</th><th>Costs</th><th>LYs</th><th>QALYs</th><th>Inc. costs</th><th>Inc. LYs</th><th>Inc. QALYs</th><th>ICER</th></tr><tr><td colspan="8">Original CS base-case</td></tr><tr><td>BSC</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>SEC</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>[redacted]</td><td>0.000</td><td>[redacted]</td><td>£28,165</td></tr><tr><td colspan="8">Original CS base-case amended to incorporate long-term health state transitions informed by Week 12–36 transition probabilities from TA392 for BSC patients</td></tr><tr><td>BSC</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>SEC</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>[redacted]</td><td>0.000</td><td>[redacted]</td><td>£32,213</td></tr></table>Abbreviations: CS: company submission; ICER: incremental cost-effectiveness ratio; Inc: incremental; LY: life year; PAS: patient access scheme; QALYs: quality-adjusted life years.
It is currently unclear whether treatment specific or treatment pooled health state utility values should be used in the economic model	Yes	Novartis thank the EAG for their consideration of the evidence already submitted supporting the use of treatment-specific utility values, and for specifying in the EAG Report what additional analyses they would like to see to further convince them that the trial data support the use of treatment-specific utility values in the model. Specifically, the EAG have requested (1) further clinical evidence on the individual components which together comprise the HiSCR endpoint, by treatment, to support treatment differences within state; and (2) further statistical analysis in the form of a repeated measures regression model of utilities, but with interaction terms between treatment and health state. Novartis are pleased to provide the information requested and trust this will prove sufficient to allow the EAG to support the use of treatment-specific utility values. **Clinical data** As highlighted in the CS, mean HiSCR is determined by a continuous variable (a reduction in inflammatory lesion count [abscesses + inflammatory nodules]) and a binary component (no increase in abscesses or draining fistulas when compared with baseline). For example, if a

patient has a reduction of more than 50% in abscesses and inflammatory nodules but has an increase in the number of abscesses or the number of draining fistulae from baseline, they would be considered a non-responder.

As requested by the EAG, Table 5 presents the mean percentage change in AN count from baseline in each HiSCR health state using the pooled data between Week 2 and Week 16. Results show that the reduction in the mean AN count from baseline for the secukinumab treatments arms for the non-response health state ([redacted]% versus [redacted]% for secukinumab Q2W and Q4W, respectively) compared with placebo ([redacted]%) is statistically significant, showing that patients on secukinumab in the non-responder health state are better.

Table 5. Mean percentage change from baseline in AN count in each HiSCR health state (pooled overall data from week 2–16)

Treatment	Mean (SD) percentage change in AN count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
Secukinumab Q2W (n=3428)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab Q4W (n=3418)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=3392)	[redacted]	[redacted]	[redacted]	[redacted]

* P-values <0.0001 vs Placebo
Abbreviations: AN: Abscesses and inflammatory nodule; HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; Q4W: every four weeks; SD: standard deviation.
Source: Pooled data from the SUNSHINE and SUNRISE trials.

Table 6 and Table 7 present the proportion of patients with no increase in abscesses and draining fistula counts using the pooled data between Week 2 and Week 16 compared to baseline, by treatment arm. While these binary data are more difficult to interpret as they cannot be interpreted in isolation, it can be seen that the secukinumab arms are [redacted]

[redacted] an increase in abscesses compared with placebo, and [redacted] in draining fistulas, providing reassurance that the difference between arms in the mean percentage change in AN count (Table 5) is not biased.

Table 6. Number (%) of patients with no increase in abscesses at Week 16 in each HiSCR health state (pooled overall data from week 2-week 16)

Treatment	Number (%) of patients with no increase in abscesses count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
Secukinumab Q2W (n=1134)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab Q4W (n=1038)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=1070)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; Q4W: every four weeks.
* P-values < 0.05 vs placebo
Source: Pooled data from the SUNSHINE and SUNRISE trials.

Table 7. Number (%) of patients with no increase in draining fistula counts at Week 16 in each HiSCR health state (pooled overall data from week 2- week 16)

Treatment	Number (%) of patients with no increase in draining fistula counts			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
Secukinumab Q2W (n=1134)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab Q4W (n=1038)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n= 1070)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; Q2W: every two weeks; Q4W: every four weeks.
Source: Pooled data from the SUNSHINE and SUNRISE trials.

The mean change in AN count and proportion of patients with no increase in abscesses and draining fistulas at Week 16 are shown in Appendix 1 for transparency.

In summary, clinical data underpinning the HiSCR endpoint provide clear evidence that clinical outcomes differ by treatment arm, with a statistically significant reduction in the mean AN count from baseline for the secukinumab arms ([redacted]% and [redacted]% for Q2W and Q4W, respectively) compared with placebo ([redacted]) for the non-response health state, with a [redacted] in the proportion of patients with no increase in abscesses and [redacted] in the proportion of patients with no increase in number of draining fistula counts.

Statistical evidence

As requested by EAG, Table 8 and Table 9 provide estimates of regression coefficients from mixed-model repeated measures (MMRM) with interaction terms specified between treatment arms and HiSCR category, using all available utility data from Weeks 2 to 16 as the response variable, for each secukinumab regimen (Q2W and Q4W) separately and pooled, respectively.

With the model stratifying by placebo, secukinumab Q2W and Q4W (Table 8), the MMRM model shows that there is strong statistical evidence to support the use of treatment-specific utilities for some of the health states, with statistical significance achieved in some, but not every, HiSCR category for each treatment arm.

Table 8: Regression coefficients from an MMRM utility analysis with separate secukinumab treatment arms

		Fixed Effect	Estimate	Standard Error	P value
		Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D		BASELINE EQ-5D	[redacted]	[redacted]	[redacted]
Health state		HiSCR<25 (reference category)	[redacted]	[redacted]	[redacted]
		HiSCR25–49	[redacted]	[redacted]	[redacted]
		HiSCR50–74	[redacted]	[redacted]	[redacted]
		HiSCR≥75	[redacted]	[redacted]	[redacted]
Treatment-Health State Interactions	Secukinumab Q2W (Placebo reference)	HiSCR<25	[redacted]	[redacted]	[redacted]
		HiSCR25–49	[redacted]	[redacted]	[redacted]
		HiSCR50–74	[redacted]	[redacted]	[redacted]
		HiSCR≥75	[redacted]	[redacted]	[redacted]
	Secukinumab Q4W (Placebo reference)	HiSCR<25	[redacted]	[redacted]	[redacted]
		HiSCR25–49	[redacted]	[redacted]	[redacted]
		HiSCR50–74	[redacted]	[redacted]	[redacted]

		HiSCR≥75	[redacted]	[redacted]	[redacted]

Bolded p values indicate statistical significance.
Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; MMRM: mixed model review analysis; Q2W: every two weeks; Q4W: every four weeks.

With the Q2W and Q4W secukinumab arms pooled to increase sample size (Table 9), there is strong statistical evidence in support of treatment-specific utilities, with statistically significant differences between secukinumab Q2W and Q4W pooled and placebo observed in each HiSCR category (the exception being HR with a p value of exactly [redacted]).

Table 9: Regression coefficients from an MMRM utility analysis with secukinumab treatment arms pooled.

		Fixed Effect	Estimate	Standard Error	P value
		Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D		BASELINE EQ-5D	[redacted]	[redacted]	[redacted]
Health state		HiSCR<25 (reference category)	[redacted]	[redacted]	[redacted]
		HiSCR25–49	[redacted]	[redacted]	[redacted]
		HiSCR50–74	[redacted]	[redacted]	[redacted]
		HiSCR≥75	[redacted]	[redacted]	[redacted]
Treatment-Health State Interactions	Secukinumab Q2W + Q4W (Placebo reference)	HiSCR<25	[redacted]	[redacted]	[redacted]
		HiSCR25–49	[redacted]	[redacted]	[redacted]
		HiSCR50–74	[redacted]	[redacted]	[redacted]
		HiSCR≥75	[redacted]	[redacted]	[redacted]

Bolded p values indicate statistical significance.
Abbreviations: HiSCR: Hidradenitis Suppurativa Clinical Response; MMRM: mixed model review analysis; Q2W: every two weeks; Q4W: every four weeks.

In summary, results from the MMRMs provide strong evidence in support for the use of treatment specific utility values in the economic model.

Conclusion

Considering the totality of the evidence presented (clinical evidence and MMRMs), there is strong and conclusive evidence in support of the use treatment-specific utilities for some health states, if not all.

Acknowledging concerns from the EAG and new evidence presented as part of TE, Novartis proposes to amend its base-case whereby treatment-specific utility values are used for the non-responders health state and pooled utility values across arm for the remaining health states (i.e., HiSCR25–49, HiSCR50–74, HiSCR≥75). Novartis would highlight that this is likely to be conservative given that results from the MMRMs provide evidence in support of the use of treatment-specific utility values for other health states.

The impact on the ICERs in the CS base-case associated with using treatment-specific utility values for the non-responder health state only (part of the Company's amended base-case following TE) is shown in Table 10 for transparency.

Table 10: ICERs for CS base-case and CS base-case with treatment-specific utilities for non-responders only

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Original CS base-case							

		<table><tr><td>**BSC**</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>**SEC**</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>[redacted]</td><td>0.000</td><td>[redacted]</td><td>£28,165</td></tr><tr><td colspan="8">**Original CS base-case with treatment-specific utilities for non-responders only**</td></tr><tr><td>**BSC**</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>**SEC**</td><td>[redacted]</td><td>22.797</td><td>[redacted]</td><td>[redacted]</td><td>0.000</td><td>[redacted]</td><td>£29,979</td></tr></table> **Abbreviations:** CS: company submission; ICER: incremental cost-effectiveness ratio; Inc.: incremental; LY: life year; PAS: patient access scheme; QALYs: quality-adjusted life years.
The rates and costs of hospital resource use for HS are highly uncertain and may be over-estimated in the company's economic model	Yes	The Company's base-case uses hospital resource use obtained from a survey of UK clinical experts (N=40), conducted for the previous NICE appraisal of adalimumab in HS (TA392). The EAG is concerned that (1) the number of surgeries over the lifetime may be over-estimated ([redacted] and [redacted] surgeries for BSC and secukinumab, respectively); and (2) there is a lack of clarity on how the resource use were estimated as well as the uncertainty in estimates not being accounted for. Owing to this, 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. The EAR notes (page xi) that a literature review may help to reduce uncertainty on this issue, however –at the clarification stage – the Company noted that the CS presented an economic SLR undertaken in 2022, to identify resource use estimates from published literature for patients with moderate-to-severe HS. NICE TA392 and Willems et al. 2020 were the only two publications identified that were relevant to the UK population. Given that the model inputs in Willems et al. 2020 were informed by TA392, TA392 was chosen as the most appropriate source to inform the resource use frequencies in the model. In the absence of further literature, and to help reduce the uncertainty, the EAG requested that the company conducts its own elicitation exercise with clinical experts, presenting variability in expert opinion and incorporating this within the probabilistic analyses.

		While a formal elicitation exercise was not possible to conduct given the time available for TE, clinical validation was sought on (1) whether the resource use presented in TA392 were still reflective of UK clinical practice and (2) setting of surgery. In summary, two of the four clinical experts consulted considered that using the resource use reported in TA392 was appropriate and did not expect significant change compared with current UK clinical practice. One clinical expert considered that resource use was likely to have gone up since TA392 due to the increased and earlier diagnosis in specialised centres (compared with diagnosis mostly done in primary care before 2016). Using resource use from TA392 is therefore likely to be an under-estimate and conservative. The fourth clinical expert consulted did not comment. The EAG also had concern that the number of surgeries predicted over the lifetime may be over-estimated ([redacted] and [redacted] surgeries for BSC and secukinumab respectively). Novartis notes that in TA392, the company's estimated a total number of 33.87 procedures in patients receiving BSC which was considered appropriate by the ERG and their clinical experts (committee papers TA392, ERG report, page 120). Another concern by the EAG was that the company assumed that all surgical procedures will be conducted as elective inpatient admissions that require overnight admission. The EAG considered this to be unrealistic and was advised by their clinical expert that many procedures for HS will take place as day case procedures. The four clinical experts consulted as part of TE were asked to comment on the type and the setting of surgeries. Mirroring the view from the EAG's clinical experts, clinical opinion sought following TE indicated that most surgeries would be minor/intermediate and undertaken as day case with the remaining requiring major/multiple elective surgery. Acknowledging concerns from the EAG and reflecting clinical opinion obtained during TE, Novartis proposes to amend its base-case to align our approach with that employed in TA392 by the ERG. In our amended base-case, it is assumed that patients have 2 lifetime wide

excisions, 67% of surgeries are intermediate and done as day case, with the remaining surgeries requiring inpatient stays (split equally between elective and non-elective short stay intermediate surgeries in line with TA392).[3, 4]

In addition to our amended base-case based on the ERG's preference in TA392,[3] three additional scenarios are presented based on those presented in the final published guidance for TA392 including:

- **Scenario 1**: 2 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days
- **Scenario 2**: 3 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days
- **Scenario 3**: 4 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days

The impact on the ICERs in the CS base-case associated with alternative approaches for costing of surgery is shown below in Table 11 for transparency.

Table 11: ICERs from CS base-case and alternative approaches for costing of surgeries

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Original CS base-case							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165

		Original CS base-case, amended based on TA392 ERG assumption: 2 lifetime wide excisions, 67% surgeries intermediate day case **BSC** [redacted] 22.797 [redacted] **SEC** [redacted] 22.797 [redacted] [redacted] 0.00 [redacted] £34,261 **Scenario 1: 2 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days** **BSC** [redacted] 22.797 [redacted] **SEC** [redacted] 22.797 [redacted] [redacted] 0.00 [redacted] £33,894 **Scenario 2: 3 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days** **BSC** [redacted] 22.797 [redacted] **SEC** [redacted] 22.797 [redacted] [redacted] 0.00 [redacted] £33,205 **Scenario 3: 4 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days** **BSC** [redacted] 22.797 [redacted] **SEC** [redacted] 22.797 [redacted] [redacted] 0.00 [redacted] £32,516 **Abbreviations**: CS: company submission; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; Inc: incremental; LY: life year; PAS: patient access scheme; QALYs: quality-adjusted life years.
The company economic model includes costs of BSC and surgery but does not include any quality-of-life benefits from these treatments	Yes	A key concern raised by the EAG is that the potential benefits associated with surgeries and treatments that are part of BSC may not have been captured in the company's base-case, despite costs being included. As discussed in Issue 1, this is because the company's base-case assumed that long-term transitions between the 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, despite receiving surgeries and BSC. The EAG suggested that an alternative approach to align benefits and costs would be to remove the costs of surgery from the model. While Novartis acknowledges the limitation with the

		approach originally employed in the CS, Novartis does not consider the scenario suggested by the EAG to be clinically plausible and reflective of NHS clinical practice given the aim of treatments in HS is to prevent surgeries. The amended base-case (see response to Issue 1 above) addresses the concerns from the EAG by allowing patients on BSC to transition between the response health states to reflect the potential improvement in symptoms and quality of life associated with BSC treatments and surgeries. In this amended base-case, the BSC transition probability matrix reported in TA392 is used (Table 2) to allow patients who are receiving BSC to keep transitioning between the different response health states. An additional concern raised by the EAG is that the costs for BSC treatments used in the economic model do not align with those included in the SUNNY trials. The EAG further considered that most treatments are given in secondary care and therefore electronic market information tool (eMIT) unit costs may be a more appropriate source. In the Company's model, the costs of BSC are modelled to reflect UK clinical practice and include topical and oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens, with the type and distribution of treatment informed by clinical expert opinion. Clinician opinion sought by the EAG considered the type and distribution of treatments to be broadly reflective of UK clinical practice (See Section 4.2.8, EAG report, page 116). Novartis considers it important for costs for BSC to reflect NHS clinical practice. While Novartis recognises the potential mismatch between treatments given in clinical practice and those given in the SUNNY trials, clinical experts indicated that treatment for HS are mostly supportive, notably following adalimumab failure. Clinical experts indicated that it was reasonable to assume the effect of the placebo arm of the SUNNY as a proxy for BSC in UK clinical practice in the absence of alternative evidence. Clinical opinion was also sought as part of TE to understand where BSC treatments are prescribed. Clinical experts considered that most antibiotics are typically prescribed in primary care, while clindamycin, rifampicin, retinoids, dapsone and immunosuppressants (e.g.,

ciclosporin, cyproterone) would be prescribed in secondary care. Consequently, the Company's base-case has been amended to reflect this.

Acknowledging concerns from the EAG and reflecting clinical opinion obtained during TE, Novartis proposes to amend its base-case source of unit costs for treatments that are part of BSC. In our new base-case, antibiotics (other than clindamycin and rifampicin) are assumed to be prescribed in primary care and therefore unit costs are taken from prescription cost analysis (PCA) for England (2021/22). In contrast, clindamycin, rifampicin, retinoids, dapsone and immunosuppressants are assumed to be prescribed in secondary care and therefore unit costs are taken from eMIT.The impact on the ICERs in the CS base-case associated with using different source for unit costs for BSC (part of the company's amended base-case following TE) is shown below in Table 12 for transparency.

Table 12: ICERs from CS base-case and CS base-case with amended BSC cost sources.

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Original CS base-case							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£28,165
Original CS base-case with amended BSC cost sources							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£29,074

Abbreviations: CS: company submission; ICER: incremental cost-effectiveness ratio; Inc: incremental; LY: life year; PAS: patient access scheme; QALYs: quality-adjusted life years

B.4 Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Inclusion of up-titration from Q4W to Q2W	Section 4.2.6, Page 54, EAR Table 28, Page 84, EAR	No	The Company's base-case includes the possibility for patients on Q4W not responding at Week 16 to be up-titrated to Q2W in line with the anticipated marketing authorisation. The EAG prefers to remove up-titration. This is justified by the EAG (Table 28, EAR, Page 84) "*because the effectiveness data from the SUNNY trials are applied to a more difficult to treat subgroup. This creates a selection 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*". While Novartis acknowledges that the SUNNY trials were not designed to assess a strategy of up-titration of treatment dosage, Novartis notes that the evidence

			from the SUNNY trials [redacted] Acknowledging the EAG concern, Novartis further considers that the approach taken in the CS is reasonable. This can be seen when continuing to apply the transition matrix for Q4W after the induction phase for non-responders (instead of up-titrating to the Q2W transition matrix): the ICER remains broadly unchanged (£28,165 with up-titration versus £28,554 without up-titration), suggesting that Q4W and up-titration of non-responders to Q2W are similarly cost-effective. Novartis are concerned that removal of up-titration from the model could lead to final guidance that disadvantages those who would respond in clinical practice if up-titration were permitted, while making little difference to the ICER.
Additional issue 2: EAG suggestion of double counting of outpatient costs	Page 67, EAR	No	The Company thanks the EAG for the revisions made to the EAR following factual accuracy checking stage but continues to dispute the EAG assertion in the revised EAR that the resource use taken from TA392 “may double count” outpatient costs. We refer to our detailed description in the factual accuracy check response (“ID4039 Company TE papers”, bookmark “4b. Factual accuracy check ACIC form_7Mar23_EAG response [ACIC]”, Section 1: Major Issues).

B.5 Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base-case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 1	Assumed no transition between response health states after Week 16 for patients receiving BSC	Added Week 12–36 transition probabilities from TA392 and used the data to inform the long-term health state transitions (Week 16+) of patients receiving BSC	ICER increased from £28,165 (original base-case ICER) to **£32,213**
Key issue 2	Assumed treatment-specific utilities for responders and non-responders	Used the pooled utility values for all responders and only applied the treatment-specific utility values to the non-responders	ICER increased from £28,165 (original base-case ICER) to **£29,979**
Key issue 3	Assumed all skin surgeries for HS patients to be elective admissions and informed by costs sourced from NHS Reference Cost database	Aligned the approach with the ERG's preferred assumption in TA392, i.e., 2 lifetime wide excisions, 67% surgeries intermediate day case, the remainder intermediate inpatient	ICER increased from £28,165 (original base-case ICER) to **£34,620**

Key issue 4	Assumed BSC would be prescribed in primary care setting	Assumed the following drugs would be prescribed in the secondary care setting while the remainder (most antibiotics) would be prescribed in primary care setting: • Clindamycin • Rifampicin • Dapsone • Acitretin • Isotretinoin • Ciclosporin • Cyproterone	ICER increased from £28,165 (original base-case ICER) to **£29,074**
Updated settings to align with minor preferences from the EAG	• Excluded costs and QoL impact of AE • Applied severity weighting of disease based on data from PIONEER II	• Included costs and QoL impact of AE • Applied severity weighting of disease based on data from SUNNY	ICER decreased from £28,165 (original base-case ICER) to **£27,893**
Company's base-case following technical engagement (or revised base-case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	ICER: **£42,415**

Sensitivity analyses around revised base-case

Table 13: ICERs from revised base-case following technical engagement and alternative approaches for costing of surgeries

Treatment	Costs	LYs	QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Revised base-case following technical engagement							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£42,415
Scenario 1: 2 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£42,022
Scenario 2: 3 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£41,285
Scenario 3: 4 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days							
BSC	[redacted]	22.797	[redacted]	-	-	-	-
SEC	[redacted]	22.797	[redacted]	[redacted]	0.000	[redacted]	£40,548

Abbreviations: CS: company submission; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; Inc: incremental; LY: life year; PAS: patient access scheme; QALYs: quality-adjusted life years.

References

1. Howes R, Ingram JR, Thomas KS, et al. The surgical management of hidradenitis suppurativa in the United Kingdom: a national survey of care pathways informing the THESEUS study. Journal of Plastic, Reconstructive & Aesthetic Surgery 2022;75:240-247.
2. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. British Journal of Dermatology 2019;180:1009-1017.
3. National Institute for Health and Care Excellence (NICE). Adalimumab for treating moderate to severe hidradenitis suppurativa (TA392). Final Appraisal Determination – Committee Papers. Available from: https://www.nice.org.uk/guidance/ta392/documents/committee-papers-2. Accessed: 07 March 2023.
4. National Institute for Health and Care Excellence (NICE). Adalimumab for treating moderate to severe hidradenitis suppurativa (TA392). Final Guidance – Chapter 3 (Evidence). Available from: https://www.nice.org.uk/guidance/ta392/chapter/3-Evidence. Accessed: 07 March 2023.

Appendix 1

Table 14: Mean percentage change from baseline in AN count at Week 16 in each HiSCR health state

Treatment	Mean (SD) percentage change in AN count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
Secukinumab Q2W (n=361)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab Q4W (n=360)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=363)	[redacted]	[redacted]	[redacted]	[redacted]

* P-values <0.05

Table 15: Number (%) of patients with no increase in abscesses at week 16 in each HiSCR health state

Treatment	Number (%) of patients with no increase in abscesses count			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
Secukinumab Q2W (n= 361)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab Q4W (n=360)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=363)	[redacted]	[redacted]	[redacted]	[redacted]

Table 16: Number (%) of patients with no increase in abscesses at week 16 in each HiSCR health state

Treatment	Number (%) of patients with no increase in draining fistula counts			
	HiSCR<25	HiSCR25–49	HiSCR50–74	HiSCR≥75
Secukinumab Q2W (n=361)	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab Q4W (n=360)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n= 363)	[redacted]	[redacted]	[redacted]	[redacted]

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Questions for patients

The evaluation of secukinumab focusses on adults with active moderate to severe hidradenitis suppurativa (HS) who cannot take adalimumab including those who is contraindicated or otherwise unsuitable, including those whose treatment didn't work or stopped working. For this specific group:

- **What is it like to live with moderate to severe hidradenitis suppurativa? If possible, please include the experiences of others for example families and carers (if applicable)**

  Living with moderate to severe HS is incredibly difficult and can be described as 'relentless. Many long-standing HS sufferers will say it has destroyed my relationships my chance of being a parent, getting married, my career and my ability to try and experience many of life's experiences and for those of us who do find acceptance it often later in life and too late to turn back the clock.

  It is perhaps easier to try and think of areas of life it does not affect rather than those it does. Primarily the challenge is pain, there are little to no effective pain management treatments for HS, I believe this to be the reason people's mental health suffers so much and why there is increased risk-taking behaviours such as over eating, smoking and substance misuse to feel comfort and mask pain. However, those behaviours impact on the known co-morbidities and can aggravate our symptoms and in the absence of adequate holistic healthcare and treatments, we find ourselves in a vicious cycle.

  Over the counter medicines barely reduce the high frequency pain caused in an acute flare, the pain as a flare drains and heals, is completely

different to that of the initial inflammation pain, a deep dulling thud and constant pain with the added soreness around wound healing and in some cases additional pain caused by infection and scarring.

Similar to pain there is also intensive itching from both new flares and old wounds healing which causes extreme frustration. Both itch and pain can really impact in how we interact with those around us, our social and intimate relationships, employment or education and our general mental wellbeing.

This leads to the impact moderate to severe HS has on mental health. Intense feelings of isolation, an incredibly difficult condition to talk to others about or to physically show the pain and difficult of living with multiple chronic, inflamed and draining wounds in personal areas. Many patients living long term on mental health medication and therapy and others left with no support.

It is common for people with HS to live with anxiety and depression and a number of patients will openly talk about self-harm, substance misuse and in some cases attempts on their own life as ways and means to stop the constant pain. Some of the generic routes for mental health, as a first stop are low level talking therapies but for many, they do not want to talk about this, they have kept quiet and suffered in silence for so long, they literally can’t talk about it. We can feel embarrassed, ashamed and have low self-worth.

There is a culture of patient blame and shame by uneducated health care professionals and other people in our personal lives who reinforce the stigma around HS being cause by poor hygiene, being overweight, that it may be contagious or linked to sexually transmitted disease. It is a truly awful place to be and for so many of us, this happens as young adults who already have a lot of body changes, a critical time for forming social and intimate relationships and we struggle to talk to others, when we do reach out to a professional, if the person isn’t aware of HS it can cause more

harm than good. We are faced with on average 7-10 years for a diagnosis and are misdiagnosed on average three times before learning of HS.

Wound management is critical, many patients still use plasters, toilet tissue, sanitary products and a range of other inappropriate ways to care for their wounds in the absence of access to appropriate wound care. Post-surgical intervention, there is usually effective wound care, this is where many people learn how to self-manage but if you haven't had surgery, you are not likely to get much support outside of a GP for infection and a dermatologist to prescribe something within the NICE treatment guidelines.

HS needs a holistic and joined up approach to care covering mental health, pain management and wound care and it simply doesn't exist; this is costing the NHS, society as a whole in some cases, it is fatally costing the lives of people.

There is an impact on those we live with and our wider family, friends and relationships at work. Patients talk about how they feel unkind towards people when in pain. That people who don't understand either minimise their pain or use toxic positivity. Small things, when people try and help can really anger us, for example saying you will feel better tomorrow, or are you feeling 'better' today. I have had very few days in 33 years of living with HS where I would describe myself as feeling well. In addition to the impact on skin we feel lethargy, chronic fatigue and flu like symptoms including headaches and fever on the onset of a flare. It is hard to maintain relationships with both he relentless and unpredictable nature. The unpredictability means we can feel unreliable, we pull out of social plans, we let people down or we recluse and don't engage in activity as we are tired of disappointing people.

Some people have very supportive partners and friends who can help them drain and dress parts of the body we can not reach and see, they help them see when they may need emergency care, they are able to practically bring them things we cannot physically do things and play a

carer role. They accompany you to appointments, help you heal post-surgery and in some cases take off time from work to do this. They may need to help financially support you if you cannot work because of your HS or contribute to higher household builds from the continuous washing of clothes and bed linen or the cost of prescriptions, parking or transport for appointments. Others have no one to help because they haven't been able to establish those positive, caring relationships and they stay in a cycle of believing they would not bring value to anyone's lives.

- **What are the current treatment options in England?**

For moderate to severe HS the two key treatments are biologics and surgical intervention although many with severe HS are told it is too severe for either of these routes to be effective. In some cases, people are offered a biologic to try and reduce disease activity in order to get them to a position when surgery may be possible. My chosen treatment is trying new biologics as they become available, ad hoc oral steroids and both planned and unplanned surgery. Planned surgery is always more effective as this is done by a surgeon familiar with HS, using the correct closure methods. They think about the fact that this may be one of many surgeries and how they can reduce scarring etc. Emergency admissions often result in a general surgeon who is less familiar with the way the disease behaves. However some patients are too scared to use a biologic, they worry about long term side effectives, adverse reactions and similarly for surgery you need to feel mentally strong to withstand the recovery and many are scared at the prospect and surgeons can often be very blunt in their manner and can further scare patients.

- **How effective are these treatments in reducing the severity of HS?**

Even when the routes above are on offer, surgical intervention is limited to the chosen anatomical area and the disease can often simply form sinus tracts and begin to attack another area of the body, not to mention the time required off work to heal post-surgery which makes it less appealing. For many though, surgical intervention has been the only relief they have from

HS, in my experience is completely stopped the disease in one axillary and helped in many other areas.

Similarly for biologics, for some it appears to enable them to live on a daily basis with reduced pain and therefore live a manageable, which in turn supports metal health, lifestyles choices and reduce the risk of other associated co-morbidities. For others it does not work.

- **Does response to these treatments change over time? If so, how? For example, if someone does not have an initial response to treatment, could their condition still improve over time?**

Biological treatment appears to work for some and not for others, like most other treatments available for people with HS. If the loading dose is not delivered fully, due to patient error, or treatment being incorrectly stored or administered, longer term this can affect the impact. Self-administration does put a lot of responsibility on a patient but for many is preferable to hospital appointments and in-patient stays, it just requires appropriate support at the beginning.

Infusions require longer periods off work, for some people it can be less effective over time and for others an ongoing maintenance dose is an effective way of managing their HS and enables them to enjoy a better quality of life. I am unaware of anyone who once stopping taking biologics, that the HS remains in remission, so they appear to be required for long term management.

I think part of the challenge is that for patients who have lived long term with HS find it difficult to know what to expect because of its unpredictable nature and progression of course, it’s hard to tell how effective a treatment has been. Patients may have unrealistic expectations that a treatment may cure their HS, many hope for remission but for others it is a way of managing the symptoms. The disappointment of not going into remission can for some patients, as in my case, feel it has been ineffective and then once the treatment has stopped you see an increase in disease activity and begin to then appreciate that it had provided a better quality of life. In

view of this what is missing, is some effective outcome measurement tools for patients and clinicians to consider shared decision making on impact. We need to move beyond clinical observation, body mapping and lesion count and consider quality of life. What can visually look bad and painful is not always the case and vice versa. Given the challenges patients have accessing biologics first time round, there is a low likelihood of getting a second chance.

- **How do these treatments impact a person's quality of life? Please tell us about improvements and any limitations.**

In my case, I have used the same biologic via self-injection, on two occasions, years apart and another biologic via infusion. The second run on the injection biologic was at a much higher dose than previously and whilst it did not stop new flares, it did, quite significantly reduced the level of inflammation. This meant not having to wear as many dressings, not change them as often, feeling more confident in my clothes and body, a lesser financial burden on myself and the NHS for dressing prescriptions. I had wound infections less frequently and therefore lower anti biotic use, took less time off work and my mental health and overall quality of life improved. In lower phases of disease activity, I was able to start relationships and do more social activities.

Limitations included the confidence to self-administere at home and it was always a challenge to dispose of the injection pens. I often wondered if the long-term risks of a biologic would be worth the better quality of life now but those are the decisions we make and should be supported by clinicians to make. I always asked a lot of questions of my consultant so I could make an informed decision and sometimes hear that others haven't really considered the risks because they simply feel that right now, they have no choice than to try and take anything which may help them.

- **If not already stated, would people in this specific group have surgery for the condition? If so, how often would this be done?**

Would an overnight stay in hospital be required or could surgery be done as a day case admission?

People with HS have both planned surgery and unplanned when it is required in an emergency. Some people are too scared to go down the surgical route. As mentioned previously, in my experience surgeons can be very abrupt in their approach. I have had some consultations which feel actively designed to deter me from the option. I think surgeons need to explain the risks and potential outcome and within that there are lots of unknowns so many patients think why I would go through the fear, the loss of earnings, absence from work on my record and a long, hard recovery, when I am told this may not actually help.

It also depends of the scale of surgery, wide scale excision and skin granting being for those with most severe disease and carrying the most intensive recovery. Skin grafts are unpredictable, and, in my case, I could not bear the thought of laying on my back for recovery when the skin to create the graft would have been taken from my back. There are practical worries about how I will cope with going to the toilet, how often will dressings be changed and by who, how will I manage the post operation pain, alongside my hs pain in other areas of my body.

For others, myself included it is an effective intervention. In some cases, the surgeon describes physical matter that has been removed that no amount of treatment would have broken down. The skin has become so damaged over time, removing tissue, and allowing it to regrow is my best chance of reducing disease activity. I have had surgery under both local and general anaesthetic and have always required an inpatient stay. I think for surgery to be an option, the HS is severe and so day patent surgery is less likely. I have gone home following emergency surgery but due to personal choice.

I found carbo dioxide laser surgery to be most effective although not all hospitals have the equipment or expertise to delivery this. Other

surgery has included deroofing and traditional surgical knife and spoon techniques. In know when I have planned surgery it signals to others around the severity of what I am living with as I can't show them, I know I will receive adequate wound care support. One of my best experiences was being given a PIQO dressing which meant I only had to change this weekly, and it seemed to heal more quickly.

People don't know what to expect from surgery so that is barrier, the recent UK Theseus Study did a video on deroofing for the patients and public which had almost 5000 views but the video of professionals received over 1.1 million views. People want to know what they are signing up for. One of the risks being, you can mark out and plan which parts of the body will receive surgery and where you can expect scarring but it is not until you are in there and they rub the dye, do they know how deep or in what directions they may need to go, so one of my own worries about surgery is the extent they have gone to, which I will only find when I come round.

Surgery is a personal choice, a choice some people don't have because its too severe or not severe enough. If more information was available and the approach more person centred, it could encourage more people to try what I would say is an effective management technique in HS.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **26 April 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Association of Dermatologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The company preferred model structure for the BSC arm applies restrictions that do not reflect UK clinical practice	No	Regarding the BSC arm, containing standard oral therapies and surgery for hidradenitis suppurativa (HS), there is a weak evidence base for efficacy in most cases. In particular, there is a lack of long-term prospective cohort studies providing evidence regarding whether progression of disease is modified. While satisfactory disease control with these options may be obtained in mild HS, they are often insufficient for moderate to severe HS, leading to disease progression, generation of more scarring, and further reduction in quality of life and functioning. Wide excision of a whole skin region (for example, removing all the skin and subcutaneous tissue of the axilla), has a relatively high cure rate (Ngaage *et al*. 2020 10.1111/iwj.13241). However, this only provides benefit for the treated region, while disease progression will not be affected in untreated skin regions. It should be noted that the retinoid, acitretin is unsuitable for women of childbearing age (the majority of HS patients in the UK, Ingram, 2020 10.1111/bjd.19435) and ciclosporin is very rarely prescribed for HS. Antibiotic stewardship issues mean that HS physicians and patients wish to reduce prescribing of antibiotics, which are currently the most used therapy for HS.
It is currently unclear whether treatment specific or treatment pooled health state utility values	No	This question is best directed to Novartis to provide an answer.

should be used in the economic model		
The rates and costs of hospital resource use for HS are highly uncertain and may be over-estimated in the company's economic model	Yes	Relevant evidence to consider if not already included: (1) Desai & Shah 10.1111/bjd.14976. (2) Howes *et al*. 2022 10.1016/j.bjps.2021.08.038. One factor to consider is that mis-coding likely produces an underestimate of HS resource utilization because approximately one-third of people with HS in the UK are un-diagnosed (Ingram *et al* 2018 10.1111/bjd.16101) and so A&E admissions and HS surgical procedures may not be linked to the diagnosis.
The company economic model includes costs of BSC and surgery but does not include any quality-of-life benefits from these treatments	No	It is difficult to define BSC and three issues should be considered: (1) Small surgical procedures improve quality of life in the short term but do not alter natural disease history in terms of new skin lesions and progression of disease. (2) Robust quality of life data for standard HS oral systemics such as antibiotics in RCTs are lacking. (3) Adalimumab is often used in combination with standard oral systemics due to: a. insufficient primary response (attainment of HiSCR 50 means that up to 50% of baseline inflammatory lesions remain untreated) or b. secondary loss of response, in the context of no other approved biologic treatment options.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

EAG critique of company response to Technical Engagement

Produced by Aberdeen HTA Group

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Contains: [redacted]

Version: **1**

This report provides the EAG's brief commentary and critique of additional economic evidence and modelling submitted by the company Novartis, received by the EAG on May 2nd in response to Technical Engagement and in advance of the first AC meeting for the appraisal of secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]. The commentary/critique provided below should be read in conjunction with the company's original submission, company technical engagement response, and the EAG report (V2.0 post factual accuracy check). The commentary focuses on remaining areas of disagreement between the company and EAG preferred analyses and follows the order of issues identified for technical engagement.

Issue 1: Company model structure and BSC transition probabilities following induction phase (after week 16)

The company have accepted the EAG amendments to the model structure to allow transitions out of the non-response (HiSCR<25) health state but have provided revised transition probabilities for patients treated with BSC (i.e., the BSC arm of the model and secukinumab arm where patients discontinue treatment to BSC).

The company has further updated the transition probabilities post week-16 in the BSC arm of the model, using data reported in TA392 (NICE appraisal of adalimumab for HS), obtained from the BSC arm of the PIONEER II study. The company prefer the use of data from the placebo arm of the PIONEER II study, as opposed to data from the placebo arms of the SUNNY trials because PIONEER II has longer follow-up of the placebo arm (36-weeks) than the placebo arm of the SUNNY trials (16 weeks). The company argue that the longer-term data better capture the true trajectory of disease beyond the treatment induction phase. The company are concerned that the approach favoured in the EAG report (extrapolation of data from the induction phase, week 0-16) generates clinically implausible estimates with less than half of the BSC cohort in the non-response state at any one time throughout the model time horizon. The company preferred approach post technical engagement applies BSC transitions from the placebo arm of the SUNNY trials up to week 16. Beyond week 16, 24 weeks of data from the PIONEER II study (measured over weeks 12-36) are applied for the treatment maintenance phase and extrapolated for the model time horizon, applied as a one-off transition every six cycles in the model.

EAG critique:
The EAG and company preferred model structures are now aligned and the EAG is satisfied that removing the semi-absorbing non-response state for BSC treated patients improves the clinical validity of the economic model allowing for the potential for periods of disease improvement and deterioration over time.

The EAG acknowledges that the transition probabilities obtained from the placebo arm of the PIONEER II study have the advantage of providing longer-term data on transitions between health states. However, the approach taken by the company relies on a naïve comparison of

the placebo arms of the SUNNY and PIONEER II studies, which adds substantial uncertainty, because it breaks the benefits of randomisation from the SUNNY trials. Furthermore, the company has not provided any reassurance that the population characteristics or disease severity are comparable between the placebo arms of the SUNNY or PIONEER II studies. Therefore, the magnitude of any potential bias associated with using SUNNY placebo data up to week 16, extrapolated to week 36 using PIONEER II placebo data is unclear. The EAG has further reviewed the different data sources to assess their comparability in terms of health state definitions as well as treatments allowed, and trial participant characteristics in the placebo arms of the studies. The EAG is satisfied that the health state definitions are consistent between the two appraisals. The concomitant treatments allowed in the placebo arms of the SUNNY and PIONEER studies were also broadly similar, in that they only included antibiotics and treatments for symptom management, rather than treatments that might be expected to alter the course of HS disease, or impact on transition probabilities between health states. For the SUNNY trials, concomitant medications included doxycycline, lymecycline, minocycline, tetracycline, clindamycin, and rifampicin. For the PIONEER studies, concomitant medications included chlorhexidine, triclosan, tramadol, benzoyl peroxide, Skinsan, Cyteal and hypochlorous acid.

A summary of key participant and disease severity characteristics is provided in Table 1 below.

Table 1: Population characteristics of the placebo groups of the SUNNY and PIONEER studies

	Placebo arm of the SUNNY trials (CS)		Placebo arm of the PIONEER trials (TA392)	
	SUNSHINE	**SUNRISE**	**PIONEER I**	**PIONEER II**
Age, mean (SD)	35.5 (10.8)	36.2 (11.3)	37.8 (11.33)	36.1 (12.18)
Female, n (%)	102 (56.7%)	105 (57.4%)	105 (68.2%)	113 (69.3%)
BMI, kg/m^2, Mean (SD)	32.0 (7.1)	31.4 (7.4)	34.5 (7.94)	32.9 (7.94)
Disease duration in years: mean (SD)	13.1 (9.2)	13.0 (9.5)	11.6 (8.86)	11.8 (9.41)
Hurley stage, n (%)				
I	8 (4.4%)	3 (1.6%)	0 (0%)	0 (0%)
II	121 (67.2%)	110 (60.1%)	81 (52.6%)	89 (54.6%)
III	51 (28.3%)	70 (38.3%)	73 (47.4%)	74 (45.5%)
AN count, mean (SD)	12.8 (8.2)	12.8 (8.5)	14.4 (14.80)	11.9 (11.02)
Prior surgery for HS, n (%)	72 (40.0%)	78 (42.6%)	13 (8.4%)	18 (11.0%)
Previous exposure to systemic biologic therapy, n (%)	46 (25.6%)	48 (26.2%)	0 (0%)	0 (0%)

Abbreviations: AN: abscess and inflammatory nodule; CS: company submission; HS: hidradenitis suppurativa; SD: standard deviation.

The data show important differences between the placebo arms of the trials. For example, the population in the PIONEER studies had more severe disease at baseline but were less likely to have had previous surgery and had no previous treatment with biologic therapies. The net impact of these differences on the magnitude of bias associated with using two different studies is unclear. The EAG therefore does not consider it appropriate to apply an extrapolation naïvely using the TA392 data. If such data were to be considered, they should be appropriately adjusted to account for the impact of differences in disease severity and previous treatment exposure. Due to the magnitude of remaining uncertainty, the EAG retains its initial preference to extrapolate the data from the placebo arm of the SUNNY trials. The EAG does however acknowledge that the follow-up duration in both studies (16 weeks for the SUNNY

trials and 36 weeks for the PIONEER II study) is short and that substantial uncertainty remains regarding the most appropriate longer-term model extrapolations.

Issue 2: Health state utility values (treatment specific vs. treatment pooled)

The original company submission applied treatment specific health state utility values in each modelled health state. However, after some additional information was provided at clarification regarding the impact of treatment on utility, adjusting for health state, the EAG were not satisfied that the company's evidence supported the use of treatment specific HSUVs in each modelled health state. In response to technical engagement, the company have provided additional clinical data and regression modelling of utilities to support their case. Specifically, the company provide data on the percentage change in AN count from baseline, percentage of participants with no increase in abscesses at week 16, and percentage of participants with no increase in draining fistula counts at week 16. Both the assessment of abscesses and AN count show significant treatment effects of both Q2W and Q4W treatment dose of secukinumab compared to placebo in the non-response health state, but no significant differences in any other health state. The company also provided the results of a repeated measures model, with interaction terms for treatment and health state to explore any impact of treatment within each health state. The conclusions are consistent with the clinical findings, demonstrating a statistically significant treatment effect of the Q4W secukinumab dose compared to placebo in the non-response (HiSCR<25) health state only. Q2W dose also appears to have a significant effect on utility in the HiSCR25-49 and HiSCR50-74 states. Given the totality of the evidence, the company propose a revised base case analysis that applies treatment specific HSUVs in the non-response (HiSCR<25) health state only.

EAG critique:

The EAG would like to thank the company for providing the additional information requested. Whilst the EAG does not consider the evidence strong enough to support treatment specific utilities across all health states, the company's proposal to apply treatment specific HSUVs in the non-response state only is appropriate. The EAG is particularly convinced given that both the clinical evidence and utility modelling are consistent and supportive of a treatment effect in the HiSCR<25 state. HSUVs from the original company submission (pooled), EAG report (treatment specific) and agreed utilities post technical engagement are summarised in Table 2 below.

Table 2: Alternative health state utility values for application in the economic model

	Treatment specific (company original submission)	Treatment pooled (preferred in EAG report)	Treatment specific applied only to non-response health state (EAG and company preferred approach post technical engagement)
Secukinumab Q4W			
HiSCR≥75	[redacted]	[redacted]	[redacted]
HiSCR50-74	[redacted]	[redacted]	[redacted]
HiSCR25-49	[redacted]	[redacted]	[redacted]
HiSCR<25	[redacted]	[redacted]	[redacted]
Secukinumab Q2W			
HiSCR≥75	[redacted]	[redacted]	[redacted]
HiSCR50-74	[redacted]	[redacted]	[redacted]
HiSCR25-49	[redacted]	[redacted]	[redacted]
HiSCR<25	[redacted]	[redacted]	[redacted]
BSC			
HiSCR≥75	[redacted]	[redacted]	[redacted]
HiSCR50-74	[redacted]	[redacted]	[redacted]
HiSCR25-49	[redacted]	[redacted]	[redacted]
HiSCR<25	[redacted]	[redacted]	[redacted]

Abbreviations: HiSCR: HiSCR: hidradenitis suppurativa clinical response; Q2W: every 2 weeks; Q4W: every 4 weeks.

Issue 3: The rates and costs of hospital resource use for HS

Frequency of hospital resource use

The original CS applied frequencies of hospital-based resource use obtained from a survey of n=40 clinical experts conducted for the NICE appraisal of adalimumab (TA392). The EAG were concerned that there was a lack of transparency with regards to how resource use was estimated that uncertainty was not incorporated probabilistically in the economic model, and

that the frequencies appeared higher that what might be expected in clinical practice. The company note that they are not aware of any literature to inform the frequency of resource use over time and have instead sought the opinion of four clinical experts during technical engagement, two of whom considered the resource use estimates appropriate, one of whom considered them an underestimate and one who provided no comment.

EAG critique

The company and EAG preferred base case were aligned prior to technical engagement. The EAG has not been provided with the details of any specific literature searches conducted for HS surgery frequencies so cannot completely verify a lack of published evidence on the frequency of hospital resource use for HS. However, it is unlikely that there is any published data on the frequency of hospital resource use in the UK stratified by model health state. The EAG also appreciates that the company have not had time to conduct a formal elicitation exercise but considers this to be an important area of residual uncertainty. Furthermore, these uncertainties have not been adequately incorporated into the probabilistic analyses. The company and EAG preferred base case analyses remain aligned post technical engagement, though substantial uncertainty remains.

Unit costs of HS surgery

During technical engagement, the company updated their preferred base case analysis to revise the average unit cost of HS surgery. The original company submission assumed all patients received surgery as elective inpatients, with the average unit cost obtained as a weighting of finished consultant episodes across HRG codes describing four different grades of skin procedure (multiple major, major, intermediate and minor). The EAG accepted the weighting across grades but disagreed with the exclusion of day-case procedures. The EAG preferred base case therefore applied a unit cost weighted according to grade of procedure and setting (elective inpatient and day-case).

The company has further revised their approach post technical engagement to align with the assumptions used in TA392. The amended base-case assumes two lifetime wide excisions with 67% of surgeries performed as intermediate grade and day case procedures, with the remaining surgeries assumed to also be intermediate procedures, split across elective inpatient and non-elective short stays.

EAG critique

The company revised base case analysis may over-estimate the costs of surgical procedures for HS. The EAG clinical expert believed most surgeries for HS are minor, and often conducted as day-case procedures. Clinical expert opinion sought by the company (page 20/21 of the company response to technical engagement) appears to validate the EAG's approach, noting that most procedures are minor or intermediate day-cases, with the remainder conducted as major or multiple major elective inpatient admissions. The EAG notes however that the company's revised base case analysis excludes all minor procedures from the costings and is likely to over-estimate surgery costs in the model. The company provides additional scenario analyses testing the impact of different numbers of lifetime wide excisions and exploring the impact of a reduction in the proportion of procedures conducted as day-cases, but all these scenario analyses retain the assumption that none of the surgeries can be classed as minor procedures. Given the risk of over-estimating surgery costs using the company's approach, the EAG retain our preferred base case assumption to derive weighted average unit costs for HS surgeries, weighting according to finished consultant episodes across all grades of procedure and across day-case and elective inpatient settings. The company original base case, post technical engagement base case and EAG preferred distributions of surgery severity and setting are compared in Table 3 for the committee's information.

Table 3: Comparison of different distributions of HRG coding and weighted average unit costs for HS surgery procedures

Procedure descriptions	HRG code	Setting	Original CS	Company post-technical engagement	EAG preferred (%) [A]
Multiple Major Skin Procedures	JC40Z	Elective inpatient	3.84%	0.00%	0.13%
Major Skin Procedures	JC41Z	Elective inpatient	15.46%	6.68%	0.52%
Intermediate Skin Procedures	JC42C	Elective inpatient	54.78%	13.16%	1.85%
Minor Skin Procedures	JC43C	Elective inpatient	25.92%	0.00%	0.87%
Multiple Major Skin Procedures	JC40Z	Day case	0.00%	0.00%	1.02%
Major Skin Procedures	JC41Z	Day case	0.00%	0.00%	3.68%
Intermediate Skin Procedures	JC42C	Day case	0.00%	67.00%	22.25%
Minor Skin Procedures	JC43C	Day case	0.00%	0.00%	69.68%
Intermediate Skin Procedures	JC42C	Non-elective short stay	0.00%	13.16%	0.00%
Weighted average cost per procedure applied in the economic model:	--	--	**£4,652.57**	**£2,401.52**	**£1,216.68**

[A] EAG preferred proportions remain unchanged post technical engagement.**Abbreviations:** CS: company submission; HRG: healthcare resource group; HS: hidradenitis suppurativa.

Issue 4: The inclusion of BSC and surgery costs, but exclusion of benefits.

The company response to technical engagement suggests that the model structural amendment, allowing transition between different response health states for BSC addresses the EAG concern that the model did not adequately capture the benefit of surgery or BSC as used in UK clinical practice. The company further acknowledges the EAG concern that BSC treatments allowed in the placebo arms of the SUNNY trials were much less intensive than those that might be used in UK clinical practice. However, the company prefers to include these costs as they are a better reflection of the real-world costs of BSC.

Whilst the EAG agree that the revised model structure does improve clinical validity and facilitates the potential inclusion of surgery and BSC treatment benefits, these benefits are not quantified or explicitly modelled. The key concern raised in the EAG report that the costs of surgery and BSC as used in UK clinical practice are included in the model, but the benefits are not remains, even with the amendments to the company's model structure. The company's underlying assumption appears to be that the transition probabilities derived from the PIONEER II study will capture some of the surgery and BSC benefit. The EAG disagree with the company argument on the grounds that there are no data from the PIONEER or SUNNY studies to suggest the impact of surgery or BSC as delivered in UK clinical practice on health state transition probabilities. It is therefore impossible for the transition probabilities from the trials to adequately capture the benefit of surgery or BSC. Modelled BSC treatments assumed in clinical practice are more intensive than those allowed in the placebo arms of either the SUNNY or PIONEER II trials. Therefore, transitions between health states derived from those studies likely underestimate the effectiveness of BSC used in clinical practice. Given that the impact of BSC treatments on transition probabilities (i.e., effectiveness) is unknown, the EAG prefers to align the costs of BSC applied in the model, with the treatments used in the placebo arms of the SUNNY trials to minimize potential biases.

Whilst likely to be pessimistic, the EAG considers a scenario analysis that removes the costs of surgery to be useful for the committee's consideration as it provides information on what the ICER might be when aligning the modelled transition probabilities with the underlying treatments from the trial.

Other issues from the EAR:

The EAG retains our preferences for the removal of up-titration from the model due to the uncertainties associated with applying treatment effectiveness estimates for a higher dose to a harder to treat subgroup of respondents who have failed lower dose secukinumab treatment.

The EAG also retains our preference to only include one set of outpatient costs from the clinical expert survey conducted as part of TA392. However, the impact of EAG compared to company preferred preferences on the ICER is small.

Summary:

The EAG has reviewed the company provided documentation and revised economic model. It was possible to reproduce both the original company submission base case and the EAG preferred base case using the company provided economic model post technical engagement. The EAG are also satisfied that the amendments to the model have been implemented as described in the company provided response to technical engagement. The company and EAG preferred base case assumptions post technical engagement are summarised in Table 4 below. Results of the EAGs preferred assumptions, applied to the company preferred base case post-technical engagement are provided in Table 5.

Table 4: Summary of company and EAG preferred assumptions post technical engagement

	Company preferred assumption post technical engagement	EAG preferred assumption post technical engagement
Model structure (Issue 1)	Adapted to allow long-term transitions for BSC between health states	Adapted to allow long-term transitions for BSC between health states
BSC transition probabilities post week 16 (Issue 1)	Obtained from the placebo arm of the PIONEER II study (data reported for 12-36 weeks of follow up)	Data extrapolated from the average transitions between week 0-16 from the SUNNY trials
HSUVs (Issue 2)	Treatment pooled for response states, treatment specific for non-response state	Treatment pooled for response states, treatment specific for non-response state
Rates of hospital resource use (Issue 3 + other issues)	Based on clinical expert survey from TA392	Based on clinical expert survey from TA392, adapted to reduce outpatient consultation frequency
Unit costs of hospital resource use (Issue 3)	Based on 2 lifetime wide excisions (major elective procedures), 67% intermediate day-case, remainder split between intermediate elective inpatient and non-elective short stay	Based on weighted average of FCEs for skin procedure HRGs, weighted across - multiple major, major, intermediate, and minor procedures and - elective inpatient and day case admissions.
BSC costs	Based on company conducted research about treatments used in UK clinical practice	Aligned with the placebo arm of the SUNNY trials.
Up-titration	Included	Excluded

Abbreviations: BSC: best supportive care; FCE: finished consultant episode; HSUV, health-state utility value; HRG: healthcare resource group.

Table 5 Impact of EAG preferred assumptions on the company revised ICER post technical engagement.

	Treatment	Cost (£)	Incremental Costs (£)	QALY	Incremental QALYs	ICER (£ / QALY)
0	**Company original base case:**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,165
	BSC	[redacted]		[redacted]		
1	**Long-term BSC health state transition probabilities from PIONEER studies (TA392)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£32,213
	BSC	[redacted]		[redacted]		
2	**Treatment-specific utilities for non-responders only**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,979
	BSC	[redacted]		[redacted]		
3	**Alternative surgery costing assumes 2 lifetime wide excisions (major), 67% surgeries intermediate day case, remainder split between elective inpatient and non-elective short stay, no minor procedures.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£34,261
	BSC	[redacted]		[redacted]		
4	**Amended BSC unit cost sources for primary care prescribing (prescription cost analysis) and secondary care prescribing (eMIT) separately.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,074
	BSC	[redacted]		[redacted]		
5	**Updated settings to align with EAG preferences around adverse event costs, QOL and disease severity weightings for resource use estimates**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£27,893
	BSC	[redacted]		[redacted]		
6	**Company revised base case post technical engagement (Combined 0-6)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£42,415
	BSC	[redacted]		[redacted]		
7	**EAG preference 1: BSC transition probabilities beyond week 16 extrapolated from the placebo arm of the SUNNY trials.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£86,504
	BSC	[redacted]		[redacted]		

	Treatment	Cost (£)	Incremental Costs (£)	QALY	Incremental QALYs	ICER (£ / QALY)
8	**EAG preference 2: Weighted (using FCEs) average unit cost of HS surgery across elective inpatient admissions and day-case settings and across all grades of procedure complexity (multiple major, major, intermediate, and minor procedures)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£45,847
	BSC	[redacted]		[redacted]		
9	**EAG preference 3: Include BSC costs of treatments allowed in the placebo arms of the SUNNY trials only.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£45,091
	BSC	[redacted]		[redacted]		
10	**EAG preference 4: remove up-titration**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£43,412
	BSC	[redacted]		[redacted]		
11	**EAG preference 5: apply EAGs preference for outpatient attendance frequencies**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£43,294
	BSC	[redacted]		[redacted]		
12	**EAG preferred base case post technical engagement (Combined 6-11)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£95,821
	BSC	[redacted]		[redacted]		

Abbreviations: BSC: best supportive care; eMIT: electronic market information tool; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; QOL: quality of life.

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

EAG additional analyses prior to ACM1

Produced by Aberdeen HTA Group

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Contains: [redacted]

Version: **2**

This document provides the following additional information for consideration at the first appraisal committee meeting for this topic:

1) Probabilistic ICERs, scatter plots of the cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) for the EAG and company preferred base case analyses post technical engagement.

2) Graphical representations of the BSC and secukinumab extrapolations for the company and EAG preferred base case models, as well as an additional scenario where the cohort, on average, retain their last observed health state distribution from the SUNNY trials (16 weeks for BSC and 52 weeks for secukinumab), carried forward for the remainder of the model time horizon (i.e., assuming that there are no further transitions between HiSCR response health states for the remainder of the model time horizon). Whilst transitions between states might occur in clinical practice, this analysis assumes that fluctuations in health state are averaged out over time.

3) Further scenario analyses applied to the EAG preferred base case, including the implications of retaining health state distributions from the last observed time point for BSC (16 weeks) and secukinumab (52 weeks), for the remainder of the model time horizon.

1. Probabilistic ICERs

Table 1 below provides the probabilistic ICERs for the company and EAG preferred base case analyses respectively. Figures 1-2 and 3-4 illustrate uncertainty on scatter plots of the cost-effectiveness plane and cost-effectiveness acceptability curves for company and EAG preferred base case analyses respectively.

Table 1 Company and EAG preferred base case ICERs

	Treatment	Cost (£)	Incremental Costs (£)	QALY	Incremental QALYs	ICER (£ / QALY)
1	**Company preferred base case ICER post technical engagement (probabilistic)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£42,268
	BSC	[redacted]		[redacted]		
2	**EAG preferred base case ICER post technical engagement (probabilistic)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£96,353
	BSC	[redacted]		[redacted]		

Figure 1: Company preferred base case scatterplot.

Figure 2: Company preferred base case cost-effectiveness acceptability curve.

Figure 3: EAG preferred base case scatterplot.

Figure 4: EAG preferred base case cost-effectiveness acceptability curve.

2. Long-term extrapolations

Figure 5 below illustrates the long-term modelled response curves for BSC and secukinumab up to 10 years. Dotted lines indicated transitions for BSC, whereas solid lines indicated transitions for secukinumab Q4W. Three alternative assumptions are explored, all applied to scenarios without up-titration:

- A) Company preferred base case, transition probabilities for secukinumab extrapolated from week 52 onwards, calculated as the average of observed 4-weekly transition probabilities from pooled data across the secukinumab arms of the SUNNY trials between week 16 and 52. Transition probabilities for BSC obtained from the pooled placebo arms of the SUNNY trials up until week 16. Transitions beyond week 16 assumed equal to transition probabilities derived from TA392 (weeks 12-36 data) and applied every 24 weeks (6 cycles) for the remainder of the modelled time horizon.

- B) EAG preferred base case: as per the company preferred base case for secukinumab (note that the EAG and company preferred secukinumab curves diverge over time due to different assumptions for BSC post treatment discontinuation on secukinumab). For BSC, data from the placebo arms of the SUNNY trials are applied up to week 16 and extrapolated for the remainder of the model time horizon.

- C) EAG alternative scenario analysis: For both arms, data applied, as observed from the SUNNY trials, up to week 16 (BSC) and week 52 (secukinumab). Longer term extrapolations are then assumed to be equal to the average distribution of the cohort at the last observed 4-weekly transition from the trial data. This scenario is applied in the model by setting transition probabilities between HiSCR health states to 0 beyond the time in which data are observed for each treatment from the trials. Whilst transitions are likely in clinical practice, this approach may reduce uncertainty by averaging out fluctuations in flare-ups in health state over time and may be an alternative assumption for the committee's consideration.

For ease of presentation, and to aide comparison to the clinical effectiveness results, the graph below shows response, defined as the proportion of the cohort in a response state over time, where response is defined as the sum of health state occupancy proportions in the HiSCR50-74 and HiSCR≥75 states. Secukinumab projections also incorporate discontinuation to BSC.

Figure 5: Alternative long-term extrapolation assumptions for secukinumab and BSC

3. Additional scenarios applied to the EAG preferred base case analysis.

Table 2 provides the results of additional scenario analyses applied to the EAG preferred base case, including several provided by the company in response to technical engagement.

Table 2 Additional scenario analyses applied to the EAG preferred base case.

	Treatment	Cost (£)	Incremental Costs (£)	QALY	Incremental QALYs	ICER (£ / QALY)
1	**EAG preferred base case ICER post technical engagement (deterministic)**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£95,821
	BSC	[redacted]		[redacted]		
2	**Assume 2 lifetime wide excisions, 49% surgeries as intermediate day case, with remainder as intermediate inpatient.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£92,303
	BSC	[redacted]		[redacted]		
3	**Assume 3 lifetime wide excisions, 49% surgeries as intermediate day case, with remainder as intermediate inpatient.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£91,625
	BSC	[redacted]		[redacted]		
4	**Assume 4 lifetime wide excisions, 49% surgeries as intermediate day case, with remainder as intermediate inpatient.**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£90,947
	BSC	[redacted]		[redacted]		
5	**Reduce non-surgery related hospital resource use by 25%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£97,100
	BSC	[redacted]		[redacted]		
6	**Reduce non-surgery related hospital resource use by 50%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£98,379
	BSC	[redacted]		[redacted]		
7	**Reduce non-surgery related hospital resource use by 75%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£99,658
	BSC	[redacted]		[redacted]		

	Treatment	Cost (£)	Incremental Costs (£)	QALY	Incremental QALYs	ICER (£ / QALY)
8	**Reduce non-surgery related hospital resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£100,937
	BSC	[redacted]		[redacted]		
9	**Reduce surgery resource use by 25%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£96,631
	BSC	[redacted]		[redacted]		
10	**Reduce surgery resource use by 50%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£97,442
	BSC	[redacted]		[redacted]		
11	**Reduce surgery resource use by 75%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£98,252
	BSC	[redacted]		[redacted]		
12	**Reduce surgery resource use by 100%**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£99,062
	BSC	[redacted]		[redacted]		
13	**EAG alternative long-term extrapolations, with average health state occupancy based on last observation carried forward from the secukinumab and BSC arms of the SUNNY trials (See 2 (C) above).**					
	Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£68,135
	BSC	[redacted]		[redacted]		

Abbreviations: BSC = Best supportive care; ICER = Incremental cost-effectiveness ratio; QALY = quality adjusted life year.

Single Technology Appraisal

Secukinumab for treating moderate to severe hidradenitis suppurativa [ID4039]

ACIC check

'Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.' (Section 5.4.9, NICE health technology evaluations: the manual).

If you do identify any errors in the marking of confidential information you must inform NICE by **12:00pm** on **Wednesday 21 June** using the below table. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Location of incorrect marking	Description of incorrect marking	Amended marking
Committee slides		
Slide 15	AIC marking on Figure 1	As data is available in the now published EPAR (Figure 31) for secukinumab in HS the AIC marking can now be removed
Slide 45	AIC marking for previous exposure to adalimumab	As data is available in the now published EPAR (Table 13) for secukinumab in HS the AIC marking can now be removed
EAG critique of company's technical engagement response		

Page 5	AIC marking for “Disease duration in years”	As data is available in the now published EPAR (Table 13) for secukinumab in HS the AIC marking can now be removed
EAG report post-FAC		
Page 13	the vast majority were treated with adalimumab ([redacted] [redacted], and [redacted] [redacted], respectively	the vast majority were treated with adalimumab (122/129 [95%], and 116/126 [92%], respectively
Table 7	AIC marking for Ethnicity, Weight, and BMI	As data is available in the now published EPAR (Table 12) for secukinumab in HS the AIC marking can now be removed
Table 8	AIC marking for Time since HS symptom(s) onset (years), Baseline HS-PGA, Baseline DLQI total score and Previous exposure to adalimumab	As data is available in the now published EPAR (Table 13) for secukinumab in HS the AIC marking can now be removed
Page 25	SUNSHINE: [redacted] in Q2W and [redacted] in Q4W vs. [redacted] in placebo; SUNRISE:[redacted] in Q2W and [redacted] in Q4W vs. [redacted] in placebo	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
Page 26	the estimated OR [redacted] (95% CI: [redacted], [redacted]) and OR [redacted] (95% CI: [redacted], [redacted]), respectively, for the secukinumab Q2W group and OR [redacted] (95% CI: [redacted], [redacted]) and OR [redacted] ([redacted], [redacted]), respectively, for the secukinumab Q4W group	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
Page 26	the biologic-experienced subgroup consisted of [redacted] ([redacted]) and [redacted] ([redacted]) of the SUNSHINE and SUNRISE study participants,	the biologic-experienced subgroup consisted of 23.8% (129/541) and

	respectively, the vast majority of whom were treated with adalimumab ([redacted] [redacted], and [redacted] [redacted], respectively	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
Page 29	Most were mild-to-moderate in severity and only [redacted] in each trial ([redacted]) discontinued the study drug.	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.
Page 50	Of the participants in the SUNNY trials, only [redacted] and [redacted] of the SUNSHINE and SUNRISE trial participants had previous adalimumab treatment	Of the participants in the SUNNY trials, only 22.6% and 21.4% of the SUNSHINE and SUNRISE trial participants had previous adalimumab treatment
Page 50	*approx.* [redacted] *of the SUNNY trials*	approx. 80% of the SUNNY trials

Secukinumab for treating moderate to severe hidradenitis suppurativa

Slides for public, redacted

Technology appraisal committee B [07 June 2023]

Chair: Baljit Singh

Lead team: Francis Drobniewski, Tony Wootton and Warren Linley

External assessment group: Aberdeen Health Technology Assessment Group

Technical team: Anna Willis, Lizzie Walker, Richard Diaz

Company: Novartis

Background on hidradenitis suppurativa (HS)

Condition

- Hidradenitis suppurativa (HS) is a painful, long-term skin condition that causes abscesses and scarring[1]
- The exact cause of HS is unknown but it occurs in skin folds where there are sweat glands, in particular the groin and armpits

Epidemiology

- Affects about 1 in 100 people and is more common in women than men[1]

Symptoms and prognosis

- Symptoms of HS can range from mild to severe:
    - Early symptoms include isolated, painful nodules; with or without intermittent inflammation
    - Disease progression is characterised by development of sinus tracts (pus-discharging tunnels) fistulas and/or abscesses
- Extent and severity of disease are often assessed using the Hurley staging system
- The focus of the company's submission is moderate (Hurley stage II) to severe (Hurley stage III) HS

Abbreviations: HS, hidradenitis suppurativa

Clinical perspectives

Submission received from the British Association of Dermatologists

- Scarring due to HS limits function and reduces the ability to work and study
- Reversal of scarring may require extensive surgery
- So preventing progression of HS is important
- Alternatives to adalimumab are needed for people where treatment has failed to work, or for people with contraindications

"Many patients on adalimumab therapy still experience substantial morbidity. In addition, secondary failure of adalimumab often occurs"

"Adalimumab and other anti-TNF-alpha drugs are contraindicated in those with a personal or family history of demyelinating diseases such as multiple sclerosis, so secukinumab [could provide] a potential option is this group."

Clinical experts: How does HS typically progress over time?

Abbreviations: HS, hidradenitis suppurativa; TNF, tumour necrosis factor

Patient perspectives

Submission from patient expert

- HS has a substantial impact on quality of life
  - Challenges include pain and intense itching, and living with chronic, inflamed and draining wounds
  - People with HS often experience anxiety and depression

- There is a stigma around HS and a culture of patient blame from some healthcare professionals
  - Average time to diagnosis of 7 to 10 years

- Financial burden on people with HS and family members
  - Some people cannot work with HS
  - High household bills from washing of clothes/bed linen or cost of prescriptions, parking or transport for appointments

- Surgical intervention can be helpful but is limited to a specific area and time off work is required to heal post-surgery
- Biologics reduce pain and level of inflammation for some people, but do not work in others

"Living with moderate to severe HS is incredibly difficult and can be described as relentless. Many long-standing HS sufferers will say it has destroyed relationships the chance of being a parent, getting married [and] their career"

"The unpredictability means we can feel unreliable, we pull out of social plans, we let people down or we recluse and don't engage in activity as we are tired of disappointing people"

NICE

Abbreviations: HS, hidradenitis suppurativa

Equality considerations

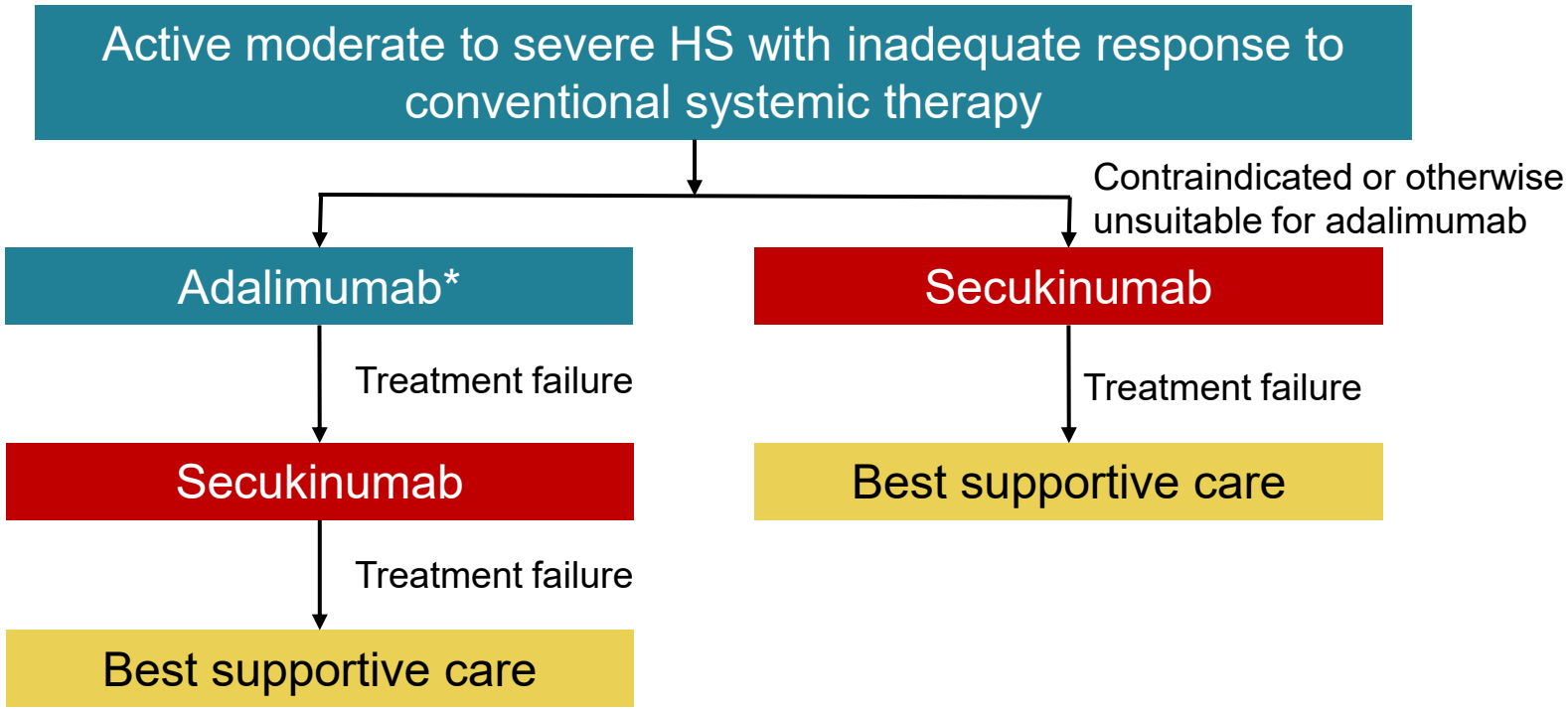
- The incidence of HS is higher in people of African-Caribbean family background as compared with people of European family background
- Peak prevalence is in females of childbearing age

Abbreviations: HS, hidradenitis suppurativa

Treatment pathway

Company's proposed positioning of secukinumab in the treatment pathway

Figure 1: Company's proposed positioning of secukinumab in the treatment pathway



Does the clinical pathway reflect NHS clinical practice?
What is best supportive care in NHS clinical practice?
What proportion of people would be contraindicated to adalimumab?

Conventional systemic therapy[1]:

- Oral tetracyclines
- Oral clindamycin and rifampicin for those unresponsive to oral tetracyclines
- Acitretin or dapsone considered in people unresponsive to earlier antibiotics

Adalimumab is recommended for moderate to severe HS in adults whose disease has not responded to conventional systemic therapy (TA392)

Contraindications to adalimumab:

- Hypersensitivity to active substance
- Active TB or other severe infections
- Moderate to severe heart failure

Best supportive care:

- Surgical procedures, antibiotics, retinoids, dapsone, ciclosporin and anti-androgens

Abbreviations: HS, hidradenitis suppurativa; TB, tuberculosis.

Secukinumab (Cosentyx, Novartis)

Marketing authorisation	• Secukinumab has an EU marketing authorisation for the treatment of "active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic hidradenitis suppurativa therapy".
Mechanism of action	• Fully human IgG1/κ monoclonal antibody, which targets IL-17A, inhibiting its interaction with the IL-17 receptor • This inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage
Administration	• Secukinumab 300 mg is self-administered by subcutaneous injection, with initial weekly dosing from week 0 to 4, followed by maintenance dosing every 4 weeks with the possibility to up-titrate to every 2 weeks
Price	• List price per 300 mg pre-filled pen: £1,218.78 • There is a commercial arrangement (simple PAS) already in place for secukinumab across all indications

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; MHRA, Medicines and Healthcare Products Regulatory Agency; PAS, patient access scheme.

Decision problem

	Final scope	Company
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
Intervention	Secukinumab	As per scope
Comparators	Adalimumab, best supportive care	Best supportive care **only**
Outcomes	Disease severity, disease progression, clinical response, inflammation and fibrosis, discomfort and pain, adverse effects, HRQL	As per scope
Subgroups	People with no response to prior adalimumab treatment	As per scope

EAG comments:

- Company has positioned secukinumab as a second-line treatment following biologics such as adalimumab. EAG has some concerns about the omission of adalimumab as a comparator.
- Agrees that infliximab is not established clinical practice

Abbreviations: HRQL, health-related quality of life; HS, hidradenitis suppurativa

Issues

Key issues	Resolved?	ICER impact
BSC transition probabilities *Should the transition probabilities for BSC be taken from week 12-36 data of PIONEER II, week 0-16 of the SUNNY trials, or be based on the last observation carried forward from the SUNNY trials?*	No	Large
Alignment of costs and benefits for BSC *Should the costs for the BSC arm of the model be aligned with the placebo arm of the SUNNY trials or with clinical expert opinion on UK clinical practice?*	No	Unknown
Hospital resource use rates *Has the uncertainty around hospital resource use rates been adequately captured?*	No	Unknown
Health state utility values *What are the most appropriate utility values: treatment specific, treatment pooled or treatment specific for the non-response health-state only?*	Yes	Large
Other issues		
Inclusion of up-titration from Q4W to Q2W dose	No	Small
Surgery costs	No	Small
Outpatient visits costs	No	Small

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Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QxW, every x weeks.

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Company's clinical effectiveness evidence comes from two identically designed phase 3 trials – SUNSHINE and SUNRISE (known collectively as the SUNNY trials)

	SUNSHINE (n=541) and SUNRISE (n=543)
Design	Phase 3 randomised, double-blind, placebo-controlled, parallel-group trials
Population	Adults (≥18 years old) with moderate to severe HS
Intervention	Secukinumab 300mg subcutaneous injection Q2W or Q4W
Comparator(s)	Placebo subcutaneous injection Q2W or Q4W
Duration	52 weeks, comparative evidence available for 16 weeks only
Primary outcome	Proportion of patients with an HS clinical response score of 50 (HiSCR50) at week 16, defined as a ≥50% decrease in abscess and inflammatory nodule (AN) count with no increase in the number of abscesses and/or draining fistulae
Key secondary outcomes	AN count, HS flares, NRS30 (skin pain); at week 16
Locations	Worldwide: 132 study sites, 12 sites in UK (n= 46, across both trials)
Used in model?	Yes (HiSCR50, EQ-5D-3L, adverse events), data naïvely pooled due to identical study design

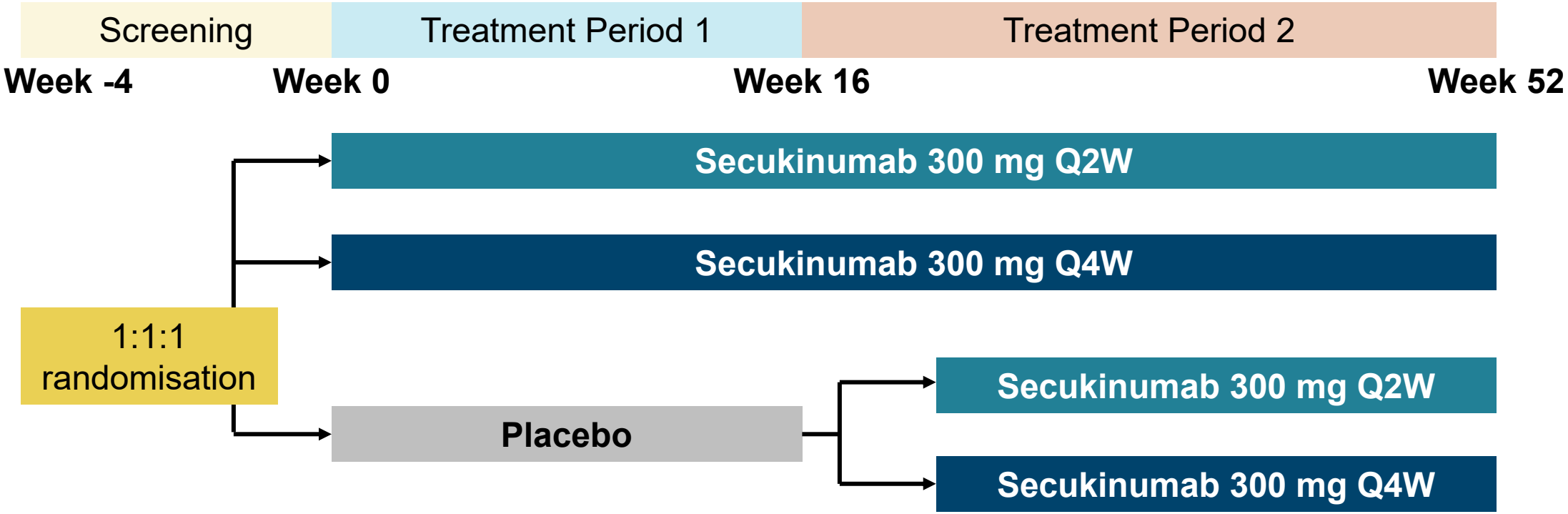
Abbreviations: AN, abscess and inflammatory nodule; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; HiSCR50, HS clinical response score of 50; HS, hidradenitis suppurativa; QxW, every x weeks; NRS, numerical rating scale.

SUNNY trial design

People in SUNNY were randomised to secukinumab Q2W or Q4W, or placebo

- Comparative clinical effectiveness data available up to Week 16 only
- Anticipated marketing authorisation is for maintenance dosing Q4W with the possibility to up-titrate to Q2W
- SUNNY trials did not specifically assess the clinical effectiveness of up-titration

Figure 1: SUNNY trial design



Abbreviations: HS, hidradenitis suppurativa; QxW, every x weeks

SUNNY trials: Results

Proportion of people with HiSCR50 at week 16 was greater for secukinumab versus placebo. Difference was statistically significant across both trials and doses, except for the Q4W dose in SUNSHINE

Table 1: SUNNY trial results, primary outcome, week 16

Study	PBO	SEC Q2W			SEC Q4W		
	% response	% response	OR vs PBO (95% CI)	p-value*	% response	OR vs PBO (95% CI)	p-value*
SUNSHINE	33.7	45.0	1.75 (1.12, 2.73)	p=0.0070**	41.8	1.48 (0.95, 2.32)	p=0.0418 (not statistically significant)
SUNRISE	31.2	42.3	1.64 (1.05, 2.55)	p=0.0149**	46.1	1.90 (1.22, 2.96)	p=0.0022**

Secondary outcomes:

- Greater reduction in skin pain (NR30), greater decrease in abscess and inflammatory nodule count and fewer people experiencing HS flares at week 16 for secukinumab versus placebo
- Mixture of statistically significant and non-statistically significant results across Q4W and Q2W treatment arms and trials

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Abbreviations: HiSCR50, hidradenitis suppurativa clinical response score of 50. **Notes** *one-sided p value; **statistically significant based on the pre-defined testing hierarchy.

Generalisability of SUNNY trials to decision problem

Background

Relevance for population in whom adalimumab is unsuitable

- ~23% of participants in SUNNY trials had previously received systemic biologic therapy, mostly adalimumab
- Pre-specified subgroup analyses of SUNNY trials show that achievement of HiSCR50 was broadly consistent in groups with and without previous exposure to biologics (see **Figure 1**, next slide)
- Company model uses data from full SUNNY population (biologic-experienced and biologic-naïve)

Generalisability of BSC arm

- 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

EAG comments:

- Overall population of SUNNY trials does not match company's positioning of secukinumab as second-line after biologics
- Adalimumab and secukinumab use a different mechanism of action, so non-response to adalimumab would not impair the response to secukinumab
- However, secukinumab is likely to be used in more difficult to treat cases that are unresponsive to adalimumab, which may have increased the effect size in favour of secukinumab
- BSC treatments in SUNNY may not align with NHS clinical practice

Are the SUNNY trials appropriate for the decision problem?

Abbreviations: BSC, best supportive care

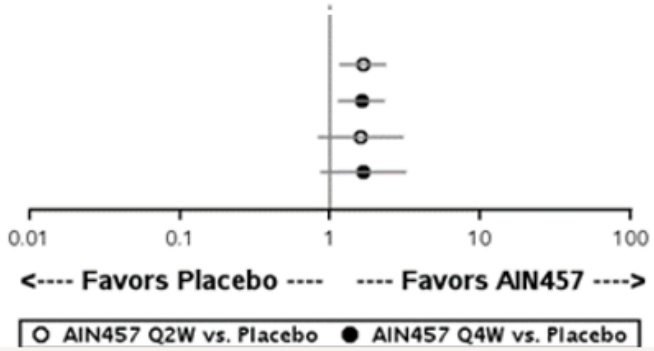
Subgroup analysis

Pre-specified subgroup analysis based on previous exposure to biologics shows similar odds ratios across biologic-experienced and biologic-naïve subgroups

Company

Figure 1: Subgroup analysis of primary outcome based on previous exposure to biologics (pooled analysis of SUNNY trials)

Subgroup	Treatment Comparison	OR (95% CI)	P-value	Placebo (n*/m, %)	AIN457 (n*/m,%)
Previous exposure to biologics					
N	AIN457 Q2W vs. Placebo	1.64 (1.15, 2.33)	0.0065	92.0/269 (34.2)	128.1/281 (45.6)
	AIN457 Q4W vs. Placebo	1.61 (1.13, 2.29)	0.0087	92.0/269 (34.2)	126.8/279 (45.4)
Y	AIN457 Q2W vs. Placebo	1.60 (0.83, 3.08)	0.1604	25.7/ 94 (27.3)	29.6/ 80 (37.0)
	AIN457 Q4W vs. Placebo	1.67 (0.86, 3.22)	0.1281	25.7/ 94 (27.3)	31.4/ 81 (38.8)



Notes: Nominal significance was not achieved in the biologic-experienced subgroup due to the smaller sample size as compared with biologic-naïve patients. **Abbreviations:** AIN457, secukinumab; BSC, best supportive care; CI, confidence interval; OR, odds ratio; QxW, every x weeks.

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model structure

Company

- Developed a Markov model with 5 health states based on HiSCR, in line with the model used in TA392. Model health states included:
  - **Non-response:** HiSCR: <25
  - **Partial response:** HiSCR: 25–49
  - **Response:** HiSCR: 50–74
  - **High response:** HiSCR: ≥75
  - **Death**

Table 1: Company's model features

Perspective	NHS/PSS
Time horizon	Lifetime
Cycle length	4 weeks
Discounting (costs and effects)	3.5% annually

- The secukinumab arm of the model included an induction phase (week 0-16), an up-titration phase (week 16-28) for non-responders at week 16, and a maintenance phase (week 16/28 onwards)
- The BSC arm of the model included induction and maintenance phases only
- Model features are presented in **Table 1** and the model structure diagram is presented on the next slide

EAG comments:

- Model structure is appropriate

Abbreviations: BSC, best supportive care; HiSCR, hidradenitis suppurativa clinical response; PSS, personal and social services.

Company's Markov model – secukinumab arm

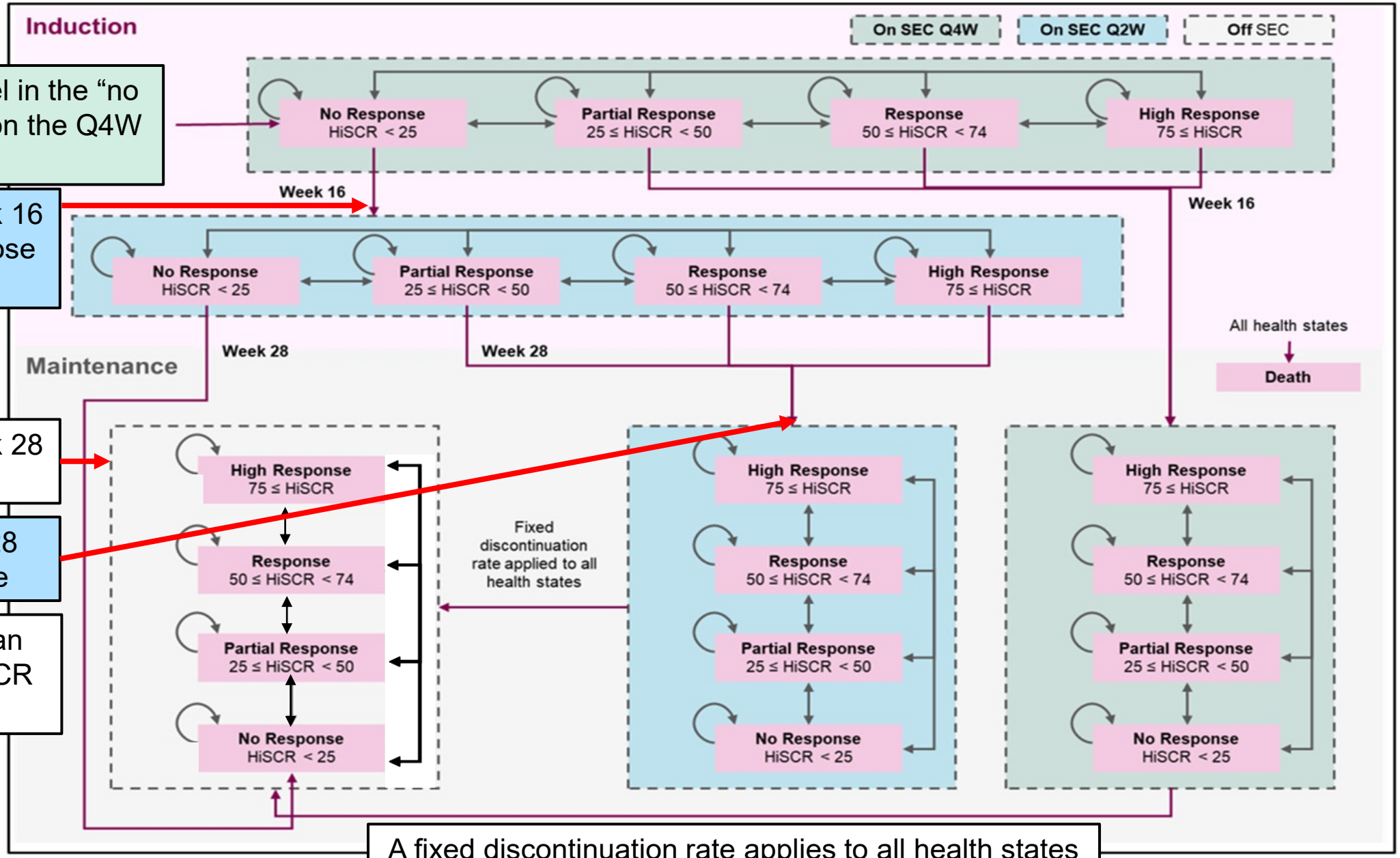
Patients enter the model in the "no response" health state on the Q4W dose

Non-responders at week 16 up-titrate to the Q2W dose until week 28

Non-responders at week 28 stop treatment

Responders at week 28 stay on the Q2W dose

Patients in all states can transition between HiSCR response states



A fixed discontinuation rate applies to all health states

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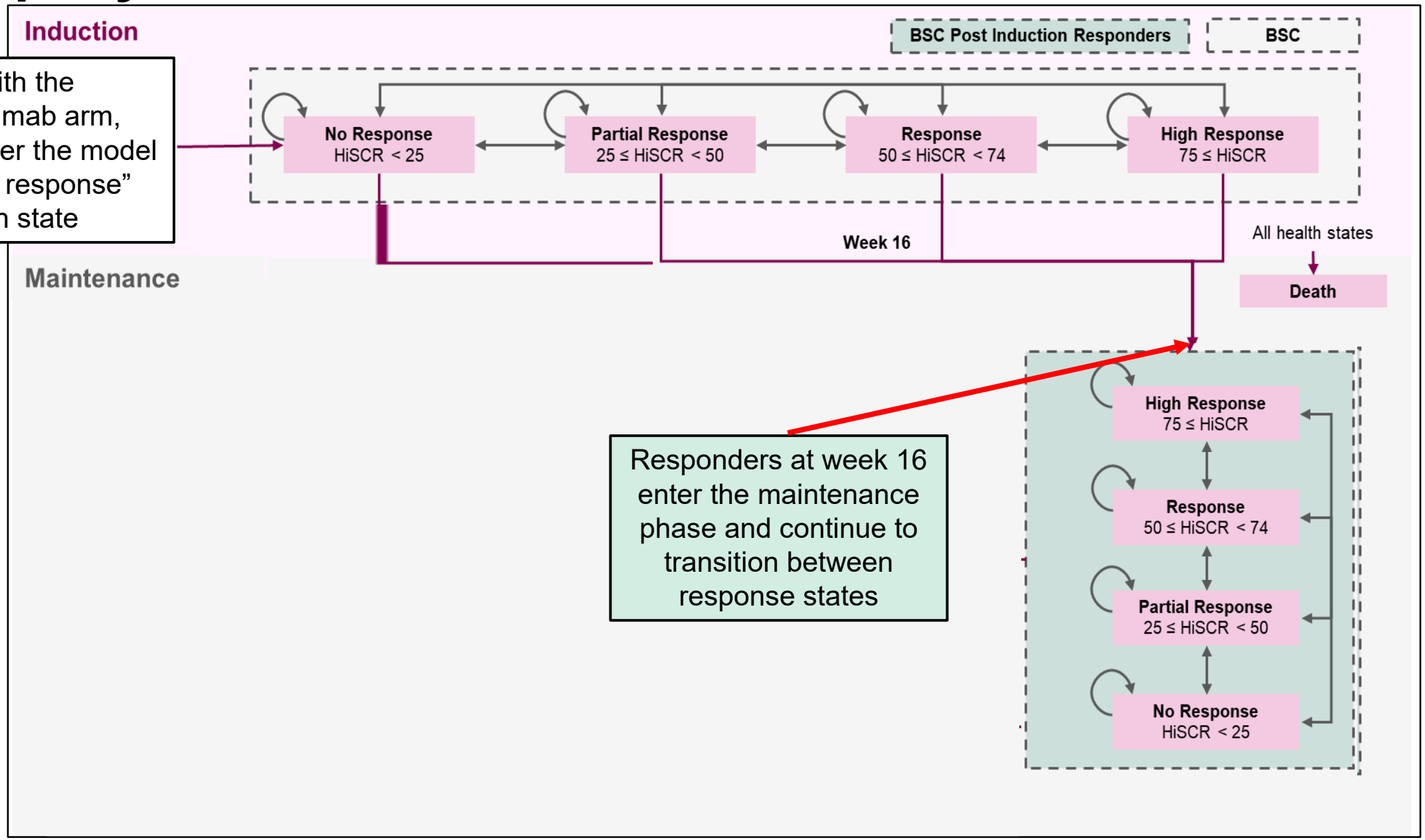
Company's Markov model – BSC arm

As with the secukinumab arm, patients enter the model in the "no response" health state



Cost and QALY impact of secukinumab

- Technology affects **costs** by:
  - **Increased** treatment acquisition costs for secukinumab
  - **Decreased** health state costs for secukinumab
    - Improved treatment effectiveness → less time in more costly, lower HiSCR response health states

- Technology affects **QALYs** by:
  - **Increased** QALYs from more time spent in less severe health states
    - Improved treatment effectiveness → more time in higher HiSCR response health states
  - **Increased** QALYs from applying treatment specific health state utility values in the "no response" health state
    - In "no response state", people receiving secukinumab have higher QALYs than people receiving BSC. In other states, treatment pooled utility values are applied

- Assumptions with greatest **ICER** effect:
  - Source of BSC transition probabilities
  - Use of treatment specific vs treatment pooled health state utility values
  - Rates and unit costs of hospitalisations assumed for each model health state

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Company's model inputs (1/2)

Input	Assumption and evidence source
Baseline characteristics	Based on SUNNY trials: • Mean age – 36.2 years; female (%) – 56.3%; mean weight – 93.47kg
Efficacy & extrapolation	**Induction phase (weeks 0 – 16):** • SUNNY trials, data from Q4W arm for secukinumab and placebo arm data for BSC **Up-titration phase (weeks 16-28, for non-responders in induction phase):** • SUNNY trials, Q2W arm for secukinumab • Not applicable for BSC **Maintenance phase (from end of induction/up-titration phase):** • SUNNY trials up to week 52 for secukinumab extrapolated over duration of model • PIONEER II (TA392) used for transition probabilities between week 16-52 and extrapolated over duration of model
Discontinuation	• All-cause discontinuation rates pooled from the SUNNY trials applied regardless of response during the maintenance phase • Per cycle discontinuation rate Year 1: [redacted], Year 2 onwards: 0.475%
Mortality	Based on age-matched general population mortality for all patients, irrespective of health state or treatment

Abbreviations: BSC, best supportive care; QxW, every x weeks.

Company's model inputs (2/2)

Input	Assumption and evidence source
Utilities	• EQ-5D-3L data collected between weeks 2-16 of the SUNNY trials • Utility values were assumed to be dependent on health state • In the non-response health state, utilities were also dependent on treatment • Utilities were age-adjusted using UK general population norms
Acquisition cost	• Costs of BSC include topical and oral antibiotics, dapsone, retinoids, ciclosporin and anti-androgens • Distribution of BSC treatments informed by clinical expert opinion
Administration cost	• One-off cost (£54.92) for training by a community-based nurse to self-administer
Health state costs and resource use	• Costs included for inpatient admissions, outpatient visits, wound care appointments and emergency care attendances • Resource use frequencies based on a survey of UK clinicians for TA392 • Resource use assumed to be health state specific and independent of treatment received
Severity	• Severity modifier not applied

Abbreviations: BSC, best supportive care; EQ-5D-3L, EuroQol 5 dimensions, 3 levels

Key issue: BSC transition probabilities (1/3)

Company and EAG disagree on data sources for BSC transition probabilities

Background

- Company's original model structure assumed that after week 16, people on BSC could only lose response, and could not regain a response for remainder of the model time horizon
- Company removed this assumption at technical engagement
- Company and EAG disagree on most appropriate source of data for BSC transition probabilities - has a large impact on ICER
- Comparison of company and EAG preferred sources for transition probabilities is presented in Table 1.

Table 1: Company and EAG preferred sources for transition probabilities

Model arm	Treatment phase	Company base case (post-TE)	EAG base case
SEC	Week 0-16	Week 0-16 data from secukinumab arm of SUNNY trials	
	Week 16-52 and Week 52+	Week 16-52 data from secukinumab arm of SUNNY trials	
BSC	Week 0-16	Week 0-16 data from placebo arm of SUNNY trials	
	Week 16-52 and Week 52+	**Week 12-36 data from placebo arm of PIONEER II study** (adalimumab vs BSC, used in TA392)	**Week 0-16 data from placebo arm of SUNNY trials**

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; SEC, secukinumab; TE, technical engagement.

Key issue: BSC transition probabilities (2/3)

Company prefers to use data from PIONEER II trials and EAG prefers data from SUNNY trials to estimate transition probabilities for BSC, after week 16

Company

- PIONEER II trial provides longer follow-up data than SUNNY trials for people treated with placebo (36 weeks versus 16 weeks)
- Approach is conservative as there are likely to be fewer non-responders to BSC in PIONEER II (TA392) as this population had not had prior biologics such as adalimumab
- Approach has been clinically validated – EAG's approach lacks face validity (see **Figure 1,** next slide)

EAG comments

- Company's approach relies on a naive comparison of placebo arms of SUNNY and PIONEER II studies and introduces bias as it breaks randomisation
- Although the concomitant treatments allowed in the placebo arms of the SUNNY and PIONEER were broadly similar, there are differences in baseline characteristics:
  - Population in PIONEER II had more severe disease at baseline but were less likely to have had previous surgery and no previous treatment with biologic therapies
  - Net effect of these differences is unclear
  - Follow-up duration in both studies is short
- The EAG present an alternative scenario assuming that people remain in the health state they were in at the last observed time point from the trial (52 weeks for secukinumab, 16 weeks for BSC)

Abbreviations: BSC, best supportive care.

Key issue: BSC transition probabilities (3/3)

Company's and EAG's assumptions for response over time

Figure 1: Proportion of responders over time with different model assumptions

Response definition:
Response is defined as the sum of health state occupancy proportions in the HiSCR50 to 74 and HiSCR≥75 states

Note: Although the same assumptions are used by the company and EAG for SEC, those who discontinue SEC go on to BSC. As the BSC assumptions in the company and EAG base cases are different, this means the SEC curves diverge over time because of discontinuations to BSC

Clinical experts: Which of the response curves look most plausible?
Committee: Should the transition probabilities for BSC be taken from week 12-36 data of PIONEER II (company base case), week 0-16 of the SUNNY trials (EAG base case), or be based on the last observation carried forward from the SUNNY trials (EAG scenario)?

Key issue: Alignment of costs and benefits for BSC (1/2)

Costs and benefits for BSC treatments are not aligned in company's model

Background

- Company used different sources for BSC costs and efficacy **(Table 1)**

Table 1: Company's BSC efficacy and cost assumptions and sources

BSC inputs in model	Description of BSC	Source
Efficacy	Simple pain management and restricted use of antibiotics	SUNNY and PIONEER II trials
Costs	Surgical procedures, topical and oral antibiotics, retinoids, dapsone, ciclosporin and anti-androgens	UK clinical opinion. Costs from prescription cost analysis (antibiotics) and eMIT

Company

- Updated its model structure at technical engagement to allow BSC patients to regain response once lost based on transition probabilities from PIONEER II (**previous key issue**)
- Model now addresses EAG's concerns as it captures the efficacy benefit of BSC treatments
- BSC treatments are supportive only, company's clinical experts support using data from placebo arm of SUNNY trials as a proxy for BSC efficacy in UK clinical practice

Abbreviations: BSC, best supportive care; eMIT, electronic market information tool.

Key issue: Alignment of costs and benefits for BSC (2/2)

EAG prefers to base BSC costs on treatments given in the placebo arms of SUNNY

EAG comments

- Although the revised model structure improves clinical validity and allows for the benefits of surgery and other BSC treatments to be included, these benefits are not quantified or explicitly modelled
- Costs of surgery and other BSC treatments used in UK practice are included in the model but the benefits are not
- The company assumes that PIONEER II data captures the benefit of these treatments, the EAG disagrees as the trial does not provide efficacy data for treatments given in UK practice
- Given that efficacy of treatments given in UK practice is unknown, the EAG base case uses costs based on treatments used in the placebo arm of the SUNNY trials (but still includes surgery costs)
- The EAG also provided a scenario where surgery costs are excluded to align completely with SUNNY trials

Clinical expert

- Small surgical procedures improve quality of life in the short term but do not alter natural disease history in terms of new skin lesions and progression of disease
- There is a lack of robust quality of life data for standard oral systemics (such as antibiotics)

Should the costs for the BSC arm of the model be aligned with the placebo arm of the SUNNY trials or with clinical expert opinion on UK clinical practice?

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Abbreviations: BSC, best supportive care

Key issue: Hospital resource use rates

Resource use estimates from survey of UK clinicians are uncertain

Background

- Hospital resource use rates for each model state based on survey of 40 UK clinical experts conducted for TA392
- Model predicts [redacted] and [redacted] surgeries over lifetime for BSC and secukinumab patients, respectively

Company

- Conducted clinical validation of TA392 estimates at technical engagement with 4 clinical experts:
  - 2 experts considered the resource use estimates appropriate, 1 considered them an underestimate and 1 provided no comment → Resource use likely to be an underestimate and conservative
- No published data available

EAG comments

- EAG and company base cases are the same, however EAG concerned that company's approach lacked transparency, that frequencies were higher than what might be expected in clinical practice, and that uncertainty was not incorporated probabilistically in the economic model
- Conducted exploratory analyses reducing resource use estimates by 25%, 50%, 75% and 100% to explore the impact on the ICER

Clinical expert

- Resource use in HS may be underestimated due to miscoding, ~third of people with HS are undiagnosed

Has the uncertainty around hospital resource use rates been adequately captured?

Key issue: Health state utility values (1/2)

Background

- In original submission, company applied treatment-specific utilities in all health states
- → assumption that within the same health state, people on secukinumab had a higher utility than people on BSC
- EAG requested further data and analyses to support this assumption

Company

- Updated base case at technical engagement to include treatment specific utilities in the "no response" (HiSCR<25) health state **only**:
  - **Clinical data** – showed significant treatment effects of both Q2W and Q4W dose of secukinumab compared to placebo in the "no response" health state, in terms of:
    - percentage change in abscess and inflammatory nodule count from baseline
    - percentage of participants with no increase in abscesses at week 16
    - percentage of participants with no increase in draining fistula counts at week 16
  - **Statistical analyses** – a repeated measures regression model, with interaction terms for treatment and health state, showed a statistically significant treatment effect of the Q4W and Q2W secukinumab dose compared to placebo in the "no response" health state

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Abbreviations: BSC, best supportive care, HiSCR, hidradenitis suppurativa clinical response; QxW, every x weeks.

Key issue: Health state utility values (2/2)

EAG comments

- Satisfied with company's updated approach
- Noted that the Q2W dose also appears to have a significant effect on utility in the HiSCR25-49 and HiSCR50-74 states
- Company's and EAG's original utility values, and updated, agreed utility values after technical engagement are presented in **Table 1**

Table 1: Alternative health state utility values for application in the economic model

Treatment arm	Health state	Treatment specific (CS)	Treatment pooled (EAG report)	Treatment specific applied to "no response" health state only (company and EAG post-TE)
SEC Q4W	HiSCR≥75	[redacted]	[redacted]	[redacted]
	HiSCR50-74	[redacted]	[redacted]	[redacted]
	HiSCR25-49	[redacted]	[redacted]	[redacted]
	HiSCR<25	[redacted]	[redacted]	[redacted]
SEC Q2W	HiSCR≥75	[redacted]	[redacted]	[redacted]
	HiSCR50-74	[redacted]	[redacted]	[redacted]
	HiSCR25-49	[redacted]	[redacted]	[redacted]
	HiSCR<25	[redacted]	[redacted]	[redacted]
BSC	HiSCR≥75	[redacted]	[redacted]	[redacted]
	HiSCR50-74	[redacted]	[redacted]	[redacted]
	HiSCR25-49	[redacted]	[redacted]	[redacted]
	HiSCR<25	[redacted]	[redacted]	[redacted]

What are the most appropriate utility values: treatment specific, treatment pooled or treatment specific for the non-response health-state only?

Abbreviations: BSC, best supportive care; CS, company submission; HiSCR, hidradenitis suppurativa clinical response; QxW, every x weeks; SEC, secukinumab; TE, technical engagement.

Other issues: Inclusion of up-titration from Q4W to Q2W dose

EAG prefers not to model up-titration to Q2W dose

Company

- In model, people in secukinumab arm start on the Q4W dosing, non-responders at week 16 can up-titrate to Q2W dosing
- Efficacy for people who are up-titrated to Q2W regimen is based on the week 16-28 transition probabilities from all participants in the Q2W arms of the SUNNY trials
- Dosing in model is aligned with the anticipated marketing authorisation (maintenance dosing Q4W with the possibility to up-titrate to Q2W)
- If Q4W transition probabilities are used for non-responders who up-titrate to Q2W (rather than Q2W transition probabilities), the impact on the ICER is small

EAG comments

- Prefers not to model up-titration as the SUNNY trials were not designed to assess this, however the impact of including up-titration on the ICER is small (~£800/QALY decrease in EAG base case)
- Non-responders to the Q4W dose at week 16 are a more difficult to treat subgroup
- Therefore, applying effectiveness based on the full sample randomised to the Q2W dose likely over-estimates effectiveness in the subgroup who are more difficult to treat

Should up-titration be modelled? If so, what data / assumptions should be used?

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Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QxW, every x weeks.

Other issues: Surgery costs

Company has aligned with EAG assumptions in TA392 to estimate cost of surgery, EAG prefers to assume most procedures will be minor

Company

- Approach to costing surgery aligned with that used by EAG in TA392
- Presented additional scenarios assuming different numbers of lifetime wide excisions (elective inpatient, major surgeries) and exploring the impact of reducing the proportion of day-case surgeries

EAG comments

- Company's updated approach (and scenarios) excludes minor procedures
- Most procedures for HS are minor, therefore the company's approach may still overestimate costs
- EAG prefers to derive the surgery cost by weighting across all grades of procedure and across day-case and elective inpatient settings
- A comparison of approaches and final costs applied in the model is presented in **Table 1**

Table 1: Company and EAG approach to costing surgery

Setting	Type of skin procedure	Company post-TE	EAG
Elective inpatient	Multiple major	0%	0.13%
	Major	6.68%	0.52%
	Intermediate	13.16%	1.85%
	Minor	0%	0.87%
Day case	Multiple major	0%	1.02%
	Major	0%	3.68%
	Intermediate	67.00%	22.25%
	Minor	0%	69.68%
Non-elective short stay	Intermediate	13.16%	0%
Weighted average cost		**£2,401.52**	**£1,216.68**

Are the company or EAG estimates for the cost of surgery more appropriate?

Other issues: Outpatient visit frequencies

The company's estimates of resource use may double count outpatient visits

Background

- The EAG was concerned that company's estimates of hospital resource use may double count resource use for outpatient appointments as "outpatient visits for HS surgery" or "visits to wound care" may already be included in "outpatient visits for any reason"

Company

- Approach to estimating resource use is aligned with TA392 where all of these components were included as separate resource use categories

EAG comments

- The EAG retains its preference to only include one set of outpatient costs
- Impact on ICER is small
- There are remaining uncertainties with the company's estimates of resource use in general (see key issue)

Are the company or EAG estimates for resource use more appropriate?

Abbreviations: ICER, incremental cost-effectiveness ratio.

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
BSC transition probabilities	Based on placebo arms of SUNNY and TA392 Responders* at 1, 5 and 10 years in BSC arm; [redacted], [redacted] and [redacted], respectively.	Based on placebo arms of SUNNY Responders* at 1, 5 and 10 years in BSC arm; [redacted].
Health-state utility values	Treatment specific for "no response" state only	
Hospital resource use rates	Survey of n=40 UK clinical experts conducted for TA392	
BSC costs	UK clinical opinion	Placebo arms of SUNNY trials
Up-titration to Q2W dose permitted	Yes	No
Surgery cost	As per TA392 – no minor procedures (£2,402)	Weighted across HRG codes for all grades of surgery (£1,217)
Outpatient visit frequencies	TA392	TA392 – with some outpatient visits removed to avoid double counting
Prescribing setting for BSC treatments	Most antibiotics prescribed in primary care, all other treatments prescribed in secondary care	

Notes: *Response is defined as the sum of health state occupancy proportions in the HiSCR50-74 and HiSCR≥75 states. **Abbreviations:** BSC, best supportive care; HRG, healthcare resource group; Q2W, every 2 weeks.

Company base case results

Company deterministic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£42,415

Company probabilistic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£42,268

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

EAG base case results

EAG deterministic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£95,821

EAG probabilistic base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£96,353

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Company and EAG base case results

Individual impact of EAG preferences on company ICER (deterministic)

No.	EAG preference (applied individually to company base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£/QALY) versus BSC
0	**Company base case**	[redacted]	[redacted]	£42,415
1	BSC transition probabilities beyond week 16 extrapolated from SUNNY trials	[redacted]	[redacted]	£86,504
2	EAG's preferred surgery costing approach	[redacted]	[redacted]	£45,847
3	BSC costs as per placebo arms of SUNNY trials	[redacted]	[redacted]	£45,091
4	Up-titration removed	[redacted]	[redacted]	£43,412
5	EAG's preferred outpatient visit frequencies	[redacted]	[redacted]	£43,294
6	EAG preferred base case (combined 0-6)	[redacted]	[redacted]	£95,821

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Company deterministic scenario analysis

Company scenario analyses (deterministic)

No.	Scenario (applied to company base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£/QALY) versus BSC
1	**Company base case**	[redacted]	[redacted]	£42,415
2	2 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days	[redacted]	[redacted]	£42,022
3	3 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days	[redacted]	[redacted]	£41,285
4	4 lifetime wide excisions, 49% surgeries as intermediate as day case with the reminder intermediate inpatient days	[redacted]	[redacted]	£40,548

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Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

EAG deterministic scenario analysis (1/2)

EAG scenario analyses (deterministic)

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£/QALY) versus BSC
1	**EAG base case**	[redacted]	[redacted]	£95,821
2	Assume 2 lifetime wide excisions, 49% surgeries as intermediate day case, with remainder as intermediate inpatient.	[redacted]	[redacted]	£92,303
3	Assume 3 lifetime wide excisions, 49% surgeries as intermediate day case, with remainder as intermediate inpatient.	[redacted]	[redacted]	£91,625
4	Assume 4 lifetime wide excisions, 49% surgeries as intermediate day case, with remainder as intermediate inpatient.	[redacted]	[redacted]	£90,947

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

EAG deterministic scenario analysis (2/2)

EAG scenario analyses (deterministic)

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus BSC	Incremental QALYs versus BSC	ICER (£/QALY) versus BSC
1	**EAG base case**	[redacted]	[redacted]	£95,821
5	Reduce non-surgery resource use by 25%	[redacted]	[redacted]	£97,100
6	Reduce non-surgery resource use by 50%	[redacted]	[redacted]	£98,379
7	Reduce non-surgery resource use by 75%	[redacted]	[redacted]	£99,658
8	Reduce non-surgery resource use by 100%	[redacted]	[redacted]	£100,937
9	Reduce surgery resource use by 25%	[redacted]	[redacted]	£96,631
10	Reduce surgery resource use by 50%	[redacted]	[redacted]	£97,442
11	Reduce surgery resource use by 75%	[redacted]	[redacted]	£98,252
12	Reduce surgery resource use by 100%	[redacted]	[redacted]	£99,062
13	Long-term extrapolations based on last observation carried forward from the both arms of SUNNY trials	[redacted]	[redacted]	£68,135

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.