Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende secukinumab til behandling af aktiv moderat til svær hidrosadenitis suppurativa

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. secukinumab
2. Forhandlingsnotat fra Amgros vedr. secukinumab
3. Ansøgers endelige ansøgning vedr. secukinumab

NOVARTIS | Reimagining Medicine

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28. februar 2025

Respons til Udkast til Medicinrådets anbefaling vedr. secukinumab til behandling af hidrosadenitis suppurativa (HS)

Forløbet samt manglende involvering af HS-specialister i den endelige vurdering af secukinumab

Novartis modtog den 8.11.2024 et første udkast og dernæst den 14.2.2025 et opdateret udkast til vurderingsrapporten for secukinumab til behandling af HS. På baggrund af første udkast anmodede Novartis om clock-stop, dels pga. en markant fejl i Medicinrådssekretariatets beregning af ICER, samt at der i mellemtiden var tilkommet nye data ift. vedvarende effekt efter behandlingsophør med secukinumab og på behandlingsspecifikke nytteværdier, som var væsentlige at inddrage. Novartis genfremsendte derfor en ansøgning den 14.1.2025 med en opdateret sundhedsøkonomisk analyse.

Såvel de nye data samt antagelserne for den sundhedsøkonomiske analyse er valideret af en af de mest erfarne HS-dermatologer i Danmark samt internationalt.

Medicinrådssekretariatet samt Fagudvalget for Atopisk Dermatit, som håndterer den endelige vurdering af secukinumab har afvist de nye data og den opdaterede sundhedsøkonomiske analyse.

Novartis gjorde i efteråret 2022 Medicinrådet opmærksom på, at vi ville indsende en ansøgning for HS, men først i januar 2025 er der nedsat et funktionsdygtigt Fagudvalg for HS. Vi accepterede tilgangen med Fagudvalget for Atopisk Dermatit for ikke yderligere at blive forsinket i processen.

Specifikke kommentarer til vurderingen af den sundhedsøkonomiske analyse

I vores sundhedsøkonomiske model anvender vi EQ-5D-3L-data fra SUNNY-studierne som input til at estimere QALY-gevinsten ved behandling med secukinumab. Som nævnt i vores ansøgning, anvender vi sundhedsstadiespecifikke og behandlingsspecifikke nytteværdier i vores base case. Denne tilgang understøttes af data, der viser, at behandlingsarmen er en signifikant prædiktor for nytteværdier. Det indikerer, at der er meningsfuld forskel i nytteværdien mellem patienter, der modtager secukinumab, og dem, der modtager placebo, selv indenfor de HiSCR specifikke sundhedsstadier. Yderligere har modellen, der inkorporerer behandlingsspecifikke nytteværdier, den laveste AIC, hvilket indikerer en bedre statistisk fit til de observerede data og derfor en mere præcis repræsentation af data.

Det er klinisk relevant, at patienter, der modtager secukinumab, selv inden for de samme sundhedsstadier, kan have forskellige nytteværdier sammenlignet med dem, der modtager placebo. De fire sundhedsstadier i modellen er brede, og forskellene i patientfordelingen i hver af de fire HiSCR-stadier fanger muligvis ikke den fulde effekt af behandlingen. Derfor muliggør brugen af behandlingsspecifikke nytteværdier en mere nuanceret og præcis refleksion af fordelene ved secukinumab, idet den fanger både inter- og intrakategoriske forskelle.

Desværre præsenteres vores tilgang ikke i vurderingsrapporten, hvilket vi finder misvisende – jf. nedenstående. Medicinrådet diskuterer kun kort vores metode med sætningen: *"Medicinrådet benytter dog de stadiespecifikke nytteværdier, da der ikke ses statistisk signifikant forskel på de behandlingsspecifikke nytteværdier."* I stedet præsenteres der i afsnit 3.3, som burde beskrive ansøgers tilgang til opgørelse af helbredsrelateret livskvalitet, en tabel med nytteværdier, som ikke findes i den endelige ansøgning til Medicinrådet.

Ydermere beskrives det i rapporten, at *"Medicinrådet benytter ansøgers overordnede tilgang til modellering af helbredsrelateret livskvalitet, med udgangspunkt i, at livskvaliteten vil være afhængig af patienternes sygdomsniveau, og ikke af den behandling, de modtager",* hvilket vi også mener er misvisende, da Medicinrådet netop ikke anvender vores tilgang, men en helt anden.

En vigtig baggrund for vores anmodning om clock-stop vedrører antagelsen om vedvarende effekt efter behandlingsophør. Efter dialog med Medicinrådet inkluderede vi data om tab af effekt fra SUNNY-studierne for korrekt at medtage den residualeffekt, som patienterne vil have, efter at de stopper med behandlingen. Baseret på den kliniske HS eksperts vurdering er antagelsen imidlertid, at personer, der seponeres fra behandling, vil opleve en respons i en efterfølgende periode. Her er vi således ikke enige med Medicinrådet.

Begge effekter påvirker ICER mærkbart. I vores base case – valideret af HS eksperten – estimerer vi, at ICER for behandling med secukinumab vil være DKK 220.320 (AIP-priser), hvilket er mindre end 1/3 af den ICER, som Medicinrådet kommer frem til. Det er derfor bemærkelsesværdigt, at Medicinrådet ikke har præsenteret resultaterne fra vores base case analyse eller særskilte sensitivitetsanalyser, hvilket ville have givet en mere transparent fremstilling af vigtigheden af ændringerne i disse antagelser. I udkastet til vurderingsrapporten er det således ikke muligt at genfinde de base case analyser, som vores endelige ansøgning er baseret på. Dette mener vi er uhensigtsmæssigt af transparans hensyn, omend vi tager ad notam, at Medicinrådet – jf. deres processer – ikke er forpligtet til at tilpasse den endelige vurderingsrapport i forhold til vores opdaterede model samt ansøgning.

Vi håber, at ovennævnte vil blive taget i betragtning og ser frem til Medicinrådets endelige beslutning om ibrugtagning af secukinumab til behandling af HS den 26. marts 2025.

Med venlig hilsen,
Novartis Healthcare A/S

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25.02.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	26-03-2025
Leverandør	Novartis
Lægemiddel	Cosentyx (secukinumab)
Ansøgt indikation	Aktiv moderat til svær hidrosadenitis suppurativa (HS) (acne inversa) hos voksne som tidligere har afprøvet anden biologisk behandling (i dansk klinisk praksis, adalimumab).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse.

Prisinformation

Amgros har følgende priser på Cosentyx (secukinumab):

Tabel 1: Aftalepriser:

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Cosentyx	75 mg	1 stk.	1.885,25	[redacted]	[redacted]
Cosentyx	150 mg	2 stk.	7.540,97	[redacted]	[redacted]
Cosentyx	300 mg	1 stk.	7.540,97	[redacted]	[redacted]

[redacted]

[redacted], med effekt fra ca. 1. november 2025

Konkurrencesituationen

To andre biologiske lægemidler, Amgevita (adalimumab) og Bimzelx (bimekizumab) er EMA-godkendt til moderat til svær HS. Bimzelx er aktuelt under vurdering i Medicinrådet.
[redacted]

Tabel 2 viser lægemiddeludgifter i relation til Amgevita, den billigste biosimilære version af adalimumab på nuværende tidspunkt. Tetracyklin, Doxycyclin, Lymecyclin, Rifampicin og Clindamycin er komparatorer i Medicinrådets udkast til vurderingsrapport.
[redacted]. Da hvert af disse lægemidler kun bruges til en lille andel af patienterne, er der ikke medtaget beregninger for dem i tabel 2.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient.

Lægemiddel	Styrke	Pakningsstørrelse	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 18 måneder (SAIP, DKK)
Cosentyx	300 mg	1 stk.	300 mg SC hver 4. uge	[redacted]	[redacted]
Cosentyx *med dosisjustering*	300 mg	1 stk.	300 mg SC hver 4. uge indtil uge 16. Derefter 300 mg hver 2. uge	[redacted]	[redacted]
Amgevita (adalimumab)	40 mg	2 stk.	Induktionsperiode med 160 mg i uge 1, 80 mg i uge 3 og herefter 40 mg ugentligt fra uge 5**	[redacted]	[redacted]

*Jf. "Udkast: Medicinrådets anbefaling vedrørende Cosentyx til behandling af aktiv til moderat til svær HS" tabel 3-3, s. 42. **jf. SPC

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til anbefaling
Sverige	Anbefalet		Link til anbefaling
England	Anbefalet	Inkluderer "complex patient access scheme" hvor behandlinger hver 2. uge koster det samme som hver 4. uge.	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of secukinumab for hidrosadenitis suppurativa (HS)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

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Abbreviations

Abbreviation	Full text
AE	Adverse event
AIC	Akaike Information Criterion
AN	Abscess and inflammatory nodule
Bio-experienced	Patients who were previously exposed to biologics
CI	Confidence interval
DSA	Deterministic sensitivity analyses
DDS	Dansk Dermatologisk Selskab (Danish Dermatology Association)
DLQI	Dermatology Life Quality Index
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
HiSCR50	Hidradenitis Suppurativa Clinical Response of ≥50% reduction
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Hidradenitis Suppurativa
HSUV	Health-state specific utility values

Abbreviation	Full text
ICER	Incremental cost-effectiveness ratio
IIT	Intention to treat
IFN-γ	Interferon gamma
IL-1β,	Interleukin-1 beta
IL-17A	Interleukin-17A
LOR	Loss of response
LSM	Least square mean
MAE	Mean absolute error
MMRM	Mixed model approach
NRS30	At least a 30% reduction in pain compared to baseline measured by the skin pain numeric rating scale (NRS).
OR	Odds ratio
PBO	Placebo
PPP	Pharmacy Purchase Price
PSA	Probabilistic sensitivity analyses
Q2W	Treatment given every 2 weeks
Q4W	Treatment given every 4 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RMSE	Root mean squared error
RR	Relative risk
SAE	Serious adverse event
SE	Standard error
SD	Standard deviation
SmPC	Summary of Product Characteristics

Abbreviation	Full text
TNFα	Tumour necrosis factor alpha

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Cosentyx®
Generic name	Secukinumab
Therapeutic indication as defined by EMA	Cosentyx is indicated for the treatment of active moderate to severe hidradenitis suppurativa in adults with an inadequate response to conventional systemic HS therapy.
Marketing authorization holder in Denmark	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
ATC code	L04AC10
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	Cosentyx received EC approval for the treatment of HS on 26th April 2023
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Adult plaque psoriasis. Paediatric plaque psoriasis. Psoriatic arthritis. Ankylosing spondylitis (AS, radiographic axial spondyloarthritis). Non-radiographic axial spondyloarthritis (nr-axSpA).

Overview of the medicine	
	Juvenile idiopathic arthritis. Juvenile psoriatic arthritis. Enthesitis-related arthritis.
Other indications that have been evaluated by the DMC (yes/no)	Yes, DMC has recommended Cosentyx for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA). In addition, Cosentyx is included in the DMC treatment guidelines and treatment recommendations for psoriasis and psoriatic arthritis. Previously DMC had treatment guidelines for ankylosing spondylitis and non-radiographic axial spondyloarthritis, in which Cosentyx was also included.
Dispensing group	NBS
Packaging – types, sizes/number of units and concentrations	Secukinumab is available as Cosentyx®, in 150/300 mg solution for injection in single-use pre-filled pen. Packs of: 1 or 2 pre-filled pens are available. In addition, 75 mg solution for injection in a single-use pre-filled pen is available in packs of 1 (not relevant for HS).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Treatment of adults with active moderate to severe HS with an inadequate response to conventional systemic HS therapy and who have previously had biological treatment. This is a subgroup from the EMA indication which included both bio-naïve and bio-experienced patients. The subgroup population was suggested by DMC in their final assessment of the full patient population.
Dosage regiment and administration	The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by a maintenance dose of 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks (Q2W) may provide additional benefit for patients.
Choice of comparator	Clinical part: Placebo. Health economic part: Standard of care (SoC) which includes systemic antibiotics, retinoids and roflumilast (biological treatment is not included, except for in a sensitivity analysis for budget impact).
Prognosis with current treatment (comparator)	Without additional biological treatment options, patients with HS who do not respond sufficiently to adalimumab would be left with very limited treatment options. This would include additional need for surgical treatment and going back to systemic treatment, such as antibiotics, which did not work sufficiently in the first place. Considering the substantial impact on quality of life (QoL) for these patients, there is a high unmet medical need for treatment with secukinumab after adalimumab.
Type of evidence for the clinical evaluation	Head-to-head studies (results for subgroup pooled from two identical studies).
Most important efficacy endpoints (Difference/gain compared to comparator)	Proportion of patients achieving Hidradenitis Suppurativa Clinical Response of ≥50% reduction (HiSCR50). Percentage reduction in abscess and inflammatory nodule (AN) count. Proportion of patients achieving least a 30% reduction in pain compared to baseline measured by the skin pain numeric rating scale (NRS30). Proportion of patients achieving ≥5 point reduction in Dermatology Life Quality Index (DLQI) and Safety. Efficacy in the subgroup was generally in line with what was seen in the full intention to treat (ITT) patient population. The SUNNY studies were not powered to show differences in the subgroups, but a statistically significant difference in favour of secukinumab was anyway seen on the outcomes related to AN count, pain and DLQI.

Summary	
Most important serious adverse events (SAE)s for the Intervention and comparator	According to the Summary of Product Characteristics (SmPC) for Cosentyx®, SAEs such as serious infections, inflammatory bowel disease and hypersensitivity reactions have been observed across indications. In the full study population in the SUNNY studies, 2/721 patients (0.3%) experienced inflammatory bowel disease as an SAE and 3/720 (0.4%) experienced an infection as a SAE while on secukinumab Q2W or Q4W, whereas 3/363 patients (0.08%) on placebo experienced an infection as a SAE (see Appendix E).
Impact on health-related quality of life (HRQoL)	Clinical documentation: In the secukinumab Q4W arm 49.2% (95% confidence interval (CI)I: 36.9%, 61.5%) of patients achieved a reduction in DLQI of at least 5 points at 16 weeks vs. 31.5% (95% CI: 20.8%, 42.2%) in the placebo arm. The absolute difference was 17.7 %-points, (95% CI: 1.4%, 34.0%) and odds ratio (OR) was 1.56 (95% CI: 1.03, 2.38). Despite the relatively small patient number, the difference between treatments is statistically significant in favour of secukinumab. Health economic model: An increase in HRQoL measured with European Quality of Life 5 Dimensions (EQ-5D) was observed in the secukinumab arms in the SUNNY studies.
Type of economic analysis	Cost-utility analysis with a Markov model.
Data sources used to model the clinical effects	The transition probabilities applied in the model were based on pooled efficacy estimates from the bio-experienced population from the SUNNY studies, using results on HiSCR response rates for the secukinumab Q4W and Q2W dosing regimens.
Data sources used to model the HRQoL	SUNNY studies and Danish value set.
Life years gained	0 years
(QALYs gained	0.66 QALY
Incremental costs	220,320 DKK
ICER (DKK/QALY)	334,772 DKK/QALY (based on pharmacy purchase price, PPP)
Uncertainty associated with the ICER estimate	The health state utility values related to different severity categories of HS and the healthcare resource use in the hospital sector were found to have the largest impact on the incremental costs and QALYs in the deterministic sensitivity analysis.
Number of eligible patients in Denmark	Incidence: 50 patients per year (after adalimumab). Prevalence: Currently approximately 100 patients are eligible for secukinumab after adalimumab.
Budget impact (in year 5)	DKK 41,687,803 over all 5 years (based on the PPP).

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

HS is a chronic inflammatory skin disease affecting hair follicles in intertriginous areas, including the axillary, inframammary, inguinal, genital, buttocks, and perianal/perineal areas [1].

HS pathophysiology involves blockage and inflammation of hair follicles triggered by both genetic and environmental factors. Follicles that have been occluded can dilate and rupture, leading to the triggering of inflammatory pathways and release of proinflammatory cytokines (e.g., IL-1β, IL-17A, TNF-α, IFN-γ) [2].

Primary lesions can develop into painful inflammatory abscesses persisting over long time periods (weeks or months), leading to additional symptoms such as burning and stinging. Recurrence of HS or flare-ups can result in the formation of sinus tracts and severe, rope-like scarring, with persistent symptoms such as pain, itching, purulent and malodorous discharge and hypertrophic scars (over months or years) [3].

HS is classified as mild, moderate and severe disease based on the Hurley staging [1]:

- Mild: Abscess formation, single or multiple, without sinus tracts or scar formation.
- Moderate: Recurrent abscesses with tract formation and scarring, single or multiple, widely separated lesions.
- Severe: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

As described in section 3.3 below, the treatment of HS depends on the severity of disease and involves both medical and surgical treatment, as well as supportive treatment such as management of pain, smoking cessation, weight loss and psychosocial support [4]. Biological treatment is used for patients with moderate to severe HS who do not respond sufficiently to conventional systemic therapy, and currently adalimumab is the only biological treatment that is recommended by DMC. For patients who do not respond adequately to adalimumab or who do not tolerate it, there are no further recommended treatment options, and patients would then generally need increased additional surgery (which may result in irreversible scarring and potential surgery complications) and would have to go back to systemic medical treatment that previously did not work sufficiently if non-approved biological alternatives, mostly non-approved, are not chosen.

HS has a highly negative impact on QoL and devastating psychological effects, with an impact greater than for many other dermatologic diseases. In addition to the pain,

malodorous fistulae discharge and scarring, patients with HS also often suffer from depression, social isolation, impaired sexual health, difficulty performing work duties and they have increased suicidal risk [5–7].

A recent Danish study showed that 27.4% of patients with HS have psychiatric comorbidity, with affective disorders (16.2%) being most prevalent [8]. HS is also associated with socio-economic and personal burdensome somatic comorbidities, i.e. metabolic syndrome consisting of cardiovascular risk factors, chronic lymphedema, inflammatory bowel disease and squamous cell carcinoma [1].

HS is also impacting work productivity. A Danish study included 100 consecutive patients attending a dermatology hospital department. Among 57 (57.0%) patients who were employed, 21.2% reported missing work and 60.4% reported loss of work productivity during the preceding week as a result of HS. The overall work productivity was reduced by 26.6%. In addition, 72% reported daily activity impairment, averaging 32.7% reduction in daily activities [9].

3.2 Patient population

The average onset of HS is in the early 20s, and the disease is three times more prevalent in women than in men [10, 11]. For this application, the relevant population are patients who have already been treated with biologics, and a Danish registry study showed that patients treated with biologics were on average 42 years old and 60% were women [9].

The true prevalence of HS is challenging to estimate due to diagnose delay and heterogenic methods. This is reflected in a large variability of reported prevalence, e.g. from 0.00033% to 4.1% [13]. However, current consensus of the prevalence in Europe is estimated to 1% [1] which translates to approximately 59,000 in Denmark in 2022 [14]. The incidence in Denmark is not known but estimated to 6/100,000 person-years in the US [15]. Approximately 68% have mild disease (Hurley stage I), 28% moderate disease (Hurley stage II) and 4% severe disease (Hurley stage III) [16] which corresponds to approximately 19,000 persons with moderate or severe HS in Denmark, and a yearly incidence of moderate or severe HS of 350 (see Table 1).

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	350	350	350	350	350
Prevalence in Denmark	57,950	58,300	58,650	59,000	59,350
Number of patients with moderate to severe HS	18,544	18,656	18,768	18,880	19,992

Sources: [11, 14, 17]

The treatment of HS is described below. Biological treatment is reserved for patients with moderate to severe HS with inadequate response to conventional systemic HS therapy and takes place in dermatological hospital departments.

Only a limited number of patients with moderate and severe HS reach the dermatology hospital departments. When biological treatment was introduced in 2016, RADS assumed that a maximum of 130 patients would fulfil the criteria for biological treatment [18]. Up to December 2018, a total of 241 HS patients had been treated with biological treatments across all hospital departments [12]. A recent update showed that a total of 452 patients had been treated with biological treatment, including non-approved biological treatments, up to December 2021, corresponding to a yearly increase of 70 patients from 2018 to 2021 [19]. Recent data from DLI show that at least 286 HS patients were treated with biological treatments in 2021 at the Danish hospitals. Based on expert input, approximately 500 HS patients are estimated to be on biological treatment today (2024) and going forward, 100 new patients will start biological treatment every year [20].

The estimation of number of patients who will be treated with secukinumab over a five-year period is shown in Table 2. The estimate builds on the assumptions that the total population on biological treatment (starting on adalimumab) will grow by approximately 100 patients per year, and 50 patients per year will switch to secukinumab. Currently it is estimated that 100 patients, who have already failed on adalimumab, will start treatment with secukinumab, if the DMC recommends it.

Table 2 Estimated number of patients eligible for treatment

Year	2024	2025	2026	2027	2028
Estimated number of HS patients in Denmark who are eligible for biological treatment in the coming years	400	500	600	700	800
Estimated number of HS patients in Denmark who are eligible for treatment with secukinumab in the coming years	100	50	50	50	50

Sources: [19–22]

3.3 Current treatment options

The treatment of HS depends on severity of the disease and the efficacy and tolerability of the treatments for the individual patient. As described in the European guidelines [1] as well as in the Danish Dermatology Association (DDS) guidelines [4], treatment options include topical treatments, oral treatment with antibiotics (due to their anti-inflammatory effect), biological treatment, laser treatment and various types of surgery. In addition, the patient should be supported in losing weight and smoking cessation [1, 4].

Patients with HS are treated in general practice, by dermatologists in private practice and at dermatology hospital departments. In addition, an unknown number of HS patients are treated by other specialists (e.g. acute incision of HS abscesses by doctors in emergency rooms, other surgeons e.g. gastro-surgeons or urologists treating anogenital abscesses, plastic surgeons, gynaecologists, and general practitioners) [16, 18].

When it comes to biological treatment in Denmark, prescription of biological treatment is as mentioned limited to the dermatology hospital departments and reserved for patients with moderate to severe HS who have not responded adequately to conventional non-biological treatment. Adalimumab is currently the only biological treatment recommended for patients with moderate to severe HS with an inadequate response to conventional systemic HS therapy, both in the (retired) RADS guideline and in the DDS guideline [4, 18].

It is well recognised that HS is a difficult to treat chronic disease [3]. Treating HS with adalimumab requires higher doses compared with psoriasis [23] and the median survival time for adalimumab in a Danish population was shown to be 36 weeks [12].

A recent Danish study, which included all HS patients in Denmark who had been treated with biological treatments at a dermatology hospital department from 2005 to 2018, showed that a substantial part of the patients who were treated with adalimumab switched - primarily thought to be due to insufficient efficacy - to other biological treatments, including treatments that have not been approved by EMA [12].

Without additional biological treatment options, patients with HS, who do not respond sufficiently to adalimumab, would be left with very limited treatment options. This would include additional/increased need for surgical treatment and going back to systemic treatment, such as antibiotics, which did not work sufficiently in the first place. Considering the substantial impact on QoL for these patients, there is a high unmet medical need for an alternative treatment like secukinumab after adalimumab.

3.4 The intervention

3.4.1 Description of the intervention

Table 3 Overview of intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Treatment of adults with active moderate to severe HS with an inadequate response to conventional systemic HS therapy and who have previously had biological treatment. The EMA indication included both bio-naïve and bio-experienced patients, and this assessment thus only include the subgroup of bio-experienced patients. The subgroup population was suggested by DMC in their final assessment of the full patient population [24].
Method of administration	Subcutaneously.
Dosing	The recommended dose is 300 mg of secukinumab by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by a maintenance dose of 300 mg monthly.

Overview of intervention	
	Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients.
Dosing in the health economic model (including relative dose intensity)	In the model, patients in the secukinumab arm received secukinumab according to the posology described in the SmPC [25]. In the base case, patients are initiated on secukinumab treatment with 300 mg SC monthly [20]. After 16 weeks, patients on secukinumab monthly who did not achieve a response (defined as HiSCR ≥50 in the base case) would be up-titrated to 300 mg secukinumab Q2W.
Should the medicine be administered with other medicines?	No.
Treatment duration / criteria for end of treatment	The treatment should continue as long as there is an effect [24].
Necessary monitoring, both during administration and during the treatment period	After initial instruction by health care personnel, the patient can self-administer the treatment and no monitoring during administration is required. During the treatment period, DDS recommends clinical monitoring by treating physician after 3 months with adalimumab [4].
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No.
Package size(s)	Secukinumab is available as Cosentyx, in 150/300 mg solution for injection in single-use pre-filled pen. Packs of 1 or 2 pre-filled pens are available. In addition, 75 mg solution for injection in a single-use pre-filled pen is available in packs of 1 (not relevant for HS).

3.4.2 The intervention in relation to Danish clinical practice

In Danish clinical practice, secukinumab is expected to be used in patients with moderate or severe HS who have previously been treated with adalimumab. In that respect, secukinumab will be an additional treatment option in the treatment algorithm. No new diagnostic tests or methods used for patient selection are required.

3.5 Choice of comparator

Placebo is chosen as comparator for this application for the subgroup of bio-experienced HS patients. This choice is based on the suggestion from the DMC in their recommendation for secukinumab for the full HS population (i.e., the full EMA indication) [24].

As described in section 3.3, many bio-experienced patients with moderate to severe HS (i.e. after adalimumab) are treated with biological treatments, including treatments that are not approved by EMA. Thus, placebo does not fully reflect the standard of Danish clinical practice.

If use of additional biologics for patients who do not respond sufficiently to adalimumab was not practiced, treatment options would as previously mentioned include additional need for surgical treatment and going back to systemic treatment, e.g. antibiotics, which did not work sufficiently in the first place (SoC, described in more details in section 11.1).

Table 4 Overview of comparator

Overview of comparator	
Generic name	N/A – as comparator is placebo
ATC code	
Mechanism of action	
Method of administration	
Dosing	
Dosing in the health economic model (including relative dose intensity)	
Should the medicine be administered with other medicines?	
Treatment duration/ criteria for end of treatment	
Need for diagnostics or other tests (i.e. companion diagnostics)	
Package size(s)	

3.6 Cost-effectiveness of the comparator(s)

The comparator is placebo. The current cost-effectiveness analysis for secukinumab vs. placebo is the first of its kind within the area of HS to be evaluated by the DMC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
HISCR50	16 weeks	Proportion of patients with at least 50% change in Hidradenitis Suppurativa Clinical Response (HiSCR50). HiSCR50 was defined as achieving ≥50% reduction in abscesses and inflammatory nodules, along with no increase in the number of abscesses and no increase in the number of draining fistulas from baseline.	HISCR was evaluated by the investigator at every study visit.
AN count	16 weeks	Percentage change in number of abscesses and noduli from baseline (AN count).	AN count was evaluated by the investigator at every study visit.
NRS30	16 weeks	Pain measured as proportion of patients with a baseline numeric rating scale of three or more, achieving an improvement of at least 30% on a numeric scale from 0-10 (NRS30).	NRS30 was assessed by the patient at every study visit.
DLQI	16 weeks	QoL measured as proportion of patients achieving an improvement of at least 5 points on the DLQI.	DLQI was assessed by the patient at every study visit.
SAE	16 weeks	Proportion of patients with an SAE.	Assessed during the entire study period.
Treatment withdrawal	Up to week 16	Proportion of patients stopping treatment before planned during the study period, regardless of reason.	Assessed during the entire study period.
Time to loss of response (LOR)	From week 52 up to week 104	LOR is defined as a 50% or greater increase in the AN count at a regular or unscheduled visit compared to the average AN count from the 3 previous visits (including core visits) or the week 52 visit, whichever is lower, and the increase is at least 3 AN count.	Assessed during the extension study

AN, abscess and inflammatory nodule; DLQI, dermatology life quality index; HiSCR, Hidradenitis Suppurativa Clinical Response; NRS skin pain, numerical rating scale of the Patient's Global Assessment of Skin Pain–at worst; SAE, serious adverse event.
* Time point for data collection used in analysis (follow up time for time-to-event measures)

As HS is a chronic disease, long term efficacy is of high relevance. For this reason, efficacy data at 52 weeks for the secukinumab Q4W arm will also be presented in this application.

Validity of outcomes

Methods of analyses and handling of missing data is described in section 6.1.4.

HISCR50

HiSCR50 is clinically relevant in the assessment of HS treatment effectiveness, as the score captures the inflammatory manifestations of the disease. Using the threshold of 50% is clinically appropriate and meaningful to patients with respect to QoL and pain level improvement [44]. The validity of the HiSCR outcome has been tested with test-retest reliability [44].

AN count

The DMC included AN count in their assessment of secukinumab in the full HS population [24], as AN count was considered a relevant efficacy outcome [26] and it is therefore included in this application.

NRS30

The DMC included skin pain (NRS30) in their assessment of secukinumab in the full HS population [24], as pain was considered a relevant efficacy outcome [26] and it is therefore included in this application. The numerical rating scale (NRS) is a segmented numeric version of the visual analogue scale in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of their pain ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). NRS30, defined as at least a 30% reduction and at least 2 units reduction from baseline, is a validated clinically important outcome, and was assessed in patients with a baseline numeric rating scale of three or more [27].

DLQI

DLQI is the most widely used QoL instrument for skin diseases which makes it relevant for use in HS. The validity of DLQI has been tested in eczema and psoriasis using the correlation between DLQI scores, measures of clinical severity and domain scores on the Nottingham Health Profile. The reliability has been tested through test-retest [45]. The minimal clinically important difference has-+ been estimated to 4 [26]. For the SUNNY studies, the definition of DLQI response is a decrease of 5 or more from baseline [28].

SAE

Safety outcomes are of great clinical relevance because it is important to know and understand the risks associated with a treatment option. Proportion of patients experiencing SAE is generally assessed by the DMC.

Withdrawal from treatment

The clinical relevance of this outcome has not been assessed, however, discontinuation may be considered to have clinical relevance, as it provides insight to treatment compliance and the most important reasons for early cessation of treatment.

4. Health economics analysis

The health economics analysis in the present application was a cost-utility analysis that assessed the cost per quality-adjusted life year (QALY) of treating patients with moderate to severe HS with secukinumab compared to treatment with SoC. In the SUNNY studies, secukinumab was compared to placebo which was used as the efficacy data for SoC in the model. SoC in the model comprised various non-biological systemic treatments informed by the Danish clinical expert, which are presented in section 11.1. In the following, we present the health economics model applied in the analysis.

4.1 Model structure

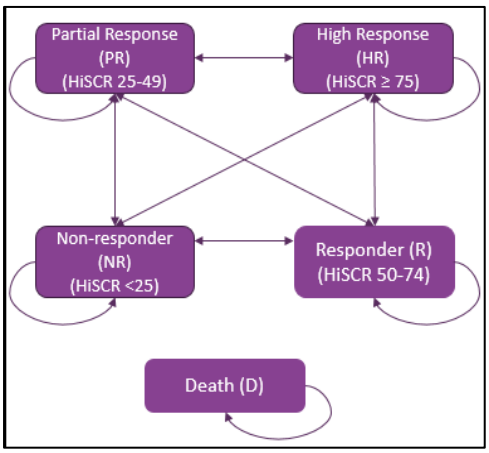
A Markov model was developed which assessed the cost-effectiveness of secukinumab compared to SoC. The rationale for the Markov approach was that it appropriately mapped the clinical pathway of care while maintaining a simple structure. The model structure is presented in Figure 1. The model comprised of an induction phase (first 16 weeks) followed by a long-term maintenance phase.

The model comprised five health states defined and categorised based on the percentage HiSCR improvement a patient achieved:

- High responders (HR): HiSCR ≥75%
- Responders (R): HiSCR 50-74%
- Partial Responders (PR): HiSCR 25-49%
- Non-Responders (NR): HiSCR <25%
- Death (D).

HiSCR threshold values were used to segregate patients into the different states. The rationale behind this was the statistically significant difference in utility values and resource usage between HR, R, PR, and NR. The model also comprised an absorbing death state, where only all-cause mortality was considered, and patients were at risk of death at any point in the model. The risk of death was independent of health state and treatment since HS does not confer an increased risk of mortality.

Figure 1 Model structure



Patient flow in the model

Patients entered the model in either a Q4W arm, where patients received a monthly secukinumab dosing regimen or a Q2W arm, where patients received secukinumab every two weeks, or SoC during the induction phase, which comprised the first 16 weeks. All patients were assessed for treatment response (HiSCR <25, HiSCR 25-49, HiSCR 50-74 and HiSCR ≥75) at the end of every cycle (4 weeks) in line with when response was assessed in clinical studies on HS. Treatment could not be discontinued in the induction phase in the base case, but the model did include a feature to allow for discontinuation in the induction phase. If discontinuation in the induction phase was not selected, a 4-week discontinuation rate based only on data from 36 weeks was applied. If discontinuation in the induction phase was selected, a 4-week discontinuation rate based on data from 52 weeks was applied.

After the first 16 weeks, patients who entered the model in the secukinumab Q4W arm (representing the monthly dosing regimen) who achieved a response (in the base case defined as HiSCR ≥50) continued monthly secukinumab treatment until the end of the time horizon, death, or discontinuation. Responders who discontinued were moved to SoC treatment. Patients in the secukinumab Q4W arm with no response (HiSCR <50) were up-titrated and moved to the secukinumab Q2W arm and continued treatment for another 16 weeks. If they remained non-responders after the 32 weeks, they discontinued secukinumab treatment and moved to SoC treatment.

Patients who entered the model in the secukinumab Q2W arm who achieved a response continued receiving secukinumab Q2W until the end of the time horizon, death or discontinuation. Responders who discontinued were moved to SoC. Patients in the secukinumab Q2W arm who did not achieve a response after 16 weeks moved to the SoC arm. When patients in both secukinumab arms moved to SoC, with the response criteria being HiSCR ≥50, they moved to 'off-treatment' and was ascribed utilities and costs equal to that of patients receiving SoC in the HiSCR<25 health state. However, treatment response was observed for a [redacted] among patients in both the Q4W and Q2W arms, respectively, who stopped treatment with secukinumab and continued with

placebo in the long-term extension of the SUNNY studies. Therefore, patients transitioning from treatment with secukinumab to off-treatment were assigned a one-off cost decrement and a utility increment accounting for this.

It was assumed, based on input from the clinical expert, that patients in the SoC arm could not discontinue SoC, but would remain on SoC treatment until the end of the time horizon or death. All patients in the SoC arm were moved to the non-responder health state after the induction phase regardless of treatment response.

Following week 52, patients who were still receiving treatment with secukinumab were subjected to an additional response assessment. During this assessment, patients who were classified as non-responders, were discontinued from secukinumab treatment and moved to off-treatment. Conversely, patients who were classified as responders and continued with secukinumab treatment beyond week 52 were assumed to remain in their current HiSCR state, until either the end of the time horizon or until they discontinued treatment. This means that no further transitions between HiSCR states were modeled for patients who remained on secukinumab therapy after week 52.

4.2 Model features

Table 6 presents a summary of the model features.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	Patients with moderate to severe HS who have previously received treatment with adalimumab (bio-experienced).	The patient population in the model was selected based on discussions with the DMC. The patient age, proportion of females and average weight in the model were 38.9 years, 57.6% and 94.5 kg, respectively, based on weighted averages of patients from the SUNNY studies.
Perspective	Limited societal perspective.	According to DMC guidelines.
Time horizon	Until patients reach 100 years.	A lifelong time horizon was applied, as HS is a chronic and lifelong condition. In addition, it is expected that some patients experience a prolonged and positive response to HS treatment and therefore, a lifelong time horizon was applied to capture this long-term effectiveness of secukinumab.
Cycle length	4 weeks.	Consistent with assessment of treatment response in clinical practice.
Half-cycle correction	Yes.	To estimate the costs more accurately across the model cycles.

Model features	Description	Justification
Discount rate	Year 0-35: 3.5% for costs and effects. Year 36-70: 2.5% for costs and effects. Year 70+: 1.5% for costs and effects.	In accordance with DMC guidelines the discounting rates from the Ministry of Finance were applied [29].
Intervention	***Induction*** Secukinumab 300 mg SC week 0, 1, 2, 3, and 4. ***Maintenance:*** Secukinumab 300 mg SC monthly or Secukinumab 300 mg SC Q2W.	In the model, secukinumab is administered either monthly or Q2W after the induction phase, in accordance with the SmPC. In the SUNNY studies, secukinumab was dosed either as Q4W or Q2W. Efficacy and safety data for patients who received secukinumab Q4W are used to model the cost-effectiveness for individuals on monthly treatment. We expect that the effects between Q4W treatment and monthly treatment will be equivalent.
Comparator(s)	SoC.	The SoC arm comprised a basket of non-biological systemic treatments, based on input from the clinical expert.
Outcomes	HiSCR. EQ-5D. Safety.	Based on how treatment response is measured in clinical HS studies and standard approach in other HS models. EQ-5D was selected in accordance with DMC guidelines.

5. Overview of literature

5.1 Literature used for the clinical assessment

No literature search was conducted, as this application is based on pooled data from two identical head-to-head studies with placebo as a comparator. All patients from the SUNNY studies who completed the full study treatment period (52 weeks) were eligible to enter into the extension study "Extension Study to Assess Effects of Non-interrupted Versus Interrupted and Long Term Treatment of Two Dose Regimes of Secukinumab in Subjects With Hidradenitis Suppurativa". This study was also applied in the clinical assessment of secukinumab. Results from this long-term extension study have not been published but are posted on Clinicaltials.gov (NCT04179175) [30]. Relevant literature is shown in Table 7.

Table 7 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study	Used in comparison of*
Main publication: 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. Kimball AB, Jemec GB, Alavi A, et.al. Lancet 2023 [28] **Publication of subgroups (prior biological treatment):** Secukinumab in patients with moderate to severe hidradenitis suppurativa based on 1 prior biological exposure: An efficacy and safety analysis from the SUNSHINE and 2 SUNRISE phase III trials. Zouboulis CC, Passeron T, Pariser D, et al Br J Dermatol 2024 [31].	SUNSHINE	NCT number: NCT03713619	Start: 31/01/19 Primary Completion: 01/10/21 Data cut-off 01/10/21 Study completion:27/07/22	Secukinumab vs. placebo for HS patients with prior biological treatment
	SUNRISE	NCT number: NCT03713632	Start: 25/02/19 Primary Completion: 23/09/21 Data cut-off 23/09/21 Study completion:19/07/22	
Data on file/clinicaltrials.gov Extension Study to Assess Effects of Non-interrupted Versus Interrupted and Long-Term Treatment of Two Dose Regimes of Secukinumab in Subjects With Hidradenitis Suppurativa [30].	Extension study of the SUNNY trials	NCT number: NCT04179175	Start: 2020/03/18 Primary completion: 2023/05/26 Study completion: 2026/07/15	

5.2 Literature used for the assessment of health-related quality of life

The HRQoL data was solely obtained from the head-to-head SUNNY studies. Thus, a literature search was not conducted.

Table 8 Relevant literature included for (documentation of) health-related quality of life N/A

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A		

5.3 Literature used for inputs for the health economic model

The health economic analysis was informed by the SUNNY studies, input from the clinical expert, DMC documents and DRG tariffs. Thus, no external literature was applied and therefore, no literature search was conducted.

Table 9 Relevant literature used for input to the health economic model N/A

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A			

6. Efficacy

6.1 Efficacy of secukinumab compared to placebo for bio-experienced HS patients

6.1.1 Relevant studies

This application is based on pooled data from the pre-defined subgroup of patients who had previously been exposed to biological treatment ("bio-experienced") in the SUNSHINE (NCT03713619) and SUNRISE (NCT03713632) studies (the SUNNY studies).

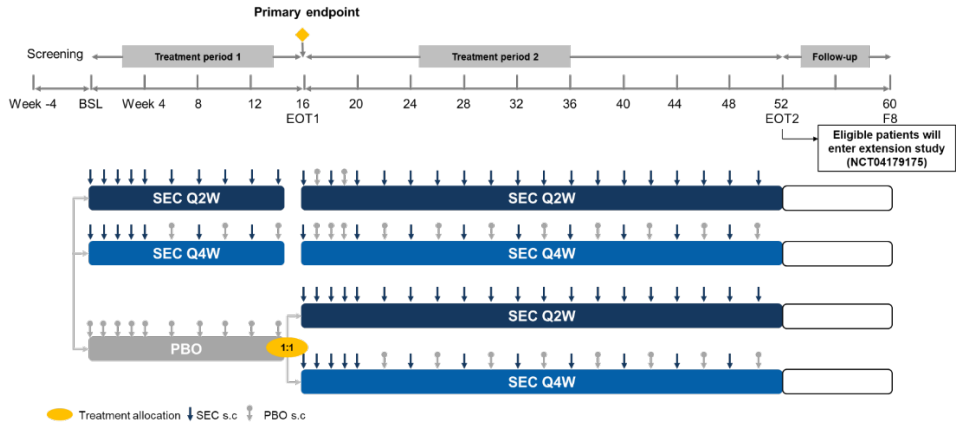
The SUNSHINE and SUNRISE studies (the SUNNY studies) are two identical Phase 3, randomised, double-blind, placebo-controlled studies conducted to evaluate the efficacy and safety of two secukinumab dose regimens in patients with moderate to severe active HS [28].

The studies were divided into three parts (plus a post-treatment follow-up period) consisting of screening, a 16-week placebo-controlled treatment period and an uncontrolled treatment period up to 52 weeks.

Patients who prematurely discontinued the studies, or who completed the studies and did not continue in the optional extension study, were required to complete a post-treatment follow-up period. At randomisation patients were stratified by region, concomitant antibiotic use and bodyweight (<90 vs. ≥90 kg).

The study design and phases for the identical studies are detailed further in Figure 2 below.

Figure 2: Study design for SUNSHINE and SUNRISE



Abbreviations; BSL: Baseline; EOT1/EOT2: End of treatment period 1/2; F8: End of 8-week follow-up period; PBO: Placebo; Q2W: Every two weeks; Q4W: Every four weeks; s.c.: Subcutaneous; SEC: Secukinumab 300 mg.

Notes; Treatment period 1: Patients were randomised to secukinumab Q2W, secukinumab Q4W, placebo Q2W or placebo Q4W in 1:1:0.5:0.5 ratio and were included in the Randomised set. **Treatment period 2:** at Week 16 visit, patients initially randomised to placebo were switched to one of the two active dose regimens (secukinumab Q2W or Q4W), while patients randomised to secukinumab during treatment period 1 continued on the same dose. **Extension study**: At the end of the studies, patients who completed the core study and who were expected to benefit from study treatment were eligible to continue into the extension study. **Post-treatment follow-up**: The post-treatment follow-up period (lasting 8 weeks) was required for patients who prematurely discontinued the studies, or who completed the studies and could not or did not wish to continue in the optional extension study.

Overall, 541 patients were randomised in SUNSHINE (181 to secukinumab 300 mg s.c. every two weeks (Q2W), 180 to secukinumab 300 mg s.c. every four weeks (Q4W) and 180 to placebo) and 543 patients in SUNRISE (180 to secukinumab Q2W, 180 to secukinumab every Q4W and 183 to placebo) studies, respectively. Two Danish sites, Bispebjerg Hospital and Aarhus University Hospital, participated in the SUNRISE study.

Of the 1,085 patients included in the SUNNY studies, 255 patients had previously been treated with biologics, 80 patients in the secukinumab Q2W arm, 81 patients in the secukinumab Q4W arm and 94 in the placebo arm.

All patients from the SUNNY studies who completed the full study treatment period (52 weeks) were eligible to enter into an extension study. The purpose of the study was to evaluate maintenance of HiSCR response with either continuous or interrupted therapy (using a randomized withdrawal period) and to assess long-term efficacy, safety and tolerability of secukinumab in patients with HS. Patients who had not achieved HiSCR50 at 52 weeks were treated with secukinumab Q2W in the long-term extension study. Patients who had achieved HiSCR50 at 52 weeks were randomised 2:1 to either continue the allocated dose of secukinumab or switch to placebo. The primary endpoint was time to loss of response (LOR) up to week 104 in patients who were HiSCR50 responders at week

52 in the core studies. Of a total of 207 HiSCR50 responders who had been treated with secukinumab Q2W in the core study, 136 were randomised to secukinumab Q2W and 71 to placebo. Of a total of 184 HiSCR50 responders who had been treated with secukinumab Q4W in the core study, 121 were randomised to secukinumab Q2W and 63 to placebo [30]. The usual maintenance dose of secukinumab for other indications is monthly [25]. However, it was originally anticipated that the dose for HS patients could be higher, i.e. Q2W due to the fact that HS is a disease which is difficult to treat and based on the higher body weights observed in HS patients. For the final analysis of the primary endpoint, the alpha level was α=0.02 for secukinumab Q2W vs. placebo and α=0.005 for Q4W vs. placebo, i.e., a stricter threshold to achieve significant difference for the QW4 arm vs. placebo [32].

Based on similar results for the Q2W and Q4W dose regimens, the recommended maintenance dose of secukinumab is monthly, and therefore, only data from the secukinumab Q4W arm and the placebo arm will be included in the comparison in this application.

Table 10 Overview of study design for studies included in the comparison

Study name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
SUNSHINE NCT03713619 [28, 31]	Randomised, double blinded, placebo controlled, phase 3 study of secukinumab vs. placebo.	16 weeks double blinded period follow by 36 weeks open label (52 weeks in total). At week 16 visit, patients on placebo were switched to one of the two active dose regimens, while patients randomised to secukinumab during treatment period 1 continued on the same dose.	Patients with moderate-to-severe HS, (defined as a total of five or more inflammatory lesions affecting at least two distinct anatomical areas) for at least 1 year. Patients were excluded, if they had 20 or more fistulae at baseline. Patients previously treated with TNFα inhibitors or on a stable dose of selected antibiotics were eligible for inclusion.	Secukinumab, (s.c.), 300 mg week 0,1,2,3,4 and either every 2 weeks (Q2W) or every 4 weeks (Q4W) thereafter.	Matching placebo (s.c. administration)	Primary and secondary outcomes: HiSCR50-response (week 16), change from baseline in AN count (week 16), flaring (week 16, not included in the application), NSR30-response (week 16), adverse events (AE)s and SAEs. In addition, the exploratory outcome DLQI-response (week 16) is included in this application. Outcomes at 52 week is also included for the Q4W treatment arm.
SUNRISE NCT03713632 [28, 31]						
Long-term extension study of the SUNNY trials NCT04179175 Data on file	This is a multicenter extension study to both the SUNNY studies (core studies). This study contains a randomised withdrawal design, double blinded and placebo controlled up to week 104 or loss of response	Up to week 104	Patients who have completed the study treatment period (52 weeks) in the core studies and had received secukinumab treatment during Treatment Period 2 (36 weeks)	Secukinumab 300 mg every 2 weeks or secukinumab 300 mg every 4 weeks	Matching placebo (s.c. administration)	Time to LOR up to week 104 in HiSCR responders. Loss of response was defined as: • At least a 50% increase in abscess and/or nodules (AN) count compared to the average AN count from the 3 previous visits or at Week 52, whichever

Study name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						is lower and the increase was at least of 3 AN. • At least a 30% increase in AN compared to the average AN count from the 3 previous visits or Week 52, whichever is lower, with an increase of at least 2 AN and a further increase in the AN count of at least 2 AN at a re-assessment visit within 2-4 weeks Number of Participants With Treatment Emergent Adverse Events.

The SUNNY studies are described in detail in Appendix A.

6.1.2 Comparability of studies

N/A as the comparison is based on pooled data from two head-to-head studies with identical study design.

6.1.2.1 Comparability of patients across studies

For the full study population, the patient populations in the SUNSHINE and SUNRISE studies were in general similar with regard to baseline characteristics. Slightly more patients in the SUNRISE study had Hurley III compared to the SUSHINE study (40.7 vs 34.0%). Baseline characteristics for the SUNNY studies are shown in Table 11.

Table 11 Baseline characteristics between the SUNSHINE and SUNRISE clinical studies [31]

Characteristic	SUNSHINE (N=541)	SUNRISE (N=543)
Age, years, mean (SD)	36.1 (11.7)	36.3 (11.4)
Age group, years, n (%)		
<30	178 (32.9)	169 (31.1)
30–<40	171 (31.6)	174 (32.0)
40–<65	185 (34.2)	193 (35.5)
≥65	7 (1.3)	7 (1.3)
Sex, female, n (%)	304 (56.2)	306 (56.4)
Race, n (%)		
White	430 (79.5)	415 (76.4)
Black or African American	37 (6.8)	49 (9.0)
Asian	66 (12.2)	51 (9.4)
Other/multiple/not reported	8 (1.5)	28 (5.2)
Body mass		
≥90 kg, n (%)	296 (54.7)	277 (51.0)
Body mass, kg, mean (SD)	94.7 (24.4)	92.2 (22.8)
Body mass index, kg/m^2, mean (SD)	32.5 (7.6)	31.8 (7.5)
Smoking status, n (%)		
Never	165 (30.5)	167 (30.8)
Current smokers	292 (54.0)	293 (54.0)
Former smokers	84 (15.5)	83 (15.3)
Hurley stage, n (%)		
I	25 (4.6)	15 (2.8)
II	332 (61.4)	307 (56.5)
III	184 (34.0)	221 (40.7)
Time since HS diagnosis, years, mean (SD)	7.1 (7.1)	7.4 (7.4)
AN count, mean (SD)	12.8 (8.7)	13.3 (9.1)

Characteristic	SUNSHINE (N=541)	SUNRISE (N=543)
IN count, mean (SD)	10.0 (7.5)	10.0 (7.4)
Abscess count, mean (SD)	2.7 (4.0)	3.3 (4.9)
Draining tunnel count, mean (SD)	2.6 (3.4)	2.7 (3.5)
NRS skin pain, mean (SD)	5.0 (2.5)	5.3 (2.4)
DLQI total score, mean (SD)	13.8 (6.7)	14.9 (7.1)
IHS4, mean (SD)	25.8 (19.6)	27.4 (20.9)
EQ-5D VAS score, mean (SD)	63.3 (20.1)	62.5 (20.3)
Prior surgery for HS, n (%)	216 (39.9)	227 (41.8)
Frequency of prior biological exposure, n (%)		
≥1 type of biologic	129 (23.8)	126 (23.2)
≥2 types of biologics	12 (2.2)	5 (0.9)
≥3 types of biologics	2 (0.4)	0 (0.0)
Previous exposure to adalimumab, n (%)	122 (22.6)	116 (21.4)
Previous exposure to systemic antibiotics, n (%)	446 (82.4)	455 (83.8)

Due to rounding, some percentages may not summate to 100%.
AN, abscess and inflammatory nodule; DLQI, dermatology life quality index; EQ-5D, European quality of life 5 dimension; HS, hidradenitis suppurativa; IHS4, international hidradenitis suppurativa severity score system; IN, inflammatory nodule; N, number of patients in group; n, number of patients with characteristic; N/A, not applicable; NRS skin pain, numerical rating scale of the Patient's Global Assessment of Skin Pain–at worst; SD, standard deviation; VAS, visual analogue score.

The bio-experienced subgroup is relevant for this application, and baseline characteristics for the pooled population from the SUNRISE and SUNSHINE studies are shown in Table 12 below for patients randomised to either secukinumab Q4W or placebo. Considering the relatively low number of patients, the groups are well balanced.

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (bio-experienced subgroup) [31]

	SUNSHINE and SUNRISE (pooled data)	
	Secukinumab Q4W (N=81)	Placebo (N=94)
Age, years, mean (SD)	38.7 (12.1)	37.8 (11.6)
Age group, years, n (%)		
<30	21 (25.9)	24 (25.5)
30–<40	22 (27.2)	32 (34.0)
40–<65	37 (45.7)	35 (37.2)
≥65	1 (1.2)	3 (3.2)
Sex, female, n (%)	46 (56.8)	57 (60.6)

	SUNSHINE and SUNRISE (pooled data)	
	Secukinumab Q4W (N=81)	Placebo (N=94)
Race, n (%)		
White	67 (82.7)	77 (81.9)
Black or African American	11 (13.6)	8 (8.5)
Asian	2 (2.5)	6 (6.4)
Other/multiple/not reported	1 (1.2)	3 (3.2)
Body mass		
Body mass, kg, mean (SD)	95.8 (23.8)	92.2 (21.8)
Body mass index, kg/m^2, mean (SD)	32.8 (8.2) (N=80)	31.6 (6.9) (N=94)
Smoking status, n (%)		
Never	29 (35.8)	27 (28.7)
Current smokers	40 (49.4)	52 (55.3)
Former smokers	12 (14.8)	15 (16.0)
Hurley stage, n (%)		
I	0 (0.0)	1 (1.1)
II	43 (53.1)	46 (48.9)
III	38 (46.9)	47 (50.0)
Time since HS diagnosis, years, mean (SD)	9.2 (8.4) (N=81)	9.4 (7.0) (N=93)
AN count, mean (SD)	15.7 (11.3)	15.5 (9.8)
IN count, mean (SD)	11.8 (10.7)	10.9 (8.3)
Abscess count, mean (SD)	3.9 (4.8)	4.5 (5.6)
Draining tunnel count, mean (SD)	4.2 (4.8)	3.0 (3.3)

	SUNSHINE and SUNRISE (pooled data)	
	Secukinumab Q4W (N=81)	**Placebo (N=94)**
NRS skin pain, mean (SD)	5.7 (2.6) (N=71)	5.7 (2.4) (N=83)
DLQI total score, mean (SD)	16.4 (6.7) (N=71)	15.1 (6.9) (N=86)
IHS4, mean (SD)	36.2 (26.0)	31.9 (21.1)
EQ-5D VAS score, mean (SD)	62.0 (18.6) (N=71)	58.3 (21.6) (N=85)
Prior surgery for HS, n (%)	38 (46.9)	45 (47.9)
Frequency of prior biological exposure, n (%)		
≥1 type of biologic	81 (100.0)	94 (100.0)
≥2 types of biologics	4 (4.9)	9 (9.6)
≥3 types of biologics	1 (1.2)	1 (1.1)
Previous exposure to adalimumab, n (%)	76 (93.8)	87 (92.6)
Previous exposure to systemic antibiotics, n (%)	73 (90.1)	85 (90.4)
Patients on permitted stable antibiotics at study entry, n (%)*	13 (16.0)	16 (17.0)

Due to rounding, some percentages may not summate to 100%.
AN, abscess and inflammatory nodule; DLQI, dermatology life quality index; EQ-5D, European quality of life 5 dimension; HS, hidradenitis suppurativa; IHS4, international hidradenitis suppurativa severity score system; IN, inflammatory nodule; N, number of patients in group; n, number of patients with characteristic; NRS skin pain, numeric rating scale of the Patient's Global Assessment of Skin Pain–at worst; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SEC, secukinumab 300 mg; VAS, visual analogue score.
*Permitted antibiotics included tetracycline up to 500 mg twice daily, minocycline up to 100 mg twice daily, or doxycycline up to 100 mg twice daily. Data on file

Rescue treatment was allowed during the study. During the 16 weeks of double-blind treatment, 3 (3.7%) patients were treated with an antibiotic and 4 (4.9%) underwent a surgical procedure as rescue treatment in the secukinumab Q4 arm, and 2 (2.1%) patients were treated with an antibiotic and 5 (5.3%) underwent a surgical procedure as rescue treatment in the placebo arm (data on file).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The subpopulation of bio-experienced patients in the SUNNY studies was to a large degree comparable with the Danish population with HS that has been treated with adalimumab [21, 31]. Characteristics for the Danish population is shown in Table 13 below, and apart from the SUNNY population being slightly younger (approximately 38 years vs. 42 years), and weighing less (approximately 94 kg vs. 103 kg), the populations are similar with regard to gender, BMI, previous treatment with antibiotics and HS surgery.

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [12]*	Value used in health economic model (SUNNY studies, data on file)
Age, mean years (SD)	41.9 (12.6)	36.20 years
Gender, women	59.4%	56.3%
BMI, mean (SD)	32.3 (8.3)	N/A
Body weight, mean (SD), kg	103.1 (28.9)	75 kg assumed
Previous antibiotics	95.0%	N/A
Previous HS surgery	84.7%	N/A

* HS patients who are treated with adalimumab

6.1.4 Efficacy – results per SUNNY studies

As explained in section 6.1.1 the SUNNY studies showed similar results for the Q2W and Q4W dose regimens. The recommended maintenance dose of secukinumab is monthly, and therefore, only data from the secukinumab Q4W arm and the placebo arm will be included in the comparison in this application.

The data presented are from the pre-defined subgroup of patients who had previously been exposed to biologics, and thus only the results for the primary endpoint HiSCR50 is presented in the EPAR [33]. There is no discrepancy between the result shown in the EPAR and in the publication by Zouboulis et al. [31].

For this application, the analyses were performed based on pooled data from the SUNSHINE and SUNRISE studies. Logistic regression models or an analysis of covariance were performed to assess the effects of secukinumab versus placebo at week 16 for HiSCR50, change from baseline in AN count, and NRS30. Covariates included treatment group, baseline AN count or baseline NRS, body weight (<90 kg, ≥90 kg), Hurley stage, geographical region, use of antibiotics, and study (SUNSHINE or SUNRISE). ORs for HiSCR and NRS30, or difference in least squares means (LSM) for change from baseline in AN count with 95% confidence intervals (CIs) are presented to assess the treatment

differences of secukinumab over placebo. For the analyses of HiSCR50, change from baseline in AN count, and NRS30 up to week 16, multiple imputation was applied to handle missing data. All additional endpoints were analysed based on observed data. Results from the extension study are based on both bio-naive and bio-experienced patients.

6.1.4.1 Efficacy at 16 weeks

The following results were found after 16 weeks of double-blind treatment [31]:

HiSCR50
In the secukinumab Q4W arm 38.8%, (95% CI: 28.2%, 49.4%) of patients achieved HiSCR50 at 16 weeks vs. 27.3% (95% CI: 18.3%, 36.3%) in the placebo arm. The absolute difference was 11.5 %-points, (95% CI: -2.4%, 25.4%), the OR was 1.67 (95% CI: 0.86, 3.22) and the RR was 1.41 (95% CI: 0.89, 2.00), favouring secukinumab.

AN count
In the secukinumab Q4W arm the percentage change (difference in LSM) from baseline in AN count was -36.4% at 16 weeks vs -14.0% in the placebo arm. The absolute difference was -21.85 %-points (95% CI: -42.50, -1.20), favouring secukinumab. The difference between treatments is statistically significant in favour of secukinumab at a 95% confidence level.

Pain assessed by NRS30
In the secukinumab Q4W arm 33.4% (95% CI: 21.4%, 45.4%) of patients achieved NSR30, at week 16 vs. 12.1% (95% CI: 4.5%, 19.7%) in the placebo arm. The absolute difference was 21.3 %-points (95% CI: 7.0%, 35.6%), the OR was 3.59 (95% CI: 1.35, 9.57) and the RR was 2.73 (95% CI: 1.3, 4.70). Despite the relatively small patient number, the difference between treatments is statistically significant in favour of secukinumab at a 95% confidence level.

QoL assessed by DLQI
In the secukinumab Q4W arm 49.2% (95% CI: 36.9%, 61.5%) of patients achieved a reduction in DLQI of at least 5 points at 16 weeks vs. 31.5% (95% CI: 20.8%, 42.2%) in the placebo arm. The absolute difference was 17.7 %-points, (95% CI: 1.4%, 34.0%) and the RR was 1.56 (95% CI: 1.03, 2.38). Despite the relatively small patient number, the difference between treatments is statistically significant in favour of secukinumab at a 95% confidence level.

SAE
In the secukinumab Q4W 6.2% (95% CI: 0.9%, 11.4%) experienced a SAE vs. 3.2% (95% CI: -0.4%, 6.7%) in the placebo arm at 16 weeks. The absolute difference was 3.0 %-points, (95% CI: -3.4%, 9.3%) and the RR was 1.93 (95% CI: 0.48, 7.85). As the numbers are small, the difference is of limited clinical significance. Further details of SAEs are listed in Appendix E.

Withdrawal
In the secukinumab Q4W arm 7.4% (95% CI: 1.7%, 13.1%) withdrew from treatment before week 16 vs. 6.4% (95% CI: 1.4%, 11.3%) in the placebo arm at week 16. The reasons for withdrawal were: AEs: 1; other reasons: 5. In the placebo arm 6 patients withdrew from

treatment before week 16. The reasons for withdrawal were: AEs: 3; other reasons: 2; lack of efficacy: 1. The absolute difference was 1.0 %-points (95% CI: -6.5%, 8.6%) and the RR was 1.16 (95% CI: 0.39, 3.46). As the numbers are small, the difference is of limited clinical significance.

Conclusion

The SUNSHINE studies were not powered for subgroup analysis. Approximately 25% of the full study population were bio-experienced and thus included in this analysis. Regardless of only considering the subgroup of bio-experienced patients, secukinumab Q4W was statistically significantly superior to placebo at the 95% confidence level, both regarding reduction in AN count, efficacy on pain measured by NRS30 response, and QoL measured by DLQI. For HiSCR50, secukinumab had numerically better results than placebo. Clear differentiation from placebo was observed from 2-4 weeks and forward [31]. Regarding proportion of patients experiencing SAEs and withdrawing from treatment, the numbers were small both in the secukinumab Q4W arm and in the placebo arm.

In conclusion, secukinumab Q4W seems more efficacious than placebo for the subgroup of bio-experienced patients.

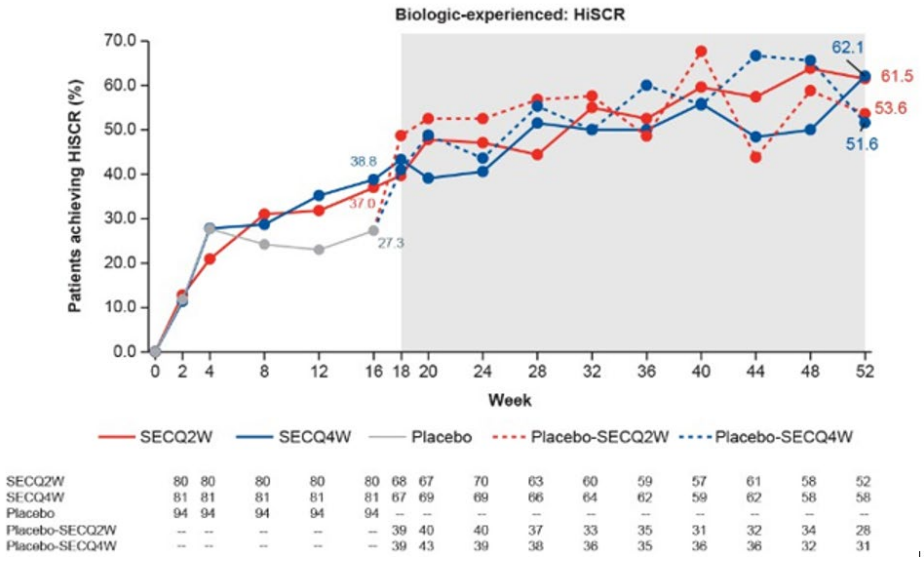
Detailed information about the results of all outcomes included in the comparative analysis is provided in Appendix B.

6.1.4.2 Efficacy at 52 weeks

As HS is a chronic disease, and the treatment with secukinumab should continue as long as there is an effect, it is relevant to present long term data.

In the SUNSHINE studies, the proportion of bio-experienced patients achieving HiSCR50 in the secukinumab treatment groups was sustained, with a trend for improvement to week 52 (see Figure 3).

Figure 3 HiSCR50 in bio-experienced patients



Furthermore, placebo-switchers also experienced a rapid improvement of HiSCR50, which was sustained to week 52. The same was the case for reduction in AN count, proportion of patients achieving NRS30 and proportion of patients experiencing DLQI response. Safety for long term treatment is presented in section 9 and in Appendix E.

6.1.5 Loss of response (LOR)

In the long-term extension study, for patients who had achieved HiSCR50 at 52 weeks, LOR was observed at a median of 365 days, (95% CI: 225, not reached) in the group that continued on secukinumab Q4W, and at a median of 171 days, (95% CI: 113, 337) in the group that stopped treatment and continued on placebo, hazard ratio (HR): 0.70 (95% CI: 0.47, 1.05), p=0.44. The results demonstrate that patients can still benefit from secukinumab treatment after cessation of treatment.

6.1.1 Efficacy – results per [study name 2] N/A

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A as the comparison is based on pooled data from two identical head-to-head studies.

7.1.3 Results from the comparative analysis

In below, the results of the comparative analyses of secukinumab vs. placebo for bio-experienced patients are listed [31]. The full study population has previously been assessed by the Medicines Council, who concluded that the efficacy and safety of secukinumab was at par with adalimumab. In order to see the results for the bio-experienced in context with those for the full study population, the results for secukinumab vs. placebo in the full study population has been included in the table (indicated with a grey background) [28, 34].

Table 14 Results from the comparative analysis of secukinumab vs. placebo for bio-experienced HS patients [31] **and for the full study population** [34, 35]

Outcome measure	Secukinumab Q4W (N=81)	Placebo (N=94)	Result
Proportion of patients achieving HiSCR50 (week 16)	31/81, 38.8% (95 % CI: 28.2, 49.4)	26/94, 27.3% (95 % CI: 18.3, 36.3)	Absolute risk: 11.5% OR: 1.67

Outcome measure	Secukinumab Q4W (N=81)	Placebo (N=94)	Result
			RR: 1.41
Full population [34] *Proportion of patients achieving HiSCR50 (week 16)*	SUNSHINE: 75/180, 41.8% (95 % CI: 34.6, 49.3) SUNRISE: 83/180, 46.1% (95 % CI: 38.8, 53.7)	SUNSHINE: 61/181, 33.7% (95 % CI: 27.0, 41.1) SUNRISE: 57/183, 31.2% (95 % CI: 24.7, 38.4)	Absolute risk: 11.8% (estimated based on RR and baseline risk from SUNSHINE of 33.7%) RR: 1.35 (from meta-analysis of the SUNNY studies)
AN count, 16 weeks	LSM change from baseline: -36.4%	LSM change from baseline: -14.0%	-21.85% (95 % CI: -42.50, -1.20)
Full population [28] *AN count, 16 weeks*	LSM change from baseline: SUNSHINE: −42.4% SUNRISE: −45.5%	LSM change from baseline: SUNSHINE: −24.3% SUNRISE: −22.4%	–18.5% (95% CI: 29.3, –7.6); p=0.0004 –22.9% (95% CI: −35.2, –10.6); p=0·0001
Proportion of patients achieving NRS30 (week 16)	20/59, 33.4% (95 % CI: 21.4, 45.4)	8.5*/70, 12.1% (95 % CI: 4.5, 19.7)	Absolute risk: 21.3% OR: 3.59 RR: 2.73
Full population [28] *Proportion of patients achieving NRS30 (week 16)*	79/222, 35% (95% CI: 29.3%, 41.9%)	62/230, 27% (95% CI: 21.2%, 32.7%)	Absolute risk: 8.6% OR: 1.50 RR: 1.32
Proportion of patients achieving ≥5 point reduction in DLQI (week 16)	31/63, 49.2% (95 % CI: 36.9, 61.5)	23/73, 31.5% (95 % CI: 20.8, 42.2)	Absolute risk: 17.7% RR: 1.56
Full population [34] *Proportion of patients achieving ≥5 point reduction in DLQI (week 16)*	SUNSHINE: 62/128, 48.4% (95 % CI: 39.6, 57.4) SUNRISE: 67/142, 47.2% (95 % CI: 38.8, 55.7)	SUNSHINE: 37/128, 28.9% (95 % CI: 21.4, 37.7) SUNRISE: 46/145, 31.7% (95 % CI: 24.4, 40.0)	Absolute risk: 16.5% (estimated based on RR and baseline risk from SUNSHINE of 28.9%) RR: 1.57 (from meta-analysis of the SUNNY studies).

Outcome measure	Secukinumab Q4W (N=81)	Placebo (N=94)	Result
Proportion of patients experiencing an SAE (week 16)	5/81, 6.2% (95 % CI: 0.9, 11.4)	3/94, 3.2% (95 % CI: 0.4, 6.7)	Absolute risk: 3.0% RR: 1.93
Full population [34] *Proportion of patients experiencing an SAE (week 16)*	SUNSHINE: 3/180, 1.7% (95 % CI: 0.4, 5.2) SUNRISE: 6/180, 3.3% (95 % CI: 1.3, 7.4)	SUNSHINE: 6/180, 3.3% (95 % CI: 1.4, 7.4) SUNRISE: 5/183, 2.7% (95 % CI: 1.0, 6.6)	Absolute risk: -0.5% (estimated based on RR and baseline risk from SUNSHINE of 3.3%) RR: 0.84 (from meta-analysis of the SUNNY studies).
Proportion of patients withdrawing from treatment, any cause (week 16)	6/81, 7.4% (95% CI: 1.7, 13.1)	6/94, 6.4% (95% CI: 1.4, 11.3)	Absolute risk: 1.0% RR: 1.16
Full population [34] *Proportion of patients withdrawing from treatment, any cause (week 16)*	SUNSHINE: 11/180, 6.1% (95% CI: 2.6%, 9.6%) SUNRISE: 11/180, 6.1% (95% CI: 2.6%, 9.6%)	SUNSHINE: 8/180, 4.4% (95% CI: 1.4%, 7.5%) SUNRISE: 16/183, 8.7% (95% CI: 4.7%, 12.8%)	Absolute risk: -0.3% (estimated based on RR and baseline risk from SUNSHINE of 4.4%) RR: 0.94 (from meta-analysis of the SUNNY study).
Full population [30] *Time to loss of response*	EXTENSION STUDY 365 days, (95% CI: 225, not reached)	EXTENSION STUDY 171 days, (95% CI: 113, 337)	Hazard ratio: 0.70 (95% CI: 0.47, 1.05), p=0.44.

AN, Abscess and inflammatory nodule; CI, confidence interval; DLQI, Dermatology Life Quality Index; HiSCR50, Hidradenitis Suppurativa Clinical Response of ≥50% reduction; LSM, Estimated least squares means; NRS30, at least a 30% reduction in pain compared to baseline measured by the skin pain numeric rating scale (NRS); OR, odds ratio; RR, relative risk; Qw4, every 4 week SAE, serious adverse event.
* Based on back-calculation from response rate

7.1.4 Efficacy – results per outcome measure

Results per outcome measure for the head-to-head comparison of secukinumab vs. placebo have already been described in sections 6.1.4.1 and 7.1.3 above, and further details are described in Table 64 and Table 65.

It is important to note that only approximately 25% of the full study population in the pivotal SUNNY studies were bio-experienced. In line with common practise, the studies were not powered for subgroup analysis.

A Danish register study has shown that efficacy in a bio-experienced population could be expected to be lower than in a bio-naïve population [19].

To strengthen the interpretation of the results of the bio-experienced subgroup, the results from the full study population are shown in Table 14 above.

In the bio-experienced subgroup, the efficacy of secukinumab Q4W is consistently numerically higher than that of placebo for HiSCR50 response, reduction in AN count, pain reduction measured by NRS30 responders, and on OoL measured by proportion of patients reaching at least 5-point reduction in DLQI. Of note, for NRS30 and DLQI, secukinumab Q4W is statistically significantly better than placebo for the subgroup of bio-experienced patients.

The responses for the bio-experienced group are thus at the same level as for the full study population, where the majority of patients were bio-naïve.

The risk of experiencing a SAE and of withdrawal from treatment for any reason is slightly higher for the secukinumab Q4W treated bio-experienced patients, compared to the full study population, however, the numbers are very low.

In conclusion, bio-experienced HS patients may benefit from treatment with secukinumab at the same level as the full study population in the SUNNY studies.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

This section presents how efficacy has been modelled in the health economic analysis and how the transition probabilities for the Markov model has been derived.

8.1.1 Extrapolation of efficacy data

N/A as no extrapolation of efficacy data has been conducted in the present application.

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 15 Summary of assumptions associated with extrapolation of [effect measure] N/A

Method/approach	Description/assumption
Data input	N/A
Model	N/A

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

- The transition probabilities applied in the model were based on pooled efficacy estimates from the bio-experienced population from the SUNNY studies, using results on HiSCR response rates for the secukinumab Q4W and Q2W dosing regimens. Patients transition between the health states, which were illustrated in Figure 4 and Table 16.

Table 16 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
High response	High response	Based on HiSCR response rates observed in study	SUNNY studies
Response	Response		
Partial response	Partial response		
Non-response	Non-response		
Death	Death		

In the induction phase, the proportion of high responders, responders, partial responders and non-responders were estimated separately for each arm and each cycle, based on the distribution of patients across these health states at each study assessment visit (see Table 17). In the maintenance phase, for patients in the secukinumab 300 mg Q4W and Q2W groups, patients who responded (HiSCR ≥50 in the base case) at 16 weeks, continued secukinumab till 52 weeks irrespective of response during weeks 16-52. The transition for these responders from 16-52 weeks in various HiSCR categories was obtained from pooled data from the SUNNY study for secukinumab (see Table 18).

As mentioned, patients who did not respond on secukinumab 300 mg Q4W at 16 weeks, could be up-titrated to secukinumab 300 mg Q2W. For up-titrated patients, efficacy from week 16 to week 32 of secukinumab Q2W from the SUNNY studies was applied to this subset of patients (Table 17). Post 32 weeks, the non-responders moved to SoC. The responders continued to transition between various health states till 52 weeks based on data from weeks 16 to 36 from secukinumab 300 mg Q2W arms (see Table 18) unless they discontinued due to reasons other than lack of efficacy.

From 52 weeks and onwards, the responders remain in the same health state until discontinuation or death and non-responders moved to SoC. For discontinued patients, with the response criterion being HiSCR ≥50 (base case), the treatment discontinued patients were moved to off-treatment (SoC) and a weighted average utility and cost of HiSCR 25-49 and HiSCR<25 was considered. In the scenario analysis with the HiSCR ≥25 response criterion, patients moved to HiSCR <25 health state of SoC.

- The proportion of patients in each health state in the model time horizon in the secukinumab arm and the SoC arm is presented in Figure 4.

Table 17 Response rates at week 16 from bio-experienced population. Source: pooled data from the SUNNY studies.

Treatment	HiSCR % Score	Week 4	Week 8	Week 12	Week 16
Secukinumab Q4W (n=81)	HiSCR ≥75	[redacted]			
	HiSCR 50-74				
	HiSCR 25-49				
	HiSCR <25				
Secukinumab Q2W (n=80)	HiSCR ≥75				
	HiSCR 50-74				
	HiSCR 25-49				
	HiSCR <25				
SoC (n=94)	HiSCR ≥75				
	HiSCR 50-74				
	HiSCR 25-49				
	HiSCR <25				

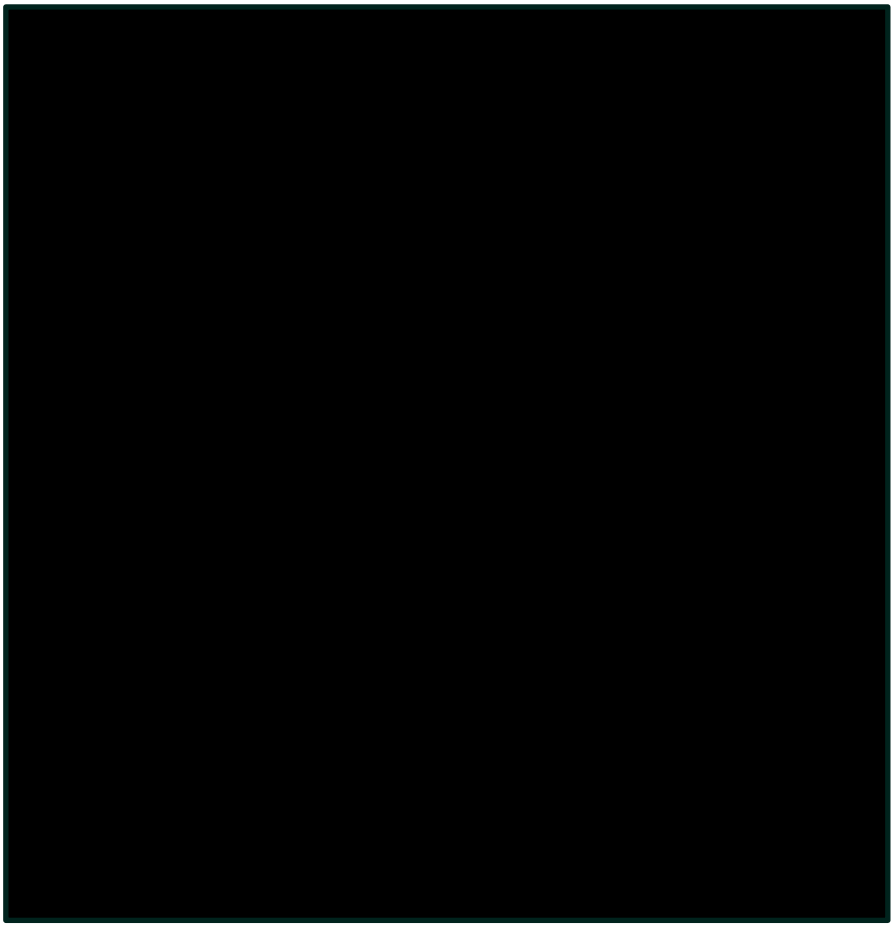
Note: 95% confidence intervals are denoted in parentheses.

Table 18 Response rate post induction phase with HiSCR ≥50 response criterion. Source: pooled data from the SUNNY studies.

	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Secukinumab Q4W									
HiSCR ≥75	[redacted]								
HiSCR 50-74									
HiSCR 25-49									
HiSCR < 25									
Secukinumab Q2W									
HiSCR ≥ 75									
HiSCR 50-74									
HiSCR 25-49									
HiSCR < 25									
SoC									
HiSCR ≥ 75	0%	0%	0%	0%	0%	0%	0%	0%	0%
HiSCR 50-74	0%	0%	0%	0%	0%	0%	0%	0%	0%
HiSCR 25-49	0%	0%	0%	0%	0%	0%	0%	0%	0%
HiSCR < 25	100%	100%	100%	100%	100%	100%	100%	100%	100%

HiSCR, Hidradenitis Suppurativa Clinical Response; Q2W, every two weeks; Q4W, every four weeks; SoC, standard of care

Figure 4 The proportion of patients in each health state in the model time horizon for secukinumab and SoC



8.1.2.1 Discontinuation

Patients who continued receiving treatment after the induction period (the first 16 weeks) could discontinue treatment. No discontinuation was included in the first 16 weeks of treatment in the base case. This was validated by the clinical expert who agreed with this assumption but stated that patients could discontinue in the first 16 weeks due to severe AEs. An option to allow for discontinuation in the first 16 weeks was added to the model to conduct a scenario analysis to test this assumption.

Patients who initiated treatment with secukinumab Q4W and were non-responders (HiSCR <50) after 16 weeks of treatment would be up-titrated to Q2W and have their response assessed after additional 16 weeks of treatment. Patients who remained non-responders after the up-titration discontinued secukinumab and moved to SoC treatment. Patients on secukinumab Q2W and Q4W who achieved a response would continue treatment. Response was assessed after 52 weeks of treatment and patients who were non-responders (HiSCR <50) after 52 weeks would discontinue secukinumab and move to SoC treatment. In addition, patients could discontinue secukinumab each cycle after the first 16 weeks in the base case. The per cycle discontinuation rate used in the model for secukinumab was based on the year-1 estimate from the SUNNY studies, which was

converted to a 4-week rate for the model. The 4-week rate varied based on whether the option to allow for discontinuation within the first 16 weeks was selected. If selected, the 4-week rate was based on 52 weeks contrary to the base case 4-week rate that was based on 36 weeks. From year 2 and onwards, the discontinuation rate was based on estimates from Corbett et al. 2016 (52 weeks estimate) [36].

The annual rates from the SUNNY studies and Corbett et al. 2016 were discussed with the clinical expert who stated that the rates could be higher in a clinical setting, as the Danish patient population might be more refractory than patients in the SUNNY studies. The rates were not adjusted based on the discussion with the clinical expert, as it was expected that the discontinuation rates were aligned with what is expected in a Danish clinical setting, as non-responders also discontinued secukinumab treatment in addition to the per cycle probability.

No discontinuation was assumed for SoC based on input from the clinical expert and the rationale that it is unlikely that HS patients will not receive any treatment at all. The discontinuation rates are presented in Table 19.

Table 19 Estimation of per cycle discontinuation rates post 16 weeks

Treatment	Annual rates		4-week discontinuation rate			Source
	Year 1	Year 2+	Year 1 (without discontinuation within first 16 weeks)	Year 1 (with discontinuation within first 16 weeks)	Year 2+	
Secukinumab Q4W	xxxxxx	6.00%	xxxxx	xxxxx	0.47%	Year 1: SUNNY studies Year 2+: Corbett et al. 2016 [36]
Secukinumab Q2W	xxxxxx	6.00%	xxxxx	xxxxx	0.47%	Year 1: SUNNY studies Year 2+: Corbett et al. 2016 [36]
SoC	0%	0%	0%	0%	0%	Assumption

SoC, standard of care; Q2W, every two weeks: Q4W, every four weeks

8.1.2.2 Loss of response

As previously described, based on the results from the long-term extension of the SUNNY studies, we assume a prolonged response for individuals who discontinue treatment with secukinumab and transition to the off-treatment stage.

All patients from the SUNNY studies who completed the full study treatment period (52 weeks) were eligible to enter into an extension study. Patients who had achieved HiSCR50

at 52 weeks and had been treated with monthly secukinumab or Q2W secukinumab were randomized 2:1 to either a secukinumab Q2W arm, secukinumab Q4W arm (monthly dosing regimen) or a placebo arm up to week 104. The primary endpoint was the time to loss of response (LOR) up to week 104 in patients who were HiSCR50 responders at week 52 in the core studies. Treatment response was observed for a [redacted] among patients who stopped treatment with secukinumab in the Q4W arm and the Q2W arm, respectively, and continued with placebo in the long-term extension of the SUNNY studies [30].

At the end of the model's 13th cycle (representing week 52 in the model), [redacted] of patients still receiving treatment with secukinumab were receiving monthly treatment, while the remaining [redacted] were receiving treatment Q2W. Therefore, we assume that the prolonged response for individuals who discontinue treatment is 7 cycles, which approximately corresponds to [redacted].

During this period, the model assumes that the patient incurs the same cost level and utility as if they had remained in the HiSCR stage from which they discontinued. For example, if a person discontinues from HiSCR >75, they will receive the same cost level and utility as they would if they had remained in the HiSCR >75 stage for seven cycles after transitioning to the off-treatment stage. After this period, the patient will incur costs and utilities corresponding to SOC in the HiSCR <25 stage. Specifically, this is modeled as a one-off utility increment and cost decrement in the cycle during which the patient transitions to the off-treatment stage.

8.1.2.3 Adverse events

Upper respiratory tract infections, headache, nasopharyngitis and diarrhoea were observed in ≥5% in one arm in the subgroup of bio-experienced patients in the SUNNY studies. According to the clinical expert, fungal infections might also be observed with secukinumab treatment.

An overview of the AEs observed in the bio-experienced subgroup after 16 weeks and 52 weeks are presented in Table 20. To assess the impact of adverse events in the analysis, the model calculates a weighted average between week 16 and week 52, accounting for differences in the timing of these events. The weighted average is determined by assigning weight to the AEs at week 16 based on the proportion of treatment going on until week 16 relative to the entire treatment period in the model. Similarly, the AEs observed at week 52 are weighted according to the proportion of treatment going on after week 16 relative to the total treatment duration.

Table 20 AEs observed in at least 5% in the bio-experienced population at week 16 and week 52. Source: SUNNY studies (data on file), [20, 31]

Adverse event	SEC Q4W	Placebo	SEC Q2W
Week 16			
Upper Respiratory tract infection	[redacted]		

Adverse event	SEC Q4W	Placebo	SEC Q2W
Diarrhoea			
Nasopharyngitis			
Headache			
Fungal infection*			
Week 52			
Upper Respiratory tract infection			
Diarrhoea			
Nasopharyngitis			
Headache			
Fungal infection**			

* Fungal infections are shown at High Level Group Term level, i.e. it includes the full range of fungal infections. For "candida infections" the rates were 1.2%, 1.1% and 3.8 %, respectively, for the SEC Q4W, SoC and SEC Q2W treatment arms.
**Rates based on inputs from the clinical expert
SEC: secukinumab, Q4W: every four weeks, Q2W: every two weeks.

8.1.2.4 Mortality

In the model, patients are at risk of all-cause mortality at every time point, but no differential mortality risk exists between the therapies being evaluated. Patients were assumed to have the same mortality rate as for the general Danish population. Mortality rates are taken from age-related statistics from Statistic Denmark and adjusted based on male-female ratio from the Excel sheet provided by the DMC, please see the 'Mortality' sheet in the model.

8.2 Presentation of efficacy data from additional documentation

No efficacy data from additional documentation was applied in the health economic model.

8.3 Modelling effects of subsequent treatments

No effects of subsequent treatments were modelled in the health economic analysis.

8.4 Other assumptions regarding efficacy in the model

No additional assumptions regarding efficacy not previously described were regarded as relevant to present in this section.

8.5 Overview of modelled average treatment length and time in model health state

Estimates for the modelled average and modelled median of the effect measures predicted by the extrapolation model were not presented, as no extrapolation was conducted in the health economic analysis. Table 22 provides the modelled average treatment length and time in model health states.

Table 21 Estimates in the model N/A

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]	N/A	N/A	N/A
[Name of comparator]	N/A	N/A	N/A

Table 22 Overview of modelled average treatment length in months and time in each model health state (months), undiscounted and not adjusted for half cycle correction

Treatment	Treatment length (average)	HR	R	PR	NR	Off-treatmet
Secukinumab	5.61	4.03	1.17	0.10	0.31	39.88
SoC	45.64	0.03	0.05	0.04	45.53	0.00

HR, high response; NR, non-response; PR, partial response, R: response; SoC, standard of care

9. Safety

9.1 Safety data from the clinical documentation

All patients who received ≥1 dose of study treatment were included in the safety analysis.

During the 16-week double blind treatment period, 65.4% of bio-experienced patients in the secukinumab Q4W arm, and 61.7% in the placebo arms experienced any AE [31] (see Table 23). In both SUNNY studies, treatment with secukinumab was well tolerated;

analysis of safety data from the placebo-controlled period showed similar results across the secukinumab and placebo groups. The most frequently reported AEs by preferred term in the full study population were headache, nasopharyngitis, and worsening of hidradenitis [28].

The proportion of bio-experienced patients who had experienced a SAE at week 16 was 6.2% in the secukinumab Q4W group compared to 3.2% in the placebo group. The rates of SAEs were low and similar between treatment groups [31]. According to the SmPC for Cosentyx, SAEs such as serious infections, inflammatory bowel disease and hypersensitivity reactions have been observed across indications [25]. In the full study population in the SUNNY studies, 2/721 patients (0.3%) experienced inflammatory bowel disease as a SAE and 3/720 (0.4%) experienced an infection as a SAE while on secukinumab Q2W or Q4W, whereas 3/363 patients (0.08%) on placebo experienced an infection as a SAE [28] (see Appendix E). For further details see Table 23.

From baseline to week 52 no new safety signals were identified. Across both studies, there were two deaths and three cases of new-onset inflammatory bowel disease [31]. The two deaths were: One patient in the secukinumab Q4W arm with pre-existing aortic valve stenosis who had a fatal myocardial infarction, and one patient in the placebo–secukinumab Q4W arm who entered the study with a history of stable Crohn's disease had a severe upper gastrointestinal hemorrhage due to duodenal ulcers during concomitant treatment with ibuprofen. The patient died on day 249 (79 days after last dose of secukinumab) due to this event. Both events were not considered to be related to study treatment due to preexisting conditions and use of concomitant medications [28]. An overview of SAEs up to 52 weeks is shown in Appendix E.

Table 23 Overview of safety events. 16 weeks.

	Secukinumab Q4W (N=81) [31]	**Placebo (N=94)** [31]	**Difference % (95 % CI)**
Number of AEs, n	Not available for bio-experienced subgroup	Not available for bio-experienced subgroup	N/A
Number and proportion of patients with ≥1 AEs, n (%)	53 (65.4%)	58 (61.7%)	3.7% (-10.5%, 18.0%)
Number of SAEs adverse events*, n	Not available for bio-experienced subgroup	Not available for bio-experienced subgroup	N/A
Number and proportion of patients with ≥ 1 SAE*, n (%)	5 (6.2%)	3 (3.2%)	3.0% (-3.4%, 9.3%)
Number of CTCAE grade ≥ 3 events, n	Not available	Not available	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	Not available	Not available	N/A

	Secukinumab Q4W (N=81) [31]	Placebo (N=94) [31]	Difference % (95 % CI)
Number of adverse reactions, n	Not available for bio-experienced subgroup	Not available for bio-experienced subgroup	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	Not available for bio-experienced subgroup	Not available for bio-experienced subgroup	N/A
Number and proportion of patients who had a dose reduction, n (%)	Not available for bio-experienced subgroup	Not available for bio-experienced subgroup	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	6 (7.4%)	6 (6.4%)	1.0% (-6.5%, 8.6%)
Number and proportion of patients who discontinue treatment due to AEs, n (%)	1 (1.2%)	3 (3.2%)	-2.0% (-6.2%, 2.3%)

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Q4W, every four weeks; SAE, serious adverse event.
*A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

No SAE occurred with a frequency of ≥5% in either treatment arm at 16 weeks. A list of all SAEs observed in the full population in the SUNNY studies is available in Appendix E.

Table 24 SAEs with a frequency of ≥5% at 16 weeks N/A

Adverse events	Secukinumab Q4W (N=81)		Placebo (N=94)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	N/A			

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

Table 25 presents the weighted average used between adverse events experienced at week 16 and week 52 as described in section 8.1.2.3.

Table 25 Adverse events used in the health economic model per cycle (4 weeks).

Adverse events	SEC Q4W	SoC	SEC Q2W		
	Frequency used in economic model for SEC Q4W	Frequency used in economic model for SoC	Frequency used in economic model for SEC Q2W	Source	Justification
Upper Respiratory tract infection	0.48%	0.54%	0.88%	SUNNY studies (data on file)	Based on clinical trial
Diarrhoea	0.73%	0.86%	0.57%	SUNNY studies (data on file)	Based on clinical trial
Nasopharyngitis	0.63%	0.99%	0.87%	SUNNY studies (data on file)	Based on clinical trial
Headache	2.07%	1.55%	1.64%	SUNNY studies (data on file)	Based on clinical trial
Fungal infection	0.64%	0.35%	1.17%	Clinical expert	Expert opinion

9.2 Safety data from external literature applied in the health economic model

No safety data from external literature was used in the health economic analysis.

Table 26 Adverse events that appear in more than X % of patients N/A

Adverse events	Intervention (N=x)	Comparator (N=x)	Difference, % (95 % CI)
N/A			

10. Documentation of health-related quality of life (HRQoL)

HRQoL was assessed in the SUNNY studies with the generic measuring instrument EQ-5D-3L. The EQ-5D is a questionnaire with 5 questions, where subjects are asked to indicate their health state at the time of survey by ticking the box next to the most appropriate statement in each of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that each has three levels (no problem, moderate problem, severe problem). In addition, a health state assessment is made using

a visual analogue scale (VAS) that records the respondent's self-rated health on a 100 mm (or 100 point) vertical VAS, where the endpoints are labelled "Best imaginable health state" (= 100) and "Worst imaginable health state" (= 0). The number and percentage of subjects in each of the 3 categories for each question was presented by visit up to the study end for each treatment group.

Table 27 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	Combined data from the SUNNY studies	Used to derive utilities and assess clinical effectiveness in terms of improving HRQoL

10.1 Presentation of the HRQoL measured with EQ-5D-3L

10.1.1 Study design and measuring instrument

As chronic pain interferes with daily activities and the patient's QoL, patient reported outcome measures were included in the SUNNY studies for assessing the patient's perception of the impact of disease and treatment on the daily life, physical, psychological and social functioning, and well-being. In accordance with DMC guidelines, HRQoL measured with the EQ-5D from the SUNNY studies was presented. The EQ-5D-3L was included in the SUNNY studies and conducted in the FAS population, which comprised all subjects from the randomised set to whom study treatment was assigned. The EQ-5D instrument is a widely used generic instrument for measuring HRQoL in dermatologic conditions and HS [37–42] and has well-established reliability and validity when used for HS patients [37]. The HRQoL was expected to increase with secukinumab treatment given the impact of treatment on HS inflammatory lesions, discharge, scarring and pain which have a significant impact on the QoL of HS patients, and a reduction in the number of such lesions could directly benefit patients.

However, there are two significant challenges when measuring the QoL in HS patients:

1. HS is a very fluctuating skin disease, and HS lesions can appear or change on a daily and weekly basis which means it is difficult to capture the 'true' QoL with EQ-5D or DLQI, as these instruments measure the patients QoL 'today' or 'the past week', respectively.
2. EQ-5D is a generic questionnaire, i.e. not diagnose-specific or skin-disease specific. EQ-5D is thus not able to capture some of the major themes and identified 'core set domains' relevant for the QoL in HS patients such as drainage and odour. The same challenge is apparent with DLQI which is skin disease-specific, but still not HS specific. This pivotal challenge was discovered when developing the HS-specific HRQoL questionnaires, where it was identified that not all major themes and 'core set domains' impacting HS patient's QoL were in fact represented or captured in non-HS-specific questionnaires [43].

10.1.2 Data collection

A total of 1,084 patients (n=541 from SUNSHINE and n=543 from SUNRISE studies) were randomised in a 1:1:1 ratio (Q2W, Q4W, placebo). There was a total of 541 patients in SUNSHINE (Q2W=181, Q4W =180,Placebo=180) and 543 patients in SUNRISE (Q2W=180, Q4W =180, Placebo=183). This was cross validated with the interim reports available for the studies. Among all the patients (n=1,084), 76.5% (n=829) was biological naive and remaining (23.5%, n=255) had a prior exposure to biologics. An overview of the assessment schedule is presented in Table 28.

Table 28 Assessment schedule for EQ-5D-3L. Source: Novartis data on file.

Study	Analysis week															
	Baseline	2	4	8	12	16	20	24	28	32	36	40	44	48	52	Follow-up
SUNNY studies	x	x	x		x	x			x						x	

Among all randomised patients, 1,081 had EQ-5D-3L utility values (99.7% of all randomised), 360/361 (99.7%) in arm Q2W, 359/360 (99.7%) in arm Q4W and 362/363 (99.7%) in the placebo arm. Across the 1,081 patients, in total there were 6,429 EQ-5D-3L utility assessments, with 980 assessments at baseline and 4,996 assessments post-baseline. There were 972 patients with both baseline and at least 1 post-baseline assessment (the EQ-5D-3L analysis population), and a total of 4,996 post-baseline assessments were included in the modelling of utilities estimation. The pattern of missing observations and completion is presented in Table 29. No imputation of missing data was conducted.

HiSCR outcomes were reported at 2,4,8,12,16, 18, 20, 24, 28, 32, 36, 40, 44, 48 and 52 weeks. Among all patients (n=1,084), 1,074 had HiSCR outcome values (99.1% of all randomised), 357/361 (98.9%) in arm Q2W, 357/360 (99.2%) in arm Q4W and 360/363 (99.2%) in the placebo arm. Across the 1,074 patients, in total there were 13,793 HiSCR assessments. On merging the EQ-5D-3L dataset with HiSCR outcomes and exposure to biologics a total of 4,926 records were analysed from 969 patients. The final dataset included only 2, 4, 12, 16, 28 and 52 weeks records from HiSCR database to match with EQ-5D data.

Table 29 Pattern of missing data and completion from combined SUNNY dataset

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	*Number of patients for whom data is missing (%*	*Number of patients "at*	*Number of patients who completed (% of*

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
		of patients at randomisation)	*risk" at time point X*	*patients expected to complete)*
Baseline	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	104 (9.6%) from total population (1,084 minus 980)	Among all randomised patients, 1,081 had EQ-5D-3L utility values available (Q2W: 361, Q4W: 360, placebo: 363)	980 (90.7%) had an EQ-5D assessment at baseline
Week 2	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	198 (18.3%) from total population (1,084 minus 886)	972 in the total population had both a baseline assessment and a post-baseline assessment	886 (91.2%) in the total population had a post-baseline assessment at week 2
Week 4	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	185 (17.1%) from total population (1,084 minus 899)	972 in the total population had both a baseline assessment and a post-baseline assessment	899 (92.5%) in the total population had a post-baseline assessment at week 4
Week 12	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	241 (22.2%) from total population (1,084 minus 843)	972 in the total population had both a baseline assessment and a post-baseline assessment	843 (86.7%) in the total population had a post-baseline assessment at week 12
Week 16	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	217 (20.0%) from total population (1,084 minus 867)	972 in the total population had both a baseline assessment and a post-baseline assessment	867 (89.2%) in the total population had a post-baseline assessment at week 16
Week 28	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	304 (28.4%) from total population (1,084 minus 780)	972 in the total population had both a baseline assessment and a	780 (80.3%) in the total population had a post-baseline

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
			post-baseline assessment	assessment at week 28
Week 52	Total: 1,084 (Q2W: 361, Q4W: 360, placebo: 363)	433 (40.0%) from total population (1,084 minus 651)	972 in the total population had both a baseline assessment and a post-baseline assessment	651 (67.0%) in the total population had a post-baseline assessment at week 52

HRQoL, health-related quality of life; Q2W, every two weeks; Q4W, every four weeks

10.1.3 HRQoL results

Descriptive summaries of the EQ-5D are provided in Table 30 from SUNSHINE and Table 31 from SUNRISE.

Table 30 EQ-5D assessment (from 0 to 100) at baseline and post-baseline up till week 52 (observed data) in the full analysis set from SUNSHINE (data on file)

	Secukinumab Q4W N=180		Secukinumab Q2W N=181		Placebo N=180		Secukinumab Q4W vs. Placebo
	N (evaluable number of subjects)	Mean (SE), post-baseline	N (evaluable number of subjects)	Mean (SE), post-baseline	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]						
Week 2	[redacted]						
Week 4	[redacted]						
Week 12	[redacted]						
Week 16	[redacted]						
Week 28	[redacted]				Not assessed		N/A
Week 52	[redacted]				Not assessed		N/A

CI, confidence intervals; Q4W: every four weeks, Q2W, every second week; SE: standard error; SoC, Standard of care.
For each post-baseline visit only subjects with a value at both baseline and the respective post-baseline visit are included. Higher score values mean a better quality of life status.

Figure 5 EQ-5D VAS scores up to week 16 and week 52 (mean +/-SE) observed data from FAS population from SUNSHINE. Source: Novartis clinical study report data on fil

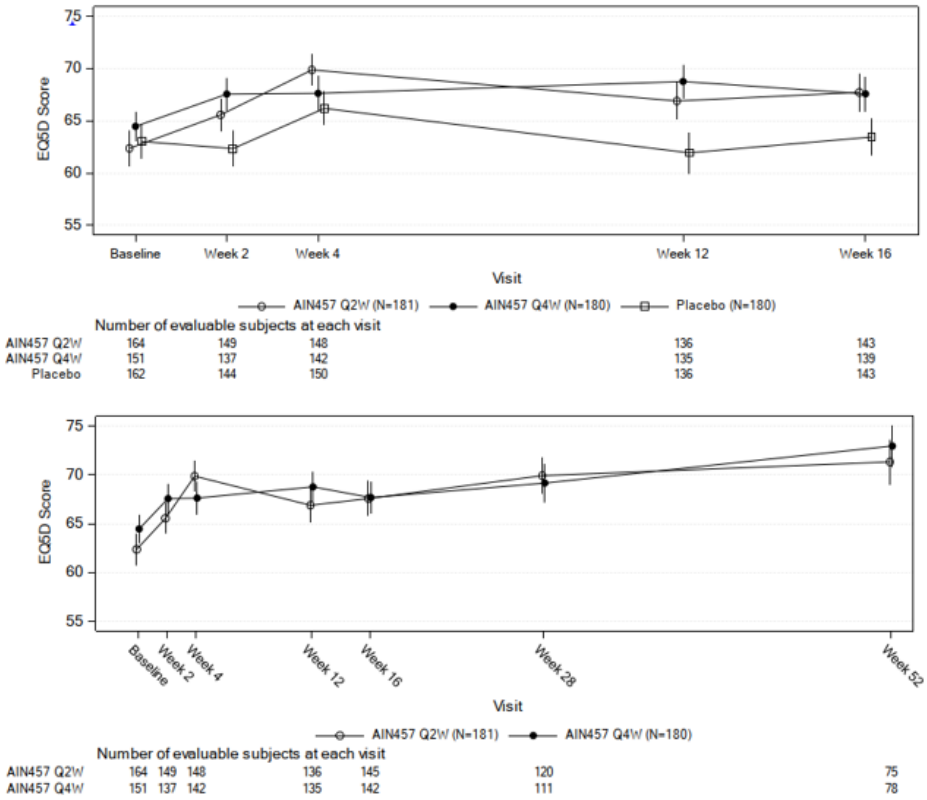


Figure note: AIN457 Q2W: secukinumab Q2W, AIN457 Q4W: secukinumab Q4W

Table 31 EQ-5D assessment (from 0 to 100) at baseline and post-baseline up till week 52 (observed data) in the full analysis set from SUNRISE (data on file)

	Secukinumab Q4W N=180		**Secukinumab Q2W N=180**		**Placebo N=183**		**Secukinumab Q4W vs. Placebo**
	N (evaluable number of subjects)	Mean (SE) post-baseline	N (evaluable number of subjects)	Mean (SE) post-baseline	N	Mean (SE)	Difference (95% CI) p-value
Baseline	Xx						
Week 2	Xx						
Week 4	Xx						

	Secukinumab Q4W N=180	Secukinumab Q2W N=180	Placebo N=183	Secukinumab Q4W vs. Placebo
Week 12	X			
Week 16	X			
Week 28	X		Not assessed	N/A
Week 52	X		Not assessed	N/A

CI, confidence intervals; Q4W: every four weeks, Q2W: every second week; SE: standard error.
For each post-baseline visit only subjects with a value at both baseline and the respective post-baseline visit are included. Higher score values mean a better quality of life status.

Figure 6 EQ-5D VAS scores up to week 16 and week 52 (mean +/-SE) observed data from FAS population from SUNRISE. Source: Novartis clinical study report data on file

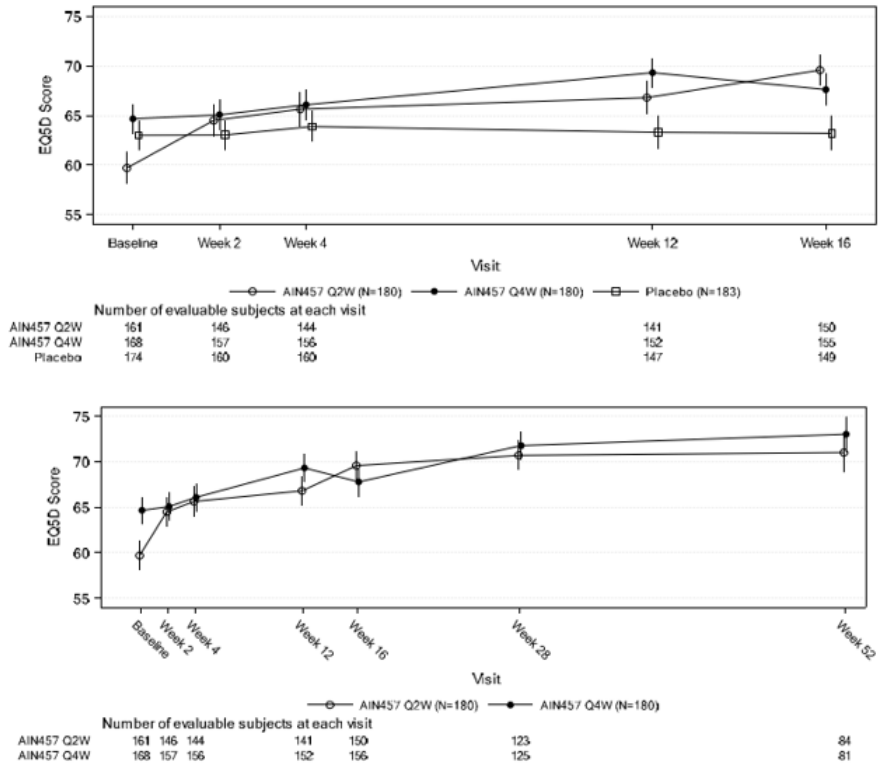


Figure note: AIN457 Q2W: secukinumab Q2W, AIN457 Q4W: secukinumab Q4W.

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The health state utility values applied in the model was calculated with a mixed model approach (MMRM) to consider the effect of repeated measures. The MMRM was modelled using HiSCR outcome and EQ-5D baseline variables (fixed effect). As baseline utility was included in the model as a covariate, only patients with baseline and post-baseline assessments were included in the model. Time (visit) variable was also included. An unstructured covariance structure was used. In case unstructured structure did not converge, auto-regressive structure or compound symmetry was used in that order. No imputation of missing data was conducted.

In our model, we include health state-specific utility values (HSUV) estimated from a model with treatment-specific utility values. The treatment arm was found to be a significant predictor of utility, indicating that whether a patient is receiving secukinumab or placebo has a meaningful impact on their utility values. Additionally, the model incorporating treatment-specific utilities had the lowest Akaike Information Criterion (AIC), suggesting a better fit to the observed data and a more accurate representation of patient outcomes.

Clinically, it makes sense that patients receiving secukinumab, even within the same health states, can have different utility values compared to those receiving placebo. This is because the four health states in the model are quite broad, and the difference in the distribution of patients in each of the four HiSCR stages alone may not necessarily capture the full effect of the treatment. There is also an effect difference within the respective categories. Therefore, using treatment-specific utility values allows for a more nuanced and accurate reflection of the benefits of secukinumab, capturing both the inter- and intra-category differences in patient outcomes.

The model was estimated using pooled data from the SUNSHINE and SUNRISE studies. Pooling the data allowed for an increased sample size and provided a more robust estimate. This approach enhanced the reliability of the results by offering a more comprehensive analysis. The goodness of fit statistics and observations per visit are presented in Table 32 and Table 33, respectively.

Table 32 Model fit statistics

-2 Log Likelihood	639.8
Akaike Information Criterion (AIC)	707.8
Corrected Akaike Information Criterion (AICC)	708.2
Bayesian Information Criterion (BIC)	873.6

The utility values applied in the model were based on the Danish value set for EQ-5D-5L published in Jensen et al. 2021 [44]. In accordance with the DMC methods guideline, the health state utilities have been age-adjusted. The estimation was based on 969 subjects and 4,926 assessments which were all used in the HSUV estimation. In the base case, study data up till week 52 was applied.

Table 33 Observations per visit

Week	Observations
2	886
4	899
12	843
16	867
28	780
52	651
Total	**4,926**

10.2.1.1 Mapping

EQ-5D-3L was mapped (reverse cross walk) to EQ-5D-5L in accordance with DMC guidelines. The method used to map EQ-5D-3L responses to EQ-5D-5L value sets was published by Van Hout 2021 and Van Hout 2012. In the following, we present the method from Van Hout 2021 in brief [45]. Different approaches to deriving value sets for the 5L were assessed utilising different 3L value sets to recommend a cross walk that would generate values for the 5L instrument. EQ-5D-3L responses and EQ-5D-5L responses were collected from participants in 6 countries (Denmark, England, Italy, the Netherlands, Poland, and Scotland) divided among 8 disease populations including COPD/asthma (n= 342), diabetes (n=275), liver disease (n=426), rheumatoid arthritis/arthritis (n=372), cardiovascular disease (n=250), stroke (n=614), depression (n=250), and personality disorders (n=384), as well as 443 students and 334 patients with nonspecific diagnoses. Different subgroups were targeted, and in most countries, a screening protocol was implemented to capture a broad spectrum of health across the EQ-5D dimensions for both the 5L and 3L descriptive systems.

Table 34 Respondents characteristics. Source: Van Hout 2012 [46]

Country	Population	n	% female	Mean age (y)	Mean VAS (SD)	Mean EQ-5D-3L index value (SD)*
Denmark	Diabetes	230	46	52.4	75 (20)	0.78 (0.24)
	Orthopaedic accident	94	34	37.8	79 (23)	0.63 (0.42)

Country	Population	n	% female	Mean age (y)	Mean VAS (SD)	Mean EQ-5D-3L index value (SD)*
	Rheumatoid arthritis	35	73	60.5	60 (25)	0.51 (0.32)
England	ADHD	69	54	34.3	63 (21)	0.59 (0.33)
	Arthritis	250	55	57.7	66 (20)	0.64 (0.23)
	Back pain	70	57	47.2	52 (19	0.47 (0.28)
	COPD	125	37	60.8	57 (21	0.56 (0.30)
	Depression	250	56	42.4	62 (21)	0.64 (0.30)
	Diabetes	45	58	50.8	69 (20)	0.72 (0.25)
	Myocardial infarction	75	27	56.7	63 (20)	0.64 (0.28)
	Parkinson's disease	32	44	49.8	66 (22)	0.46 (0.43)
	Stroke	85	39	57.4	53 (24)	0.52 (0.29)
Italy	Liver disease	426	31	56.0	70 (20)	0.80 (0.23)
Netherlands	Kidney dialysis	49	41	61.7	62 (21	0.60 (0.37)
	Personality disorders	384	67	31.7	59 (18)	0.61 (0.27)
Poland	Stroke	529	49	69.9	52 (26)	0.38 (0.41)
	Student population	443	79	22.1	79 (16)	0.87 (0.14)
Scotland	Asthma	21	57	72.8	64 (18	0.64 (0.24)
	Cardiovascular disease	176	54	71.4	60 (21)	0.54 (0.33)
	COPD	196	62	70.1	58 (21)	0.53 (0.34)
	Multiple sclerosis	15	53	63.9	52 (21)	0.47 (0.37)
	Parkinson's disease	5	60	63.0	41 (30)	0.25 (0.43)

Country	Population	n	% female	Mean age (y)	Mean VAS (SD)	Mean EQ-5D-3L index value (SD)*
	Rheumatoid arthritis	87	71	69.4	56 (22)	0.48 (0.34)
Overall	-	3,691	53	51.5	64 (23)	0.62 (0.33)

ADHD, attention deficit/hyperactivity disease; COPD, chronic obstructive pulmonary disease; EQ-5D-3L, three-level version of the EuroQol five-dimensional questionnaire; VAS, visual analogue scale. * Values based on UK value set.

The general approach to model development was to predict for each EQ-5D-3L health state the probability of being in any one of the 3,125 EQ-5D-5L health states with probabilities summing to one. Predicted utilities for the 243 EQ-5D-3L health states were subsequently obtained by summing the products of the 3,125 probabilities and corresponding EQ-5D-5L health state values within a given EQ-5D-3L health state. Respondents were excluded from model estimation, if they demonstrated inconsistent behaviour by indicating (1) no problems using the EQ-5D-3L and severe or extreme problems using the EQ-5D-5L, (2) some problems using the EQ-5D-3L, but no or extreme problems using the EQ-5D-5L, or (3) extreme problems using the EQ-5D-3L and no or slight problems using the EQ-5D-5L [46].

Table 35 presents indicants of goodness of fit as measured withAIC and predictive accuracy for the non-parametric and ordinal logistic regression models adjusting for problems in other EQ-5D-3L dimensions with or without the inclusion of age, age-squared, gender, and the latent factor (common covariate to all dimensions, to capture unobserved heterogeneity). For each set of comparisons, the first row in Table 35 presents in-sample results for all respondents, including those deemed to provide inconsistent data. The following rows present results based on out-of sample predictions. Including dummy variables coding for problems in other dimensions as well as the latent factor yielded reductions in AIC, mean absolute error (MAE) and the root mean squared error (RMSE) as compared to the non-parametric model. Adding age, age-squared, and gender also resulted in improvements in indices despite the variance in statistically significant relationships. When considering in-sample predictions, the model excluding demographic characteristics and the latent factor had the lowest MAE and RMSE, while based on out-of-sample predictions MAE and RMSE were lowest for the model including the latent factor without age and gender. Thus, the ordinal logistic regression that excludes age and gender and accounts for unobserved heterogeneity using a latent factor was regarded as the best approach.

Table 35 Mean absolute error, root mean squared error, and AIC by disease group; 3L to 5L*. Source: Van Hout 2021 [45].

	Non-parametric	Ordered logistic regression + complementary dimensions			Ordered logistic regression + complementary dimensions + latent factor		
			Age and gender	Age, age^2 and gender		Age and gender	Age, age^2 and gender
Mean absolute error							
All	0.0811	**0.0706**	0.0708	0.0707	0.0756	0.0772	0.0753
COPD/asthma	0.1010	0.0874	0.0881	0.0882	**0.0815**	0.0873	0.0876
Diabetes	0.0688	0.0554	0.0550	0.0549	**0.0500**	0.0512	0.0510
Liver disease	0.0667	0.0535	0.0523	0.0523	**0.0434**	0.0469	0.0467
RA/arthritis	0.0984	0.0838	0.0837	0.0837	**0.0781**	0.0824	0.0826
CVD	0.1042	0.0981	0.0989	0.0990	**0.0912**	0.0986	0.0989
Stroke	0.1206	0.1047	0.1048	0.1048	**0.0954**	0.1020	0.1021
Depression	0.0848	0.0720	0.0716	0.0712	**0.0613**	0.0687	0.0684
Personality disorders	0.0718	0.0656	0.0657	0.0658	**0.0601**	0.0644	0.0644
Students	0.1075	0.1040	0.1039	0.1038	**0.0804**	0.1012	0.1010
Other	0.0639	0.0529	0.0547	0.0555	**0.0417**	0.0521	0.0530
Root mean squared error							
All	0.1101	**0.1016**	0.1019	0.1018	0.1145	0.1163	0.1151
COPD/asthma	0.1356	0.1223	0.1236	0.1237	**0.1208**	0.1259	0.1261
Diabetes	0.0934	0.0836	0.0833	0.0833	**0.0794**	0.0827	0.0825
Liver disease	0.0834	0.0761	0.0757	0.0757	**0.0672**	0.0725	0.0725
RA/arthritis	0.1296	0.1185	0.1185	0.1186	**0.1109**	0.1200	0.1204
CVD	0.1479	0.1447	0.1457	0.1460	**0.1328**	0.1479	0.1483
Stroke	0.1595	0.1392	0.1388	0.1389	**0.1337**	0.1390	0.1390
Depression	0.1137	0.1052	0.1051	0.1052	**0.0949**	0.1056	0.1059
Personality disorders	0.0924	0.0941	0.0938	0.0937	**0.0909**	0.0954	0.0953
Students	0.1550	0.1579	0.1580	0.1579	**0.1118**	0.1586	0.1582
Other	0.0826	0.0773	0.0779	0.0781	0.0648	0.0778	0.0778
AIC							
All	21315	19950	19647	19639	19459	19138	**19127**
COPD/asthma	18836	17689	17435	17428	17262	16997	**16987**
Diabetes	20114	18825	18555	18549	18367	18077	**18068**
Liver disease	19848	18597	18308	18300	18157	17850	**17839**
RA/arthritis	18533	17436	17171	17167	17024	16745	**16740**
CVD	19505	18186	17907	17902	17752	17459	**17452**
Stroke	16866	15919	15648	15643	15522	15232	**15222**
Depression	19853	18611	18323	18316	18154	17851	**17841**
Personality disorders	19260	17810	17540	17535	17299	17017	**17009**
Students	19241	17881	17594	17583	17457	17150	**17135**
Other	19778	18501	18260	18248	18017	17758	**17740**

*Minimum figures are presented in boldface font.

10.2.2 Disutilities

Disutilities due to adverse events were not included in the model. Disutility due to surgery was not considered due to lack of data. Real-world surgery rates can potentially be lower for patients who have received secukinumab than for patients receiving placebo, given the effectiveness of secukinumab vs placebo in studies. In this case, the exclusion of disutilities for surgery will be expected to provide a conservative estimate of the benefit of secukinumab in this model.

10.2.3 HSUV results

The utilities shown in Table 36 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. The applied utilities were age-adjusted to account for the decrease in HRQoL related to increasing age. The applied weights were constructed using the general

population health state utilities values provided by the DMC. The reference age interval was set to 30-39 to match the weighted average age of the SUNNY studies.

Table 36 Overview of health state utility values (week 52)

Health State	Treatment	LSM (95% CI)	SE	Instrument	Tariff (value set) used
HiSCR ≥75	Secukinumab Q2W	X X		EQ-5D-5L	DK
	Secukinumab Q4W	X X		EQ-5D-5L	DK
	Placebo	X X		EQ-5D-5L	DK
HiSCR 50-74	Secukinumab Q2W	X X		EQ-5D-5L	DK
	Secukinumab Q4W	X X		EQ-5D-5L	DK
	Placebo	X X		EQ-5D-5L	DK
HiSCR 25-49	Secukinumab Q2W	X X		EQ-5D-5L	DK
	Secukinumab Q4W	X X		EQ-5D-5L	DK
	Placebo	X X		EQ-5D-5L	DK
HiSCR <25	Secukinumab Q2W	X X		EQ-5D-5L	DK
	Secukinumab Q4W	X X		EQ-5D-5L	DK
	Placebo	X X		EQ-5D-5L	DK

10.2.3.1 Utility Increment for Patients Discontinuing Treatment

As described earlier, we assume a prolonged response for individuals who discontinue treatment with secukinumab and transition to the off-treatment stage. Based on data from the long-term extension of the SUNNY studies, we assume that the prolonged response for individuals who discontinue treatment is 7 cycles. Specifically, this is

modeled as a one-off utility increment in the cycle during which the patient transitions to the off-treatment stage.

To ensure that this increment accurately reflects the difference in utility, it should correspond to the difference between being in the off-treatment stage for 7 weeks (with utility corresponding to SoC in the HiSCR < 25 stage) and being in the same response category from which the patient discontinued.

At the end of the model's 13th cycle (representing week 52 in the model), XXXXX of patients still receiving treatment with secukinumab were in the HiSCR >75 stage, while the remaining XXXXX were in the HiSCR 50-74 stage. Therefore, the utility increment for the 7 cycles, where we assume a prolonged response, can be calculated as follows:

For patients in the Q4W arm:

[redacted]

For patients in the Q2W arm:

[redacted]

This corresponds to a utility increment of XXXXX for patients in the Q4W arm and XXXXX for patients in the Q2W arm per patient who discontinues treatment.

Table 37 Utility increment for patients discontinuing treatment

Treatment arm	HiSCR >75	HiSCR 50-74	HiSCR 25-49	HiSCR < 25	Off-treatment	One-off increment
Q4W arm	[redacted]					
Q2W arm	[redacted]					

10.3 Health state utility values measured in other studies than the clinical studies forming the basis for relative efficacy

No other studies than the study forming the basis for relative efficacy have been used for health state utility values.

10.3.1 Study design N/A

10.3.2 Data collection N/A

10.3.3 HRQoL Results N/A

10.3.4 HSUV and disutility results N/A

Table 38 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

Table 39 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

All costs related to treating patients with moderate to severe HS with secukinumab and SoC were included in the model. To estimate the resource use and identify unit costs, input from the clinical expert were applied, the SmPC on secukinumab and other similar documents for SoC, data from the SUNNY studies, and assumptions. Below, descriptions of each cost element and how the element was valued in the health economics analysis are presented.

11.1 Medicine costs - intervention and comparator

The medicines included in the model base case were secukinumab and SoC (comprising a basket of non-biological systemic treatments). All drug costs included in the model were based on the PPPs obtained in January 2025. The PPPs of the included packages of secukinumab and applied SoC treatments are presented in Table 40.

Table 40 Package information on secukinumab and SoC. Source: Medicinpriser.dk (3 January 2025).

Pharmaceutical	Strength	Package size	PPP, DKK
Cosentyx®	300 mg	1 syringe	7,540.97
Oral tetracycline "Tetracyclin Actavis"	250 mg	100 tablets	100.00

Pharmaceutical	Strength	Package size	PPP, DKK
Clindamycin "Dalacin C"	300 mg	24 capsules	88.00
Rifampicin "Rimactan"	300 mg	100 capsules	264.08
Doxycyclin "Paranova"	100 mg	100 tablets	203.00
Lymecyclin "Actavis"	300 mg	100 tablets	348.00
Roflumilast "Daxas"	0,5 mg	90 tablets	780.58

Ertapenem was also included in the SoC treatment basket, however, since ertapenem is administered during an inpatient stay, no medicine costs were included for ertapenem, as these costs were included in the DRG tariff.

11.1.1 Secukinumab medicine costs

Patients in the secukinumab arm received secukinumab according to the posology described in the SmPC on secukinumab [25]. In the base case, all patients in the Q4W arm initiated treatment with monthly administrations of 300 mg SC secukinumab. This assumption was based on dialogue with the DMC. After 16 weeks, patients in the secukinumab Q4W arm who did not achieve a response (defined as HiSCR ≥50 in the base case) would be up-titrated to 300 mg secukinumab Q2W. Table 41 presents dosing information on secukinumab as applied in the health economic analysis.

Table 41 Secukinumab medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Secukinumab	Initial dosing: 300 mg at week 0, 1, 2, 3 and 4. Maintenace dosing: 300 mg montly or Q2W.	Not included	Monthly or Q2W	Not applied as patients should receive a full vial per administration

11.1.2 SoC medicine costs

Patients in the SoC arm received a basket of non-biological systemic treatments that might be used after adalimumab in a Danish clinical setting. The clinical expert was consulted in terms of which non-biological systemic treatments patients might receive in Danish clinical practice. The SoC treatments that were included based on input from the clinical expert and later revised based on inputs from DMC are presented in Table 42. In addition to the treatments in Table 42, ciclosporin, oral prednisolone and dapsone are also used in a Danish clinical setting, however, the clinical expert estimated that these treatments are used by 1% each and are not suitable for long-term use. Thus, these treatments were excluded from the SoC treatment basket. The table below presents the doses applied in the model and the proportions in the SoC arm receiving each treatment.

Table 42 SoC medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Proportion receiving treatment	Vial sharing
Oral tetracycline [4]	500 mg per os	Not included	Twice daily	5%	Not included
Clindamycin	300 mg per os	Not included	Twice daily	5%	Not included
Rifampicin [4]	300 mg per os	Not included	Twice daily	5%	Not included
Doxycyclin [47]	100 mg per os	Not included	Twice daily	20%	Not included
Lymecyclin [48]	300 mg per os	Not included	Twice daily	20%	Not included
Roflumilast [49]	500 mg per os	Not included	Once daily	10%	Not included
Ertapenem [49]	1 g i.v	Not included	Once daily	5%	Not included

Please note that the proportions in the table does not sum to 100%, as a proportion of patients receiving SoC will receive either no treatment or other non-systemic and relatively cheap treatments. Ertapenem is administered during an inpatient stay and therefore the dose information in this table is not applied in the model, as the medicine cost is included in the DRG tariff. The dose of isotretinoin is based on weight and an average patient weight of 75 kg was assumed.

Based on discussions with the DMC, a sensitivity analysis in the budget impact analysis was conducted and presented in section 13, where biological treatments used in Danish clinical practice were included as comparators in addition to SoC. The biological treatments were informed by the clinical expert and the article by Ring et al. 2024 [19, 20], and the sensitivity analysis is described in section 13. In Table 43, we present the PPPs of the biological treatments included in the budget impact sensitivity analysis.

Table 43 Medicine costs of biological treatments. Source: medicinpriser.dk (3 January 2025)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Infliximab "Flixabi"	100 mg	1 vial	2,212.69	Not included	Not accounted for in the sensitivity analysis
Ustekinumab "STEQEYMA"	45 mg	1 vial	8,952.00	Not included	Not accounted for in the

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
					sensitivity analysis
Anakinra "Kineret"	100 mg/0.67 ml	7 syringes	1,905.20	Not included	Not accounted for in the sensitivity analysis
Ixekizumab "Taltz"	80 mg	1 syringe	6,943.91	Not included	Not accounted for in the sensitivity analysis
Bimekizumab "Bimzelx"	160 mg	2 pens	15,295.82	Not included	Not accounted for in the sensitivity analysis
Guselkumab "Tremfya"	100 mg	1 pen	14,492.51	Not included	Not accounted for in the sensitivity analysis
Adalimumab "Humira"	40 mg	2 pens	2,739.23	Not included	Not accounted for in the sensitivity analysis

11.2 Medicine costs – co-administration

Not applicable, as none of the treatments require co-administration.

11.3 Administration costs

Administration costs were included for treatments administered by subcutaneous injections and by intravenous injections at the hospital. Orally administered treatments were not ascribed an administration cost, as patients were assumed to administer these at home. A macro-costing approach was applied in the model for administration costs.

According to the SmPC on secukinumab, patients may self-inject secukinumab after proper training in subcutaneous injection technique or secukinumab may be injected by a caregiver, if a physician determines that this is appropriate. This assumption was validated by the clinical expert and therefore, only one subcutaneous administration at the hospital was included for secukinumab. The DRG tariff applied as the unit cost of the subcutaneous administration of secukinumab at the hospital was '17MA98', as it was assumed that this would be done at an outpatient visit.

As shown in Table 42, ertapenem is part of the SoC treatment basket and administered via intravenous injections. Based on input from the clinical expert, it was assumed that ertapenem was administered during an inpatient stay. The cost of ertapenem treatment was based on the DRG 2024 tariff 09MA03 which was derived by combining the diagnose code DL732 with the procedure code BPHB2 in interactive DRG [49].

Table 44 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Subcutaneous administration of secukinumab	One administration at the hospital	1,989	17MA98	DRG 2024
Intravenous administration of ertapenem (inpatient stay)	One inpatient stay	20,231	09MA03	DRG 2024

11.4 Disease management costs

In the model, the resource use associated with disease management was categorised as non-surgery and surgery-related resource use. The model assumes that resource use is health state dependent, i.e. independent of treatments received. Therefore, the resource use by health states in the model was based on the resource use in the secukinumab NICE submission (TA 935), where a survey of physicians (n=40) who actively treat moderate to severe HS patients in the UK was applied to estimate the resource use. Physicians were surveyed regarding the frequency of each type of resource use, stratified by health state. The information was collected for patients with moderate and severe HS, separately, and weighted based on the proportions of patients in each disease severity category [50]. The resource use from the survey is presented in Table 46.

To ensure that the resource use was relevant in a Danish clinical practice, the resource use was validated by the clinical expert and later revised based on inputs from the DMC. According to the clinical expert, the annual resource use from the UK survey presented in Table 46 could be used as a proxy for the resource use in a Danish clinical setting. However, the number of annual bandage visits was adjusted based on input from the clinical expert to provide an accurate representation of the differing use of bandage associated with each severity category. Due to the method of estimating the resource use, it was not possible to present the frequency in non-numerical terms (e.g. as visits per month) as requested by the DMC, but the resource use in Table 46 should be interpreted as e.g. 0.11 annual inpatient stays not related to surgery for patients in the HiSCR ≥75 category translates to 1 out of 9 patients in the HiSCR ≥75 having an annual inpatient stay.

According to the clinical expert, non-surgery related outpatient visits were typically control visits, while inpatient stays could be due to infections and emergency room visits could be due to abscesses. Outpatient visits related to surgery were typically due to control visits, deroofing, intralesional steroid injections or CO2-laser treatment, while the

inpatient stays related to surgery were typically due to plastic surgery while other causes of inpatient hospitalisation could be incision of abscesses.

Table 45 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Non-surgery related				
Outpatient visit (due to any reason)	Please see Table 46	1,989	17MA98	DRG 2024
Inpatient stay	Please see Table 46	20,231	09MA03	DRG 2024. Combination of the diagnose code DL732 and the procedure code ZZ0202B in interactive DRG.
Visit to wound-care not related to HS surgery	Please see Table 46	1,625	09MA98	DRG 2024. Combination of DL732 and BNPA in interactive DRG
Emergency room visit	Please see Table 46	1,989	17MA98	DRG 2024
Telephone consultation [51]	Please see Table 46	86.92	Tariff for dermatologic telephone consultation	2024 tariff
Bandage visit	Please see Table 46	1,625	09MA98	DRG 2024. Combination of DL732 and BNPC in interactive DRG
Surgery related				
Outpatient visit due HS-related surgeries: control visit, deroofing, intralesional steroid injections, CO2-laser treatment	Please see Table 46	1,989	17MA98	DRG 2024. According to the clinical expert, deroofing, intralesional steroid injections, CO2-laser treatment is done at outpatient visits
Inpatient stay due to HS-related surgery: plastic surgery	Please see Table 46	72,018	09MP13	DRG 2024

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Visit to wound-care related to surgery	Please see Table 46	1,625	09MA98	DRG 2024. Combination of DL732 and BNPA in interactive DRG

Table 46 Annual resource use in each HiSCR category

	HiSCR ≥75	HiSCR 50-74	HiSCR 25-49	HiSCR <25
Non-surgery related visits				
Number of annual outpatient visit (due to any reason)	3.10	3.51	4.44	4.68
Number of annual inpatient stays not related to surgery	0.11	0.23	0.29	0.45
Number of annual visits to wound-care not related to HS surgery	0.67	0.47	0.64	0.45
Number of annual emergency room visits	0.12	0.20	0.47	0.57
Number of annual telephone consultations	0.24	0.40	0.94	1.14
Number of annual bandage visits	0.05	0.10	0.10	0.20
Surgery-related				
Number of annual inpatient stays due to HS-related surgery	0.13	0.22	0.54	0.80
Number of annual outpatient visit due HS-related surgeries	0.22	0.35	0.67	0.94
Number of annual visit to wound-care related to surgery	0.12	0.17	0.4	0.85

The clinical expert was consulted in terms of the distribution of the surgery-related outpatient visits (deroofing, intralesional steroid injection and CO2-laser treatment) and the surgery-related inpatient stays (plastic surgery and incision of abscesses) in each HiSCR category. The distributions are presented in Table 47.

Table 47 Distribution of the surgery-related outpatient visits and inpatient stays

	HiSCR ≥75	HiSCR 50-74	HiSCR 25-49	HiSCR <25
Distribution of outpatient visits related to surgery				
Deroofing	50%	67%	50%	50%

Intralesional steroid	0%	0%	0%	0%
C02-laser treatment	50%	33%	50%	50%
Distribution of inpatient stays related to surgery				
Plastic surgery	100%	100%	100%	100%
Incision of abscesses	0%	0%	0%	0%

HiSCR, Hidradenitis Suppurativa Clinical Response.

11.4.1 Costs related to managing the mental health of HS patients

Living with a visible chronic skin condition like HS that can cause pain, itch, and an unpleasant smell from the purulent discharge, as well as the stigmatisation the patients often experience because of their disease, have a profound impact on patients' QoL and their mental health status [52]. HS patients can experience episodes with depression and anxiety, feel embarrassed due to the visible skin lesions, experience social isolation and decreased sexual health. Thus, in addition to the resource use associated with disease management presented above, the resource use associated with managing the mental health of patients with moderate to severe HS was also included in the model.

The resource use associated with managing the mental health of HS patients was based on input from the clinical expert, who provided insights to the healthcare personnel that is typically involved in the management of decreased mental health in HS patients. The healthcare personnel involved and the expected annual number of visits to each healthcare personnel in each HiSCR category is presented in Table 48. Table 49 presents the unit costs applied in the model for each visit to the healthcare personnel presented in Table 48.

Table 48 Annual resource use (visits) related to management of the mental health of HS patients

	HiSCR ≥75	HiSCR 50-74	HiSCR 25-49	HiSCR <25
Psychiatrist	1	2	3	4
Social worker	2	4	6	8
General practitioner	1	2	3	4
Dermatologist	0.5	1	1.5	2

HiSCR, Hidradenitis Suppurativa Clinical Response

Table 49 Costs used in the model related to managing the mental health of HS patients

Activity	Frequency	Unit cost [DKK]	Tariff	Reference
Psychiatrist	See Table 48	2,089	Psychiatric outpatient tariff	Psychiatric DRG tariff 2024
Social worker	See Table 48	263	KRL 2024	Average of the hourly wage of a social worker employed by the government in March 2024. The average monthly salary was sourced using filters for position, total salary, and municipal employment. The average monthly salary was computed based on an average of 160.33 hours per month.
General practitioner	See Table 48	153.61	0101 GP consultation	DMC unit cost catalogue [53]
Dermatologist	See Table 48	378	2024 dermatologic tariff	Dermatologic 2024 tariffs. The unit cost per visit was estimated as the mean of the cost of the first visit and the cost of subsequent visits [51]

11.5 Costs associated with management of adverse events

The AEs observed in ≥5% in one treatment arm in the bio-experienced subgroup in the SUNNY studies were presented in Table 20.

The clinical expert expected that around 25% of patients experiencing any of the AEs presented in the table might have a visit to the general practitioner. As such, the costs of managing an adverse event in the analysis were assumed to correspond to 25% of the costs of a standard consultation with a general practitioner (DKK 160.72, PLO tariff 0101), corresponding to DKK 40.18.

The clinical expert noted that some upper respiratory tract infections might need antibiotics, however we only included the cost of the general practitioner visit due to the low price of antibiotics.

According to the clinical expert, fungal infections might be observed with secukinumab treatment, but since the treatment of fungal infections typically is low-cost antifungal treatment, this was not included in the model either.

Table 50 Cost associated with management of adverse events. Source: PLO tariffs, 2024

	PLO code	Unit cost
Upper Respiratory tract infection	0101	DKK 40.18*
Diarrhoea	0101	DKK 40.18*
Nasopharyngitis	0101	DKK 40.18*
Headache	0101	DKK 40.18*
Fungal infection	0101	DKK 40.18*

*Note that the unit costs correspond to 25% of DKK 160.72, PLO tariff 0101.

11.6 Subsequent treatment costs

In the cost-utility analysis, subsequent treatments were not accounted for. When patient discontinued secukinumab, they moved to SoC treatment and patients in the SoC arm could not discontinue SoC.

Table 51 Medicine costs of subsequent treatments N/A

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
[Name of subsequent treatment]	N/A				

11.7 Patient costs

In accordance with DMC guidelines, patient-related time use and costs and transportation costs were included in the model. No caregiver time or costs were included in the model. The patient time associated with secukinumab and SoC treatment was based on the time spent on treatment-related activities and traveling to and from the hospital. Based on the DMC guideline [53], a cost of DKK 203 per patient hour was applied.

In terms of transportation, a distance of 20 km to and from the hospital (40 km in total per visit) was assumed, and a unit cost per km of DKK 3.73 was applied in accordance with DMC guidelines [53]. Thus, a transportation cost of DKK 149 was applied for each hospital visit. It was assumed that patients spend 30 minutes on transportation to and from the hospital, i.e. 60 minutes per visit. The activities to which patient time use and transportation were ascribed, and the time spent by the patient on each activity including one hour of transportation, are presented in Table 52. Each activity was ascribed a transportation cost of DKK 149.

The patient time spent on each activity was informed by the clinical expert and dialogue with the DMC. Inpatient days were assumed to be 48 hours patient time and for ertapenem, 4 inpatient days were assumed based on the trim point of the DRG tariff applied for ertapenem treatment and the SmPC on Invanz® [49]. According to the clinical expert, plastic surgery is associated with hospitalisation for one to two weeks, however, 3 days were applied in the model based on dialogue with the DMC. The patient time spend on visits related to management of the mental health of HS patients was based on assumptions.

Table 52 Patient costs used in the model

Activity	Time spent [minutes or hours]*
Non-surgery related	
Outpatient visit (due to any reason)	0.5 hours
Inpatient stay	48 hours
Ertapenem inpatient stay	48 hours
Visit to wound-care not related to surgery	1.5 hours
Emergency room visit	24 hours
Telephone consultation	0 minutes (assumed to be done at home)
Bandage visit	1.5 hours
Training in subcutaneous injection technique	0.5 hours
Surgery related	
Outpatient visit due to deroofing	2 hours
Outpatient visit due to CO2 laser treatment	2 hours
Inpatient days due to plastic surgery	72 hours
Visit to wound-care related to surgery	1.5 hours

Activity	Time spent [minutes or hours]*
Management of mental health	
Psychiatrist	2 hours
Psychologist	2 hours
Social worker	1.5 hours
General practitioner	1.5 hours
Dermatologist	1.5 hours

*Please note that the patient time presented in the table is inclusive one hour of transportation time.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

11.8.1 One-off cost decrement for patients discontinuing treatment

As outlined in section 10.2.3.1, we assume a prolonged response for individuals who discontinue treatment with secukinumab and transition to the off-treatment stage. Based on data from the long-term extension of the SUNNY studies, we assume that the prolonged response for individuals who discontinue treatment is 7 cycles. Specifically, this is modelled as a one-off cost decrement in the cycle during which the patient transitions to the off-treatment stage.

To ensure that this decrement accurately reflects the difference in costs, it should correspond to the difference between being in the off-treatment stage for 7 weeks (with costs corresponding to SoC in HiSCR <25) and being in the same response category from which the individual discontinued.

At the end of the model's 13th cycle (representing week 52 in the model), XXXXX of patients still receiving treatment with secukinumab were in HiSCR > 75, while the remaining XXXXX were in HiSCR 50-74.

Table 53 shows an example of how the one-off cost decrement is calculated for non-surgery related healthcare resource use. The table presents the total cost per cycle for each cost category included in non-surgery related resource use, distributed across the four HiSCR stages, as well as for the off-treatment stage.

- The cost decrement caused by the prolonged response for 'outpatient visits (due to any reason)' is calculated as follows:

[redacted]

Using the same approach, the cost decrement is calculated for all remaining cost categories. Table 54 shows the cost decrement caused by the prolonged response for all cost categories in the model.

Table 53 Example calculation of one-off cost decrement

Cost category	HiSCR >75	HiSCR 50-74	HiSCR 25-49	HiSCR < 25	Off-treatment	One-off increment
Outpatient visits	474.30	537.03	679.32	716.04	716.04	**-1,559.52**
Non-surgical inpatient visits	171.19	357.93	451.31	700.30	700.30	**-3,308.90**
Visits to wound-care	83.75	58.75	80.00	56.25	56.25	**139.63**
Emergency room visits	18.36	30.60	71.91	87.21	87.21	**-456.07**
Bandage visits	6.25	12.50	12.50	25.00	25.00	**-118.03**
Telephone consultations	1.60	2.67	6.28	7.62	7.62	**-39.86**

Table 54 One-off cost decrement by cost category applied in the model

	Total one-off cost decrement, DKK
Non surgery related healthcare resource use	
Resource use	-5,342.75
Patient time	-2,945.51
Transportation	-162.56
Surgery related healthcare resource use	
Resource use	-26,282.07
Patient time	-5,325.05
Transportation	-163.54
Primary sector healthcare resource use	

	Total one-off cost decrement, DKK
Resource use	-4,297.12
Patient time	-2,138.03
Transportation	-974.04

12. Results

12.1 Base case overview

Table 55 provides an overview of the settings applied in the base case of the cost-effectiveness analysis.

Table 55 Base case overview

Feature	Description
Comparator	SoC
Type of model	Five-state Markov model
Time horizon	Lifelong (until patients reach 100 years)
Treatment line	Bio-experienced patients after adalimumab treatment
Measurement and valuation of health effects	HRQoL measured with EQ-5D-3L in the SUNNY studies. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Administration costs Disease management costs Patient costs and transportation costs
Dosage of medicine	Secukinumab: Please see Table 41 SoC: Please see Table 42
Average time on treatment	Secukinumab: 66.10 months SoC: 513.70 months
Parametric function for PFS	N/A
Parametric function for OS	N/A

Feature	Description
Inclusion of waste	Not included
Average time in model health state	Secukinumab HR: 41.84 months R: 18.58 months PR: 1.21 months NR: 4.47 months Placebo HR: 0.45 months R: 0.49 months PR: 0.47 months NR: 512.29 months

HR, high response; HRQoL, health-related quality of life; NR, no response; PR, partial response; R, response; SoC, standard of care

12.1.1 Base case results

In the base case, the incremental cost and incremental QALY per patient for secukinumab compared to SoC was DKK 220,320 and 0.66, respectively, over a lifelong time horizon. Table 56 presents an overview of the base case results.

Table 56 Base case results, discounted estimates

	Secukinumab	SoC	Difference
Medicine costs	576,161	32,923	543,238
Medicine costs – co-administration	-	-	-
Administration	1,989	0	453
Disease management costs	1,843,252	2,088,380	-245,128
Costs associated with adverse events	511	502	9
Subsequent treatment costs	-	-	-
Patient costs	532,934	604,038	-71,104
Palliative care costs	-	-	-
Total costs	**3,035,263**	**2,814,943**	**220,320**
Life years gained (HiSCR ≥ 75)	2.42	0.04	2.02
Life years gained (HiSCR 50-74)	1.09	0.04	0.92
Life years gained (HiSCR 25-49)	0.10	0.04	0.05

	Secukinumab	SoC	Difference
Life years gained (HiSCR < 25)	0.37	22.30	-22.78
Off-treatment	18.43	0.00	19.78
Total life years	**22.41**	**22.41**	**0**
QALYs (HiSCR ≥ 75)	1.70	0.03	1.67
QALYs (HiSCR 50-74)	0.70	0.03	0.67
QALYs (HiSCR 25-49)	0.06	0.02	0.04
QALYs (HiSCR < 25)	0.21	11.20	-10.99
Off-treatment	11.93	0.00	9.27
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**11.93**	**11.27**	**0.66**
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**334,772**	

12.2 Sensitivity analyses

Uncertainty in the input parameters in the model has been explored through deterministic sensitivity analyses (DSA) and a probabilistic sensitivity analysis (PSA) and scenario analyses which are presented in this section.

12.2.1 Deterministic sensitivity analyses

The DSAs included in the present application are presented in Table 57. Sensitivity was assessed by varying the input parameters of the model by selecting the 2.5th percentile to represent the lower bound and the 97.5th percentile to represent the upper bound.

Table 57 One-way sensitivity analyses results, secukinumab verses SoC

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	220,320	0.66	334,772
Health state utility value	2.5th percentile	Included to assess the	220,320	1.06	206,886

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
related to HiSCR < 25 for placebo		impact of this parameter			
	97.5th percentile	Included to assess the impact of this parameter	220,320	0.25	865,260
Health state utility value related to HiSCR > 75 for Q4W	2.5th percentile	Included to assess the impact of this parameter	220,320	0.47	467,503
	97.5th percentile	Included to assess the impact of this parameter	220,320	0.86	255,015
Health state utility value related to HiSCR > 75 for Q4W	2.5th percentile	Included to assess the impact of this parameter	220,320	0.49	448,057
	97.5th percentile	Included to assess the impact of this parameter	220,320	0.80	275,324
Number of inpatient stays due to HS-related surgery in HiSCR < 25	2.5th percentile	Included to assess the impact of this parameter	268,166	0.66	407,473
	97.5th percentile	Included to assess the impact of this parameter	167,614	0.66	254,686
Cost of inpatient stays due to HS-related surgery in the HiSCR < 25 severity category	2.5th percentile	Included to assess the impact of this parameter	260,026	0.66	395,104
	97.5th percentile	Included to assess the impact of this parameter	176,582	0.66	268,312

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Health state utility value related to HiSCR 50-74 for Q4W	2.5th percentile	Included to assess the impact of this parameter	220,320	0.55	399,548
	97.5th percentile	Included to assess the impact of this parameter	220,320	0.76	291,316
Health state utility value related to HiSCR 50-74 for Q2W	2.5th percentile	Included to assess the impact of this parameter	220,320	0.61	359,027
	97.5th percentile	Included to assess the impact of this parameter	220,320	0.70	315,908
Unit cost Patient hour	2.5th percentile	Included to assess the impact of this parameter	233,571	0.66	354,906
	97.5th percentile	Included to assess the impact of this parameter	205,723	0.66	312,592
Number of inpatient stays not due to HS-related surgery among the HiSCR < 25 category	2.5th percentile	Included to assess the impact of this parameter	229,662	0.66	348,967
	97.5th percentile	Included to assess the impact of this parameter	210,029	0.66	319,135
Discontinuation rate following year 1	2.5th percentile	Included to assess the impact of this parameter	221,913	0.69	319,658
	97.5th percentile	Included to assess the	218,775	0.63	349,397

Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	impact of this parameter			

HiSCR, Hidradenitis Suppurativa Clinical Response; ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.

The results were most sensitive to changes to the health state utility values related to different severity categories of HS and to the healthcare resource use in the hospital sector. Figure 7 illustrates the tornado diagram containing the results of the DSA.

Figure 7: One-way sensitivity analysis results for secukinumab compared to SoC

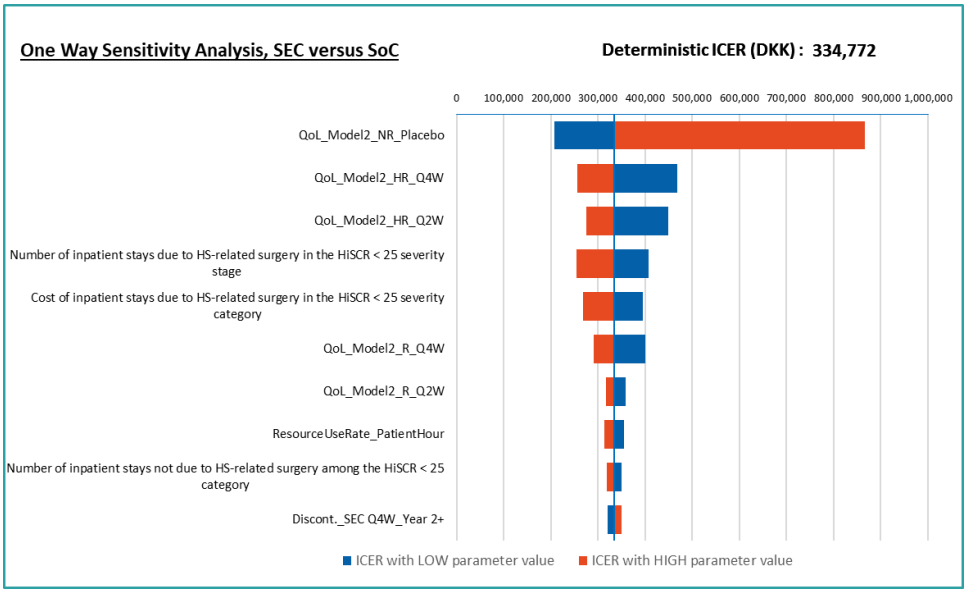


Table 58 presents the incremental cost, incremental QALYs and the associated Incremental cost-effectiveness ratio (ICER) for six scenario analyses. In addition to changing the time horizon of the model, we present the results from a scenario analysis, where we have applied a response criterion of HiSCR ≥25, a scenario analysis, where the transition probabilities are based on efficacy data for both bio-naïve and bio-experienced patients, and a scenario analysis, where discontinuation is allowed during the induction phase.

It is observed that the ICER decreases as the model's time horizon extends. This trend is expected, since the majority of the costs associated with secukinumab treatment occur within the first 16 weeks. The decreasing ICER reflects the long-term effectiveness among those individuals who experience a prolonged and positive response to secukinumab. For this reason, we also believe that the most accurate representation is obtained with a lifelong time horizon, as assumed in the model's base case.

Table 58 Scenario sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	220,320	0.66	334,772
Time horizon of 1 year	Reducing the time horizon to 1 year	In accordance with DMC guidelines	95,464	0.08	1,153,433
Time horizon of 10 years	Reducing the time horizon to 10 years	In accordance with DMC guidelines	170,268	0.43	396,214
Time horizon of 20 years	Reducing the time horizon to 20 years	In accordance with DMC guidelines	203,174	0.58	350,023
Response criteria HiSCR ≥25	Applying a response criterion of HiSCR ≥25 instead of HiSCR ≥50 as in the base case	According to the clinical expert, HiSCR ≥50 is based on guidelines but for some patients, HISCR ≥25 might be good enough	267,103	0.67	397,562
Efficacy from full population	Applying efficacy data from the full population (bio-naïve and bio-experienced) to estimate transition probabilities	Similar efficacy was detected among bio-naïve and bio-experienced patients. Using full population data to ensure robustness of results	220,676	0.73	300,363
Discontinuation from secukinumab in all Year 1 cycles	Allowing for discontinuation from secukinumab in all Year 1 cycles.	Allowing for discontinuation within first 16 weeks of treatment with secukinumab to investigate impact of	214,656	0.66	327,464

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		discontinuation.			

12.2.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 1,000 iterations. The PSA evaluated the result of the health economics analysis when several parameters of the models were varied simultaneously.

Figure 8 presents the cost-effectiveness acceptability curves (CEAC) that illustrates the cost-effectiveness probability at different willingness-to-pay thresholds.

Figure 9 presents the scatter plot from the PSA. As seen, most of the simulated ICERs from the PSA are located in the north-east quadrant, where secukinumab is more effective and more costly compared to SoC. A proportion of the ICERs are in the north-west quadrant, where secukinumab is less effective and more costly compared to SoC.

Figure 10 presents a convergence plot of the estimated ICER mean as a function of the number of PSA simulations.

Figure 11 presents the impact of the PPP of secukinumab on the estimated ICER value.

Figure 8: Cost-effectiveness acceptability curves

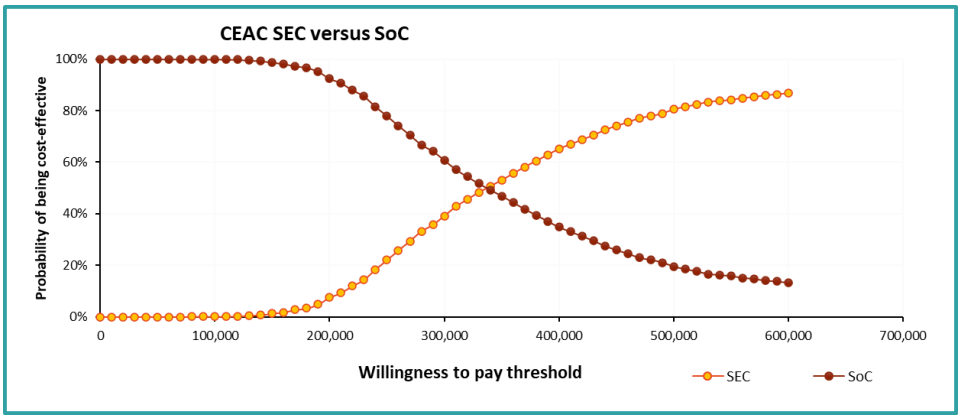


Figure 9: Scatter plot from PSA

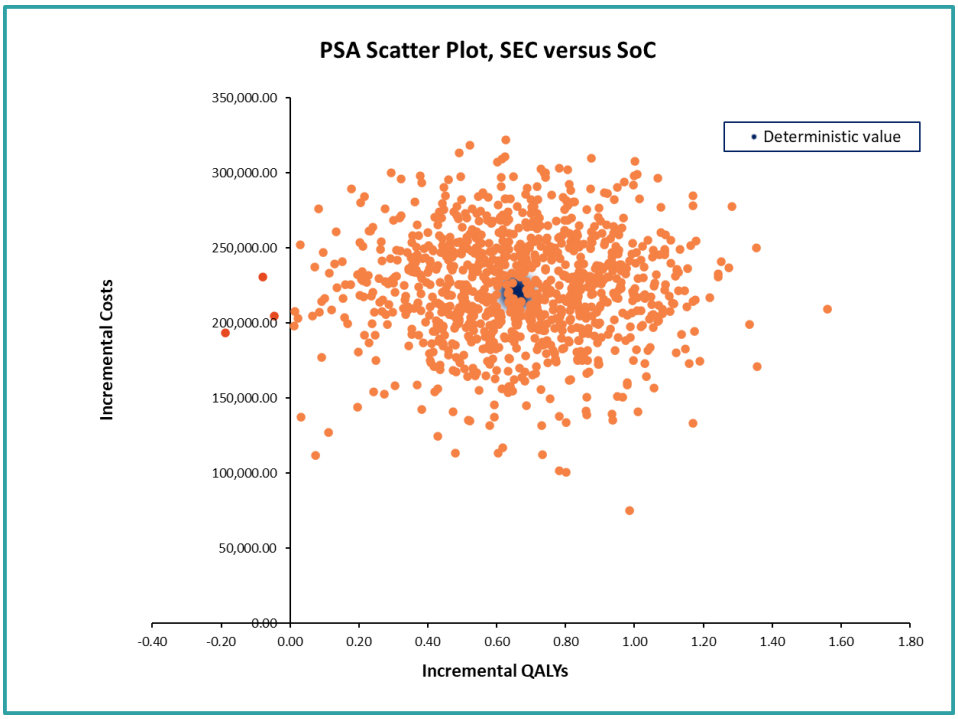


Figure 10: Convergence plot for the estimated mean

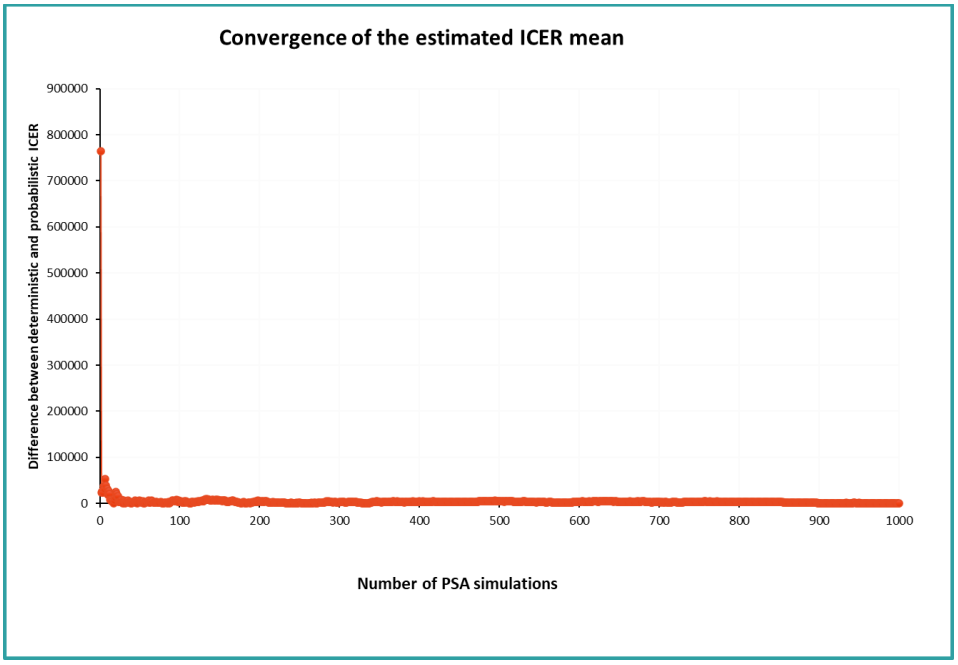
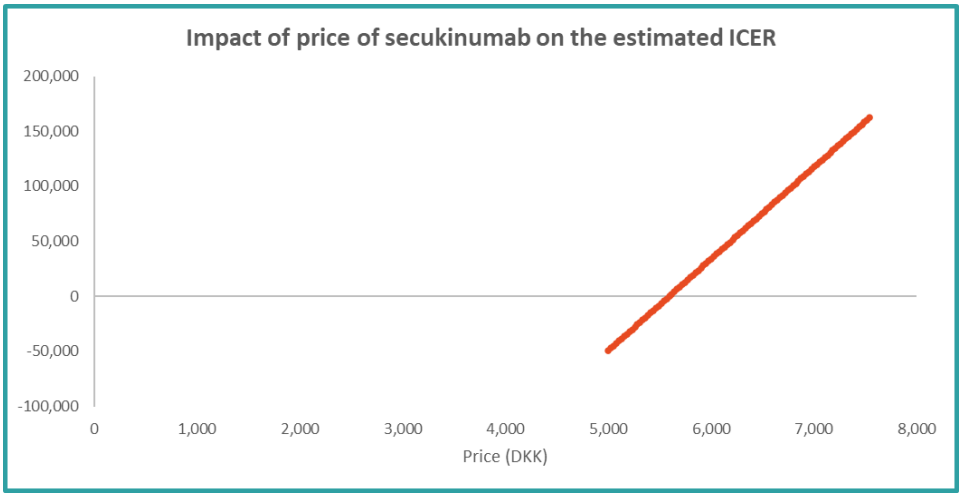


Figure 11: Impact of PPP of secukinumab on the estimated ICER



13. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending secukinumab as standard treatment for patients with moderate to severe HS after treatment with adalimumab. The budget impact was estimated per year in the first 5 years after the recommendation of secukinumab. The budget impact analysis compares the expenditures in the scenario, where secukinumab is recommended as a possible standard treatment and the scenario, where secukinumab is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

The patient numbers in the budget impact model were informed by the clinical expert. According to the clinical expert, there are currently around 100 patients with moderate to severe HS who are candidates to secukinumab treatment after treatment with adalimumab, i.e. are bio-experienced. In addition, the clinical expert expected that 50 new patients with moderate to severe HS each year will be candidates to secukinumab after adalimumab treatment. In the scenario where secukinumab is recommended as standard treatment of moderate to severe HS after adalimumab treatment, Novartis expects a 100% uptake of candidates due to no other recommended biological alternatives. In the scenario where secukinumab is not recommended, a patient uptake of 5% was expected in order to reflect the real-world usage of non-approved biological therapies.

Table 59 Number of new patients expected to be treated over the next five-year period if secukinumab is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab	100	50	50	50	50
SoC	0	0	0	0	0
			Non-recommendation		
Secukinumab	5	2.5	2.5	2.5	2.5
SoC	95	47.5	47.5	47.5	47.5

Budget impact

An overview of the results of the budget impact analysis is presented in Table 60. Based on the settings applied in the base case and the PPP on secukinumab and the other included medicines, the budget impact was estimated to DKK 41,687,803 over all 5 years in the budget impact analysis.

Table 60 Expected budget impact of recommending secukinumab for the indication, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab is recommended	19,379,089	21,124,650	26,693,167	32,216,238	37,686,242
Secukinumab is NOT recommended	9,500,066	14,326,645	19,098,617	23,863,934	28,622,322
Budget impact of the recommendation	**9,879,023**	**6,798,005**	**7,594,550**	**8,352,305**	**9,063,920**

13.1.1 Budget impact sensitivity analysis

Based on discussions with the DMC, a sensitivity analysis in the budget impact analysis was conducted, where biological treatments used in Danish clinical practice were included as comparators in addition to SoC. The sensitivity analysis was conducted in recognition of the use of biological therapies for the treatment of patients with HS, despite these therapies not being officially approved for this indication. The biological treatments were informed by the clinical expert and the PPPs of included biologics were presented in Table 43. In the sensitivity analysis, the biological treatments used in Danish clinical practice were assumed to have the same effect as secukinumab Q4W.

In the sensitivity analysis with inclusion of the biological treatments, a patient uptake for secukinumab of 100% was assumed in the scenario where secukinumab is recommended as standard treatment. A patient uptake of 5% for secukinumab was assumed in the scenario, where secukinumab is not recommended in order to reflect the real-world usage of non-approved biological therapies. In addition to this, a patient uptake of 45% and 50% for biologics and SoC, respectively, was assumed. Table 61 presents the proportions

receiving each biological treatment in the sensitivity analysis as informed by the clinical expert.

Treatment costs for the biological treatments were estimated based on the PPP of each biological treatment, the recommended dosage for each biological treatment in both induction and maintenance phases, and the proportion of patients receiving each biological treatment.

Table 61 Proportions receiving each biological treatment in the budget impact sensitivity analysis

Biological treatments	Proportions
Infliximab	15%
Ustekinumab	10%
Anakinra	1%
Ixekizumab	5%
Bimekizumab	2%
Guselkumab	2%
Adalimumab	10%
Secukinumab	5%

Budget impact in the sensitivity analysis

An overview of the results of the budget impact sensitivity analysis is presented in Table 62. Over all 5 years in the budget impact sensitivity analysis, the budget impact is DKK 38,560,556.

Table 62 Expected budget impact of recommending secukinumab for the indication in the sensitivity analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab is recommended	19,379,089	21,124,650	26,693,167	32,216,238	37,686,242
Secukinumab is NOT recommended	10,788,573	14,857,824	19,580,147	24,298,841	29,013,445
Budget impact of the recommendation	**8,590,516**	**6,266,826**	**7,113,019**	**7,917,397**	**8,672,797**

14. List of experts

Simon Francis Thomsen, Senior Consultant, Professor, Doctor of Medicine, Department of Dermato-Venereology and Wound Healing Center, Bispebjerg Hospital, has been consulted, in order to validate the assumptions and input used in the health economic parts of this application and the health economic model. The input is based on his extensive clinical and research experience within HS and on data from the HS registry at Bispebjerg Hospital.

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Appendix A. Main characteristics of studies included

As the analyses of outcomes for the subgroup of bio-experienced patients are based on pooled data from two identical studies, the SUNSHINE and SUNRISE studies are presented in one table.

Table 63 Main characteristics of the SUNSHINE and SUNRISE studies

Study names: SUNSHINE and SUNRISE	**NCT number: NCT03713619** **NCT number: NCT03713632**
Objective	The objective of this study was to assess the efficacy, safety and tolerability of secukinumab compared to placebo in treatment of moderate to severe HS.
Publications – title, author, journal, year	**Main publication:** 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 studies. Kimball AB, Jemec GB, Alavi A, et.al. Lancet 2023 **Publication of subgroups (prior biological treatment):** Secukinumab in patients with moderate to severe hidradenitis suppurativa based on 1 prior biological exposure: An efficacy and safety analysis from the SUNSHINE and 2 SUNRISE phase III studies. Zouboulis CC, Passeron T, Pariser D, et al (2024) Br J Dermatol. https://doi.org/10.1093/bjd/ljae098
Study type and design	The study was a phase 3, multicentre, randomised, double-blind, placebo-controlled parallel-group study. Patients were randomised in a 1:1:0.5:0.5 ratio to receive either 300 mg secukinumab every 2 weeks (Q2W), 300 mg secukinumab every 4 weeks (Q4W), placebo every 2 weeks or placebo every 4 weeks. During the study, subjects, site staff, persons doing the assessments and the clinical study team were blinded to the treatment. The study is completed. Randomisation was performed using an Interactive Response Technology to assign a randomisation number to the patient. Randomisation was stratified by region, concomitant antibiotic use and body weight. The study consisted of 3 phases: • Screening: up to 4 weeks • Treatment period 1: 16 weeks • Treatment period 2: 36 weeks • Post-treatment follow-up: 8 weeks for all participants, including those who prematurely discontinued

Study names: SUNSHINE and SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632

Those who received placebo in treatment period 1 and continued in treatment period 2 were reassigned to receive the active drug and thus randomised in a 1:1 ratio to receive either 300 mg secukinumab Q2W or 300 mg secukinumab Q4W.

Sample size (n)

Full study population:

The SUNSHINE study included 541 participants in the sample size. In treatment period 1, the 2 placebo groups (Q2W and Q4W) were analysed as 1 group.

	Secukinumab Q2W	Secukinumab Q4W	Placebo
Randomised analysis set	181	180	180
Full analysis set	181	180	180
Safety set	181	180	180

The SUNRISE study included 541 participants in the sample size. In treatment period 1, the 2 placebo groups (Q2W and Q4W) were analysed as 1 group.

	Secukinumab Q2W	Secukinumab Q4W	Placebo
Randomised analysis set	180	180	183
Full analysis set	180	180	183
Safety set	180	180	183

Subgroup population: Bio-experienced patients

	Secukinumab Q2W	Secukinumab Q4W	Placebo
Randomised analysis set	80	81	94
Full analysis set	80	81	94

Study names: SUNSHINE and SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632			
	Safety set	80	81	94
Main inclusion criteria	Inclusion criteria (from clinicaltrials.gov): • 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 5 inflammatory lesions, i.e., abscesses and/or inflammatory nodules ○ Inflammatory lesions should affect at least 2 distinct anatomic areas • Patients agree to daily use of topical over-the-counter antiseptics on the areas affected by HS lesions while on study treatment			
Main exclusion criteria	Exclusion criteria (from clinicaltrials.gov): • 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 • Use or planned use of prohibited treatment. Washout periods detailed in the protocol have to be adhered to • History of hypersensitivity to any of the study drug constituents • History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed) • Pregnant or lactating women			
Intervention	The intervention assessed in the study was subcutaneous injections with 300 mg secukinumab. The dosing schedule consists of injections on week 0, 1. 2. 3 and 4, followed by either every 2 weeks or every 4 weeks. In the subgroup of bio-experienced patients, 161 participants			

Study names: SUNSHINE and SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632
	were randomised to secukinumab; 80 received treatment every 2 weeks, and 81 received treatment every 4 weeks.
Comparator(s)	2 control groups with placebo were included to match the 2 different dosing schedules of the intervention. Thus, placebo was given either every 2 weeks or every 4 weeks. However, in the analysis, the 2 placebo groups are analysed as 1. In total, the placebo group in the bio-experienced subgroup consisted of 94 participants.
Follow-up time	Maximum length of follow-up was 60 weeks, including the 8-week safety follow-up.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint** The primary endpoint was the achievement of HiSCR50 at week 16, which is a collective endpoint including: • ≥50% reduction in AN count • No increase of abscesses • No increase of draining fistulas **Secondary endpoints** The secondary endpoints included the following: • Percentage change from baseline in AN count at week 16 • Flaring up to week 16 • Achievement of NRS30 **Exploratory endpoints** Exploratory endpoints included the following • Achievement of clinical response as defined by HiSCR, absolute and percentage change from baseline in AN count, flares, achievement of pain relief as defined by skin pain NRS30 • Absolute and percentage change from baseline in modified Hidradenitis Suppurativa score • Hidradenitis Suppurativa Global Assessment response • DLQI absolute and percentage change from baseline • DLQI response with a decrease in score greater than 5.0 points from baseline • EQ-5D-3L category and summary scores • Patient global impression of severity and change categories • Absolute and percentage change from baseline in work productivity and activity impairment-specific health problems • HS symptom diary items score change from baseline

Study names: SUNSHINE and SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632
	• Absolute and percentage change from baseline in the inflammatory markers C-reactive protein and erythrocyte sedimentation rate • Level of drug (AIN457) in serum • Anti-AIN457 antibodies in serum • Biomarkers in serum • Achievement of HiSCR at week 16 and up to week 52 in bio-naïve patients • Achievement of HiSCR at week 16 and up to week 52 in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg) **Safety endpoints** Safety was evaluated on the basis of monitoring both AEs and SAEs, including injection site injections. For safety, blood samples, clinical chemistry, vital signs, height, weight and physical examinations were performed. **Endpoints included in this application:** • Percentage of patients achieving HiSCR50, • Percentage change from baseline in AN count • Achievement of NRS30 • Percentage achieving DLQI response with a decrease in score greater than 5.0 points from baseline • Percentage experiencing an SAE • Percentage discontinuing treatment
Method of analysis	In the data analysis, the following analysis sets were included: • Randomised analysis set: all randomised patients analysed according to the assigned treatment at randomisation • Full analysis set: all subjects who had been assigned a treatment and analysed according to the treatment assigned at randomisation • Safety analysis set: all patients who received ≥1 dose of study treatment. In the safety analysis patients were analysed according to the treatment they actually received and not what they were randomised to The primary endpoint was analysed using logistic regression with treatment group, Hurley stage and baseline AN count as explanatory variables. ORs were calculated to compare the secukinumab doses with placebo. A statistical testing hierarchy was used. All safety analyses were performed on the safety analysis set, in which the number and percentage of participants experiencing AEs was collected and summarised for each treatment group.

Study names: SUNSHINE and SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632
	Missing data were multiply imputed based on the estimand strategy related to intercurrent events or missing at random.
Subgroup analyses	Primary and secondary endpoints were investigated in predefined subgroups based on the randomisation stratification. Thus, subgroup analyses of concomitant antibiotic use, body weight (+/- 90 kg), geographical region were conducted. Additionally, age, gender, race, previous use of systemic biologics, CPR levels, ESR levels, Hurley stage, baseline AN count and baseline disease duration were considered subgroup variables. For this application, the analyses were performed based on pooled data from the SUNSHINE and SUNRISE studies. Logistic regression models or an analysis of covariance were performed to assess the effects of secukinumab versus placebo at week 16 for HiSCR, change from baseline in AN count, flares, and NRS30. Covariates included treatment group, baseline AN count or baseline NRS, body weight (<90 kg, ≥90kg), Hurley stage, geographical region, use of antibiotics, and study (SUNSHINE or SUNRISE). Odds ratios (ORs) for HiSCR, flares and NRS30, or difference in LSM for change from baseline in AN count with 95% confidence intervals (CIs) are presented to assess the treatment differences of secukinumab over placebo. For the analyses of HiSCR, change from baseline in AN count, flares, and NRS30 up to week 16, multiple imputation was applied to handle missing data. All additional endpoints were analysed based on observed data.
Other relevant information	None.

Appendix B. Efficacy results per study

Results per study

Table 64 presents the results from the pooled analysis of data from the SUNNY-studies (SUNSHINE and SUNRISE) for bio-experienced HS patients.

Table 64 Results per study (pooled data)

Results of SUNSHINE and SUNRISE (pooled data). NCT03713619 and NCT03713632											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
HiSCR50 at week 16	Secukinumab Q4W	81	38.8% (95% CI: 28.2%, 49.4%)	11.5 %-points	-2.4%, 25.4%	Not reported	OR: 1.67 RR: 1.41	OR: 0.86, 3.22 RR: 0.89, 2.00	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the OR and RR. The RR was estimated based on the OR applying the placebo result of 27.3% as the baseline risk.	Zouboulis et al. 2024 [31]
	Placebo	94	27.3% (95% CI: 18.3%, 36.3%)								
AN count at week 16	Secukinumab Q4W	81	-36.4%	-21.85 %-points	-42.50, -1.20	Not reported	N/A	N/A	N/A	Difference in LSM for change from baseline.	Zouboulis et al. 2024 [31]
	Placebo	94	-14.0%								

Results of SUNSHINE and SUNRISE (pooled data). NCT03713619 and NCT03713632											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
NRS30 at week 16	Secukinumab Q4W	59	33.4% (95% CI: 21.4%, 45.4%)	21.3 %-points	7.0%, 35.6%	Not reported	OR: 3.59 RR: 2.73	OR: 1.35, 9.57 RR: 1.30, 4.70	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the OR and RR. The RR was estimated based on the OR applying the placebo result of 12.1% as the baseline risk.	Zouboulis et al. 2024 [31]
	Placebo	70	12.1% (95% CI: 4.5%, 19.7%)								
DLQI at week 16	Secukinumab Q4W	63	49.2% (95% CI: 36.9%, 61.5%)	17.7 %-points	1.4%, 34.0%	Not reported	RR: 1.56	1.03, 2.38	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the RR.	Zouboulis et al. 2024 suppplemen-tary data [31]
	Placebo	73	31.5% (95% CI: 20.8%, 42.2%)								
SAEs at week 16	Secukinumab Q4W	81	6.2% (95% CI: 0.9%, 11.4%)	3.0 %-points	-3.4%, 9.3%	Not reported	RR: 1.93	0.48, 7.85	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the RR.	Zouboulis et al. 2024 [31]
	Placebo	94	3.2% (95% CI: -0.4%, 6.7%)								
With-drawal	Secukinumab Q4W	81	7.4% (95% CI: 1.7%, 13.1%)	1.0 %-points	-6.5%, 8.6%	Not reported	RR: 1.16	0.39, 3.46	Not reported	The absolute difference in percentages was estimated.	Zouboulis et al. 2024 [31]

Results of SUNSHINE and SUNRISE (pooled data). NCT03713619 and NCT03713632											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
at week 16	Placebo	94	6.4% (95% CI: 1.4%, 11.3%)							The relative difference was presented as the RR.	
Time to loss of response from week 52 and up to week 104 (Median days)	Q4W-Q4W	121	365 (225, not reached)	50	Not reported	Not reported	HR: 0.70	(0.47,1.05)	0.044	The absolute difference in days to LOR was estimated. The relative difference was presented as the HR.	Clinicaltrials.gov. NCT04179174 [30]
	Q4W-PB0	71	171 (113, 337)								

AN, abscess and inflammatory nodule; CI, confidence interval; DLQI, dermatology life quality index; HiSCR50, Hidradenitis Suppurativa Clinical Response of ≥50% reduction; HR, hazard ratio; LSM, least square mean; NRS skin pain, numerical rating scale of the Patient's Global Assessment of Skin Pain–at worst; OR, odds ratio; PBO, placebo; Q4W, every 4 weeks; Q4W-PBO, ransomised to Q4W in the mailn study and to placebo in the extension study; Q4W-Q4W, randomised to Q4W in the main study and in the extension study; RR, relative risk; SAE, serious adverse event.

Appendix C. Comparative analysis of efficacy

Table 65 Comparative analysis of studies comparing secukinumab to placebo for bio-experienced HS patients

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
HiSCR50 at week 16	SUNSHINE and SUNRISE	11.5 %-points	-2.4%, 25.4%	Not reported	OR: 1.67 RR: 1.41	OR: 0.86, 3.22 RR: 0.89, 2.00	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the OR and RR.	Yes
AN count at week 16	SUNSHINE and SUNRISE	-21.85 %-points	-42.50, -1.20	Not reported	N/A	N/A	N/A	Difference in LSM for change from baseline.	No
NRS30 at week 16	SUNSHINE and SUNRISE	21.3 %-points	7.0%, 35.6%	Not reported	OR: 3.59 RR: 2.73	OR: 1.35, 9.57 RR: 1.30, 4.70	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the OR and RR.	No

DLQI at week 16	SUNSHINE and SUNRISE	17.7 %-points	1.4%, 34.0%	Not reported	RR: 1.56	1.03, 2.38	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the RR.	No
SAEs at week 16	SUNSHINE and SUNRISE	3.0 %-points	-3.4%, 9.3%	Not reported	RR: 1.93	0.48, 7.85	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the RR.	No
Withdrawal at week 16	SUNSHINE and SUNRISE	1.0 %-points	-6.5%, 8.6%	Not reported	RR: 1.16	0.39, 3.46	Not reported	The absolute difference in percentages was estimated. The relative difference was presented as the RR.	No
Time to loss of response from week 52 and up to week 104 (Median days)	SUNSHINE and SUNRISE extension study	50 days	Not reported	Not reported	HR: 0.70	(0.47,1.05)	0.044	The relative difference was presented as the HR.	Yes

AN, abscess and inflammatory nodule; CI, confidence interval; DLQI, dermatology life quality index; HiSCR50, Hidradenitis Suppurativa Clinical Response of ≥50% reduction; HR. hazard ratio; LSM, least square mean; NRS skin pain, numerical rating scale of the Patient's Global Assessment of Skin Pain–at worst; OR, odds ratio; RR, relative risk; SAE, serious adverse event.

Appendix D. Extrapolation

Not applicable since no extrapolation was carried out in the model.

D.1 Extrapolation of [effect measure 1]

N/A

D.1.1 Data input

N/A

D.1.2 Model

N/A

D.1.3 Proportional hazards

N/A

D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

For the subgroup of bio-experienced patients in the SUNSHINE and SUNRISE the number of patients who experienced an SAE are shown in Table 66 for 16 weeks and Table 68 for 52 weeks. The preferred term of the SAE has not been published. For this reason, the list of SAEs for the full study population is shown in Table 67 for 16 weeks and Table 69 for 52 weeks.

E.1 Serious adverse events at 16 weeks

Table 66 Bio-experienced patients in SUNRISE and SUNSHINE with an SAE at 16 weeks [31]

	SECQ2W (N=80)	SECQ4W (N=81)	Placebo (N=94)
Patients with serious or other significant events, n (%)			
Death	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal SAEs	4 (5.0)	5 (6.2)	3 (3.2)

SAE: Serious Adverse Event, SECQ2W: secukinumab every 2 weeks, SECQ4W: secukinumab every 4 weeks

Table 67 SAEs by preferred term for the full study population in SUNRISE and SUNSHINE at 16 weeks [28]

	SUNSHINE (N=541)			SUNRISE (N=543)		
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Placebo (N=180)	SECQ2W (N=180)	SECQ4W (N=180)	Placebo (N=183)
Any PT	**3 (1.7)**	**3 (1.7)**	**6 (3.3)**	**6 (3.3)**	**6 (3.3)**	**5 (2.7)**
Hidradenitis	1 (0.6)		2 (1.1)	1 (0.6)		
Amyloidosis					1 (0.6)	
Appendicitis		1 (0.6)				
Arrhythmia				1 (0.6)		
Asthma						1 (0.5)

	SUNSHINE (N=541)			SUNRISE (N=543)		
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Placebo (N=180)	SECQ2W (N=180)	SECQ4W (N=180)	Placebo (N=183)
Basal cell carcinoma					1 (0.6)	
Cellulitis		1 (0.6)				
Cholecystitis				1 (0.6)		
Colitis ulcerative				1 (0.6)		
Confusional state					1 (0.6)	
COVID-19 pneumonia						1 (0.5)
Glomerular vascular disorder						1 (0.5)
Inflammatory bowel disease					1 (0.6)	
Inguinal hernia	1 (0.6)					
Intentional overdose					1 (0.6)	
Osteoarthritis				1 (0.6)		
Otitis externa					1 (0.6)	
Pelvi-ureteric obstruction				1 (0.6)		
Pyrexia						1 (0.5)
Suicide attempt	1 (0.6)					
Sweat gland infection		1 (0.6)				
Urinary tract infection				1 (0.6)		1 (0.5)

	SUNSHINE (N=541)			SUNRISE (N=543)		
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Placebo (N=180)	SECQ2W (N=180)	SECQ4W (N=180)	Placebo (N=183)
Clostridium difficile colitis			1 (0.6)			
Diarrhoea haemorrhagic			1 (0.6)			
Foot fracture			1 (0.6)			
Lung cancer metastatic			1 (0.6)			
Ureterolithiasis			1 (0.6)			

A patient with multiple SAEs with the same PT is counted only once for that PT. Blank fields indicate "0 (0.0)".
COVID-19, coronavirus disease 2019; N, number of patients in arm; n, number of patients with outcome; PT, preferred term; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; SEC, secukinumab 300 mg.

E.2 Serious adverse events at 52 weeks

Table 68 Bio-experienced patients in SUNRISE and SUNSHINE with an SAE at 52 weeks [31]

	SECQ2W (N=80)	SECQ4W (N=81)	Any SECQ2W (N=122)	Any SECQ4W (N=127)
Patients with serious or other significant events, n (%))				
Death	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)*
Non-fatal SAEs	12 (15.0)	10 (12.3)	14 (11.5)	15 (11.8)

SAE: Serious Adverse Event, SECQ2W: secukinumab every 2 weeks, SECQ4W: secukinumab every 4 weeks, Any SECQ2W/Any SECQ4W: includes all patients exposed to secukinumab, including patients randomised to placebo who switched to secukinumab every 2/4 weeks at 16 weeks.
* One patient in the placebo–secukinumab every 4 weeks group who entered the study with a history of stable Crohn's disease had a severe upper gastrointestinal haemorrhage due to duodenal ulcers on day 219 (49 days after last dose of secukinumab) during concomitant treatment with ibuprofen; the patient died on day 249 (79 days after last dose of secukinumab) due to this event. The event were not considered to be related to study treatment due to pre-existing conditions and use of concomitant medications [28]

Table 69 SAEs by preferred term for the full study population in SUNRISE and SUNSHINE at 16 weeks [28]

	SUNSHINE (N=541)				SUNRISE (N=543)			
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Any SECQ2W (N=266)	Any SECQ4W (N=267)	SECQ2W (N=180)	SECQ4W (N=180)	Any SECQ2W (N=261)	Any SECQ4W (N=266)
Any PT	13 (7.2)	9 (5.0)	18 (6.8)	19 (7.1)	19 (10.6)	15 (8.3)	22 (8.4)	23 (8.6)
Hidradenitis	3 (1.7)	3 (1.7)	4 (1.5)	4 (1.5)	4 (2.2)		5 (1.9)	
Sweat gland infection	1 (0.6)	3 (1.7)	1 (0.4)	3 (1.1)	1 (0.6)	0 (0.0)	1 (0.4)	1 (0.4)
Pneumonia				2 (0.7)				
Pyrexia				1 (0.4)	2 (1.1)		2 (0.8)	
Acute kidney injury					2 (1.1)		2 (0.8)	
Intervertebral disc protrusion								2 (0.8)
Appendicitis		1 (0.6)	1 (0.4)	1 (0.4)				
COVID-19	1 (0.6)		1 (0.4)	1 (0.4)				
Cellulitis	1 (0.6)	1 (0.6)	1 (0.4)	1 (0.4)		1 (0.6)		1 (0.4)
Abdominal pain				1 (0.4)				
Breast cellulitis		1 (0.6)		1 (0.4)				
C3 glomerulopathy		1 (0.6)		1 (0.4)				
Constipation				1 (0.4)				
Dizziness				1 (0.4)				
Fatigue				1 (0.4)				
Foot deformity			1 (0.4)	0 (0.0)				
Headache				1 (0.4)				
Hypertensive emergency		1 (0.6)		1 (0.4)				
Infection				1 (0.4)				
Influenza				1 (0.4)				
Inguinal hernia	1 (0.6)		1 (0.4)					
Large intestine infection	1 (0.6)		1 (0.4)					

	SUNSHINE (N=541)				SUNRISE (N=543)			
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Any SECQ2W (N=266)	Any SECQ4W (N=267)	SECQ2W (N=180)	SECQ4W (N=180)	Any SECQ2W (N=261)	Any SECQ4W (N=266)
Meniscus injury	1 (0.6)		1 (0.4)					
Non-small cell lung cancer metastatic	1 (0.6)		1 (0.4)					
Pericarditis		1 (0.6)	0 (0.0)	1 (0.4)				
Peritonsillar abscess				1 (0.4)				
Post procedural infection		1 (0.6)		1 (0.4)				
Pulmonary embolism	1 (0.6)		1 (0.4)					
Sciatica				1 (0.4)	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)
Sepsis				1 (0.4)				
Skin candida			1 (0.4)					
Sleep apnoea syndrome			1 (0.4)					
Suicidal ideation	1 (0.6)		1 (0.4)					
Suicide attempt	1 (0.6)		1 (0.4)					
Tachycardia				1 (0.4)				
Thrombosis	1 (0.6)		1 (0.4)					
Urinary tract infection		1 (0.6)		1 (0.4)	1 (0.6)		1 (0.4)	
Vomiting				1 (0.4)				
Lower limb fracture					1 (0.6)	1 (0.6)	1 (0.4)	1 (0.4)
Nephrolithiasis					1 (0.6)	1 (0.6)	1 (0.4)	1 (0.4)
Abscess							1 (0.4)	
Abscess limb								1 (0.4)
Amyloidosis						1 (0.6)		1 (0.4)
Ankle fracture						1 (0.6)		1 (0.4)
Arrhythmia					1 (0.6)		1 (0.4)	

	SUNSHINE (N=541)				SUNRISE (N=543)			
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Any SECQ2W (N=266)	Any SECQ4W (N=267)	SECQ2W (N=180)	SECQ4W (N=180)	Any SECQ2W (N=261)	Any SECQ4W (N=266)
Basal cell carcinoma						1 (0.6)		1 (0.4)
Breast cancer					1 (0.6)		1 (0.4)	
Cholecystitis					1 (0.6)		1 (0.4)	
Cholecystitis acute					1 (0.6)		1 (0.4)	
Cholelithiasis					1 (0.6)		1 (0.4)	
Clostridium difficile colitis								1 (0.4)
Colitis ulcerative					1 (0.6)		1 (0.4)	)
Colonic abscess						1 (0.6)		1 (0.4)
Confusional state						1 (0.6)		1 (0.4)
Depression					1 (0.6)		1 (0.4)	
Dermatitis infected						1 (0.6)		1 (0.4)
Enterocolitis infectious						1 (0.6)		1 (0.4)
Fibula fracture						1 (0.6)		1 (0.4)
Gastrointestinal haemorrhage								1 (0.4)
Hypotension					1 (0.6)		1 (0.4)	
Inflammatory bowel disease						1 (0.6)		1 (0.4)
Injection site abscess							1 (0.4)	
Intentional overdose						1 (0.6)		1 (0.4)
Joint dislocation						1 (0.6)		1 (0.4)
Localised infection					1 (0.6)		1 (0.4)	
Muscle spasms					1 (0.6)		1 (0.4)	

	SUNSHINE (N=541)				SUNRISE (N=543)			
PT, n (%)	SECQ2W (N=181)	SECQ4W (N=180)	Any SECQ2W (N=266)	Any SECQ4W (N=267)	SECQ2W (N=180)	SECQ4W (N=180)	Any SECQ2W (N=261)	Any SECQ4W (N=266)
Myocardial infarction					0 (0.0)	1 (0.6)		1 (0.4)
Obsessive-compulsive disorder					1 (0.6)		1 (0.4)	
Osteoarthritis					1 (0.6)		1 (0.4)	
Otitis externa						1 (0.6)		1 (0.4)
Pelvi-ureteric obstruction					1 (0.6)		1 (0.4)	
Pyelonephritis					1 (0.6)		1 (0.4)	
Scrotal infection						1 (0.6)		1 (0.4)
Scrotal inflammation								1 (0.4)
Skull fracture						1 (0.6)		1 (0.4)
Soft tissue infection								1 (0.4)
Systematic inflammatory response syndrome					1 (0.6)		1 (0.4)	0 (0.0)
Unevaluable event					1 (0.6)		1 (0.4)	
Viral upper respiratory tract infection								1 (0.4)

A patient with multiple SAEs with the same PT is counted only once for that PT. Blank fields indicate "0 (0.0)".

COVID-19, coronavirus disease 2019; N, number of patients in arm; n, number of patients with outcome; PT, preferred term; SAE, serious adverse event; SECQ2W: secukinumab every 2 weeks, SECQ4W: secukinumab every 4 weeks, Any SECQ2W/Any SECQ4W: includes all patients exposed to secukinumab, including patients randomised to placebo who switched to secukinumab every 2/4 weeks at 16 weeks

Appendix F. Health-related quality of life

Not applicable as it was not regarded as relevant to highlight specific domains from the assessment instrument.

Appendix G. Probabilistic sensitivity analyses

Table 70 shows all parameters included in the PSA including the point estimate, and lower and upper bound and selected probability distributions used in the PSA.

Table 70 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
Settings				
Age_Model2	36,00	29,00	43,00	Normal
Female_Proportion_Model2	0,56	0,45	0,67	Normal
Probabilities				
SEC Q4W -TP Wk 4: HR	0,13	38.87	3.89	Gamma
SEC Q4W -TP Wk 4: R	0,15	0.58	0.06	Gamma
SEC Q4W -TP Wk 4: PR	0,17	639.60	0.00	Gamma
SEC Q4W -TP Wk 4: NR	0,56	544.44	0.00	Gamma
SoC -TP Wk 4: HR	0,08	513.43	0.00	Gamma
SoC -TP Wk 4: R	0,13	300.85	0.00	Gamma
SoC -TP Wk 4: PR	0,16	784.00	0.00	Gamma
SoC -TP Wk 4: NR	0,63	615.54	0.00	Gamma
SEC Q2W -TP Wk 4: HR	0,03	656.43	0.00	Gamma
SEC Q2W -TP Wk 4: R	0,18	355.18	0.00	Gamma
SEC Q2W -TP Wk 4: PR	0,16	2077.66	0.00	Gamma
SEC Q2W -TP Wk 4: NR	0,63	474.27	0.00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SEC Q4W -TP Wk 8: HR	0,12	519.42	0.00	Gamma
SEC Q4W -TP Wk 8: R	0,17	317.49	0.00	Gamma
SEC Q4W -TP Wk 8: PR	0,24	682.95	0.00	Gamma
SEC Q4W -TP Wk 8: NR	0,48	507.54	0.00	Gamma
SoC -TP Wk 8: HR	0,11	404.11	0.00	Gamma
SoC -TP Wk 8: R	0,13	300.85	0.00	Gamma
SoC -TP Wk 8: PR	0,14	751.45	0.00	Gamma
SoC -TP Wk 8: NR	0,62	772.92	0.00	Gamma
SEC Q2W -TP Wk 8: HR	0,11	564.42	0.00	Gamma
SEC Q2W -TP Wk 8: R	0,13	355.18	0.00	Gamma
SEC Q2W -TP Wk 8: PR	0,14	615.54	0.00	Gamma
SEC Q2W -TP Wk 8: NR	0,62	479.59	0.00	Gamma
SEC Q4W -TP Wk 12: HR	0,18	795.32	0.00	Gamma
SEC Q4W -TP Wk 12: R	0,17	306.25	0.00	Gamma
SEC Q4W -TP Wk 12: PR	0,14	484.99	0.00	Gamma
SEC Q4W -TP Wk 12: NR	0,51	507.54	0.00	Gamma
SoC -TP Wk 12: HR	0,11	585.52	0.00	Gamma
SoC -TP Wk 12: R	0,15	298.21	0.00	Gamma
SoC -TP Wk 12: PR	0,09	762.07	0.00	Gamma
SoC -TP Wk 12: NR	0,65	830.80	0.00	Gamma
SEC Q2W -TP Wk 12: HR	0,11	1103.59	0.00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SEC Q2W -TP Wk 12: R	0,15	408.29	0.00	Gamma
SEC Q2W -TP Wk 12: PR	0,09	538.02	0.00	Gamma
SEC Q2W -TP Wk 12: NR	0,65	519.42	0.00	Gamma
SEC Q4W -TP Wk 16: HR	0,22	855.78	0.00	Gamma
SEC Q4W -TP Wk 16: R	0,17	306.25	0.00	Gamma
SEC Q4W -TP Wk 16: PR	0,10	425.66	0.00	Gamma
SEC Q4W -TP Wk 16: NR	0,51	513.43	0.00	Gamma
SoC -TP Wk 16: HR	0,15	762.07	0.00	Gamma
SoC -TP Wk 16: R	0,17	300.85	0.00	Gamma
SoC -TP Wk 16: PR	0,09	720.89	0.00	Gamma
SoC -TP Wk 16: NR	0,58	673.94	0.00	Gamma
SEC Q2W -TP Wk 16: HR	0,15	895.43	0.00	Gamma
SEC Q2W -TP Wk 16: R	0,17	372.89	0.00	Gamma
SEC Q2W -TP Wk 16: PR	0,09	430.18	0.00	Gamma
SEC Q2W -TP Wk 16: NR	0,58	525.51	0.00	Gamma
SEC Q4W -TP Wk 20: HR	0,48	100,00	0,00	Gamma
SEC Q4W -TP Wk 20: R	0,24	100,00	0,00	Gamma
SEC Q4W -TP Wk 20: PR	0,07	100,00	0,00	Gamma
SEC Q4W -TP Wk 20: NR	0,21	100,00	0,00	Gamma
SoC -TP Wk 20: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 20: R	0,00	0,00	0,00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SoC -TP Wk 20: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 20: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 20: HR	0,57	100,00	0,01	Gamma
SEC Q2W -TP Wk 20: R	0,14	100,00	0,00	Gamma
SEC Q2W -TP Wk 20: PR	0,09	100,00	0,00	Gamma
SEC Q2W -TP Wk 20: NR	0,20	100,00	0,00	Gamma
SEC Q4W -TP Wk 24: HR	0,52	100,00	0,01	Gamma
SEC Q4W -TP Wk 24: R	0,21	100,00	0,00	Gamma
SEC Q4W -TP Wk 24: PR	0,09	100,00	0,00	Gamma
SEC Q4W -TP Wk 24: NR	0,19	100,00	0,00	Gamma
SoC -TP Wk 24: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 24: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 24: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 24: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 24: HR	0,64	100,00	0,01	Gamma
SEC Q2W -TP Wk 24: R	0,14	100,00	0,00	Gamma
SEC Q2W -TP Wk 24: PR	0,07	100,00	0,00	Gamma
SEC Q2W -TP Wk 24: NR	0,14	100,00	0,00	Gamma
SEC Q4W -TP Wk 28: HR	0,45	100,00	0,00	Gamma
SEC Q4W -TP Wk 28: R	0,28	100,00	0,00	Gamma
SEC Q4W -TP Wk 28: PR	0,07	100,00	0,00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SEC Q4W -TP Wk 28: NR	0,21	100,00	0,00	Gamma
SoC -TP Wk 28: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 28: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 28: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 28: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 28: HR	0,57	100,00	0,01	Gamma
SEC Q2W -TP Wk 28: R	0,07	100,00	0,00	Gamma
SEC Q2W -TP Wk 28: PR	0,13	100,00	0,00	Gamma
SEC Q2W -TP Wk 28: NR	0,23	100,00	0,00	Gamma
SEC Q4W -TP Wk 32: HR	0,41	100,00	0,00	Gamma
SEC Q4W -TP Wk 32: R	0,21	100,00	0,00	Gamma
SEC Q4W -TP Wk 32: PR	0,12	100,00	0,00	Gamma
SEC Q4W -TP Wk 32: NR	0,26	100,00	0,00	Gamma
SoC -TP Wk 32: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 32: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 32: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 32: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 32: HR	0,46	100,00	0,00	Gamma
SEC Q2W -TP Wk 32: R	0,18	100,00	0,00	Gamma
SEC Q2W -TP Wk 32: PR	0,11	100,00	0,00	Gamma
SEC Q2W -TP Wk 32: NR	0,25	100,00	0,00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SEC Q4W -TP Wk 36: HR	0,45	100,00	0,00	Gamma
SEC Q4W -TP Wk 36: R	0,17	100,00	0,00	Gamma
SEC Q4W -TP Wk 36: PR	0,10	100,00	0,00	Gamma
SEC Q4W -TP Wk 36: NR	0,28	100,00	0,00	Gamma
SoC -TP Wk 36: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 36: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 36: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 36: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 36: HR	0,57	100,00	0,01	Gamma
SEC Q2W -TP Wk 36: R	0,14	100,00	0,00	Gamma
SEC Q2W -TP Wk 36: PR	0,09	100,00	0,00	Gamma
SEC Q2W -TP Wk 36: NR	0,20	100,00	0,00	Gamma
SEC Q4W -TP Wk 40: HR	0,41	100,00	0,00	Gamma
SEC Q4W -TP Wk 40: R	0,17	100,00	0,00	Gamma
SEC Q4W -TP Wk 40: PR	0,14	100,00	0,00	Gamma
SEC Q4W -TP Wk 40: NR	0,28	100,00	0,00	Gamma
SoC -TP Wk 40: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 40: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 40: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 40: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 40: HR	0,50	100,00	0,01	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SEC Q2W -TP Wk 40: R	0,21	100,00	0,00	Gamma
SEC Q2W -TP Wk 40: PR	0,14	100,00	0,00	Gamma
SEC Q2W -TP Wk 40: NR	0,14	100,00	0,00	Gamma
SEC Q4W -TP Wk 44: HR	0,55	100,00	0,01	Gamma
SEC Q4W -TP Wk 44: R	0,03	100,00	0,00	Gamma
SEC Q4W -TP Wk 44: PR	0,14	100,00	0,00	Gamma
SEC Q4W -TP Wk 44: NR	0,28	100,00	0,00	Gamma
SoC -TP Wk 44: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 44: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 44: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 44: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 44: HR	0,50	100,00	0,01	Gamma
SEC Q2W -TP Wk 44: R	0,11	100,00	0,00	Gamma
SEC Q2W -TP Wk 44: PR	0,18	100,00	0,00	Gamma
SEC Q2W -TP Wk 44: NR	0,21	100,00	0,00	Gamma
SEC Q4W -TP Wk 48: HR	0,38	100,00	0,00	Gamma
SEC Q4W -TP Wk 48: R	0,17	100,00	0,00	Gamma
SEC Q4W -TP Wk 48: PR	0,17	100,00	0,00	Gamma
SEC Q4W -TP Wk 48: NR	0,28	100,00	0,00	Gamma
SoC -TP Wk 48: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 48: R	0,00	0,00	0,00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
SoC -TP Wk 48: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 48: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 48: HR	0,32	100,00	0,00	Gamma
SEC Q2W -TP Wk 48: R	0,36	100,00	0,00	Gamma
SEC Q2W -TP Wk 48: PR	0,09	100,00	0,00	Gamma
SEC Q2W -TP Wk 48: NR	0,23	100,00	0,00	Gamma
SEC Q4W -TP Wk 52: HR	0,41	100,00	0,00	Gamma
SEC Q4W -TP Wk 52: R	0,24	100,00	0,00	Gamma
SEC Q4W -TP Wk 52: PR	0,12	100,00	0,00	Gamma
SEC Q4W -TP Wk 52: NR	0,22	100,00	0,00	Gamma
SoC -TP Wk 52: HR	0,00	0,00	0,00	Gamma
SoC -TP Wk 52: R	0,00	0,00	0,00	Gamma
SoC -TP Wk 52: PR	0,00	0,00	0,00	Gamma
SoC -TP Wk 52: NR	1,00	100,00	0,01	Gamma
SEC Q2W -TP Wk 52: HR	0,50	100,00	0,01	Gamma
SEC Q2W -TP Wk 52: R	0,18	100,00	0,00	Gamma
SEC Q2W -TP Wk 52: PR	0,14	100,00	0,00	Gamma
SEC Q2W -TP Wk 52: NR	0,18	100,00	0,00	Gamma
Discont._SEC Q4W_Pre-response	0.00	0.00	0.00	Beta
Discont._SEC Q4W_Year 1_Post-response	0.03	0.02	0.03	Beta
Discont._SEC Q4W_Year 1_All_cycles	0.02	0.02	0.02	Beta

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
Discont._SEC Q4W_Year 2+	0.00	0.00	0.01	Beta
Discont._SoC_Pre-response	0.00	0.00	0.00	Beta
Discont._SoC_Year 1	0.00	0.00	0.00	Beta
Discont._SoC_Year 2+	0.00	0.00	0.00	Beta
Discont._SEC Q2W_Pre-response	0.00	0.00	0.00	Beta
Discont._SEC Q2W_Year 1_Post-response	0.03	0.02	0.03	Beta
Discont._SEC Q2W_Year 1_All_cycles	0.02	0.01	0.02	Beta
Discont._SEC Q2W_Year 2+	0.00	0.00	0.01	Beta
HSUV				
QoL_Model2_HR	0,71	0,58	0,86	Gamma
QoL_Model2_R	0,66	0,52	0,78	Beta
QoL_Model2_PR	0,61	0,49	0,73	Beta
QoL_Model2_NR	0,57	0,46	0,68	Beta
Age_Adjustments_18_29	1.02712	1.03	1.03	Beta
Age_Adjustments_30_39	1.00000	1.00	1.00	Beta
Age_Adjustments_40_49	0.98349	0.80	1.00	Beta
Age_Adjustments_50_69	0.96	0.65	1.00	Beta
Age_Adjustments_70_79	0.96	0.65	1.00	Beta
Age_Adjustments_Over_80	0.85	0.65	0.97	Beta
Costs				

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
AdminCost_SC	453,00	368,58	546,00	Gamma
AdminCost_IV	1625,00	1322,16	1958,60	Gamma
ResourceUseRate_NonSurgery_Model2_OutpatientVisits_HR	3,10	2,52	3,74	Gamma
ResourceUseRate_NonSurgery_Model2_Hospitalizations_HR	0,11	0,09	0,13	Gamma
ResourceUseRate_NonSurgery_Model2_WoundCareVisits_HR	0,67	0,55	0,81	Gamma
ResourceUseRate_NonSurgery_Model2_EmergencyRoomVisits_HR	0,12	0,10	0,14	Gamma
ResourceUseRate_NonSurgery_Model2_Misc1_HR	0,05	0,04	0,06	Gamma
ResourceUseRate_NonSurgery_Model2_Misc2_HR	0,24	0,20	0,29	Gamma
ResourceUseRate_NonSurgery_Model2_OutpatientVisits_R	3,51	2,86	4,23	Gamma
ResourceUseRate_NonSurgery_Model2_Hospitalizations_R	0,23	0,19	0,28	Gamma
ResourceUseRate_NonSurgery_Model2_WoundCareVisits_R	0,47	0,38	0,57	Gamma
ResourceUseRate_NonSurgery_Model2_EmergencyRoomVisits_R	0,20	0,16	0,24	Gamma
ResourceUseRate_NonSurgery_Model2_Misc1_R	0,10	0,08	0,12	Gamma
ResourceUseRate_NonSurgery_Model2_Misc2_R	0,40	0,33	0,48	Gamma
ResourceUseRate_NonSurgery_Model2_OutpatientVisits_PR	4,44	3,61	5,35	Gamma
ResourceUseRate_NonSurgery_Model2_Hospitalizations_PR	0,29	0,24	0,35	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_NonSurgery_Model2_WoundCareVisits_PR	0,64	0,52	0,77	Gamma
ResourceUseRate_NonSurgery_Model2_EmergencyRoomVisits_PR	0,47	0,38	0,57	Gamma
ResourceUseRate_NonSurgery_Model2_Misc1_PR	0,10	0,08	0,12	Gamma
ResourceUseRate_NonSurgery_Model2_Misc2_PR	0,94	0,76	1,13	Gamma
ResourceUseRate_NonSurgery_Model2_OutpatientVisits_NR	4,68	3,81	5,64	Gamma
ResourceUseRate_NonSurgery_Model2_Hospitalizations_NR	0,45	0,37	0,54	Gamma
ResourceUseRate_NonSurgery_Model2_WoundCareVisits_NR	0,45	0,37	0,54	Gamma
ResourceUseRate_NonSurgery_Model2_EmergencyRoomVisits_NR	0,57	0,46	0,69	Gamma
ResourceUseRate_NonSurgery_Model2_Misc1_NR	0,20	0,16	0,24	Gamma
ResourceUseRate_NonSurgery_Model2_Misc2_NR	1,14	0,93	1,37	Gamma
ResourceUseRate_Surgery_Model2_Hospitalizations_HR	0,13	0,11	0,16	Gamma
ResourceUseRate_Surgery_Model2_OutpatientVisits_HR	0,22	0,18	0,27	Gamma
ResourceUseRate_Surgery_Model2_WoundCareVisits_HR	0,12	0,10	0,14	Gamma
ResourceUseRate_Surgery_Model2_Misc1_HR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc2_HR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc3_HR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Hospitalizations_R	0,22	0,18	0,27	Gamma
ResourceUseRate_Surgery_Model2_OutpatientVisits_R	0,35	0,28	0,42	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_Surgery_Model2_WoundCareVisits_R	0,17	0,14	0,20	Gamma
ResourceUseRate_Surgery_Model2_Misc1_R	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc2_R	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc3_R	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Hospitalizations_PR	0,54	0,44	0,65	Gamma
ResourceUseRate_Surgery_Model2_OutpatientVisits_PR	0,67	0,55	0,81	Gamma
ResourceUseRate_Surgery_Model2_WoundCareVisits_PR	0,40	0,33	0,48	Gamma
ResourceUseRate_Surgery_Model2_Misc1_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc2_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc3_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Hospitalizations_NR	0,80	0,65	0,96	Gamma
ResourceUseRate_Surgery_Model2_OutpatientVisits_NR	0,94	0,76	1,13	Gamma
ResourceUseRate_Surgery_Model2_WoundCareVisits_NR	0,85	0,69	1,02	Gamma
ResourceUseRate_Surgery_Model2_Misc1_NR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc2_NR	0,00	0,00	0,00	Gamma
ResourceUseRate_Surgery_Model2_Misc3_NR	0,00	0,00	0,00	Gamma
ResourceUseCosts_NonSurgery_OutpatientVisits	1989,00	1618,33	2397,32	Gamma
ResourceUseCosts_NonSurgery_InpatientVisits	20231,00	16460,75	24384,21	Gamma
ResourceUseCosts_NonSurgery_WoundCareVisits	1625,00	1322,16	1958,60	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseCosts_NonSurgery_EmergencyRoomVisits	1989,00	1618,33	2397,32	Gamma
ResourceUseCosts_NonSurgery_Misc1	1625,00	1322,16	1958,60	Gamma
ResourceUseCosts_NonSurgery_Misc2	36,92	30,04	44,50	Gamma
ResourceUseCosts_Surgery_InpatientVisits_HR	20231,00	16460,75	24384,21	Gamma
ResourceUseCosts_Surgery_InpatientVisits_R	20231,00	16460,75	24384,21	Gamma
ResourceUseCosts_Surgery_InpatientVisits_PR	28862,17	23483,41	34787,27	Gamma
ResourceUseCosts_Surgery_InpatientVisits_NR	24938,91	20291,29	30058,60	Gamma
ResourceUseCosts_Surgery_OutpatientVisits_HR	1989,00	1618,33	2397,32	Gamma
ResourceUseCosts_Surgery_OutpatientVisits_R	1989,00	1618,33	2397,32	Gamma
ResourceUseCosts_Surgery_OutpatientVisits_PR	1989,00	1618,33	2397,32	Gamma
ResourceUseCosts_Surgery_OutpatientVisits_NR	1989,00	1618,33	2397,32	Gamma
ResourceUseCosts_Surgery_WoundCareVisits	1625,00	1322,16	1958,60	Gamma
ResourceUseCosts_Surgery_Misc1	0,00	0,00	0,00	Gamma
ResourceUseCosts_Surgery_Misc2	0,00	0,00	0,00	Gamma
ResourceUseCosts_Surgery_Misc3	0,00	0,00	0,00	Gamma
ResourceUseRate_Psychiatrist_HR	1,00	0,81	1,21	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_Psychologist_HR	1,00	0,81	1,21	Gamma
ResourceUseRate_SocialWorker_HR	2,00	1,63	2,41	Gamma
ResourceUseRate_GP_HR	1,00	0,81	1,21	Gamma
ResourceUseRate_Dermatologist_HR	0,50	0,41	0,60	Gamma
ResourceUseRate_Psychiatrist_R	2,00	1,63	2,41	Gamma
ResourceUseRate_Psychologist_R	2,00	1,63	2,41	Gamma
ResourceUseRate_SocialWorker_R	4,00	3,25	4,82	Gamma
ResourceUseRate_GP_R	2,00	1,63	2,41	Gamma
ResourceUseRate_Dermatologist_R	1,00	0,81	1,21	Gamma
ResourceUseRate_Psychiatrist_PR	3,00	2,44	3,62	Gamma
ResourceUseRate_Psychologist_PR	3,00	2,44	3,62	Gamma
ResourceUseRate_SocialWorker_PR	6,00	4,88	7,23	Gamma
ResourceUseRate_GP_PR	3,00	2,44	3,62	Gamma
ResourceUseRate_Dermatologist_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_Psychiatrist_NR	4,00	3,25	4,82	Gamma
ResourceUseRate_Psychologist_NR	4,00	3,25	4,82	Gamma
ResourceUseRate_SocialWorker_NR	8,00	6,51	9,64	Gamma
ResourceUseRate_GP_NR	4,00	3,25	4,82	Gamma
ResourceUseRate_Dermatologist_NR	2,00	1,63	2,41	Gamma
ResourceUseCost_Psychiatrist	2089,00	1699,69	2517,85	Gamma
ResourceUseCost_Psychologist	636,00	517,47	766,56	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseCost_SocialWorker	263,00	218,87	324,22	Gamma
ResourceUseCost_GP	153,61	124,98	185,14	Gamma
ResourceUseCost_Dermatologist	378,00	307,56	455,60	Gamma
ResourceUseRate_PatientHour	203,00	165,17	244,67	Gamma
ResourceUseRate_PatientHour_NonSurgery_OutpatientVisits_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Hospitalizations_HR	48,00	39,05	57,85	Gamma
ResourceUseRate_PatientHour_NonSurgery_WoundCareVisits_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_EmergencyRoomVisits_HR	24,00	19,53	28,93	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc1_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc2_HR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_NonSurgery_OutpatientVisits_R	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Hospitalizations_R	48,00	39,05	57,85	Gamma
ResourceUseRate_PatientHour_NonSurgery_WoundCareVisits_R	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_EmergencyRoomVisits_R	24,00	19,53	28,93	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc1_R	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc2_R	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_NonSurgery_OutpatientVisits_PR	1,50	1,22	1,81	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_PatientHour_NonSurgery_Hospitalizations_PR	48,00	39,05	57,85	Gamma
ResourceUseRate_PatientHour_NonSurgery_WoundCareVisits_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_EmergencyRoomVisits_PR	24,00	19,53	28,93	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc1_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc2_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_NonSurgery_OutpatientVisits_NR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Hospitalizations_NR	48,00	39,05	57,85	Gamma
ResourceUseRate_PatientHour_NonSurgery_WoundCareVisits_NR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_EmergencyRoomVisits_NR	24,00	19,53	28,93	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc1_NR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_NonSurgery_Misc2_NR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Hospitalizations_HR	24,00	19,53	28,93	Gamma
ResourceUseRate_PatientHour_Surgery_OutpatientVisits_HR	1,83	1,49	2,21	Gamma
ResourceUseRate_PatientHour_Surgery_WoundCareVisits_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Surgery_Misc1_HR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc2_HR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc3_HR	0,00	0,00	0,00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_PatientHour_Surgery_Hospitalizations_R	24,00	19,53	28,93	Gamma
ResourceUseRate_PatientHour_Surgery_OutpatientVisits_R	1,79	1,46	2,16	Gamma
ResourceUseRate_PatientHour_Surgery_WoundCareVisits_R	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Surgery_Misc1_R	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc2_R	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc3_R	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Hospitalizations_PR	60,00	48,82	72,32	Gamma
ResourceUseRate_PatientHour_Surgery_OutpatientVisits_PR	1,83	1,49	2,21	Gamma
ResourceUseRate_PatientHour_Surgery_WoundCareVisits_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Surgery_Misc1_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc2_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc3_PR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Hospitalizations_NR	43,64	35,50	52,59	Gamma
ResourceUseRate_PatientHour_Surgery_OutpatientVisits_NR	1,83	1,49	2,21	Gamma
ResourceUseRate_PatientHour_Surgery_WoundCareVisits_NR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Surgery_Misc1_NR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Surgery_Misc2_NR	0,00	0,00	0,00	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_PatientHour_Surgery_Misc3_NR	0,00	0,00	0,00	Gamma
ResourceUseRate_PatientHour_Psychiatrist_HR	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_Psychologist_HR	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_SocialWorker_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_GP_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Dermatologist_HR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Psychiatrist_R	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_Psychologist_R	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_SocialWorker_R	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_GP_R	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Dermatologist_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Psychiatrist_PR	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_Psychologist_PR	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_SocialWorker_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_GP_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Dermatologist_PR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Psychiatrist_NR	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_Psychologist_NR	2,00	1,63	2,41	Gamma
ResourceUseRate_PatientHour_SocialWorker_NR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_GP_NR	1,50	1,22	1,81	Gamma
ResourceUseRate_PatientHour_Dermatologist_NR	1,50	1,22	1,81	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseRate_PatientHour_Inpatient_Ertapenem	48,00	39,05	57,85	Gamma
ResourceUseRate_PatientHour_Administration	1,50	1,22	1,81	Gamma
ResourceUseCosts_NonSurgery_Transportation_OutpatientVisits	149,00	121,23	179,59	Gamma
ResourceUseCosts_NonSurgery_Transportation_InpatientVisits	149,00	121,23	179,59	Gamma
ResourceUseCosts_NonSurgery_Transportation_WoundCareVisits	149,00	121,23	179,59	Gamma
ResourceUseCosts_NonSurgery_Transportation_EmergencyRoomVisits	149,00	121,23	179,59	Gamma
ResourceUseCosts_NonSurgery_Transportation_Misc1	0,00	0,00	0,00	Gamma
ResourceUseCosts_NonSurgery_Transportation_Misc2	0,00	0,00	0,00	Gamma
ResourceUseCosts_Surgery_Transportation_Hospitalizations	149,00	121,23	179,59	Gamma
ResourceUseCosts_Surgery_Transportation_OutpatientVisits	149,00	121,23	179,59	Gamma
ResourceUseCosts_Surgery_Transportation_WoundCareVisits	149,00	121,23	179,59	Gamma
ResourceUseCosts_Surgery_Transportation_Misc1	0,00	0,00	0,00	Gamma
ResourceUseCosts_Surgery_Transportation_Misc2	0,00	0,00	0,00	Gamma
ResourceUseCosts_Surgery_Transportation_Misc3	0,00	0,00	0,00	Gamma
ResourceUseCosts_Transportation_Psychiatrist	149,00	121,23	179,59	Gamma
ResourceUseCosts_Transportation_Psychologist	149,00	121,23	179,59	Gamma
ResourceUseCosts_Transportation_SocialWorker	149,00	121,23	179,59	Gamma
ResourceUseCosts_Transportation_GP	149,00	121,23	179,59	Gamma

Input parameter	Point estimate	Lower bound /Alpha	Upper bound /Beta	Probability distribution
ResourceUseCosts_Transportation_Dermatologist	149,00	121,23	179,59	Gamma
ResourceUseCosts_Transportation_Inpatient_Ertapenem	149,00	121,23	179,59	Gamma
ResourceUseCosts_Transportation_Administration	149,00	121,23	179,59	Gamma
AE_UnitCosts_Headache	40.18	32.69	48.43	Gamma
AE_UnitCosts_Nasopharingitis	40.18	32.69	48.43	Gamma
AE_UnitCosts_URT	40.18	32.69	48.43	Gamma
AE_UnitCosts_Diarrhoea	40.18	32.69	48.43	Gamma
AE_UnitCosts_Gastroenteritis	40.18	32.69	48.43	Gamma
AE_UnitCosts_Influenza	0.00	0.00	0.00	Gamma
AE_UnitCosts_Toothache	0.00	0.00	0.00	Gamma
AE_UnitCosts_Bronchitis	0.00	0.00	0.00	Gamma
AE_UnitCosts_ViralGastro	0.00	0.00	0.00	Gamma

Appendix H. Literature searches for the clinical assessment.

H.1 Efficacy and safety of the intervention and comparator(s)

N/A. Literature search not performed due to head-to-head study.

Table 71 Bibliographic databases included in the literature search N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A		
Medline			
CENTRAL			

Abbreviations:

Table 72 Other sources included in the literature search N/A

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A		
e.g. EMA website			

Abbreviations:

Table 73 Conference material included in the literature search N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A			

H.1.1 Search strategies

N/A

Table 74 of search strategy table for [name of database] N/A

No.	Query	Results
#1	N/A	

H.1.2 Systematic selection of studies

N/A

Table 75 Inclusion and exclusion criteria used for assessment of studies N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	N/A	
Intervention		
Comparators		
Outcomes		
Study design/publication type		
Language restrictions		

Table 76 Overview of study design for studies included in the analyses N/A

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A					
Study 2						

H.1.3 Excluded full text references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

Not applicable since the HRQoL data came from the SUNNY studies.

I.1 Health-related quality-of-life search

N/A

Table 77 Bibliographic databases included in the literature search N/A

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
Specific health economics databases[1]	N/A	N/A	N/A

Abbreviations:

Table 78 Other sources included in the literature search N/A

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
ScHARRHUD	N/A	N/A	N/A

Table 79 Conference material included in the literature search N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

I.1.1 Search strategies

N/A

Table 80 Search strategy for [name of database] N/A

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

Not applicable since no external literature was used to inform the health economic model.

J.1 External literature for input to the health economic model

N/A

J.1.1 Ex. Systematic search for […]

N/A

Table 81 Sources included in the search N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

J.1.2 Ex. Targeted literature search for [estimates]

N/A

Table 82 Sources included in the targeted literature search N/A

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
	N/A	N/A	N/A

Abbreviations

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