Medicinrådet

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

Vers. 1.0

Bilagsoversigt

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

Den 23. februar 2024

Notat vedrørende Udkast til Medicinrådets anbefaling vedr. secukinumab til behandling af hidrosadenitis suppurativa

Vi takker for udkastet til Medicinrådets anbefaling vedr. secukinumab til behandling af hidrosadenitis suppurativa, modtaget fredag den 9. februar 2024.

Som det er anført i udkastet til Medicinrådets anbefaling, er adalimumab – udover secukinumab - det eneste biologiske lægemiddel, som har EMA indikation til HS. Den relativt udbredte brug af andre off-label biologiske lægemidler til behandling af HS underbygger, at der er et udækket behov for nye godkendte behandlinger.

Vi har enkelte kommentarer til udkastet, hvor en tilretning af teksten og den sundhedsøkonomiske model vil give et mere retvisende billede af evidensen og de sundhedsøkonomiske aspekter for secukinumab.

Effekt på tunneller

Da Medicinrådet i udkastet til Medicinrådets anbefaling har valgt at se på bl.a. effekt på tunneller, gør vi opmærksom på, at der netop er publiceret en peer-reviewed kommentar til SUNNY studierne i Lancet [1].

Denne kommentar har følgende budskaber: 1) at drænerende tunneller er særligt associeret med IL17-pathway, hvilket fremhæver rationalet for brug af en IL17-hæmmer i HS og 2) at det er sandsynligt at secukinumabs effekt vist i SUNNY studierne er undervurderet, da der benyttes HiSCR, som ikke tager højde for effekten på de allerede eksisterende drænerende tunneller.

Langtidsdata for secukinumab

I udkastet er drug-survival beskrevet med real-world data fra en dansk patientpopulation, hvor man så drug-survival for secukinumab på 13 uger. Dette er baseret på data fra relativt få patienter (n=27), hvoraf færre end 3 var bio-naive [2].

Vi har i ansøgningen indsendt langtidsdata for secukinumab fra SUNNY studierne, og vi bemærker, at disse ikke er medtaget i udkastet på trods af, at Medicinrådet sædvanligvis tillægger data for langtidseffekt stor værdi.

Som beskrevet i ansøgningen fuldførte 255 (71%) ud af 360 patienter i SUNNY studierne, som var i behandling med secukinumab hver 4. uge, 52 ugers behandling. Responsraten efter 16 uger var let stigende, og i uge 52 havde hhv. 56.3% i SUNRISE studiet og 62.2% i SUNSHINE studiet opnået HiSCR50 [3]. Dette ser umiddelbart ud til at være lidt bedre end for adalimumab (se ansøgningen).

Det er værd at notere, at mange patienter, som opnåede HiSCR50 i uge 16 fastholdt responset i uge 52, (hhv. 81% i SUNSHINE studiet og 77% i SUNRISE studiet) [3]. Dette er i overensstemmelse med, hvad man ser i danske real-world data, som antyder, at effekten persisterer hos de patienter, som har effekt af secukinumab [2].

Den sundhedsøkonomiske analyse

Der er i den sundhedsøkonomiske model ændret på antagelsen om at inkludere flere linjers behandling i analysen. Argumentationen herfor er, at *"adalimumab og secukinumab grundet sammenlignelig effekt og bivirkningsprofil vil kunne benyttes i vilkårlig rækkefølge hos behandlingsnaive og -erfarne patienter."* Dette mener vi udelukkende er en teoretisk tilgang til den forventede behandlingsalgoritme i dansk klinisk praksis, da der, grundet den forventede prisforskel mellem biosimilært adalimumab og secukinumab,

forventes at være en entydig prioritering af at bruge adalimumab før secukinumab. Derfor vurderer vi, at det er en urealistisk præmis i dansk praksis at ændre i antagelsen omkring flere behandlingslinjer og at det mest retvisende billede i dansk kontekst vil være at inkludere flere behandlingslinjer i den sundhedsøkonomiske model.

I relation til de omkostningselementer, der er inkluderet i den sundhedsøkonomiske analyse, er der ændret på inklusion af patientomkostninger relateret til behandling med henholdsvis adalimumab eller secukinumab. Dette skyldes, at *"de øvrige omkostninger forventes at være sammenlignelige for secukinumab og adalimumab, herunder at begge lægemidler forventes at kunne selvadministreres af patienterne efter oplæring."* Da adalimumab efter induktionsperioden administreres ugentligt sammenlignet med hver fjerde uge for secukinumab, er den tid patienten bruger på selvadministration ikke ens for de to behandlinger. Ud fra et metodisk synspunkt mener vi derfor, at omkostninger til patienttid burde inkluderes i den sundhedsøkonomiske analyse. Dette vil også være i linje med tidligere vurderinger indenfor biologiske behandlinger til andre kroniske inflammatoriske sygdomme og bl.a. også i omkostningsanalysen relateret behandlingsvejledningen for moderat til svær plaque psoriasis [4, 5].

For lægemiddelomkostninger i den sundhedsøkonomiske model, opjusteres 10% af patienter i secukinumab-behandling. Det er vores klare indtryk, at der i samme grad finder opjustering sted hos adalimumab-behandlede patienter, hvorfor vi mener, at opjustering også burde inkluderes for disse patienter i analysen.

Vi anerkender, at ikke alle omkostningselementer vil have lige stor påvirkning af det samlede resultat, men påpeger, at der med Medicinrådets antagelser er op mod 50% forskel mellem vores base-case og Medicinrådets analyse. Et forslag kunne derfor være at inkludere en følsomhedsanalyse, hvor ovenstående kommentarer er imødekommet.

Vi ser frem til Medicinrådets endelige beslutning om ibrugtagning af secukinumab i hidrosadenitis suppurativa i marts 2024.

Med venlig hilsen,
Novartis Healthcare A/S

Alice Brinch Mørch
Value & Access Manager

Joachim Lindholm Bjerg
Nordic HEOR Manager

Referencer

1. Maul J-T, Kolios AGA, Thomsen SF, Ring HC (2024) Secukinumab treatment of hidradenitis suppurativa: questions remain. The Lancet 403:616–617. https://doi.org/10.1016/S0140-6736(23)01616-1

2. Christian Ring H, Thorsen J, Kirby B, et al (2024) Long-term drug survival of adalimumab, infliximab, secukinumab and 1 ustekinumab in hidradenitis suppurativa: A Danish nationwide cohort study 2 3. Br J Dermatol . https://doi.org/10.1093/bjd/ljae042/7596608

3. Kimball AB, Jemec GBE, Alavi A, et al (2023) 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. Lancet 401:747–61. https://doi.org/10.1016/S0140-6736(23)00022-3

4. Medicinrådet (2022) Omkostningsanalyse vedrørende lægemidler til moderat til svær plaque psoriasis . https://medicinraadet-classic.azureedge.net/media/xc2nfblv/medicinr%C3%A5dets_omkostningsanalyse_vedr-_l%C3%A6gemidler_til_moderat_til_sv%C3%A6r_plaque_psoriasis_-_vers-_1-0_adlegacy.pdf. Accessed 22 Feb 2024

5. Medicinrådet (2022) Medicinrådets anbefaling vedr. risankizumab til behandling af psoriasisartrit. https://medicinraadet-classic.azureedge.net/media/4xnllerc/medicinr%C3%A5dets-anbefaling-vedr-risankizumab-til-psoriasisartrit-vers-1-0-x.pdf. Accessed 22 Feb 2024

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

20.02.2024

DBS/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	20.03.2024
Leverandør	Novartis
Lægemiddel	Cosentyx (secukinumab)
Ansøgt indikation	Cosentyx til behandling af aktiv moderat til svær hidrosadenitis suppurativa (HS)
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Cosentyx (secukinumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Rabatprocent ift. AIP
Cosentyx	75 mg	1 stk.	1.888,25	[redacted]	[redacted]
Cosentyx	150 mg	2 stk.	7.540,97	[redacted]	[redacted]
Cosentyx	300 mg	1 stk.	7.540,97	[redacted]	[redacted]

Cosentyx er en del at det biologiske udbud indenfor områderne reumatologi, gastroenterologi og dermatologi. I aftalen er det muligt at regulere prisen to gange om året hhv. den 31. marts og den 30. september. Den eksisterende aftale løber indtil den 30.09.2024.

Konkurrencesituationen

Én anden biologisk behandling, adalimumab, har EMA indikation til moderat til svær HS.

Tabel 2 viser lægemiddeludgifter i relation til andre lægemidler (Medicinrådets vurderingsrapport).

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 ved uge 0,1,2,3,4 og efterfølgende 300 mg hver 4. uge	[redacted]	[redacted]
Hyrimoz (adalimumab)	40 mg	2 stk.	Induktionsperiode med 160 mg i første uge, 80 mg i uge tre og herefter 40 mg ugentligt fra uge 5	[redacted]	[redacted]
Amgevita* (adalimumab)	40 mg	2 stk	Induktionsperiode med 160 mg i første uge, 80 mg i uge tre og herefter 40 mg ugentligt fra uge 5	[redacted]	[redacted]

*Amgevita bliver brugt i situationer hvor der er restordre indtil 31.01.2024. Fra den 01.04.2024 er Amgevita første valg.

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	[redacted]	Link til anbefaling

Konklusion

Leverandøren har valgt at fastholde nuværende pris til denne patientpopulation. I dag er omsætning på [redacted] på de allerede anbefalede indikationer (psoriasis, psoriasis artritis, spondyartritis og juvenil idiopatisk artrit).

Medicinrådet

Application for the assessment of secukinumab (Cosentyx®) in active moderate to severe hidradenitis suppurativa (HS)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table of contents

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Color scheme for text highlighting	
[redacted]	Confidential information

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

1. Basic information

Contact information	
Name	Alice Brinch Mørch
Title	Value and Access Manager
Phone number	+45 28 43 18 25
E-mail	alice_brinch.moerch@novartis.com
Name	Joachim Lindholm Bjerg
Title	Nordic HEOR Manager
Phone number	+45 28 35 18 29
E-mail	joachim.bjerg@novartis.com

Overview of the pharmaceutical	
Proprietary name	Cosentyx®
Generic name	Secukinumab
Marketing authorisation holder in Denmark	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
ATC code	L04AC10
Pharmacotherapeutic group	Immunosuppressants, interleukin inhibitors
Active substance(s)	Secukinumab
Pharmaceutical form(s)	Subcutaneous injection
Mechanism of action	Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases.

Overview of the pharmaceutical	
Dosage regimen	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 every 4 weeks. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, 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.
Other approved therapeutic indications	Adult plaque psoriasis Paediatric plaque psoriasis Psoriatic arthritis Ankylosing spondylitis (AS, radiographic axial spondyloarthritis) Non-radiographic axial spondyloarthritis (nr-axSpA) Juvenile idiopathic arthritis Juvenile psoriatic arthritis Enthesitis-related arthritis
Will dispensing be restricted to hospitals?	NBS – similar to other indications
Combination therapy and/or co-medication	No
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.
Orphan drug designation	No

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

2. Abbreviations

Abbreviation	Full text
AE	Adverse event
AIP	List price
a.m.	Ad modum (in such way, like)
AN	Abscess and inflammatory nodule
CHMP	Committee for Medicinal Products for Human Use
CRP	C-reactive protein
CSR	Clinical study report
DDS	Dansk Dermatologisk Selskab (Danish Dermatology Association)
DLIMI	DLIMI is part of the Danish Association of the Pharmaceutical Industry, working with health care data
DLQI	Dermatology Life Quality Index
HiSCR50	Hidradenitis Suppurativa Clinical Response of ≥50% reduction
HRQoL	Health related quality of life
HS	Hidradenitis Suppurativa
Hs-CPR	High-sensitivity C-reactive protein
IL-17A	Interleukin-17A
MD	Mean difference
OLE	Open label extension
OR	Odds ratio
PGA	Physician global assessment
Q1W	Treatment given every week
Q2W	Treatment given every 2 weeks
Q4W	Treatment given every 4 weeks
QoL	Quality of life
RR	Relative risk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TNF/TNFα-i	Tumour necrosis factor/Tumour necrosis factor alpha inhibitor

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

3. Tables and Figures

List of tables

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

List of figures

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

4. Summary

4.1 Indication

This application concerns secukinumab for the treatment of active moderate to severe hidradenitis suppurativa (HS) in adults with an inadequate response to conventional systemic HS therapy.

4.2 Disease overview

HS is a chronic, disabling inflammatory skin disease, characterised by recurrent painful deep-seated nodules, abscesses, draining fistulae and disfiguring scarring in intertriginous areas [1].

HS has a highly negative impact on quality of life (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, and difficulty performing work duties, and have increased suicidal risk [2–4]. HS is also associated with socio-economic and personal burdensome somatic comorbidities i.e., the metabolic syndrome consisting of cardiovascular risk factors, chronic lymphedema, inflammatory bowel diseases and squamous cell carcinoma [1].

The average onset of HS is in the early 20s, and the disease is three times more prevalent in women than in men [5, 6].

4.3 Current treatment and unmet need

HS is well recognised as a difficult to treat chronic disease [7]. Treatment options include topical treatments, oral treatment with antibiotics (exploiting both the antibacterial as well as the anti-inflammatory effect of either tetracycline or a combination therapy with rifampicin/clindamycin), biological treatment, laser treatment and surgery. In addition, the patient should be supported in losing weight and smoking cessation [1, 8].

Patients with moderate to severe HS, who have not responded adequately to conventional non-biological treatment may be treated with biologic treatment.

Currently, adalimumab, a tumour necrosis factor (TNF) alpha inhibitor (TNFα-i), is the only biologic therapy approved for the treatment of adults with moderate to severe HS. Two similarly designed phase 3 studies demonstrated the superiority of weekly adalimumab over placebo with respect to Hidradenitis Suppurativa Clinical Response (HiSCR50) rate at week 12: 41.8% adalimumab vs. 26.0% placebo in PIONEER I, and 58.9% adalimumab vs. 27.6% placebo in PIONEER II. A Danish registry study showed an average drug survival of 36 weeks [9].

The very limited treatment options for patients with moderate to severe HS who do not respond adequately to conventional non-biologic treatment constitute an unmet need for additional biologic therapies with a favourable benefit-risk profile, and furthermore a different mode-of-action.

4.4 Intervention and comparator

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). 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 every 4 weeks. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients [10].

The comparator adalimumab, a TNFα-i, is the only approved biological treatment for active moderate to severe HS in adults with an inadequate response to conventional systemic HS therapy. The recommended adalimumab dose regimen for adult patients with HS is 160 mg initially at day 1 (given as four 40 mg injections in one day or as two 40

mg injections per day for two consecutive days), followed by 80 mg two weeks later at day 15 (given as two 40 mg injections in one day). Two weeks later (day 29) treatment is continued with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in one day) [11].

4.5 Efficacy and safety

The comparison of efficacy and safety is based on the SUNNY studies (SUNSHINE and SUNRISE) including secukinumab [12] and the PIONEER studies (PIONEER I and II) including adalimumab [13].

The endpoints in the comparative analysis were:

- HiSCR50 responders (primary endpoint in the studies)
- Dermatology Life Quality Index (DLQI) responders, where response is defined by a decrease of 5 or more points vs. baseline
- Proportion of patients with a serious adverse event (SAE)
- Proportion of patients discontinuing treatment

For these endpoints, indirect comparisons a.m. Bucher [14] were performed. In addition, safety profiles and long term efficacy were compared narratively.

The indirect comparisons did not show any statistically significant differences with regard to efficacy, expressed as HiSCR50 responders, effect on QoL, expressed as DLQI responders, proportion of patients who experienced an SAE or proportion of patients who discontinued the treatment, as shown in Table 37.

Of notice, the efficacy of secukinumab seems to increase over time, with more patients achieving HiSCR50 at 52 weeks. In addition, 77-81% of patients who achieved HiSCR50 at 16 weeks with secukinumab 77-81% maintained their response at 52 weeks (data as observed). This is considerably more than the 48.1% observed with adalimumab at 36 weeks.

Based on the indirect and narrative comparisons across the studies, secukinumab is equally efficacious and has a similar safety profile when compared with adalimumab. There is still a significant unmet need in the treatment of HS, and a new treatment alternative with a different mode-of-action and a verified large proportion of patients with long-term efficacy is therefore highly relevant.

4.6 Economic evidence

As there were no significant differences in efficacy and safety between secukinumab and the relevant comparator, adalimumab, the health economic analysis was carried out as a cost minimisation analysis and is based on list prices (AIP) for all treatments included. The base case results indicated that secukinumab is associated with cost per patient savings over the model time horizon of 18 months. The budget impact analysis, based on the cost per patient results, also indicated that a recommendation of secukinumab is associated with cost savings over a five year period.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

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) [15].

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) [7].

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.

The average onset of HS is in the early 20s, and the disease is three times more prevalent in women than in men [5, 6].

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, and difficulty performing work duties, and have increased suicidal risk [2–4]. HS is also associated with socio-economic and personal burdensome somatic comorbidities i.e., the metabolic syndrome consisting of cardiovascular risk factors, chronic lymphedema, inflammatory bowel diseases and squamous cell carcinoma [1].

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% [16]. However, current consensus of the prevalence in Europe is estimated to 1% [1], which translates to ~ 59.000 in Denmark in 2022 of the population [17]. The incidence in Denmark is not known, but estimated to 6/100,000 person-year in the US [18]. Approximately 68% have mild disease (Hurley stage I), 28% moderate disease (Hurley stage II) and 4% severe disease (Hurley stage III) [19], which corresponds to approximately 19,000 persons with moderate or severe HS in Denmark.

Table 1 Incidence and prevalence in the past 5 years

Year	2018	2019	2020	2021	2022
Incidence in Denmark	350	350	350	350	350
Prevalence in Denmark	57,600	57,950	58,300	58,650	59,000
Prevalence of patients with moderate-severe HS	18,432	18,544	18,656	18,768	18,880

Sources: [6, 17, 20]

The treatment of HS is described below, however, 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 [21]. Up to December 2018, a total of 241 HS patients had been treated with biological treatments across all hospital departments [9]. Danish patients treated with adalimumab were on average 42 years old, and 60% were women [9]. 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 330 HS patients are on biological treatment today.

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 will grow by approximately 70 patients per year, a drug survival for adalimumab of 36 weeks [9], and that the majority of patients who stop treatment with adalimumab will be switched to secukinumab, as secukinumab will be the only other approved biological treatment alternative to adalimumab.

Table 2 Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026	2027
Number of HS patients in Denmark who are expected to be treated with biologics in the coming years	400	470	540	610	680
Number of HS patients in Denmark who are expected to be treated with secukinumab in the coming years	18	81	128	180	225

Sources: [9, 22]

5.1.1 Patient populations relevant for this application

Adult patients with active moderate to severe HS with an inadequate response to conventional systemic therapy are relevant for this application.

5.2 Current treatment options and choice of comparator

5.2.1 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 DDS guidelines [8], treatment options include topical treatments, oral treatment with antibiotics , biological treatment, laser treatment and various types of surgery. In addition, the patient should be supported in losing weight and smoking cessation [1, 8].

Patients with HS are treated in general practice and 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 ano-genital abscesses, plastic surgeons, gynaecologists and general practitioners) [19, 21].

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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 approved biological treatment for HS and has been recommended as the treatment choice 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 [8, 21].

It is well recognised that HS is a difficult to treat chronic disease [7]. Treating HS with adalimumab requires higher doses compared with psoriasis [11]. In addition, 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 to other biological off-label treatments, primarily thought to be due to insufficient efficacy. The median survival time for adalimumab was 36 weeks [9]. Thus, considering the very limited treatment options, an unmet need exists for additional systemic therapies with a favourable benefit-risk profile.

Secukinumab is currently approved and used for psoriasis at the dermatology hospital departments. Secukinumab received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the treatment of HS on 26 April 2023, and is expected to be approved by EMA shortly. Regarding efficacy and safety, secukinumab is expected to be equal to adalimumab in an indirect treatment comparison. With a different mode of action, secukinumab will be an alternative to adalimumab in a disease area, where drug survival with adalimumab is relatively short and there therefore is an unmet need for alternative treatment options.

5.2.2 Choice of comparator

Adalimumab is the only approved biological treatment for HS and was recommended as first choice in the latest (now retired) treatment recommendation from the Danish Medicines Council (DMC) [23]. Secukinumab will be an additional treatment choice for HS patients.

5.2.3 Description of the comparator

The following information about adalimumab is based on the Summary of Product Characteristics (SmPC) for Humira [11].

Table 3 Description of adalimumab

Adalimumab	
Generic name (ATC-code)	Adalimumab (ATC-code L04AB04).
Mode of action	Adalimumab targets tumour necrosis factor-alpha (TNF-α), which is involved in causing inflammation and is found at high levels in patients with HS. By blocking TNF-α, adalimumab reduces the inflammation and other symptoms of the disease.
Pharmaceutical form	Solution for injection.
Method of administration	Subcutaneous injection
Dosing	The recommended adalimumab dose regimen for adult patients with HS is 160 mg initially at day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at day 15 (given as two 40 mg

	injections in one day). Two weeks later (day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in one day).
Should the pharmaceutical be administered with other medicines?	No, however it is recommended that the patient should use a topical antiseptic wash on their HS lesions daily during treatment with adalimumab.
Treatment duration/criteria for end of treatment	Disease flare/worsening or lack of response by week 12 according to most recent RADS recommendation (retired).
Necessary monitoring, both during administration and during the treatment period	Standard routine clinical monitoring by treating physician.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Packaging	Adalimumab is available as AMGEVITA, Humira, Hyrimoz and Imraldi, in 20/40 mg solution for injection in single-use pre-filled syringes. Packs of: 2 pre-filled syringes.

5.3 The intervention

The following information about secukinumab is based on the SmPC for Cosentyx [10].

Table 4 Description of secukinumab

Generic name (ATC-code)	Secukinumab (ATC code L04AC10).
Mode of action	Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases.
Pharmaceutical form	Solution for injection in prefilled pen.
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 every 4 weeks. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients.
Method of administration	Subcutaneous injection
Should the pharmaceutical be administered with other medicines?	No, however it is recommended that the patient should use a topical antiseptic wash on their HS lesions daily during treatment with Cosentyx.
Treatment duration/criteria for end of treatment	No formal stopping criteria. Continuous treatment is recommended for as long as the patient is benefitting of treatment in the opinion of the treating physician.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Necessary monitoring, both during administration and during the treatment period	Standard routine clinical monitoring by treating physician.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Packaging	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.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review was conducted to identify relevant publications to assess the efficacy and safety of secukinumab vs. adalimumab for the treatment of HS. The literature searches were performed on 15 November 2022. The searches were performed in PubMed via the National Library of Medicine (NLM) and in CENTRAL (Cochrane Central Register of Controlled Trials (Wiley)). The search strategies are provided in Appendix A.

In addition, the results from the pivotal phase 3 studies for secukinumab in HS, SUNSHINE and SUNRISE, were published by Kimball et al, on 3 February 2023, and the publication has been included in the PRISMA flow.

The eligibility criteria used for the systematic literature review are defined in terms of the population, interventions, comparisons, outcomes (PICOs) and study design framework as well as language and time frame (see Table 21 in Appendix A).

A total of 111 records were identified through PubMed and CENTRAL. Together with the Kimball 2023 publication, a total of 112 records were included in the selection process. With duplicates removed (n = 24), 88 records were left to be screened. Two reviewers, working independently, reviewed the identified records for inclusion by title or abstract according to the PICO selection criteria; this resulted in 73 excluded records. The 15 records that passed the first screening underwent a full-text screening to assess any data of interest according to PICO. Of these, four publications corresponding to four clinical studies were found relevant, which are further described in section 0. There was no disagreement between the reviewers during the full-text screening and study selection process. All 11 records excluded after full-text review are presented with reason for exclusion in Table 22 in Appendix A.

The process of study identification and selection is summarised in Figure 5 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

In addition, clinicaltrials.gov and the EU Clinical Trials Register have been searched for ongoing studies and finalised studies not yet published (see Table 20 in Appendix A), and the Assessment Report for secukinumab has been consulted [24].

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

6.2 List of relevant studies

The included studies are listed below in Table 5.

Table 5 Relevant studies included in the assessment

Reference (title, author, journal, year)	Study name	NCT number	Dates of study (start and expected completion date)
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	SUNSHINE and SUNRISE	NCT03713619 NCT037136322	31 January, 2019-26 July, 2022 25 February, 2019-19 July. 2022
Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa Kimball AB, Okun MM, Williams DA, et al. New England Journal of Medicine 2016 Adalimumab medium-term dosing strategy in moderate-to-severe hidradenitis suppurativa: integrated results from the phase III randomized placebo-controlled PIONEER trials Jemec GBE, Okun MM, Forman SB et al. Br. J. Dermatol. 2019 Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open label extension study. Zouboulis, CC; Okun, MM; Prens, EP et al. J Am Acad Dermatol 2019	PIONEER I and PIONEER II	NCT01468207 NCT01468233	November 2011-January 2014 November 2011-April 2014

For detailed information about included studies, see Appendix B.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

7. Efficacy and safety

7.1 Efficacy and safety of secukinumab compared to adalimumab for active moderate to severe HS

7.1.1 Relevant studies

A brief overview of the relevant studies documenting efficacy and safety of secukinumab and adalimumab compared to placebo for active moderate to severe HS is given below. Detailed study characteristics are described in details in Appendix B. Detailed baseline characteristics of patients included in each study are listed in Appendix C.

SUNSHINE and SUNRISE – phase 3 studies of secukinumab vs. placebo in active moderate to severe HS

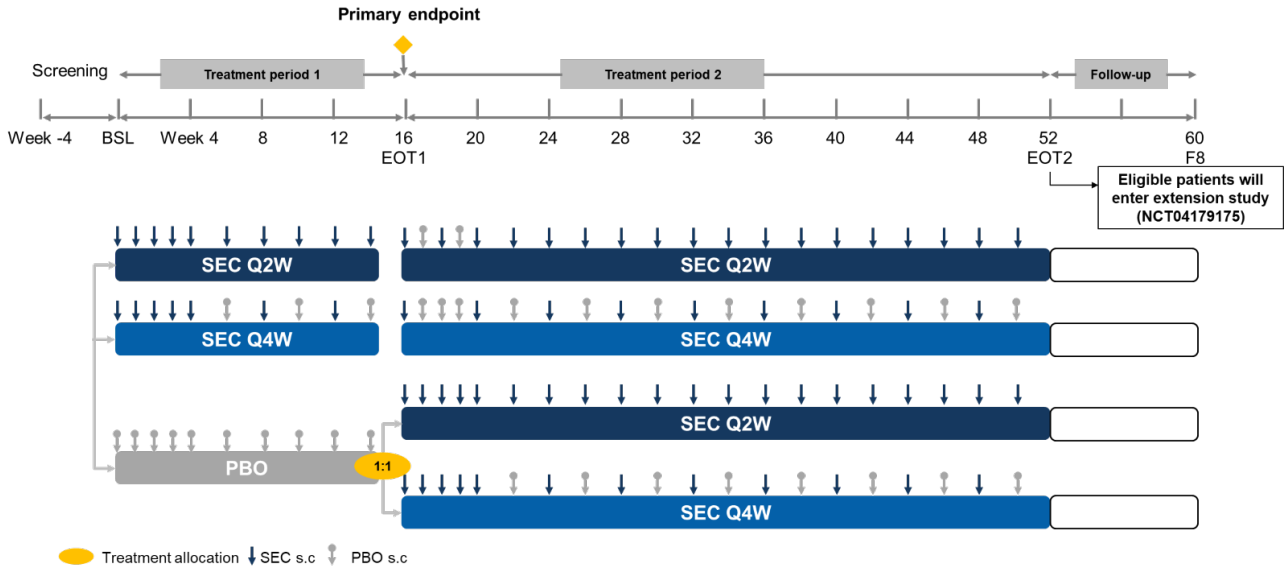
The SUNSHINE (NCT03713619) and SUNRISE (NCT03713632) studies (the SUNNY studies) are two identical Phase 3, randomised, double-blind, placebo-controlled studies conducted to evaluate the efficacy and safety of two secukinumab dose regimens in patients with moderate to severe active HS [12].

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 1 below.

Figure 1: 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 every two weeks (Q2W), 180 to secukinumab every four week (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.

The usual dose of secukinumab for other indications is Q4W. However, it was originally anticipated that the dose for HS patients would need to 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 [12].

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

PIONEER I and II – phase 3 studies of adalimumab vs. placebo in active moderate to severe HS

PIONEER I (NCT01468207) and PIONEER II (NCT01468233) studies (hereafter PIONEER studies) were multicentre, 36-week, phase 3 studies conducted to evaluate the efficacy and safety of adalimumab in patients with moderate to severe active HS [13].

The two studies were similar in eligibility criteria and design, except that:

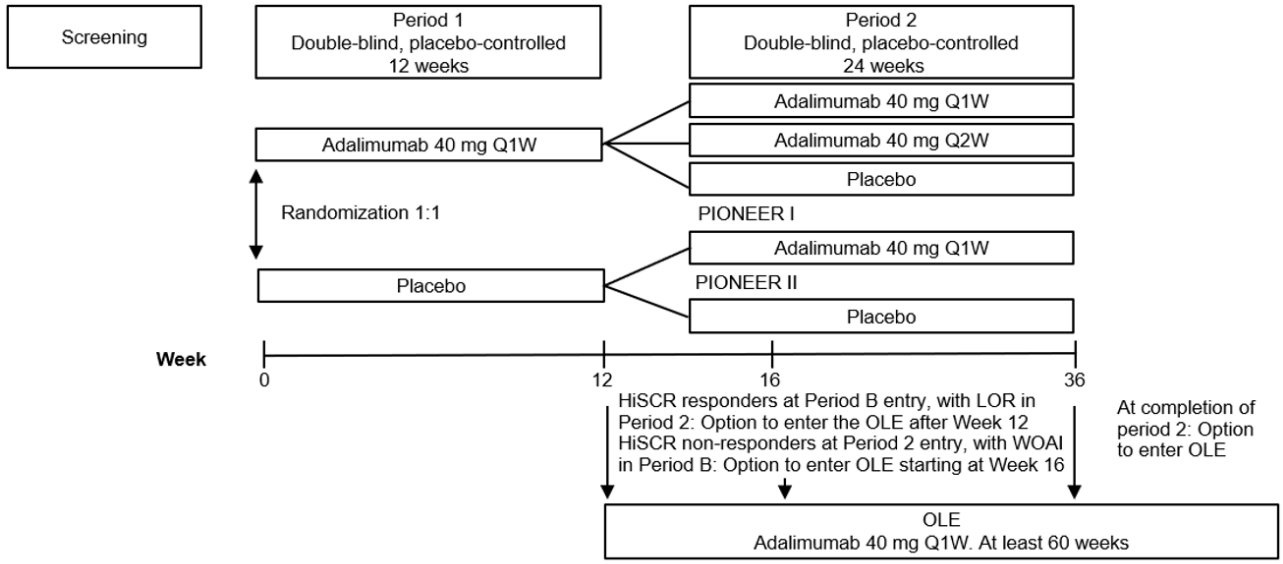
- Concomitant treatment with systemic antibiotics was not allowed in PIONEER I, but was allowed in PIONEER II. Stratification at randomisation based on concomitant use of systemic antibiotics was applied in PIONEER II. In addition, patients were stratified based on Hurley stage 2 or 3 in both studies.
- At re-randomisation after week 12, patients originally randomised to placebo were continuing on adalimumab 40 mg weekly in PIONEER I and on placebo in PIONEER II.

The studies were divided into three parts (plus a post-treatment follow-up period) consisting of screening, a 12-week placebo-controlled period 1 and a 24-week placebo-controlled period 2. All patients who received adalimumab in period 1 and continued to period 2 underwent a second randomisation at week 12. Patients who received placebo in period 1 were reassigned to adalimumab weekly (in PIONEER I) or to placebo (in PIONEER II) in a blinded fashion and received that regimen for 24 weeks.

Patients could enter the multi-centre 60-week phase 3 open label extension (OLE) study if 1) they completed Period B of their respective PIONEER trial; 2) achieved HiSCR50 at entry to Period B of their respective PIONEER study and then experienced a loss of response; or 3) did not achieve HiSCR50 at entry of Period B and then experienced worsening or absence of improvement.

The design for the PIONEER studies is detailed further in below and phases are detailed in Figure 2 below.

Figure 2 Study design for PIONEER I and PIONEER II [25]



Q1W: weekly; Q2W: every other week; HiSCR: Hidradenitis Suppurativa Clinical Response; LOR: loss of response; OLE, open-label extension; WOAI, worsening or absence of improvement

Overall, 307 patients were enrolled in PIONEER I (153 adalimumab and 154 placebo) and 326 in PIONEER II (163 placebo and 163 adalimumab), respectively.

Cross-study comparison

Table 6 summarises the main differences between the SUNNY studies and the PIONEER studies.

Table 6 Comparison between the SUNNY studies and the PIONEER studies

Differences	SUNNY studies	PIONEER studies
Duration of double blind treatment	16 weeks	12 weeks
Eligibility criteria	Concomitant antibiotics allowed Previous biological treatment allowed	Concomitant antibiotics not allowed in PIONEER I
Baseline characteristics	42.6-44.4% male 30.7-40.5% with Hurley stage III 10-14% on concomitant antibiotics 21.7 to 26.2% on previous biological treatment	30.7-40.5% male 45.4-47.4% with Hurley stage III No patients on concomitant antibiotics in PIONEER I, 19% in PIONEER II
Predefined subgroups	Defined in protocol	Not defined
Long term treatment	Possible to follow Q4W treatment in the same population for 52 weeks	Due to re-randomisation after 12 weeks it is only possible to follow a small group of patients on treatment given every week (Q1W) for longer than 12 weeks

In conclusion, the studies are comparable with a few exceptions that may affect study outcome: more severe disease may result in lower efficacy, concurrent antibiotic use may favour the placebo arm, and patients who have previously been treated with biological treatment (and possibly failed) may be more difficult to treat subsequently.

In the SUNSHINE study, the disease severity was slightly higher in the secukinumab arm vs. placebo arm, as 35.0% in the secukinumab arm had Hurley stage III vs. 28.3% in the placebo arm. Apart from this, all four studies had high internal validity with low risk of bias (see Table 23 in Appendix A), and high external validity, as the study populations to a high degree reflected the Danish HS population who is eligible for biological treatment.

7.1.2 Efficacy and safety – results per study

For this application the following outcomes have been evaluated:

- Proportion of patients 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 (HiSCR50)
- Proportion of patients achieving response in DLQI, where response is defined as a decrease in the DLQI score greater than 5.0 points from baseline to follow-up at week 12 or 16
- Safety profile and proportion of patients experiencing an SAE
- Proportion of patients who withdrew during the placebo controlled treatment period
- Long term efficacy (HiSCR50).

In the treatment guideline from RADS, DLQI, Physician Global Assessment (PGA), HiSCR50 and SAEs are included as outcomes. For DLQI, a decrease of four is considered clinically relevant [26], however, DLQI response is defined as a decrease of five or more from baseline in all four included studies [12, 27]. Proportion of patients achieving HiSCR50 is the primary endpoint both in the SUNNY studies and in the PIONEER studies. PGA results were not published for any of the studies. The endpoints are described in more details in Appendix D.

7.1.2.1 Results from secukinumab studies – SUNSHINE and SUNRISE

HiSCR50 responders

Week 16

In the SUNSHINE study, the proportion of patients achieving a HiSCR50 response at week 16 was 41.8% (95% CI: 34.6%–49.3%) in the secukinumab group compared to 33.77% (95% CI: 27.0%–41.2%) in the placebo group, resulting in an absolute difference in effect of 8.24% (95% CI: -1.72%–18.20%) and an odds ratio (OR) of 1.48 (95% CI: 0.95–2.32; p=0.042) [12].

In the SUNRISE study, the proportion of patients achieving a HiSCR50 response at week 16 was 46.1% (95% CI: 38.8%–53.7%) in the secukinumab group compared to 31.2% (95% CI: 24.7%–38.4%) in the placebo group, resulting in an absolute difference in effect of 14.96% (95% CI: 5.06%–24.87%) and an OR of 1.90 (95% CI: 1.22–2.96; p=0.002) [12]. For further details, see Table 29 and Table 30 in Appendix D.

The placebo responses are high in the two studies. High placebo rates for clinical efficacy endpoints are a well-known observation in HS clinical studies, and the high rates appear to be linked to natural disease fluctuation, concomitant medications (e.g., antibiotics, as continuation of stable doses for antibiotic treatment was allowed), or scoring systems used in clinical studies. These factors might have contributed to the high placebo response observed in these studies. High placebo response rates have also been observed in clinical studies in other dermatological diseases [12].

As observed, the result for Q4W in the SUNSHINE study was not statistically significant. A contributing factor for the high placebo response in the SUNSHINE study could be that the disease severity was lower in the placebo arm (28.3%

with Hurley III) vs. the secukinumab arm (35.0% with Hurley III) at baseline [12]. For both studies, statistical significance was achieved for the Q2W dosing regimen, and it should be noted that in SUNSHINE, the difference in response rates between the Q2W and Q4W regimens was only 3 percentage points, and in SUNRISE, the treatment difference vs. placebo was numerically larger for the Q4W regimen than the Q2W regimen. The meta-analysis of the two studies showed a p value of 0.002 (see Table 35). As such, the short-term efficacy has in principle been adequately demonstrated.

To minimise the impact of natural disease fluctuation in the indirect comparison, the results at 12 weeks (same treatment length as for adalimumab) were also analysed for exploratory reasons.

Week 12

In the SUNSHINE study, the proportion of patients achieving a HiSCR50 response at week 12 was [redacted] in the secukinumab group compared to [redacted] in the placebo group, resulting in an absolute difference in effect of [redacted] and an OR of [redacted] (data on file).

In the SUNRISE study, the proportion of patients achieving a HiSCR50 response at week 12 was [redacted] in the secukinumab group compared to [redacted] in the placebo group, resulting in an absolute difference in effect of [redacted] and an OR of [redacted] (data on file or EPAR).

At 12 weeks, the efficacy of secukinumab was statistically superior to placebo in both SUNNY studies. For further details, see Table 29 and Table 30 in Appendix D.

Subgroups

Response rates for HiSCR50 for pre-defined subgroups were analysed. The studies were not powered for subgroup analyses, however, the efficacy of secukinumab vs. placebo seems similar, most notably when it comes to dosing (Q2W and Q4W) and weight (<90 kg/≥90 kg), but also for age (<40years/≥40 years), gender (female/male), concomitant use of antibiotics (yes/no), or previous treatment with biological treatment (yes/no) at baseline [24]. For further details, see Figure 6 in Appendix D.

DLQI responders

In the SUNSHINE study, the proportion of patients achieving a DLQI response at week 16 was 48.4% (95% CI: 39.6%–57.4%) in the secukinumab group compared to 28.9% (95% CI: 21.4%–37.7%) in the placebo group, resulting in an absolute difference in effect of 19.53% (95% CI: 7.84%–31.22%) and an OR of 3.09 (95% CI: 1.76–5,43; p<0.001) [12].

In the SUNSHINE study, the proportion of patients achieving a DLQI response at week 16 was 47.2% (95% CI: 38.8%–55.7%) in the secukinumab group compared to 31.7% (95% CI: 24.4%–40.0%) in the placebo group, resulting in an absolute difference in effect of 15.46% (95% CI: 4.29%–26.63%) and an OR of 1.92 (95% CI: 1.16–3.17; p=0.0112) [12]. For further details, see Table 29 and Table 30 in Appendix D.

At 16 weeks, the DLQI response, in terms of responders, of secukinumab was statistically superior to placebo in both SUNNY studies.

Safety profile

Narrative assessment of adverse events

During the 16 week double blind treatment period, 65.6% and 63.3% of patients in the secukinumab arms, and 66.7% and 63.4% in the placebo arms experienced any AE. The most frequently reported adverse events by preferred term in both studies were headache, nasopharyngitis, and worsening of hidradenitis. No new treatment-emergent adverse events were identified up to week 52 [12].

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.

Serious adverse events

In the SUNSHINE study, the proportion of patients who had experienced an SAE at week 16 was 1.7% (95% CI: 0.4%–5.2%) in the secukinumab group compared to 3.3% (95% CI: 1.4%–7.4%) in the placebo group, resulting in an absolute difference of -1.67% (95% CI: -4.89%–1.55%) and a risk ratio of 0.50 (95% CI: 0.13–1.97; p=0.322) [28].

In the SUNRISE study, the proportion of patients who had experienced an SAE at week 16 was 3.3% (95% CI: 1.4%–7.4%) in the secukinumab group compared to 2.7% (95% CI: 1.0%–6.6%) in the placebo group, resulting in an absolute difference of 0.60% (95% CI: -2.93%–4.13%) and a risk ratio of 1.22 (95% CI: 0.38–3.93; p=0.739) [28].

The rate of SAEs were low and similar between treatment groups. For further details, see Table 29 and Table 30 in Appendix D.

Treatment discontinuations due to adverse events

At week 16, the proportion of patients who discontinued treatment due to AEs was 0% (no events) and 2.2% (four events) in the secukinumab arms vs. 0.6% (one event) and 2.2% (four events) in the placebo arms [12]. The discontinuation rate due to adverse events was low with no difference between treatment groups. For further details, see Table 33 in Appendix E.

Discontinuation for any reason

In the SUNSHINE study, the proportion of patients who had discontinued treatment for any reason at week 16 was 6.1% in the secukinumab group compared to 4.4% in the placebo group, resulting in an absolute difference of 1.67% (95% CI: -2.95%–6.28%) and a risk ratio of 1.38 (95% CI: 0.57–3.34; p=0.482) [12].

In the SUNRISE study, the proportion of patients who had discontinued treatment for any reason at week 16 was 6.1% in the secukinumab group compared to 8.7% in the placebo group, resulting in an absolute difference of -2.63% (95% CI: -8.02%–2.75%) and a risk ratio of 0.70 (95% CI: 0.33–1.46; p=0.343) [12].

The discontinuation rates were low with no differences between treatment arms. For further details, see Table 29 and Table 30 in Appendix D.

Long-term efficacy

In the SUNNY studies, patients on secukinumab continued treatment for up to 52 weeks, while patients initially receiving placebo were re-randomised to receive secukinumab Q2W or Q4W from week 16 up to week 52.

In both studies, the clinical efficacy observed at week 16 was sustained to week 52. HiSCR50 clinical response values observed at week 16 were improved over time to week 52 in both SUNNY studies with respectively 56.3% in the SUNRISE study, and 62.2% in the SUNSHINE study obtaining HiSCR50 at week 52. In the groups switching from placebo to secukinumab at week 16, HiSCR50 response rates increased from 30-37% at week 16 to 48-55% at week 52 (see Figure 3, observed data) [24].

Figure 3 The effects for secukinumab and placebo on HISCR50 [12]

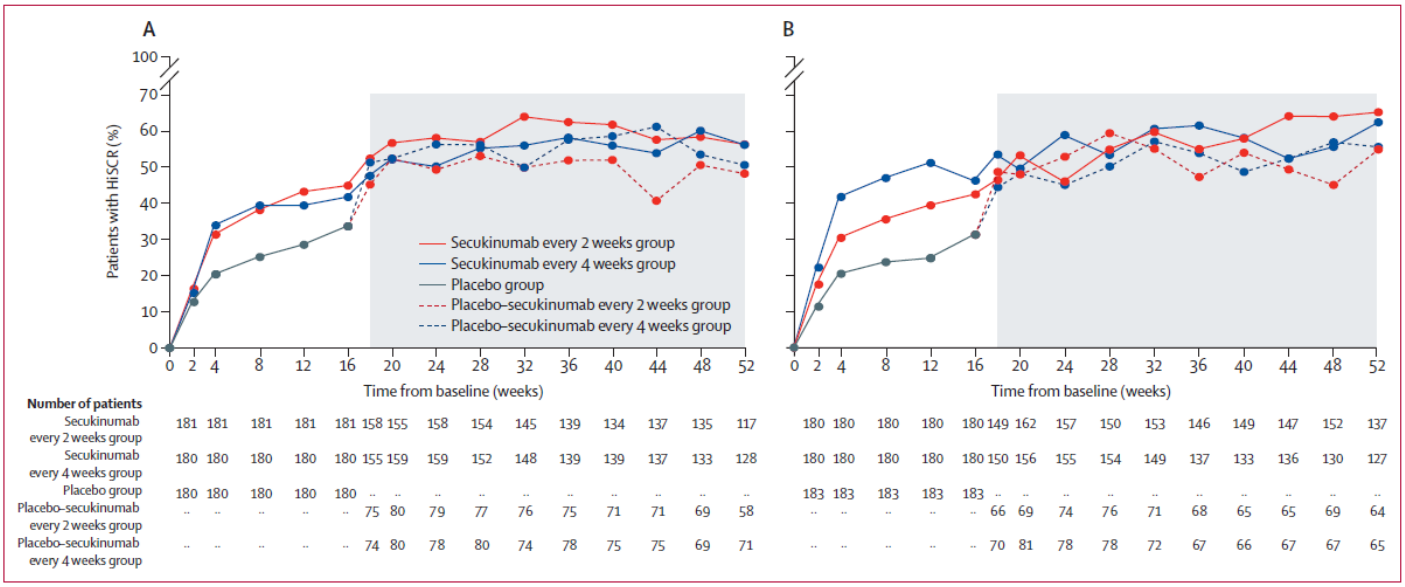


Figure 2: **The effects of secukinumab and placebo on HiSCR**
The effects of secukinumab every 2 weeks, secukinumab every 4 weeks, and placebo on HiSCR from baseline to week 52 in the SUNSHINE (A) and SUNRISE (B) trials. Data for baseline to week 16 are based on the primary estimand and multiple imputation from the week 16 database lock. Data for week 18 to 52 are based on observed data from the week 52 database lock. Dashed lines represent patients switching from placebo at week 16. Grey box represents observed data. HiSCR=hidradenitis suppurativa clinical response.

Of note, in a post-hoc analysis, many patients with a hidradenitis suppurativa clinical response at week 16 maintained the response at week 52 in both the SUNSHINE (42 (81%) of 52 patients on secukinumab Q4W) and the SUNRISE studies (50 (77%) of 65 patients on secukinumab Q4W) [12].

7.1.2.2 Results from adalimumab studies – PIONEER I and PIONEER II

HiSCR50 responders

Week 12

In PIONEER I, the proportion of patients achieving a HiSCR50 response at week 12 was 41.8% in the adalimumab group compared to 26.0% in the placebo group, resulting in an absolute difference in effect of 15.8% (95% CI: 5.41%–26.30%) and a relative risk of 1.61 (95% CI: 1.16–2.23; p=0.004) [13].

In PIONEER II, the proportion of patients achieving a HiSCR50 response at week 12 was 58.9% in the adalimumab group compared to 27.6% in the placebo group, resulting in an absolute difference in effect of 31.29% (95% CI: 21.08%–41.49%) and a relative risk of 2.13 (95% CI: 1.61–2.82; p<0.001) [13].

At 12 weeks, the efficacy of adalimumab was statistically superior to placebo in both PIONEER studies. For further details, see Table 31 and Table 32 in Appendix D.

Baseline differences in the study populations may have contributed to the difference in the observed treatment effect between the two PIONEER studies. The higher disease burden at baseline for patients in PIONEER I (higher mean abscess, inflammatory-nodule, and draining-fistula counts and a higher mean modified Sartorius score) may have led to lower responsiveness to therapy at week 12, thereby contributing to between-study differences in HiSCR50 [13].

DLQI responders

In POINEER I, the proportion of patients achieving a DLQI response at week 12 was 50.7% in the adalimumab group compared to 33.8% in the placebo group, resulting in an absolute difference in effect of 16.9% (95% CI: 5.90%–27.89%) and a relative risk of 1.50 (95% CI: 1.14-1.97; p=0.004) [27].

In PIONEER II, the proportion of patients achieving a DLQI response at week 12 was 49% in the adalimumab group compared to 34% in the placebo group, resulting in an absolute difference in effect of 14.8% (95% CI: 4.15%–25.45%) and a relative risk of 1.44 (95% CI: 1.10–1.88; p=0.008) [27].

At 12 weeks, DLQI response, in terms of responders, of adalimumab was statistically superior to placebo in both PIONEER studies. For further details, see Table 31 and Table 32 in Appendix D.

Safety profile

Narrative assessment of adverse events

During the 12 week double blind treatment period, 50.3% and 57.1% of patients in the adalimumab arms, and 58.6% and 63.2% in the placebo arms experienced any AE. The most frequently reported AEs by preferred term in both studies were headache and nasopharyngitis [13].

In both PIONEER studies, treatment with adalimumab was well tolerated; analysis of safety data from the placebo-controlled period showed similar results across the adalimumab and placebo groups.

Serious adverse events

In the PIONEER I study, the proportion of patients who had experienced an SAE at week 12 was 1.3% in the adalimumab group compared to 1.3% in the placebo group, resulting in an absolute difference of -0.01% (95% CI: -2.56%–2.54%) and a risk ratio of 0.99 (95% CI: 0.14–6.96; p=0.995) [13].

In the PIONEER II study, the proportion of patients who had experienced an SAE at week 12 was 1.8% in the adalimumab group compared to 3.7% in the placebo group, resulting in an absolute difference of -1.84% (95% CI: -5.39%–1.71%) and a risk ratio of 0.50 (95% CI: 0.13–1.97; p=0.321) [13].

The rate of SAEs were low and similar between treatment groups. For further details, see Table 31 and Table 32 in Appendix D.

Treatment discontinuations due to adverse events

At week 12, the proportion of patients who discontinued treatment due to AEs was 0% (no events) and 2.5% (four events) in the adalimumab arms vs. 1.3% (two events) and 3.7% (six events) in the placebo arms [13].

The discontinuation rate due to adverse events was low with no difference between treatment groups. For further details, see Table 33 in Appendix E.

Discontinuation for any reason

In the PIONEER I study, the proportion of patients who had discontinued treatment for any reason at week 12 was 5.2% in the adalimumab group compared to 4.6% in the placebo group, resulting in an absolute difference of 0.65% (95% CI: -4.18%–5.49%) and a risk ratio of 1.14 (95% CI: 0.42–3.07; p=0.791) [13].

In the PIONEER II study, the proportion of patients who had discontinued treatment for any reason at week 12 was 4.9% in the adalimumab group compared to 7.4% in the placebo group, resulting in an absolute difference of -2.45% (95% CI: -7.66%–2.75%) and a risk ratio of 0.67 (95% CI: 0.28–1.59; p=0.360) [13].

The discontinuation rates were low with no differences between treatment arms. For further details, see Table 31 and Table 32 in Appendix D.

Long-term efficacy

In the PIONEER studies, patients were re-randomised after 12 weeks and continued in a 24-week controlled study (36 weeks in total, see Figure 2).

Of the 316 patients randomised to adalimumab Q1W in the PIONEER studies, 300 were re-randomised, and a total of 99 patients continued treatment with adalimumab Q1W during the second treatment phase. Of the 99 patients, 43.4% achieved HiSCR50 at week 36. For patients who had achieved HiSCR50 at 12 weeks, 48.1% maintained the response at week 36 [25].

Following the PIONEER studies, patients could continue treatment with adalimumab Q1W in an OLE study. A total of 88 patients, who had been treated with adalimumab Q1W in both treatment periods in the PIONEER studies, entered the OLE study. The proportion of the 88 patients that had achieved HiSCR50 over time, was 58.0% at 48 weeks (observed data). It should be noted that patients on Q1W during the 12 week double-blind study period, who did not continue in the OLE study were not part of the 88 patients. [29].

7.1.3 Comparative analyses of efficacy and safety

7.1.3.1 Method of synthesis

The comparative analyses of efficacy and safety outcomes were conducted with meta-analyses and indirect treatment comparisons according to DMC guidelines. In addition, the differences in the safety profiles and the long-term efficacy are presented by narrative.

The meta-analyses assessed the relative difference between secukinumab and placebo in the SUNNY studies, and adalimumab and placebo in the PIONEER studies. The relative differences are estimated with inverse variance weights meta-analyses. The random effects meta-analysis was chosen, as it allows for between study differences in the treatment effects, whereas a fixed effects meta-analysis assumes that all studies estimate the same treatment effect. In Appendix C, the comparability of the study populations is described. For the indirect treatment comparison between secukinumab and adalimumab, Bucher's method [14] with inputs from the random effects meta-analyses was used.

7.1.3.2 Results from the comparative analyses

HiSCR50 responders

The relative risk for secukinumab at 16 weeks vs. adalimumab at 12 weeks was 0.72, with 95% CI: 0.52-1.01 and p=0.055. The difference is not statistically significant.

As described in section 7.1.2, high placebo responses were observed in the SUNNY studies, which could be linked to natural disease fluctuation, among other causes, such as concomitant medications (e.g., antibiotics), or scoring systems used in clinical studies [12].

For this reason, two additional sensitivity analyses were performed, one comparing 12-week data for all four studies, and one that included data for adalimumab from two placebo-controlled studies: Bechara 2021 [30], which was excluded because the patient population differs (the patients required surgery), and Glatt 2021 [31], which was a small phase 2 study that was excluded because of major bias in baseline characteristics.

At 12 weeks, the relative risk for secukinumab at 16 weeks vs. adalimumab was 0.90, with 95% CI: 0.56-1.45 and p=0.66. When including Bechara 2021 and Glatt 2021 in the meta-analysis for adalimumab, the relative risk at 12 weeks for secukinumab vs. adalimumab was 0.96, with 95% CI: 0.61-1.51 and p=0.860.

These additional analyses further support that the efficacy of secukinumab and adalimumab are in a similar range, and in conclusion, there is no statistically significant difference between secukinumab and adalimumab with regard to HiSCR50 response in HS.

For additional information, see Table 37 in Appendix F.

DLQI responders

The relative risk for secukinumab at 16 weeks vs. adalimumab at 12 weeks was 1.07, with 95% CI: 0.80-1.43 and p=0.65. The difference is not statistically significant.

For additional information, see Table 37 in Appendix F.

Safety profile

Narrative assessment of adverse events

The proportion of patients experiencing an AE and proportion of patients discontinuing due to an AE was approximately the same in SUNNY studies and the PIONEER studies, taking into account the longer follow up time in SUNNY studies (16 weeks) when compared with the PIONEER studies (12 weeks). The details are shown in Table 7.

Table 7 Proportion of patients with an adverse event or a serious adverse event

Study	SUNSHINE		SUNRISE		PIONEER I		PIONEER II	
Treatment arm	SEC n=180	PLA n=180	SEC n=180	PLA n=183	ADA n=153	PLA n=152	ADA n=163	PLA n=163
Exposure time	16 weeks				12 weeks			
Proportion of patients with at least one Adverse Event, n (%)	118 (65.6)	120 (66.7)	114 (63.3)	116 (63.4)	77 (50.3)	89 (58.6)	93 (57.1)	103 (63.2)
Proportion of patients discontinuing treatment due to an adverse event, n (%)	0	1 (0.6)	4 (2.2)	4 (2.2)	0	2 (1.3)	4 (2.5)	6 (2.7)

SEC: secukinumab Q4W, PLA: placebo, ADA: adalimumab Q1W

The most frequently reported AEs for both secukinumab and adalimumab were nasopharyngitis and headache.

In the following, the safety profiles of secukinumab and adalimumab are compared based on the SmPCs [10, 11]. As the SmPCs of both the products cover multiple indications, calculations of frequency are affected by the sample sizes of studies; moreover, the data in the SmPCs is derived from multiple data sources, including spontaneous reporting, making it very difficult to make any direct comparison between the interventions based on the SmPCs.

Secukinumab

According to the SmPC for Cosentyx, which is based on data across all approved indications, the most frequently reported adverse drug reactions for secukinumab are upper respiratory tract infections (most frequently nasopharyngitis, rhinitis).

Serious infections were reported in 1.2% of the patients treated with secukinumab (in 3,430 patients treated for up to 52 weeks). In psoriasis phase III clinical studies, neutropenia was more frequently observed with secukinumab than

with placebo, but most cases were mild, transient and reversible. Neutropenia <1.0–0.5 × 10^9/L (Common Terminology Criteria for Adverse Events grade 3) was reported in 18 out of 3430 (0.5%) patients on secukinumab, with no dose dependence and no temporal relationship to infections in 15 out of the 18 cases. There were no reported cases of more severe neutropenia. The frequency of neutropenia in psoriatic arthritis and axSpA (AS and nr-axSpA) was similar to psoriasis.

Adalimumab

According to the SmPC for Humira, the most reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache, and musculoskeletal pain.

Serious adverse reactions have been reported for adalimumab. TNFα-i, such as adalimumab, affect the immune system and their use may affect the body's defence against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and tuberculosis), hepatitis B virus reactivation and various malignancies (including leukaemia, lymphoma and hepatosplenic T-cell lymphoma) have also been reported with the use of adalimumab.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

When comparing the safety data in the SmPCs of the two products, it should be kept in mind, that in general, the SmPC of adalimumab holds data from indications which are not covered by secukinumab. In addition, adalimumab was first marketed in 2003, whereas secukinumab was first marketed in 2015; thus, changes in how evaluations were made may play a role, influencing the direct comparability.

For further details, see Appendix E.

Patients experiencing an SAE

The relative risk for secukinumab at 16 weeks vs. adalimumab at 12 weeks was 1.34, with 95% CI: 0.32-5.58 and p=0.69. The difference is not statistically significant. For additional information, see Table 37 in Appendix F.

Discontinuation for any cause

The relative risk for secukinumab at 16 weeks vs. adalimumab at 12 weeks was 1.11, with 95% CI: 0.44-2.81 and p=0.819. The difference is not statistically significant. For additional information, see Table 37 in Appendix F.

Long term efficacy

In the SUNNY studies, the HiSCR50 clinical response values observed with secukinumab at week 16 were improved over time to week 52, where 56.3-and 62.2% had achieved HiSCR50, and in the groups switching from placebo to secukinumab at week 16, HiSCR50 response rates increased from 30- 37% at week 16 to 48-55% at week 52 (observed data). In addition, many patients with a hidradenitis suppurativa clinical response at week 16 maintained the response at week 52 in both the SUNSHINE (42 (81%) of 52 patients on secukinumab Q4W) and the SUNRISE studies (50 (77%) of 65 patients on secukinumab Q4W) [12]. In the PIONEER studies, the rate of HiSCR50-responders for patients on Q1W adalimumab was 43.4% at 32 weeks [25]. At 48 weeks, 58.0% of the 88 included patients had achieved HiSCR50 (observed data), however, the 88 patients were the patients who continued in the OLE study. Patients who withdrew during the 12 week double-blind treatment period are not included in the analysis [29]. For patients who had achieved HiSCR50 at 12 weeks, 48.1% maintained the response at week 36 [25].

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Due to the difference in study design, comparisons should be made with caution. This said, secukinumab seems to have a favourable effect vs. adalimumab with regard to maintenance of response and increase in response over longer treatment time.

Conclusion

Secukinumab seems equally effective vs. adalimumab in the treatment of moderate to severe HS, and with a safety profile which is tolerable when compared with adalimumab.

The indirect comparisons did not show any statistically significant differences with regard to efficacy, expressed as HiSCR50 responders, effect on QoL, expressed as DLQI responders, proportion of patients who experienced an SAE or proportion of patients who discontinued the treatment.

Of notice, the efficacy of secukinumab seems to increase over time, with more patients achieving HiSCR50 at 52 weeks. In addition, 77-81% of patients who achieved HiSCR50 at 16 weeks with secukinumab maintained their response at 52 weeks (data as observed). This is considerably more than the 48.1% observed with adalimumab at 36 weeks.

Both secukinumab and adalimumab have tolerable and manageable safety profiles.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8. Health economic analysis

As previously mentioned in 7.1.3, the results of the indirect treatment comparison demonstrated equal parity of secukinumab and adalimumab, both in terms of safety and efficacy when compared to the relevant comparator with indication for treating active severe to moderate HS.

Based on the parity on both the clinical efficacy and the safety profile, a cost-minimisation analysis was deemed the most appropriate health economic model in the evaluation of secukinumab compared to adalimumab in the perspective of the Danish healthcare system.

8.1 Cost-minimisation model

The health economic model is based on a simple cost-minimisation analysis. Costs included in the model are drug acquisition costs for primary treatment and following treatment, costs related to administration, and patient costs. The perspective of the model is a limited societal perspective only including relevant costs directly associated with treatment of both the intervention and the comparator. All societal costs, benefits etc. are not included, however, in accordance with the national guidelines, patient costs are included to value the time used by patients on any treatment related activity.

The time horizon of the model is 18 months. This is in line with the time horizon in recent assessments of biological treatments made by the Danish Medicines Council and the clinical comparison in the treatment guideline for plaque psoriasis and chronic rheumatoid arthritis, where both secukinumab and adalimumab are included, as well as the treatments used subsequently in this health economic model [32–34]. The model uses a weekly cycle length, and because of this very short length, no half-cycle correction is applied. The discounting for all costs after the first year is 3.5% in accordance with guidelines.

8.1.1 Structure of the model

In the simple cost-minimisation model, patients can be either on primary treatment or following treatment. The intervention is secukinumab and adalimumab is the comparator. Due to the usual treatment regime for biological treatment of HS, where patients often switch treatment, primarily thought to be due to insufficient efficacy, patients will - after the primary treatment - switch to another biological treatment (or discontinue treatment) to mimic the current clinical practice in Denmark. Switching only occurs once in the model, i.e. from primary treatment to following treatment, due to the relatively short time horizon, where it was assessed clinically irrelevant to include several switches.

Primary treatment

Patients enter the model in the primary treatment state. The time in this state, i.e. the drug survival on primary treatment, is determined using data from a Danish registry study of drug survival for biological treatment in patients with HS [9]. The study is an independent registry study of biological treatment in a real-world setting during 2005-2018 from five academic hospitals in Denmark, hence covering all biological treatments of HS in Denmark, and well reflecting how biological treatment of HS take place in a Danish real-world clinical setting. As stated in the study, *"drug survival is a well-established proxy measure for real-life drug performance"*.

The drug survival is illustrated using Kaplan-Meier curves, with median drug survival presented for adalimumab, infliximab, ustekinumab and etanercept. Due to its limited usage in Danish clinical practice and significantly higher risk of treatment discontinuation compared to the other three treatments, etanercept is not incorporated into the health economic model. Table 8 shows the median drug survivals for all biologics available in the model.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

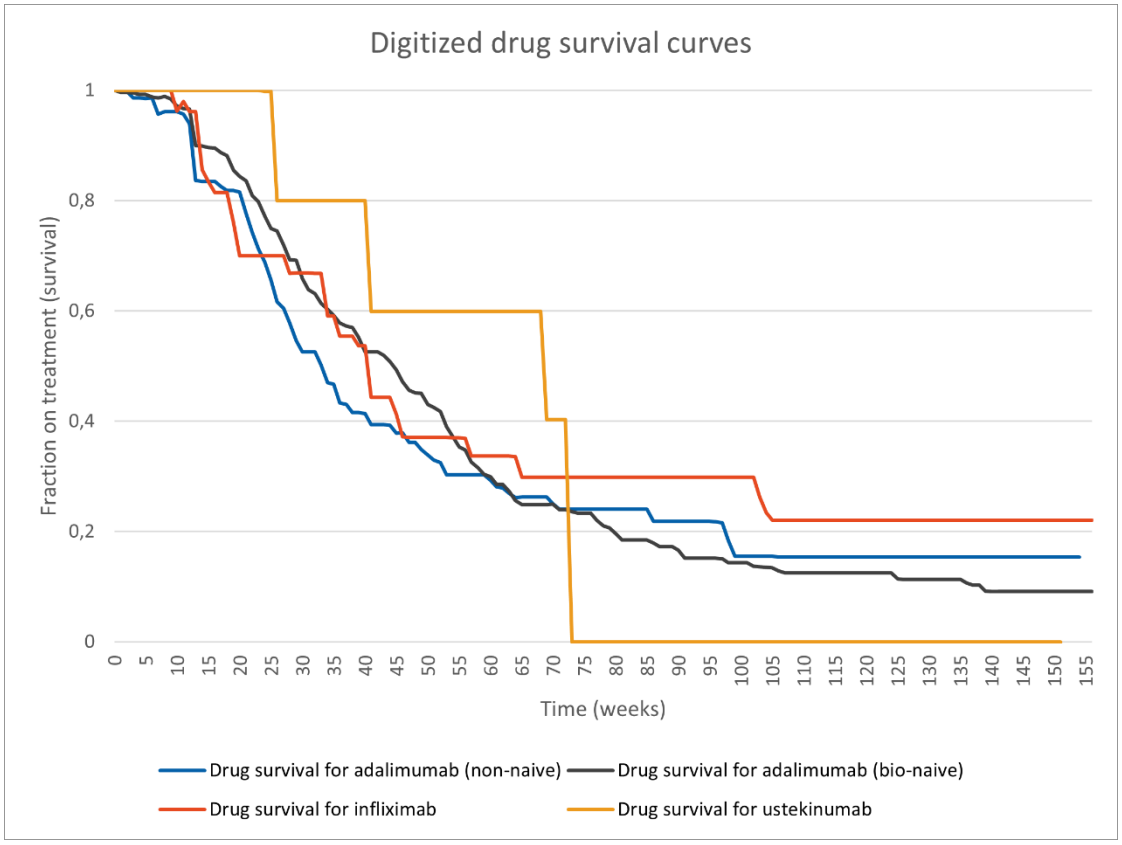
Table 8 Median drug survival for biologics used for treatment HS in Denmark [9]

Biological treatment*	Overall median drug survival (all)	Median drug survival (bio-naïve)	Median drug survival (non-naïve)	P-value bio-naïve vs. non-naïve
Adalimumab	36.0 weeks (n = 256)	39.6 weeks (n = 189)	28.9 weeks (n = 67)	p = 0.2504
Infliximab	28.7 weeks (n = 66)	33.7 weeks (n = 32)	27.1 weeks (n = 34)	p = 0.6302
Ustekinumab	26.0 weeks (n = 22)	40.6 weeks (n = 9)	26.0 weeks (n = 13)	p = 0.2322

*N represents number of treatment series and not the actual patient count

The Kaplan-Meier curves for bio-naïve and non-naïve patients, available from the online supplementary content [35], were used in the model directly because of the short time horizon in the model compared to that of the study. The online WebPlotDigitizer software [36] was used to convert the graphs to data points ready to be used in the model. For adalimumab, both the bio-naïve and non-naïve graphs were digitised, but only the non-naïve graphs were digitised for infliximab and ustekinumab. This was due to the fact that infliximab and ustekinumab graphs are only used in the following treatment state i.e., in non-naïve patients. The digitised drug survival curves are shown in Figure 4.

Figure 4 Digitised drug survival curves for all treatments



The drug survival of patients in the primary treatment state receiving adalimumab is determined through the use of the digitised adalimumab curve (bio-naïve). As there is no available data on drug survival for secukinumab in the Ring et al. 2022 publication, the digitised adalimumab curve (bio-naïve) is utilised for drug survival analysis of patients receiving secukinumab as primary treatment. Note, drug survival from Ring 2022, representing the time patients are

on treatment in real world, is a combined representation of the efficacy and tolerability. Thus, comparing to the clinical controlled trials, which had specific criteria for discontinuing treatment, comes with some limitations. Specifically the SUNNY studies, where patients in general stayed on treatment to investigate the long term efficacy on the HiSCR50 response (52 weeks), the 52 weeks efficacy data does not represent a useful measure of drug survival to be used in this health economic model. The selection of adalimumab as a proxy for drug survival of secukinumab is supported by the findings that only etanercept exhibited significantly lower drug survival than all other biologics included in the Ring 2022 study [9], whereas all others showed comparable drug survival.

In addition to the digitised Kaplan-Meier data, the model permits the utilisation of a calculated curve based on median drug survival. This calculated curve is obtained from an exponential function, as only median survival data is available, thereby allowing for the calculation of a scale parameter for the exponential function. This is achieved by isolating the scale parameter from the exponential survival function (as depicted in the function below).

$$scale\ parameter = \frac{\ln(2)}{median\ survival}$$

The digitised data is chosen as it represents the true drug survival of Danish patients and to minimise any uncertainty around the exponential function and also because the follow-up of the study is sufficiently long to cover the entire time horizon of the model. In Appendix K drug survival curves for all biological treatments are shown together with the calculated curves.

Following treatment

When patients fail on the primary treatment, patients move to the following treatment state, where they receive other treatments depending on which primary treatment they initially received in the model (either secukinumab or adalimumab). In Table 9 the distribution for both the intervention arm and comparator arm in the model.

Table 9 Distribution of following treatments

Following treatment	Secukinumab as primary treatment	Adalimumab as primary treatment
Secukinumab	0%	70%
Adalimumab (non-naive)	70%	0%
Infliximab	10%	10%
Ustekinumab	10%	10%
Discontinuation	10%	10%

Based on 2021 sales numbers from DLIMI, just over 70% of patients on biological treatment for HS were treated with adalimumab and around 10% were treated with either infliximab or ustekinumab. These percentages are used in the model, where 70% of patients will receive secukinumab as following treatment after adalimumab as primary treatment and 10% will receive infliximab, ustekinumab, or will discontinue biological treatment. The assumption of only 10% discontinuing biological treatment is in contrast to the findings by Ring et al. 2022 [9], where a large proportion of patients discontinue on biological treatment (no specific percentage available), primarily thought to be due to insufficient efficacy. However, since more treatment options are becoming available for treatment of a chronic condition like moderate to severe HS, it is expected that fewer patients discontinue biological treatment after the first treatment and instead are offered more treatment. With the introduction of secukinumab as a biological treatment indicated for HS, it was assumed that only 10% will now discontinue treatment after adalimumab. The patients

receiving infliximab after adalimumab is assumed to experience secondary failure on the primary treatment which is why they are eligible to receive another TNFα-i. The same distributions are applied to patients on secukinumab treatment with the only difference being that 70% of these patients will receive adalimumab as following treatment. No patients are assumed to switch back to the primary treatment. All distributions are editable in the model.

Because of the current market landscape with biosimilars available for adalimumab, secukinumab is expected to be second line choice in biological treatment of active moderate to severe HS after adalimumab if recommended as standard treatment. The assumption that the distribution of following treatment is identical between adalimumab and secukinumab is therefore a conservative approach. A sensitivity analysis with secukinumab positioned as second line treatment is therefore presented in section 8.7.

8.1.2 Summary of the model and results

Table 10 Model overview

Summary of base-case assumptions and results of the health economic model	
Model type	Cost-minimisation model
Perspective	Limited societal perspective
Time horizon	18 months
Discounting	3,5%
Population	Moderate to severe HS
Intervention	Secukinumab, 300 mg week 0, 1, 2,3, and 4 followed by 400 mg every 4 weeks
Comparator	Adalimumab, 160 mg week 0, 80 mg week 2, and 40 mg week 4 followed by 40 mg every week
Included costs	Drug acquisition costs for primary and following treatment Administration costs for i.v. treatment Patient costs
Time to treatment shift	Adalimumab: KM data on drug survival for adalimumab (bio-naïve) Secukinumab: KM data on drug survival for adalimumab (bio-naïve)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Following treatment matrix		Secukinumab as primary	Adalimumab as primary
	Secukinumab	0%	70%
	Adalimumab (non-naive)	70%	0%
	Infliximab	10%	10%
	Ustekinumab	10%	10%
	Discontinuation	10%	10%
Result output	Per-patient costs for intervention and comparator (discounted) including drug acquisition costs, administration costs and patient costs Incremental per-patient costs of intervention vs. comparator (discounted)		

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

N/A

8.3 Extrapolation of relative efficacy

N/A

8.4 Documentation of health-related QoL (HRQoL)

N/A

8.5 Resource use and costs

8.5.1 Drug acquisition costs

The drug acquisition costs for all treatments included in the health economic model were based on the recommended dosage and list price (AIP). Information on dosage was obtained from the pertinent SmPCs and all costs were sourced from medicinpriser.dk. For off-label use, the dosage for plaque psoriasis was used. Drug wastage is not included in the model, as this is not expected for any of the included treatments. Table 11 summarises all drug acquisition costs.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 11 Strength, pack size, AIP price and dosing schedule for all treatments in the health economic model

Drug	Strength	Pack size	AIP	Dosing schedule	Reference
Secukinumab	300 mg	1	7,710.60 DKK	300 mg week 0, 1, 2,3, and 4 followed by 400 mg every 4 weeks	[37]
Adalimumab	40 mg	2	4,367.57 DKK	160 mg week 0, 80 mg week 2, and 40 mg week 4 followed by 40 mg every week	[38]
Infliximab	100 mg	1	2,262.46 DKK	5 mg/kg in week 0, 2, and 6 followed by 5 mg/kg every 8 weeks	[39]
Ustekinumab	45 mg	1	20,493.37 DKK	45 mg in week 0 and 4 followed by 45 mg every 12 weeks	[40]

Primary treatment

The costs for primary treatment in the health economic model are calculated using a cycle cost based on the total dose for the first year (with induction dosage) and the following years (maintenance dosage). For both secukinumab and adalimumab, the total dosage for induction dosage and maintenance dosage was divided by the cycle length to get the per cycle drug cost. This is shown in Table 12. The per cycle drug cost in the first 12 months of the model is based on the induction dosage and for the last six months of the model, the per cycle drug cost is based on the maintenance dosage.

Table 12 Dosage and per cycle drug acquisition costs for induction and maintenance phase

Drug	Secukinumab	Adalimumab
First year dose (induction dose)	4,800 mg	2,160 mg
Per cycle cost first year (AIP)	2,372.49 DKK	2,267.78 DKK
Following years dose (maintenance dose)	3,900 mg	2,080 mg
Per cycle cost following years (AIP)	1,927.65 DKK	2,183.79 DKK

Following treatment

Due to the memory less property of the health economic model, it is not possible to determine when exactly a patient will move from the primary treatment to the following treatment state. Consequently, it is not possible to calculate an exact induction and maintenance dosage for this state in the model. Instead, one-off per patient drug costs are calculated based on the distribution (see Table 9) and the mean drug survival for each of the following treatments (see Table 8). The mean drug survival is calculated via the exponential functions for each of the following treatments. In Table 13, the per patient costs for each of the following treatments are shown.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 13 Drug acquisition costs for all following treatments (AIP prices)

	Secukinumab*	Adalimumab (non-naive)**	Infliximab***	Ustekinumab	Discontinuation
Mean drug survival	41.69 week(s)	41.69 week(s)	48.62 week(s)	58.57 week(s)	-
Total dose in period	5,400 mg	1,760 mg	3,600 mg	270 mg	-
Per patient cost	107,948.40 DKK	96,086.54 DKK	81,448.56 DKK	122,960.22 DKK	0 DKK

* Adalimumab non-naïve is chosen

** Non-naïve is chosen for following treatment

*** Average body weight assumed to be 90 kg based on the average body weight from the clinical comparison in the treatment guideline for plaque psoriasis

8.5.2 Patient costs

Costs associated with patient time are included in the model. The unit costs for patient time are 203.00 DKK/hour based on the catalogue for unit costs (version 1.7). Patient time for self-administration of all subcutaneous treatments is included as a 10 min. administration. For simplicity, the multiple administration of adalimumab during induction phase is not taken into consideration, since this has little to no effect on the overall result. Transport costs for intravenous infusion of infliximab is included with 149.20 DKK per transport based on the catalogue for unit costs (version 1.7).

All patient costs are calculated as a first year (induction phase) and following year (maintenance phase) cost per cycle (see the sheet “Other costs” in the model). An average of the two is used in the model for simplicity, since this has very little impact on the overall result.

8.5.3 Administration costs

Costs of drug administration for all subcutaneous administered drugs are excluded from the model based on the assumption that the initiation of all treatments would be the same, and afterwards all patients can administer the treatment themselves. Only administration costs for intravenous infliximab in the following treatment state are included. The DRG rate 09MA98 (diagnosis "(DL732) Suppurerende hidrosadenitis" and procedure "(BOHJ18A1) Behandling med infliximab") of 2,041.00 DKK is used and calculated as a first year (induction phase) and following year (maintenance phase) cost per cycle. An average of the two is used in the model for simplicity, since this has no impact on the overall result.

It is assumed that an infusion takes 120 min. based on an approximation from the patient guidance for treatment with infliximab at Aarhus University Hospital [41].

8.5.4 Monitoring costs/hospital costs

According to the cost analysis in moderate to severe plaque psoriasis from the DMC, the costs related to initiation of treatment (pre-treatment examination, training of patients in home administration etc.) and monitoring (monitoring visits, blood tests etc.) are identical between all biological treatments. Based on this, it is assumed that the monitoring and hospital costs are identical between secukinumab and adalimumab and are therefore not included in the health economic model.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.5.5 Adverse event costs

In section 7.1.3.2, the safety profile is described in detail. From here it is evident that the proportion of patients experiencing an AE and the proportion of patients discontinuing due to an AE is approximately the same in SUNNY studies and PIONEER studies – even taking into account the longer follow up time in SUNNY studies (details are shown in Table 7). No significant difference between patients experiencing SAEs (p = 0.69) and discontinuation for any cause (p = 0.819) was observed (details in Table 37 in Appendix F).

Because of the similar and tolerable safety profiles between adalimumab and secukinumab, no costs related to AEs are included in the model. This is also in line with the nature of the cost-minimisation model where the underlying assumption is equal effect and safety.

8.6 Results

8.6.1 Base case results

The base case results indicate that the use of secukinumab for treating moderate to severe HS (173,363.20 DKK) is associated with an incremental saving compared to adalimumab (178,002.28 DKK) of 4,639.08 DKK per patient over the time horizon of 18 months in this health economic model.

Drug acquisition costs are the main driver of the result, and it is important to note that the results are based on the AIP prices of all treatments. The patient costs for adalimumab are higher than for secukinumab, primarily due to the more frequent administration every week compared to every four weeks. The base case results are presented in Table 14.

Table 14 Base case results (discounted)

Cost component	Secukinumab	Adalimumab	Incremental
Drug acquisition costs	171,119.83 DKK	175,167.59 DKK	-4,047.76 DKK
Patient costs	1,495.74 DKK	2,087.06 DKK	-591.33 DKK
Administration costs	747.63 DKK	747.63 DKK	0.00 DKK
Total costs	173,363.20 DKK	178,002.28 DKK	-4,639.08 DKK

8.7 Sensitivity analyses

As mentioned in section 8.1.1, it is expected that secukinumab will be positioned as second line option after adalimumab in Danish clinical practice due to biosimilars being available. To reflect the expected Danish clinical practice in the best possible way, a sensitivity analysis with distributions for following treatment of patients treated with secukinumab positioned as second line was performed. In this scenario, if patients fail on secukinumab, there are limited treatment options available. Based on the results from Ring et al. 2022 [9], where a large proportion discontinues after trying the available biological treatment with the indication, it was assumed that 40% of the patients will discontinue treatment. In addition, it is assumed that 40% of the patients will be put on ustekinumab because of a different mode of action and the rest of the patients (20%) will receive infliximab. No patients are assumed to switch back to adalimumab. The drug survival for primary treatment with secukinumab is based on the survival function of adalimumab (non-naïve).

The results from this sensitivity analysis, mimicking the expected clinical practice, indicate that the use of secukinumab for treating moderate to severe HS (145,326.01 DKK) is associated with an incremental saving compared to adalimumab (178,002.28 DKK) of -32,676.28 DKK per patient over the time horizon of 18 months in this health economic model.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

9. Budget impact analysis

The budgetary impact of using secukinumab as a treatment option for moderate to severe HS is estimated using a five-year budget impact model based on the undiscounted cost per patient from the health economic model. The budget impact model is embedded in the cost per patient model, and any changes in the settings of the cost per patient model would affect the results of the budget impact model.

The budget impact analysis estimates two scenarios where:

- secukinumab is recommended as a standard treatment for patients with moderate to severe HS

or

- secukinumab is not recommended as a standard treatment for patients with moderate to severe HS

9.1 Estimating patient population

The patient numbers in the budget impact model follow the initially stated numbers from the request for assessment of secukinumab for HS. Table 15 shows the estimated number of HS patients expected to be treated with biological treatment (see section 5.1 for more information).

Table 15 Patient population in year 1-5

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	400	470	540	610	680

The expected patient numbers are based on input from an advisory board with participants from five of the six dermatology departments from the university hospitals. Aalborg University hospital did not participate in this advisory board since they had not received permission to use biological treatment for treatment of HS until after the advisory board.

9.2 Market share and patient numbers

9.2.1 Market share

The market shares with a recommendation of secukinumab is based on input from the same advisory board as previously mentioned and are shown in Table 16. In the situation of no recommendation of secukinumab, the market share is expected to very slowly increase and eventually be 10% in year five.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 16 Market shares in biological treatment of HS

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab is recommended					
Secukinumab	5%	17%	24%	30%	33%
Adalimumab	96%	83%	76%	70%	67%
Secukinumab is not recommended					
Secukinumab	1%	3%	5%	7%	10%
Adalimumab	99%	97%	95%	93%	90%

There are no separate market shares included for the off-label use of infliximab and ustekinumab because they are included in the cost per patient model already.

9.2.2 Patient numbers

The patient numbers are based on the total numbers of patients and the market shares and are shown in Table 17.

Table 17 Number of patients based on market shares

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab is recommended					
Secukinumab	18	81	128	180	225
Adalimumab	382	389	412	430	455
Secukinumab is not recommended					
Secukinumab	4	14	27	43	68
Adalimumab	396	456	513	567	612

9.2.3 Budget impact results

Based on the base case settings in the health economic model, the market shares and the patient numbers, the budget impact of recommending secukinumab as a treatment option for patients with moderate to severe HS in Denmark at AIP was -12,194.69 DKK in year 1 and -163,729.31 DKK in year 5 (see Table 18).

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 18 Budget impact results, AIP prices

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab is recommended	55,749,120.43 DKK	26,319,705.72 DKK	12,383,997.20 DKK	12,444,245.65 DKK	12,430,154.34 DKK
Secukinumab is not recommended	55,761,315.11 DKK	26,422,312.45 DKK	12,627,295.95 DKK	12,613,551.37 DKK	12,593,883.65 DKK
Budget impact	-12,194.69 DKK	-102,606.73 DKK	-243,298.75 DKK	-169,305.71 DKK	-163,729.31 DKK

The budget impact of off-label use of infliximab and ustekinumab is represented in the budget impact of secukinumab and adalimumab due to the following treatment state in the health economic model.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

10. Discussion on the submitted documentation

This assessment of efficacy and safety of secukinumab in patients with moderate to severe HS is based on the two phase 3 studies, SUNSHINE and SUNRISE, where patients are randomised to either secukinumab Q2W, secukinumab Q4W or placebo. The design of the studies was straightforward and can be considered adequate as basis for evaluating secukinumab in HS. A total treatment period of 52 weeks was considered sufficient for safety assessment purposes and enabled assessment of maintenance of effect.

To be enrolled in the study, patients had to have a disease severity of moderate to severe, defined as having a total of at least 5 inflammatory lesions, i.e., abscesses and/or inflammatory nodules, affecting at least 2 distinct anatomic areas. This definition focuses on the degree and extent of inflammatory activity at baseline instead of using the level of scarring in the worst affected area (as in the previously used Hurley stages). Consistent with this definition, the majority of the study population were Hurley stages II and III, with only a small proportion of subjects in Hurley stage I. Of note, patients enrolled in the SUNNY studies were not stratified by Hurley stage, which in some cases resulted in an uneven distribution of severity across treatment arms.

Mean age at baseline was about 36 years, and very few subjects aged 65 years or above were enrolled. About 56% of subjects were female, and almost 80% were White. Almost 70% were either current or former smokers. Mean BMI was about 32 kg/m^2. This population is similar to the Danish population with HS on biologic treatment as described by Ring et al. Indeed, two Danish sites participated in the SUNRISE study.

The primary signs and symptoms of HS are abscesses, inflammatory nodules or draining fistulas and these are assessed by the HiSCR50. HiSCR50 has been used as the primary endpoint for demonstrating clinical efficacy of adalimumab and was also endorsed by the CHMP when the protocol was discussed at a scientific advice meeting. DLQI was chosen as outcome, as it was an outcome in the previous RADS treatment guideline.

The placebo responses for HiSCR50 were high in the two studies. High placebo rates for clinical efficacy endpoints is a well-known observation in HS clinical studies, and the high rates appear to be linked to natural disease fluctuation, concomitant medications (e.g., antibiotics, as continuation of stable doses for antibiotic treatment was allowed), or scoring systems used in clinical studies. Regarding HiSCR50, it identifies responders as those who achieve at least a 50% reduction in abscess and nodule count without an increase in the number of abscesses or draining fistulas relative to baseline and thus does not assess the anti-inflammatory effect on draining fistulas. Draining fistulas are central in the pathogenesis of HS and seem to be a source of inflammation in HS [42]. The drawback of not dynamically assessing draining fistulas was recently demonstrated in a clinical trial with vilobelumab vs. placebo. While participants in the highest dosed treatment group achieved a significantly greater reduction in AN-count and draining fistulas relative to the placebo group at Week 16, the HiSCR rate was not statistically different between these groups [43].

The factors above may have contributed to the high placebo response observed in these studies. High placebo response rates have also been observed in clinical studies in other dermatological diseases.

As observed, the difference between secukinumab and placebo for HiSCR50 for Q4W in the SUNSHINE study was not statistically significant. A contributing factor for the high placebo response in the SUNSHINE study could be that the disease severity was lower in the placebo arm (28.3% with Hurley III) vs. the secukinumab arm (35.0% with Hurley III) at baseline. For both studies, statistical significance was achieved for the Q2W dosing regimen, and it should be noted that in SUNSHINE, the difference in response rates between the Q2W and Q4W regimens was only three percentage points, and in SUNRISE, the treatment difference vs. placebo was numerically larger for the Q4W regimen than the Q2W regimen. The meta-analysis of the two studies showed a p value of 0.002 for secukinumab vs. placebo for the Q4W treatment arms. As such, the short-term efficacy has in principle been adequately demonstrated.

Response rates for HiSCR50 for pre-defined subgroups were analysed. The studies were not powered for subgroup analyses, however, the efficacy of secukinumab vs. placebo seems similar, most notably when it comes to dosing (Q2W and Q4W) and weight (<90 kg/≥90 kg), but also for age (<40years/≥40 years), gender (female/male), concomitant use of antibiotics (yes/no), or previous treatment with biological treatment (yes/no) at baseline. Based on the similar response for Q2W and Q4W, the Q4W dose regimen is the approved dosing of secukinumab for HS.

The short-term treatment effect at week 16 (about 11 percentage points vs. placebo in the pooled data) can be considered quite modest. However, the majority of patients on secukinumab that achieved HiSCR50 at week 16 maintained their response until week 52. Furthermore, a large proportion of week 16 non-responders became responders by week 52, and among the subjects switching from placebo to secukinumab at week 16, 45% of placebo non-responders developed a response by week 52. With the limited treatment options currently available, the observed effect is considered clinically meaningful.

Adverse events that were suspected to be related to study drug were reported at similar frequencies in the secukinumab groups compared to placebo during the 16 weeks placebo-controlled study period, and between secukinumab dose groups in the entire study period, with no unexpected findings. The long-term safety of secukinumab appeared overall similar to that in short-term and as previously reported.

Based on the findings of no statistical differences in efficacy and safety between secukinumab and adalimumab, the health economic analysis was carried out as a cost minimisation analysis.

The simple cost-minimisation model represents Danish clinical practice by utilising a novel Danish real-world evidence study to mimic the real-life drug survival of biological treatment of HS. This holds a strength to it since it makes the results of the health economic model represent the current Danish treatment landscape as accurately as possible. An even more simple approach could have been taken by excluding the following treatment state thereby minimising the albeit small uncertainties to this. However, this would not take the real treatment patterns into consideration and is therefore not assessed as clinically relevant to investigate this setup.

11. List of experts

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

12. References

1. Zouboulis CC, Desai N, Emtestam L, et al (2015) European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. Journal of the European Academy of Dermatology and Venereology 29:619–644. https://doi.org/10.1111/jdv.12966
2. Machado MO, Stergiopoulos V, Maes M, et al (2019) Depression and Anxiety in Adults with Hidradenitis Suppurativa: A Systematic Review and Meta-analysis. JAMA Dermatol 155:939–945. https://doi.org/10.1001/jamadermatol.2019.0759
3. McKenzie SA, Harview CL, Truong AK, et al (2020) Physical symptoms and psychosocial problems associated with hidradenitis suppurativa: Correlation with hurley stage. Dermatol Online J 26:. https://doi.org/10.5070/d3269050156
4. Thorlacius L, Cohen AD, Gislason GH, et al (2018) Increased Suicide Risk in Patients with Hidradenitis Suppurativa. Journal of Investigative Dermatology 138:52–57. https://doi.org/10.1016/j.jid.2017.09.008
5. Canoui-Poitrine F, Revuz JE, Wolkenstein P, et al (2009) Clinical characteristics of a series of 302 French patients with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol 61:51–57. https://doi.org/10.1016/j.jaad.2009.02.013
6. Revuz J (2009) Hidradenitis suppurativa. Journal of the European Academy of Dermatology and Venereology 23:985–998. https://doi.org/10.1111/j.1468-3083.2009.03356.x
7. Sabat R, Jemec G, Matusiak Ł, et al (2020) Hidradenitis suppurativa. Nat Rev Dis Primers 6:
8. Saunte DML, Dufour DN, Kofoed K, et al (2020) Guidelines vedr. behandling af hidrosadenitis suppurativa. Udarbejdet for Dansk Dermatologisk Selskab. 2020. https://dds.nu/wp-content/uploads/2020/12/DDS-HS-guidelines-_opdatering-final-2.pdf
9. Ring HC, Maul JT, Yao Y, et al (2022) Drug Survival of Biologics in Patients with Hidradenitis Suppurativa. JAMA Dermatol 158:184–188. https://doi.org/10.1001/jamadermatol.2021.4805
10. EMA (2023) Cosentyx. Summary of Product Charachteristics
11. EMA (2022) Humira. Summary of Product Characteristics
12. Kimball AB, Jemec GBE, Alavi A, et al (2023) 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. Lancet 401:747–61. https://doi.org/10.1016/S0140-6736(23)00022-3
13. Kimball AB, Okun MM, Williams DA, et al (2016) Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. N Engl J Med 375:422–434. https://doi.org/10.1056/NEJMoa1504370
14. Bucher HC, Guyatt GH, Griffith LE, Walter SD (1997) The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 50:683–691. https://doi.org/10.1016/S0895-4356(97)00049-8
15. Kelly G, Sweeney CM, Tobin AM, Kirby B (2014) Hidradenitis suppurativa: The role of immune dysregulation. Int J Dermatol 53:1186–1196. https://doi.org/10.1111/ijd.12550
16. Miller IM, McAndrew RJ, Hamzavi I (2016) Prevalence, Risk Factors, and Comorbidities of Hidradenitis Suppurativa. Dermatol Clin 34:7–16. https://doi.org/10.1016/j.det.2015.08.002
17. Jemec GBE, Heidenheim M, Nielsen NH (1996) The prevalence of hidradenitis suppurativa and its potential precursor lesions. J Am Acad Dermatol 35:191–194. https://doi.org/10.1016/s0190-9622(96)90321-7

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

18. Vazquez BG, Alikhan A, Weaver AL, et al (2013) Incidence of hidradenitis suppurativa and associated factors: A population-based study of Olmsted County, Minnesota. Journal of Investigative Dermatology 133:97–103. https://doi.org/10.1038/jid.2012.255

19. Ring HC, Saunte DM, Riis PT, et al (2017) Diagnostik og behandling af hidrosadenitis suppurativa. Ugeskr Laeger 179:1318–1322

20. Danmarks Statistik. Befolkningstal 2022. https://statistikbanken.dk/statbank5a/default.asp?w=1920

21. RADS (2016) Baggrundsnotat for biologisk behandling af hidrosadenitis suppurativa (HS). 1–20

22. Data from DLI Market Intelligence (DLIMI)

23. Medicinrådet (2021) Behandlingsvejledning inkl. lægemiddelrekommandation for anvendelse af biologisk behandling af hidrosadenitis suppurativa (HS) (retired)

24. EMA (2023) Extension of indication variation assessment report. Cosentyx

25. Jemec G, Okun M, Forman S, et al (2019) Adalimumab medium-term dosing strategy in moderate-to-severe hidradenitis suppurativa: integrated results from the phase III randomized placebo-controlled PIONEER trials. British Journal of Dermatology 181:967–975

26. Basra MKA, Salek MS, Camilleri L, et al (2015) Determining the minimal clinically important difference and responsiveness of the dermatology life quality index (DLQI): Further data. Dermatology 230:27–33. https://doi.org/10.1159/000365390

27. (2016) Kimball A, Okun M, Williams D et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. NEJM 2016. In: New England Journal of Medicine. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1504370/suppl_file/nejmoa1504370_appendix.pdf

28. Kimball AB, Jemec GBE, Alavi A, et al. Secukinumab in moderate-to- severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials. Supplementar. https://ars.els-cdn.com/content/image/1-s2.0-S0140673623000223-mmc1.pdf

29. Zouboulis CC, Okun MM, Prens EP, et al (2019) Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. J Am Acad Dermatol 80:60-69.e2. https://doi.org/10.1016/j.jaad.2018.05.040

30. Bechara FG, Podda M, Prens EP, et al (2021) Efficacy and Safety of Adalimumab in Conjunction With Surgery in Moderate to Severe Hidradenitis Suppurativa: The SHARPS Randomized Clinical Trial. JAMA Surg 156:1001–1009. https://doi.org/10.1001/jamasurg.2021.3655

31. Glatt S, Jemec GBE, Forman S, et al (2021) Efficacy and Safety of Bimekizumab in Moderate to Severe Hidradenitis Suppurativa: A Phase 2, Double-blind, Placebo-Controlled Randomized Clinical Trial. JAMA Dermatol 157:1279–1288. https://doi.org/10.1001/jamadermatol.2021.2905

32. Medicinrådet (2018) Gennemgang af terapiområdet kronisk leddegigt - valg af biologisk og targeterede syntetiske lægemidler

33. Medicinrådet (2020) Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til moderat til svær plaque psoriasis

34. Medicinrådet (2022) Bilag til Medicinrådets anbefaling vedrørende risankizumab til behandling af psoriasisartrit

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

35. Ring HC, Maul J-T, Yao Y Ring HC, Maul J, Yao Y et al. Drug survival of biologics in patients with hidradenitis suppurativa. JAMA dermatology 2022. Supplement online. https://cdn.jamanetwork.com/ama/content_public/journal/derm/9388602AOXB4WvzBj8BirzG8bfopXA

36. WebPlotDigitizer 4.6. Link: https://apps.automeris.io/wpd/. https://apps.automeris.io/wpd/

37. Lægemiddelstyrelsen Cosentyx produktvisning. https://medicinpriser.dk/Default.aspx?id=15&vnr=445576. Accessed 29 Mar 2023

38. Lægemiddelstyrelsen Imraldi produktvisning. https://medicinpriser.dk/Default.aspx?id=15&vnr=447013. Accessed 29 Mar 2023

39. Lægemiddelstyrelsen Flixabi produktvisning. https://medicinpriser.dk/Default.aspx?id=15&vnr=148231. Accessed 29 Mar 2023

40. Lægemiddelstyrelsen Stelara produktvisning. https://medicinpriser.dk/Default.aspx?id=15&vnr=093827. Accessed 29 Mar 2023

41. Aarhus Universitetshospital. Patientvejledning. Infliximab (Remicade, Remsima og Zessly), IV-behandling (Hud- og Kønssygdomme). https://www.auh.dk/patientvejledninger/hud-og-konssygdomme/medicin/infliximab/#p2

42. Navrazhina K, Frew JW, Gilleaudeau P, et al (2021) Epithelialized tunnels are a source of inflammation in hidradenitis suppurativa. Journal of Allergy and Clinical Immunology 147:2213–2224. https://doi.org/10.1016/j.jaci.2020.12.651

43. van Straalen KR, Ingram JR, Augustin M, Zouboulis CC (2022) New treatments and new assessment instruments for Hidradenitis suppurativa. Exp Dermatol 31:33–39. https://doi.org/10.1111/exd.14609

44. Kimball AB, Jemec GBE, Yang M, et al (2014) Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol 171:1434–1442. https://doi.org/10.1111/bjd.13270

45. Badia X, Mascaró JM, Lozano R (1999) Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: Clinical validity, reliability and sensitivity to change of the DLQI. British Journal of Dermatology 141:698–702. https://doi.org/10.1046/j.1365-2133.1999.03112.x

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

The objective of the literature search was to identify randomised controlled studies with adalimumab and secukinumab for treatment of HS.

Search strategy

Table 19 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE	PubMED	Until date of search	15.11.2022
CENTRAL	Cochrane	Until date of search	15.11.2022

Table 20 Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Same as for published studies, except not peer-reviewed	13.03.2023
EU Clinical Trials Register	EU Clinical Trials Register	Same as for published studies, except not peer-reviewed	13.03.2023

The search strategy developed to meet the objective of the literature search was defined by the inclusion and exclusion criteria in Table 21.

Table 21 Inclusion and exclusion criteria for literature selection

Inclusion criteria
• Population: Patients with hidradenitis suppurativa • Intervention: secukinumab • Comparator: adalimumab • Outcomes: HiSCR50, DLQI (responders), serious adverse events, discontinuation • Settings: Peer-reviewed publication • Study design: Randomised controlled trial • Language restrictions: English, Danish • Other search limits or restrictions applied: see exclusion criteria
Exclusion criteria
• Population: If not listed in the inclusion criteria above • Interventions: If not listed in the inclusion criteria above • Comparators: If not listed in the inclusion criteria above • Settings: Other than peer-reviewed publication

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

- Study design: Not RCT
- Language restrictions: Any other language than English, Danish
- Other search limits or restrictions applied: Non-human studies; publication types such as guidelines, non-systematic reviews, expert opinion pieces, letters and comments, editorials, press releases, and publications in the grey literature

Abbreviations: HiSCR50: Hidradenitis Suppurativa Clinical Response of ≥50% reduction ; DLQI: Dermatology Life Quality Index

The search strings and results are shown with screen shots below.

History and Search Details

Download Delete

Search	Actions	Details	Query	Results	Time
#14	•••	›	Search: **#10 NOT #13** Sort by: **Most Recent**	44	06:33:26
#13	•••	›	Search: **#11 OR #12** Sort by: **Most Recent**	9,159,819	06:33:04
#12	•••	›	Search: **Case report[ti] OR case reports[ti] OR comment[pt] OR review[pt]** Sort by: **Most Recent**	4,305,708	06:32:37
#11	•••	›	Search: **Animals[Mesh terms] NOT humans[Mesh terms]** Sort by: **Most Recent**	5,062,402	06:31:09
#10	•••	›	Search: **#8 AND #9** Sort by: **Most Recent**	70	06:29:47
#9	•••	›	Search: **Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR clinical trials as Topic[mh:noexp] OR randomly[tiab] OR trial[tiab]** Sort by: **Most Recent**	1,761,696	06:28:57
#8	•••	›	Search: **#6 OR #7** Sort by: **Most Recent**	402	06:24:40
#7	•••	›	Search: **#3 AND #5** Sort by: **Most Recent**	382	06:23:50
#6	•••	›	Search: **#3 AND #4** Sort by: **Most Recent**	44	06:23:31
#5	•••	›	Search: **adalimumab OR Humira*** Sort by: **Most Recent**	10,467	06:22:50
#4	•••	›	Search: **secukinumab OR cosentyx** Sort by: **Most Recent**	1,794	06:22:32
#3	•••	›	Search: **#1 OR #2** Sort by: **Most Recent**	3,973	06:21:45
#2	•••	›	Search: **hidradenitis suppurativa** Sort by: **Most Recent**	3,973	06:21:25
#1	•••	›	Search: **"Hidradenitis Suppurativa"[Mesh]** Sort by: **Most Recent**	2,876	06:20:38

Showing 1 to 14 of 14 entries

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Cosentyx HS final

Last saved on: 15/11/2022 11:18:01

View fewer lines | Print search history

#1	MeSH descriptor: [Hidradenitis Suppurativa] explode all trees	MeSH	128
#2	"acne inversa":ab,ti,kw OR "acne inversas":ab,ti,kw OR "hidradenitis suppurativa":ab,ti,kw	Limits	303
#3	cosentyx:ab,ti,kw OR secukinumab:ab,ti,kw	Limits	1053
#4	adalimumab:ab,ti,kw OR humira*:ab,ti,kw	Limits	3743
#5	#1 OR #2	Limits	303
#6	#3 OR #4	Limits	4730
#7	#5 AND #6	Limits	119
#8	("conference abstract" OR review):ti,ab,kw	Limits	163658
#9	NCT*:au	Limits	238778
#10	(EUCTR* OR clinicaltrials.gov OR trialsearch):so	Limits	444847
#11	#8 OR #9 OR #10	Limits	596146
#12	#7 NOT #11	Limits	67
#13	Type a search term or use the S or MeSH buttons to compose	S / MeSH / Limits	N/A

Clear all | Highlight orphan lines

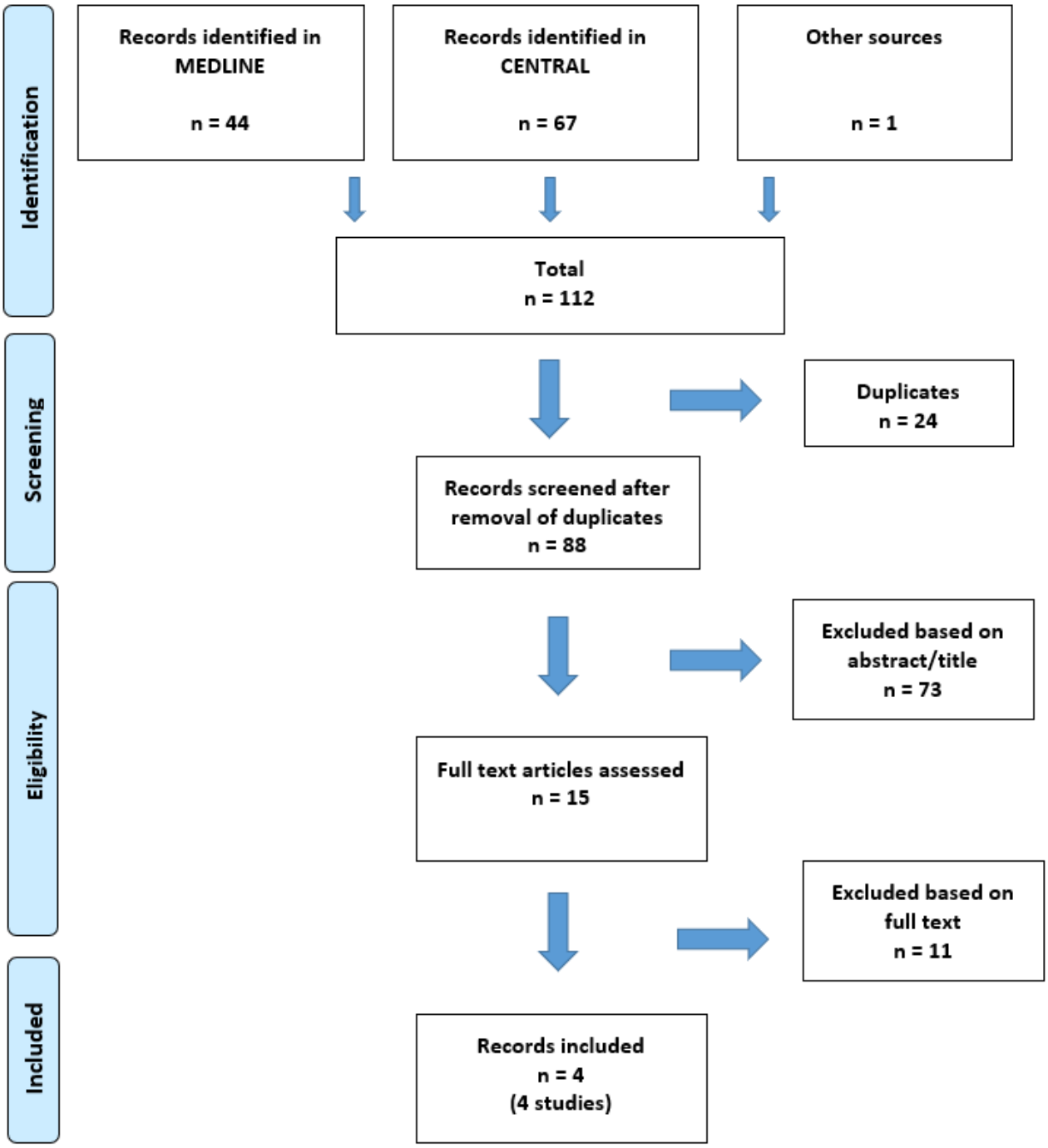
In addition to the publications identified in the searches above, the recent publication of the SUNSHINE and SUNRISE study results (Kimball et al., 3 February 2023 [12]) has been included and added to the PRISMA flow below.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Systematic selection of studies

The outcome of the search is shown in the PRISMA flow in Figure 5 below.

Figure 5 PRISMA flow



Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials

For a list of included studies and publications, see Table 5 in section 6.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 22 Excluded references

Publication	Reason for exclusion
Frew JW, Jiang CS, Singh N et al. Clinical response rates, placebo response rates, and significantly associated covariates are dependent on choice of outcome measure in hidradenitis suppurativa: A post hoc analysis of PIONEER 1 and 2 individual patient data. J. Am. Acad. Dermatol. 2020; 82(5):1150–1157.	Relevant data reported elsewhere
Bechara FG, Podda M, Prens EP et al. Efficacy and Safety of Adalimumab in Conjunction With Surgery in Moderate to Severe Hidradenitis Suppurativa: The SHARPS Randomized Clinical Trial. JAMA Surg. 2021; 156(11):1001–1009.	Different patient population, HS patients requiring radical surgery
Giamarellos-Bourboulis EJ, Sobell J, Ryan C et al. Infection-free Clinical Response Among Patients With Hidradenitis Suppurativa Who Were Treated With Adalimumab: Results from Two Phase 3 Studies. Wounds a Compend. Clin. Res. Pract. 2017; 29(11):E98–E102.	Relevant data reported elsewhere
Glatt S, Jemec GBE, Forman S et al. Efficacy and Safety of Bimekizumab in Moderate to Severe Hidradenitis Suppurativa: A Phase 2, Double-blind, Placebo-Controlled Randomized Clinical Trial. JAMA dermatology 2021; 157(11):1279–1288.	Skewed baseline characteristics and small study (n=21 pr arm)
Glatt S, Jemec GB, Forman S. Erratum: efficacy and safety of bimekizumab in moderate to severe hidradenitis suppurativa: a phase 2, double-blind, placebo-controlled randomized clinical trial (JAMA Dermatol (2021) DOI: 10.1001/jamadermatol.2021.2905). JAMA dermatology 2021; 157(11):1384-.	See above
Gottlieb A, Menter A, Armstrong A et al. Adalimumab Treatment in Women With Moderate-to-Severe Hidradenitis Suppurativa from the Placebo-Controlled Portion of a Phase 2, Randomized, Double-Blind Study. J. Drugs Dermatol. 2016; 15(10):1192–1196.	Data for subgroup, not relevant for ITC
Ingram JR. Interventions for Hidradenitis Suppurativa: Updated Summary of an Original Cochrane Review. JAMA dermatology 2017; 153(5):458–459.	Relevant data reported elsewhere
Kimball AB, Kerdel F, Adams D et al. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann. Intern. Med. 2012; 157(12):846–855.	No relevant efficacy data
Kimball AB, Sundaram M, Shields AL et al. Adalimumab alleviates skin pain in patients with moderate-to-severe hidradenitis suppurativa: Secondary efficacy results from the PIONEER I and PIONEER II randomized controlled trials. J. Am. Acad. Dermatol. 2018; 79(6):1141–1143.	Research letter, no relevant data
Lu J-W, Huang Y-W, Chen T-L. Efficacy and safety of adalimumab in hidradenitis suppurativa: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2021; 100(22):e26190.	No additional studies identified
Miller I, Lynggaard CD, Lophaven S et al. A double-blind placebo-controlled randomized trial of adalimumab in the treatment of hidradenitis suppurativa. Br. J. Dermatol. 2011; 165(2):391–398.	No relevant efficacy data

Ongoing studies and studies that have not yet been published

A search of clinicaltrials.gov with the search term "Hidradenitis suppurativa OR acne inversa" and "secukinumab OR adalimumab" was undertaken on 13 March 2023.

A search of EU Clinical Trials Register with the search teams (hidradenitis suppurativa OR acne inversa) AND (adalimumab OR secukinumab) was undertaken on 13 March 2023.

Both searches revealed the following two studies, where adalimumab and placebo are included as comparative arms:

NCT05322473/2021-005928-38

Evaluation of Sonelokimab for the Treatment of Patients With Active Moderate to Severe Hidradenitis Suppurativa. Phase 2. Estimated primary completion date: July 2023

NCT04988308/2020-002607-19

A Phase 2a/2b, Multicenter, Randomized, Placebo and Active Comparator-controlled, Double-Blind, Dose-ranging Study to Evaluate the Safety and Efficacy of Bermekimab (JNJ-77474462) for the Treatment of Subjects with Moderate to Severe Hidradenitis Suppurativa. Prematurely terminated as the Interim Analysis 1 efficacy results met the prespecified futility criteria related to the primary endpoint. Date of completion: 2022-11-23 (results not published).

None of the ongoing studies were found to be relevant for this application.

Internal validity of selected studies

Risk of bias for included studies is evaluated in Table 23 below. Based on this the internal validity of the studies was high.

Table 23 Risk of bias for included studies

Study name/ ID	SUNSHINE	SUNRISE	PIONEER I	PIONEER II
Was randomisation carried out appropriately	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes*	Yes	Yes**	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes

*SUNSHINE: Disease severity was slightly higher in the secukinumab arm vs. placebo arm, as 35.0% in the secukinumab arm had Hurley stage III vs. 28.3% in the placebo arm.

**PIOENEER I: The distribution between gender was uneven, with 40.5% male in the adalimumab arm vs. 31.8% in the placebo arm.

Quality assessment

The literature search has in general been performed and documented in accordance with the methodology recommended by the Medicines Council.

Unpublished data

Data from the clinical study reports for the SUNSHINE and SUNRISE studies for HiSCR50 week 12 has been included in this application.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix B Main characteristics of included studies

Table 24 Main characteristics of the SUNSHINE and SUNRISE studies [12]

Study name: SUNSHINE **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	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
Study type and design	The study was a phase 3, multicentre, randomised, double-blind, placebo-controlled parallel-group trial. 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 trial 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 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.

Study name: SUNSHINE	NCT number: NCT03713619
SUNRISE	NCT number: NCT03713632

Sample size (n)

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	Total
Randomised analysis set	181	180	180	541
Full analysis set	181	180	180	541
Safety set	181	180	180	541

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	Total
Randomised analysis set	180	180	183	543
Full analysis set	180	180	183	543
Safety set	180	180	183	543

Study name: SUNSHINE SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632

Main inclusion and exclusion 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
	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 either every 2 weeks or every 4 weeks. 361 participants were randomised to secukinumab; 181 received treatment every 2 weeks, and 180 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 consisted of 180 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?	No

Primary, secondary and exploratory endpoints

Endpoints included in this application are:

- Percentage of patients achieving HiSCR50,
- Percentage achieving DLQI response with a decrease in score greater than 5.0 points from baseline
- Percentage experiencing an SAE
- Percentage discontinuing treatment

Primary endpoint

The primary endpoint was the achievement of Hidradenitis Suppurativa Clinical Response of ≥50% reduction (HiSCR50) at week 16, which is a collective endpoint including:

- ≥50% reduction in abscess and inflammatory nodule (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
- Dermatology Life Quality Index (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
- Absolute and percentage change from baseline in the inflammatory markers C-reactive protein (CRP) 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.

Study name: SUNSHINE SUNRISE	NCT number: NCT03713619 NCT number: NCT03713632
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 adverse events was collected and summarised for each treatment group. 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 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.
Other relevant information	None

Table 25: Main characteristics of the PIONEER I and II studies [13]

Study name: PIONEER I	**NCT number: NCT01468207**
PIONEER II	**NCT number: NCT01468233**
Objective	The objective of these studies was to investigate the efficacy and safety of adalimumab in adults suffering from moderate to severe HS.
Publications – title, author, journal, year	**Publications of results:** Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa Kimball AB, Okun MM, Williams DA, et al. New England Journal of Medicine 2016 Adalimumab medium-term dosing strategy in moderate-to-severe hidradenitis suppurativa: integrated results from the phase III randomized placebo-controlled PIONEER trials Jemec GBE, Okun MM, Forman SB et al. Br. J. Dermatol. 2019 Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open label extension study. Zouboulis, CC; Okun, MM; Prens, EP et al. J Am Acad Dermatol 2019
Study type and design	PIONEER I and II were phase 3 multicentre studies, almost identical in design, with 2 double-blind, placebo-controlled periods. Participants were randomised centrally and stratified by Hurley stage, and ***for PIONEER II*** also by concomitant use of oral antibiotics. The randomisation schedules were generated before start of the study and based on an Interactive Voice Response System. All participants, study site personnel, personnel with direct oversight of the study conduct and management and the investigator were blinded to the study treatment. The study consists of the following phases: • Screening period: 7—30 days • Period 1: 12 weeks, where participants were randomly assigned in a 1:1 ratio between adalimumab Q1W and placebo • Period 2: 24 weeks, where participants who received adalimumab were re-randomised in a 1:1:1 ratio to receive adalimumab Q1W, adalimumab every Q2W or placebo. The randomisation before period 2 was stratified by Hurley stage and HiSCR score. ***For PIONEER I***, those who received placebo in period 1 were reassigned to receive adalimumab weekly in a random manner, ***for PIONEER II***, those who received placebo in period 1 were reassigned in a blinded fashion to continue placebo The study has been completed. Patients who completed treatment period 2 could enter an OLE study. In addition, during treatment period 2, patients could continue in the OLE study, if they if they met the primary efficacy end point and subsequently lost 50% or more of the improvement gained in period 1 or if they did not meet the primary efficacy end point and subsequently had a total abscess and inflammatory-nodule count on two consecutive visits that was greater than or equal to the count at baseline.
Sample size (n)	307 participants underwent randomisation in period 1 in PIONEER I.

Study name: PIONEER I	NCT number: NCT01468207
PIONEER II	NCT number: NCT01468233

	Adalimumab Q1W	Placebo	Total
Randomised analysis set	153	154	307
Full analysis set	153	154	307
Safety set	153	152	305

326 participants underwent randomisation in period 1 in PIONEER II.

	Adalimumab Q1W	Placebo	Total
Randomised analysis set	163	163	326
Full analysis set	163	163	326
Safety set	163	163	326

Main inclusion and exclusion criteria

Inclusion criteria (from clinicaltrials.gov):

- Adults must have a diagnosis of HS for at least 1 year prior to baseline
- HS lesions must be present in at least 2 distinct anatomical areas, one of which must be at least Hurley Stage II or Hurley Stage III
- Subject must have stable HS for at least 60 days prior to screening visit and at baseline visit
- Subject must have experienced an inadequate response to at least a 90-day treatment with oral antibiotics for treatment of HS
- Subject must have a total AN count of greater than or equal to 3 at baseline

Exclusion criteria (from clinicaltrials.gov):

- Subject was previously treated with adalimumab or another anti-tumour necrosis factor (anti-TNF) therapy (e.g., infliximab or etanercept)
- ***For PIONEER I:*** Subject received any oral antibiotic treatment for HS within 28 days prior to baseline
- ***For PIONEER II:*** Subjects on permitted oral antibiotic treatment for HS who have not been on a stable dose for at least 28 days prior to the baseline visit
- Subject received oral concomitant analgesics (including opioids) for HS-related pain within 14 days prior to baseline visit
- If entering the study on concomitant oral analgesics for non-HS related pain:

Study name: PIONEER I	NCT number: NCT01468207
PIONEER II	NCT number: NCT01468233

	○ Subject on opioid analgesics within 14 days prior to baseline visit Subject not on a stable dose of non-opioid oral analgesics for at least 14 days prior to the baseline visit ("as needed" is not considered a stable dose)
Intervention	The intervention in both period 1 and 2 was adalimumab, which was administered through subcutaneous injections. Treatment assignments by study and treatment period are shown in the table below. Patients who were assigned to receive adalimumab for the first time (either in treatment period 1 or 2), received an initial dose of 160 mg at week 0, followed by a dose of 80 mg at week 2. From week 4, participants received 40 mg adalimumab weekly.

Study	Treatment in period 1	Treatment in period 2
PIONEER I	Adalimumab Q1W, n=153	Adalimumab Q1W, n=48 Adalimumab Q2W, and alternating placebo Q2W, n=48 Placebo, n=49
	Placebo, n=154	Adalimumab Q1W, n=145
PIONEER II	Adalimumab Q1W, n=163	Adalimumab Q1W, n=51 Adalimumab Q2W, and alternating placebo Q2W, n=53 Placebo, n=51
	Placebo, n=163	Placebo, n=151

Q1W: Every week; Q2W: every other week

Comparator(s)	Placebo was used as the comparator in both periods and given in a dosing schedule matching adalimumab. For treatment assignment, see table above.
Follow-up time	36 weeks. Patients who fulfilled inclusion criteria described in the section "Study type and design", could enter an OLE study with a total follow up period up to three years.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Primary endpoint** The primary endpoint was the achievement of HiSCR50, which is achieved by collectively having: • ≥50% reduction in AN count • No increase in abscess and draining fistula from baseline

Study name: PIONEER I	NCT number: NCT01468207
PIONEER II	NCT number: NCT01468233

Secondary endpoints

The following secondary endpoints were evaluated:

- Recurrent abscesses (single or multiple) with sinus tract formation and scarring, scored as total AN count of 0, 1 or 2
- Reduction in pain score of ≥30% from baseline
- Change from baseline in modified Sartorius score
- Number of observed interventions – any lesions type
- Proportion of patients with improvement of Hurley stage in ≥1 affected body region
- Proportion of patients with baseline Hurley stage of <3 that experienced worsening of Hurley stage in ≥1 affected body region
- Proportion of patients with ≥1 of disease flare
- Mean number of days on disease flare
- Proportion of patients starting oral antibiotic rescue therapy in period 1
- Proportion of patients with erythema score 0 or 1 in all affected regions
- Mean change in high-sensitivity CRP (hs-CRP)
- Proportion of patients who achieved complete elimination of lesions
- Percentage mean change in number of lesions from baseline
- Mean change in number of lesions between groups from baseline
- Between groups change in AN count from baseline
- Proportion of patients with ≥25% increased lesion count from baseline
- Change in patients' global assessment of disease-related skin pain numeric rating scale from baseline
- Proportion of patients with DLQI score of 0 at week 12
- Proportion of patients with DLQI score of 0 or 1 at week 12
- Mean change of DLQI score from baseline
- Mean change of WPAI-SHP from baseline
- Mean change of treatment satisfaction questionnaire from baseline
- Mean change of short form-36 health status survey from baseline
- Mean percentage change of short form-36 health status survey from baseline
- Mean change of hospital anxiety and depression scale from baseline
- Mean change of in EQ-5D score from baseline
- Mean percentage change of short form-36 health status survey from baseline

Exploratory endpoints

No exploratory endpoints were evaluated.

Study name: PIONEER I PIONEER II	NCT number: NCT01468207 NCT number: NCT01468233
	Safety endpoints Safety was evaluated based on the AEs that emerged within 70 days of study drug discontinuation. In addition, the safety analysis was based on clinical laboratory measurements, vital signs and physical examination. The study also included pharmacokinetic and immunogenicity assessments, based on the presence of anti-adalimumab antibodies.
Method of analysis	Efficacy outcomes were investigated in the intention-to-treat population, whereas safety was assessed in all participants who received at least 1 dose of study treatment. The between-group difference of the primary and secondary endpoints was analysed using the Cochran-Mantel-Haenszel test for categorical variables and by an analysis of covariance with treatment, baseline value, and Hurley stage for continuous variables. The primary approach to handle missing data was nonresponse imputation.
Subgroup analyses	None
Other relevant information	None

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 27: Baseline characteristics of patients in the trials included in the indirect treatment comparison [12, 13]

	SUNSHINE trial		SUNRISE trial		PIONEER I		PIONEER II	
	SEC Q4W	PLA	SEC Q4W	PLA	ADA Q1W	PLA	ADA Q1W	PLA
	n=180	n=180	n=180	n=183	n=153	n=154	n=163	n=163
Age (years)								
Mean (SD)	35.7 (11.71)	35.5 (10.75)	35.5 (11.41)	36.2 (11.25)	36.2 (10.83)	37.8 (11.33)	34.9 (9.96)	36.1 (12.18)
Gender, n (%)								
Female	100 (55.6)	102 (56.7)	103 (57.2)	105 (57.4)	91 (59.5)	105 (68.2)	108 (66.3)	113 (69.3)
Male	80 (44.4)	78 (43.3)	77 (42.8)	78 (42.6)	62 (40.5)	49 (31.8)	55 (33.7)	50 (30.7)
Race, n (%)								
White	146 (81.1)	139 (77.2)	139 (77.2)	143 (78.1)	116 (75.8)	118 (76.6)	143 (87.7)	130 (79.8)
Black or African American	10 (5.6)	12 (6.7)	19 (10.6)	12 (6.6)	33 (21.6)	29 (18.8)	9 (5.5)	20 (12.3)
Asian*	23 (12.8)	24 (13.3)	16 (8.9)	19 (10.4)	-	-	-	-
Other	1 (0.6)	5 (2.8)	6 (3.4)	9 (4.9)	4 (2.6)	7 (4.5)	11 (6.7)	13 (8.0)
Body weight, kg								
Mean (SD)	95.43 (25.894)	92.88 (22.098)	93.13 (22.271)	90.96 (22.020)	97.1 (24.9)	99.3 (25.13)	90.2 (21.74)	95.7 (25.87)

	SUNSHINE trial		SUNRISE trial		PIONEER I		PIONEER II	
	SEC Q4W n=180	PLA n=180	SEC Q4W n=180	PLA n=183	ADA Q1W n=153	PLA n=154	ADA Q1W n=163	PLA n=163
BMI								
Mean (SD)	32.78 (7.897)	31.97 (7.053)	31.98 (7.478)	31.42 (7.382)	33.0 (7.62)	34.5 (7.94)	31.3 (7.41)	32.9 (7.94)
Smoking, n (%)								
Current smoker	96 (53.3)	101 (56.1)	90 (50.0)	106 (57.9)	81 (52.9)	92 (59.7)	105 (64.4)	109 (67.3)
Disease duration, years								
Mean (SD)	6.6 (6.73)	7.5 (7.0)	8.2 (8.42)	7.0 (6.65)				
Median (range)					8.8 (1.1–40.4)	9.4 (1.0–43.0)	9.0 (1.0–43.5)	9.9 (1.2–68.5)
Hurley stage, n (%)								
I	10 (5.6)	8 (4.4)	6 (3.3)	3 (1.6)				
I or II								
II	107 (59.4)	121 (67.2)	106 (58.9)	110 (60.1)	80 (52.3)	81 (52.6)	86 (52.8)	89 (54.6)
III	63 (35.0)	51 (28.3)	68 (37.8)	70 (38.3)	73 (47.4)	73 (47.4)	77 (47.2)	74 (45.4)

	SUNSHINE trial		SUNRISE trial		PIONEER I		PIONEER II	
	SEC Q4W n=180	PLA n=180	SEC Q4W n=180	PLA n=183	ADA Q1W n=153	PLA n=154	ADA Q1W n=163	PLA n=163
Lesions count								
AN count, mean (SD)	12.6 (8.38)	12.8 (8.15)	13.3 (8.77)	12.8 (8.45)	14.3 (11.92)	14.4 (14.8)	10.7 (8.1)	11.9 (11.02)
Abscesses, mean (SD)	2.7 (3.96)	2.7 (3.76)	2.9 (4.13)	3.2 (4.96)	2.8 (3.47)	2.7 (3.69)	2.0 (2.6)	2.4 (3.34)
Draining fistulas, mean (SD)	2.5 (3.52)	2.4 (3.76)	2.5 (3.5)	2.6 (3.24)	4.6 (5.2)	3.8 (4.4)	3.0 (4.11)	3.7 (5.2)
Inflammatory nodules, mean (SD)	9.9 (7.6)	10.1 (6.99)	10.4 (7.60)	9.6 (6.77)	11.5 (10.92)	11.6 (13.85)	8.6 (6.92)	9.4 (9.6)
DLQI scores								
mean (SD)	13.4 (6.15)	13.8 (7.17)	14.6 (7.21)	14.5 (6.92)	16.3 (6.6)	16.0 (7.1)	14.1 (7.7)	14.9 (7.3)
Treatments, n (%)								
Prior surgery	73 (40.6)	72 (40.0)	70 (38.9)	78 (42.6)	21 (13.7)	13 (8.4)	27 (16.6)	18 (11.0)
Prior systemic biologics	39 (21.7)	46 (25.6)	42 (23.3)	48 (26.2)	-	-	-	-
Prior systemic antibiotics	149 (82.8)	150 (83.3)	152 (84.4)	151 (82.5)	71 (46.4)	63 (40.1)	82 (50.3)	76 (46.6)
Concomitant antibiotic therapy	25 (14)	18 (10)	21 (12)	19 (10)	Not allowed		19%	

Note: SEC: Secukinumab, PLA: Placebo, ADA: Adalimumab. Q1W: drug given every week, Q4W: drug given every 4 weeks.AN: Abscesses and nodules. * In the adalimumab studies, “Asian” in included on “Other”.

Comparability of patients across studies

Within the individual study, the populations were well balanced between treatment arms, except for

- PIOENEER I: The distribution between gender was uneven, with 40.5% male in the adalimumab arm vs. 31.8% in the placebo arm.
- SUNSHINE: Disease severity was slightly higher in the secukinumab arm vs. placebo arm, as 35.0% in the secukinumab arm had Hurley stage III vs. 28.3% in the placebo arm.

When comparing across studies with secukinumab and the adalimumab studies, the following differences are observed:

- There are slightly more male in SUNSHINE and SUNRISE (42.6-44.4%) vs. in PIONEER I and II (30.7-40.5%)
- The distribution HURLEY stage differs, with more (severe) Hurley stage 3 patients in the PIONEER I and II (45.4-47.4%) vs. in SUNSHINE and SUNRISE (28.3-38.3%). More severe disease may result in lower efficacy.
- Concurrent systemic antibiotics were not allowed in PIONEER I, and in the remaining studies, the proportion of patients treated with systemic antibiotics at study entry was 10-14% in SUNSHINE and SUNRISE vs. 19% in PIONEER II. The concurrent use of systemic antibiotics may have favoured the placebo arm.
- In SUNSHINE and SUNRISE, 21.7 to 26.2% had been treated with biological treatment previously. Patients who had inadequate response on previous treatment may respond less to subsequent therapy.

Comparability of the study populations with Danish patients eligible for treatment

The Danish HS population that has been treated with biological treatment has been described by Ring et al. [9].

The mean age at treatment start is 41.9 years, and the population consists of 59.4% women and 40.6% men. The mean (SD) BMI was 32.3 (8.3). It is assumed that most Danish patients are Caucasian. Patients with moderate to severe HS are eligible for biological treatment in Denmark. Based on this, the study population in the included studies are comparable with the Danish HS patients.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 28 Definition, validity and clinical relevance of outcome measures

Outcome measure	Definition	Validity	Clinical relevance
HiSCR50	Defines the response to treatment according to 3 types of lesions: abscesses, inflammatory nodules and draining fistula. To achieve HiSCR50, participants should experience ≥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. Patients who required rescue medication (oral antibiotics), or who withdrew due to adverse events or lack of efficacy were categorised as "non-responders".	The validity of the HiSCR outcome has been tested with test-retest reliability [44].	HiSCR50 is clinically relevant in the assessment of HS treatment effectiveness, as the score capture the inflammatory manifestations of the disease. Using the threshold of 50% is clinically appropriate and meaningful to patients with respect to quality of life and pain level improvement [44].
DLQI response	Defined as a decrease in the DLQI score greater than 5.0 points from baseline to follow-up at week 12 or 16.	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].	DLQI is the most widely used quality-of-life instrument for skin diseases, which makes it relevant for use in HS. The minimal clinically important difference have been estimated to 4 [26]. For all four included clinical studies, the definition of DLQI response Is a decrease of 5 or more from baseline [12, 27].

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Outcome measure	Definition	Validity	Clinical relevance
SAEs	SUNSHINE and SUNRISE studies: Include SAEs that occur during the study treatment or within 84 days of treatment discontinuation. PIONEER I and II: No specification of SAEs were present in the studies. AEs were included when onset or worsening occurred until 70 days after discontinuation. It was tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 16.1 system organ classes and preferred terms.	Not assessed	Safety outcomes are of great clinical relevance, because it is important to know and understand the risks associated with a treatment option.
Discontinuation	Included as the number of patients who prematurely discontinued the study for any reason.	Not assessed	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.

Results per study

Table 29: Results of the SUNSHINE study

SUNSHINE study (NCT03713619)				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 – 16 weeks	300 mg Secukinumab Q4W	180	41.8% (34.6%, 49.3%)	Secukinumab Q4W vs placebo: 8.24%	-1.72%, 18.20%	0.105	OR: 1.48	0.95, 2.32	0.042	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was presented as the OR in the clinical study report (CSR).	Kimball et al. 2023 [12] CSR of the SUNSHINE study
	Placebo	181	33.7% (27.0%, 41.2%)								
HiSCR50 – 12 weeks	300 mg Secukinumab Q4W	180	[redacted]	Secukinumab Q4W vs placebo: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was presented as the OR in the CSR.	CSR of the SUNSHINE study
	Placebo	181	[redacted]								
DLQI response – 16 weeks	300 mg Secukinumab Q4W	128	48.4% (39.6%, 57.4%)	Secukinumab Q4W vs placebo: 19.53%	7.84, 31.22	<0.001	OR: 3.09	1.76, 5,43	<0.001	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was presented as the OR in the CSR.	Kimball et al. 2023 [12] CSR of the SUNSHINE study
	Placebo	128	28.9% (21.4%, 37.7%)								

SUNSHINE study (NCT03713619)				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**		
SAEs – 16 weeks	300 mg Secukinumab Q4W	180	1.7% (0.4%, 5.2%)	Secukinumab Q4W vs placebo: -1.67%	-4.89%, 1.55%	0.311	RR: 0.50	0.13, 1.97	0.322	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2023 Appendix1 [28]
	Placebo	180	3.3% (1.4%, 7.4%)								
Discontinuation – 16 weeks	300 mg Secukinumab Q4W	180	6.1%	Secukinumab Q4W vs placebo: 1.67%	-2.95%, 6.28%	0.479	RR: 1.38	0.57, 3.34	0.482	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2023 [12]
	Placebo	180	4.4%								

Note: Q4W: treatment given every 4 weeks. OR: Odds ratio. RR: Relative risk. CSR: Clinical study report

* A 5% two-sided α level was used to control for the type I error. Two secukinumab doses were tested versus placebo with respect to the primary and secondary endpoints. The α level was split unequally: 4% for the secukinumab every 2 weeks group versus the placebo group and 1% for the secukinumab every 4 weeks group versus the placebo group. One-sided p values were reported for hypothesis testing for all primary and secondary endpoints with a 2·5% level of significance, given that the aim of both trials was to show superiority of either secukinumab dose compared with placebo.

Table 30: Results of the SUNRISE (NCT03713632)

Sunrise study (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 – 16 weeks	300 mg Secukinumab Q4W	180	46.1% (38.8%, 53.7%)	Secukinumab Q4W vs placebo: 14.96%	5.06%, 24.87%	0.003	OR: 1.90	1.22, 2.96	0.002	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was presented as the OR in the CSR.	Kimball et al. 2023 [12] CSR of the SUNRISE study
	Placebo	183	31.2% (24.7%, 38.4%)								
HiSCR50 – 12 weeks	300 mg Secukinumab Q4W	180	[redacted]	Secukinumab Q4W vs placebo: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was presented as the OR in the CSR	CSR of the SUNRISE study
	Placebo	183	[redacted]								
DLQI response – 16 weeks	300 mg Secukinumab Q4W	142	47.2% (38.8%, 55.7%)	Secukinumab Q4W vs placebo: 15.46%	4.29%, 26.63%	0.0112	OR: 1.92	1.16, 3.17	0.0112	The absolute difference in effect was estimated using a two-sided t-test.	Kimball et al. 2023 [12]

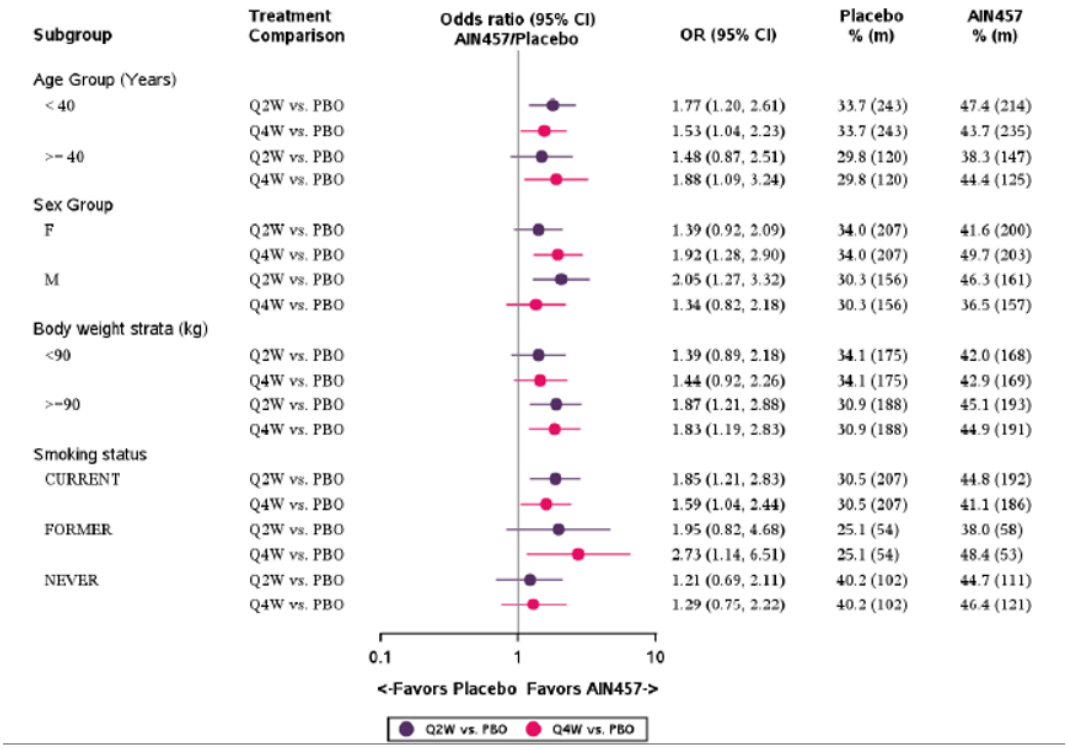
Sunrise study (NCT03713632)				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation*	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*-value**	**Difference**	**95% CI**	***P*-value**		
	Placebo	145	31.7% (24.4%, 40.0%)							The relative difference was presented as the OR in the CSR.	CSR of the SUNRISE study
SAEs – 16 weeks	300 mg Secukinumab Q4W	180	3.3% (1.4%, 7.4%)	Secukinumab Q4W vs placebo: 0.60%	-2.93%, 4.13%	0.739	RR: 1.22	0.38, 3.93	0.739	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2023 Appendix1 [28]
	Placebo	183	2.7% (1.0%, 6.6%)								
Discontinuation – 16 weeks	300 mg Secukinumab Q4W	180	6.1%	Secukinumab Q4W vs placebo: -2.63%	-8.02%, 2.75%	0.338	RR: 0.70	0.33, 1.46	0.343	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2023 [12]
	Placebo	183	8.7%								

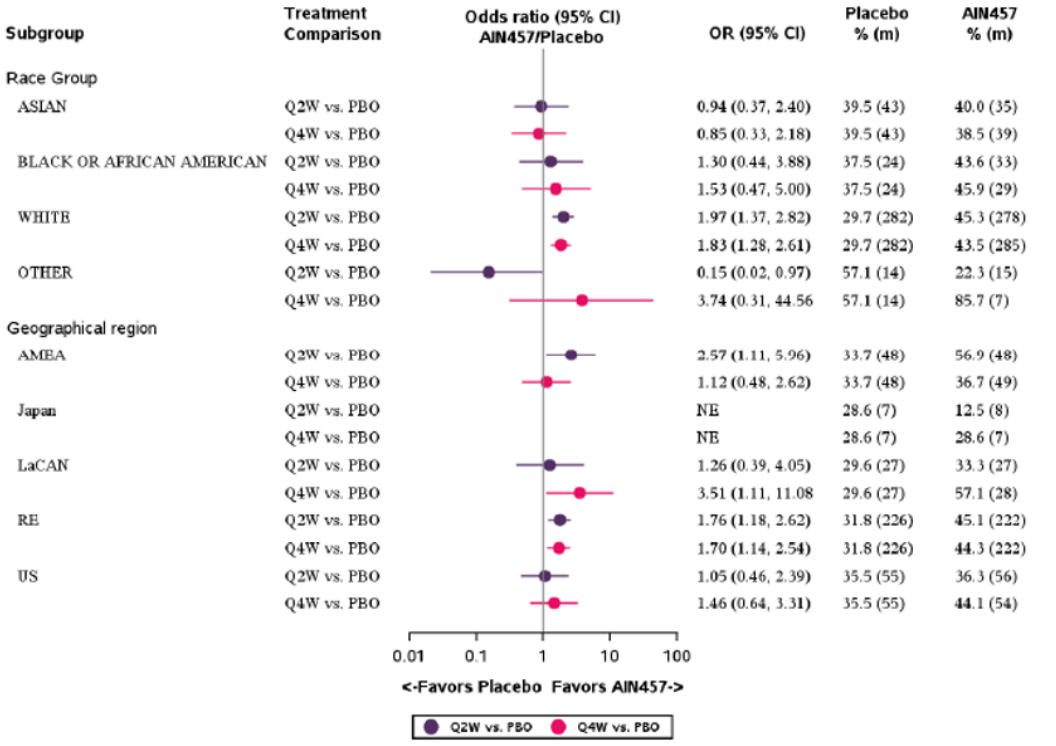
Note: Q4W: treatment given every 4weeks. OR: Odds ratio. RR: Relative risk. CSR: Clinical study report

* A 5% two-sided α level was used to control for the type I error. Two secukinumab doses were tested versus placebo with respect to the primary and secondary endpoints. The α level was split unequally: 4% for the secukinumab every 2 weeks group versus the placebo group and 1% for the secukinumab every 4 weeks group versus the placebo group. One-sided p values were reported for hypothesis testing for all primary and secondary endpoints with a 2·5% level of significance, given that the aim of both trials was to show superiority of either secukinumab dose compared with placebo.

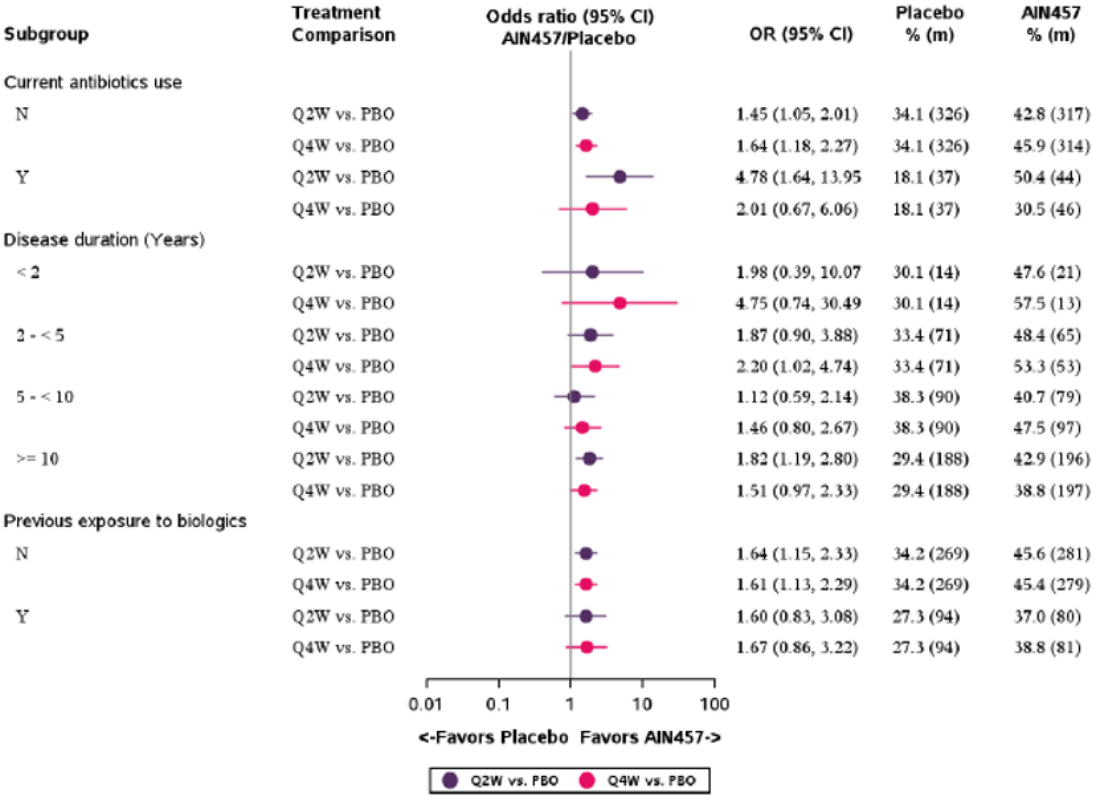
.

Figure 6 Predefined subgroup analysis, HiSCR50 [24]





Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00
medicinraadet@medicinraadet.dk www.medicinraadet.dk


Subgroup
Treatment Comparison
Odds ratio (95% CI) AIN457/Placebo
OR (95% CI)
Placebo % (m)
AIN457 % (m)
Current antibiotics use
N
Q2W vs. PBO 1.45 (1.05, 2.01) 34.1 (326) 42.8 (317)
Q4W vs. PBO 1.64 (1.18, 2.27) 34.1 (326) 45.9 (314)
Y
Q2W vs. PBO 4.78 (1.64, 13.95) 18.1 (37) 50.4 (44)
Q4W vs. PBO 2.01 (0.67, 6.06) 18.1 (37) 30.5 (46)
Disease duration (Years)
< 2
Q2W vs. PBO 1.98 (0.39, 10.07) 30.1 (14) 47.6 (21)
Q4W vs. PBO 4.75 (0.74, 30.49) 30.1 (14) 57.5 (13)
2 - < 5
Q2W vs. PBO 1.87 (0.90, 3.88) 33.4 (71) 48.4 (65)
Q4W vs. PBO 2.20 (1.02, 4.74) 33.4 (71) 53.3 (53)
5 - < 10
Q2W vs. PBO 1.12 (0.59, 2.14) 38.3 (90) 40.7 (79)
Q4W vs. PBO 1.46 (0.80, 2.67) 38.3 (90) 47.5 (97)
>= 10
Q2W vs. PBO 1.82 (1.19, 2.80) 29.4 (188) 42.9 (196)
Q4W vs. PBO 1.51 (0.97, 2.33) 29.4 (188) 38.8 (197)
Previous exposure to biologics
N
Q2W vs. PBO 1.64 (1.15, 2.33) 34.2 (269) 45.6 (281)
Q4W vs. PBO 1.61 (1.13, 2.29) 34.2 (269) 45.4 (279)
Y
Q2W vs. PBO 1.60 (0.83, 3.08) 27.3 (94) 37.0 (80)
Q4W vs. PBO 1.67 (0.86, 3.22) 27.3 (94) 38.8 (81)
0.01
0.1
1
10
100
<-Favors Placebo Favors AIN457->
Q2W vs. PBO
Q4W vs. PBO

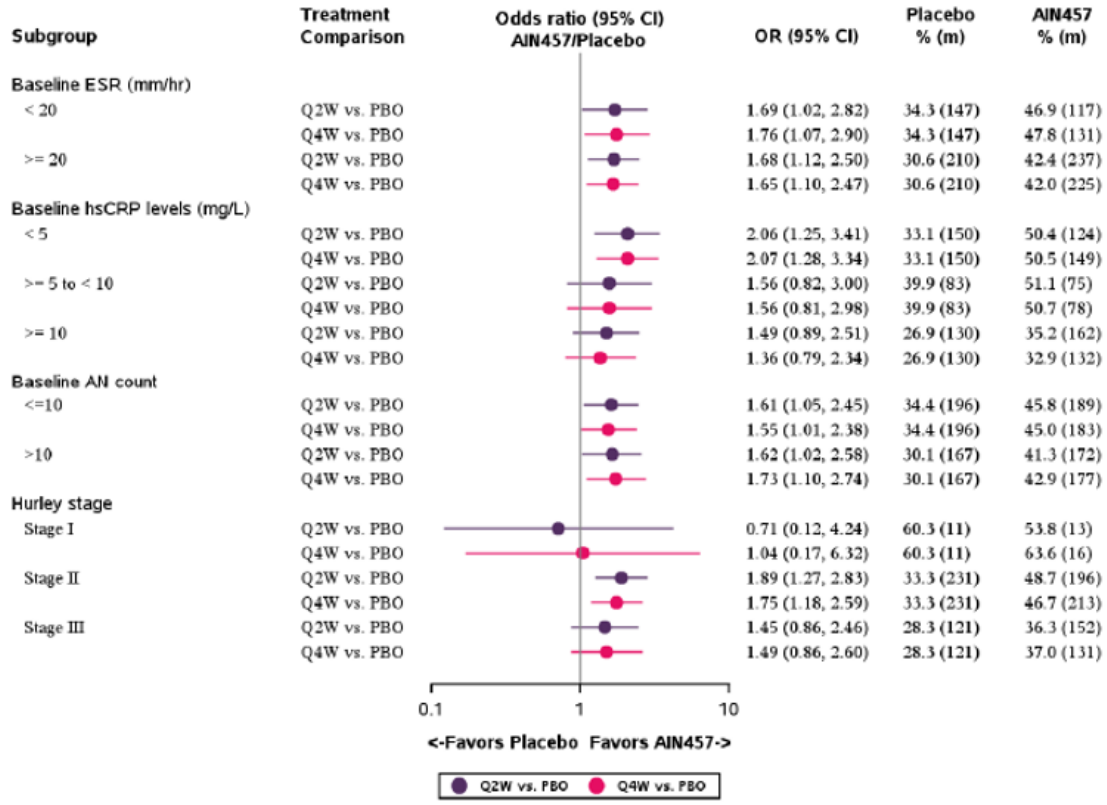

Subgroup
Treatment Comparison
Odds ratio (95% CI) AIN457/Placebo
OR (95% CI)
Placebo % (m)
AIN457 % (m)
Baseline ESR (mm/hr)
< 20
Q2W vs. PBO 1.69 (1.02, 2.82) 34.3 (147) 46.9 (117)
Q4W vs. PBO 1.76 (1.07, 2.90) 34.3 (147) 47.8 (131)
>= 20
Q2W vs. PBO 1.68 (1.12, 2.50) 30.6 (210) 42.4 (237)
Q4W vs. PBO 1.65 (1.10, 2.47) 30.6 (210) 42.0 (225)
Baseline hsCRP levels (mg/L)
< 5
Q2W vs. PBO 2.06 (1.25, 3.41) 33.1 (150) 50.4 (124)
Q4W vs. PBO 2.07 (1.28, 3.34) 33.1 (150) 50.5 (149)
>= 5 to < 10
Q2W vs. PBO 1.56 (0.82, 3.00) 39.9 (83) 51.1 (75)
Q4W vs. PBO 1.56 (0.81, 2.98) 39.9 (83) 50.7 (78)
>= 10
Q2W vs. PBO 1.49 (0.89, 2.51) 26.9 (130) 35.2 (162)
Q4W vs. PBO 1.36 (0.79, 2.34) 26.9 (130) 32.9 (132)
Baseline AN count
<=10
Q2W vs. PBO 1.61 (1.05, 2.45) 34.4 (196) 45.8 (189)
Q4W vs. PBO 1.55 (1.01, 2.38) 34.4 (196) 45.0 (183)
>10
Q2W vs. PBO 1.62 (1.02, 2.58) 30.1 (167) 41.3 (172)
Q4W vs. PBO 1.73 (1.10, 2.74) 30.1 (167) 42.9 (177)
Hurley stage
Stage I
Q2W vs. PBO 0.71 (0.12, 4.24) 60.3 (11) 53.8 (13)
Q4W vs. PBO 1.04 (0.17, 6.32) 60.3 (11) 63.6 (16)
Stage II
Q2W vs. PBO 1.89 (1.27, 2.83) 33.3 (231) 48.7 (196)
Q4W vs. PBO 1.75 (1.18, 2.59) 33.3 (231) 46.7 (213)
Stage III
Q2W vs. PBO 1.45 (0.86, 2.46) 28.3 (121) 36.3 (152)
Q4W vs. PBO 1.49 (0.86, 2.60) 28.3 (121) 37.0 (131)
0.1
1
10
<-Favors Placebo Favors AIN457->
Q2W vs. PBO
Q4W vs. PBO

Table 31 Results of PIONEER I (NCT01468207)

PIONEER I (NCT01468207)				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	Adalimumab Q1W	153	41.8%	15.8%	5.41%, 26.30%	0.003	RR: 1.61	1.16,2.23	0.004	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR..	Kimball et al. 2016 [13]
	Placebo	154	26.0%								
DLQI response	Adalimumab Q1W	150	50.7%	16.9%	5.90%, 27.89%	0.004	RR: 1.50	1.14, 1.97	0.004	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 Supplement [27]
	Placebo	151	33.8%								
SAEs	Adalimumab Q1W	153	1.3%	-0.01%	-2.56%, 2.54%	0.995	RR: 0.99	0.14, 6.96	0.995	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 [13]
	Placebo	152	1.3%								
Discontinuation	Adalimumab Q1W	153	5.2%	0.65%	-4.18%, 5.49%	0.791	RR: 1.14	0.42, 3.07	0.791	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 [13]
	Placebo	152	4.6%								

Note: Q1W: treatment given every week. RR: Relative risk.

Table 32 Results of PIONEER II (NCT01468233)

PIONEER II (NCT01468233)				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	Adalimumab Q1W	163	58.9%	31.29%	21.08%, 41.49%	<0.001	RR: 2.13	1.61, 2.82	<0.001	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 [13]
	Placebo	163	27.6%								
DLQI response	Adalimumab Q1W	162	49%	14.8%	4.15%, 25.45%	0.011	RR: 1.44	1.10, 1.88	0.008	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 Supplement [27]
	Placebo	159	34%								
SAEs	Adalimumab Q1W	163	1.8%	-1.84%	-5.39%, 1.71%	0.310	RR: 0.50	0.13, 1.97	0.321	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 [13]
	Placebo	163	3.7%								
Discontinuation	Adalimumab Q1W	163	4.9%	-2.45%	-7.66%, 2.75%	0.355	RR: 0.67	0.28, 1.59	0.360	The absolute difference in effect was estimated using a two-sided t-test. The relative difference was estimated as the RR.	Kimball et al. 2016 [13]
	Placebo	163	7.4%								

Note: Q1W: treatment given every week. RR: Relative risk.

Appendix E Safety data for intervention and comparator

Proportion of patients with at least one adverse event, at least one serious adverse event, discontinuing treatment for any reason and discontinuing treatment due to an adverse event, is shown in

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 33. Note that the exposure time for secukinumab was 16 weeks vs. 12 weeks for adalimumab.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 33 Proportion of patients with at least one adverse event and one serious adverse event [12, 13, 28]

Study	SUNSHINE		SUNRISE		PIONEER I		PIONEER II	
Treatment arm	Secukinumab Q4 W n=180	Placebo n=180	Secukinumab Q4 W n=180	Placebo n=183	Adalimumab Q1W n=153	Placebo n=152	Adalimumab Q1W n=163	Placebo n=163
Exposure time	16 weeks				12 weeks			
Proportion of patients with at least one Adverse Event, n (%)	118 (65.6)	120 (66.7)	114 (63.3)	116 (63.4)	77 (50.3)	89 (58.6)	93 (57.1)	103 (63.2)
Proportion of patients with at least one Serious Adverse Event, n (%)	3 (1.7)	6 (3.3)	3 (3.3)	5 (2.7)	2 (1.3)	2 (1.3)	3 (1.8)	6 (3.7)
Proportion of patients discontinuing treatment, any reason n (%)	11 (6.1)	8 (4.4)	11 (6.1)	16 (8.7)	7 (4.6)	8 (5.3)	8 (4.9)	12 (7.4)
Proportion of patients discontinuing treatment due to an adverse event, n (%)	0	1 (0.6)	4 (2.2)	4 (2.2)	0	2 (1.3)	4 (2.5)	6 (2.7)

There are no published data on proportion of patients with adverse drug reactions. However, adverse events considered related to the secukinumab and adalimumab drugs are shown in Table 34, across all approved indications, based on the approved SmPCs for Cosentyx and Humira [10, 11] .

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 34 Safety information for secukinumab and adalimumab from the SmPCs

	Secukinumab	Adalimumab
Mechanism of action	IL-17 inhibitor	TNF-α inhibitor
Contraindications	• Hypersensitivity to the active substance or to any of the excipients • Clinically important, active infection, e.g. active tuberculosis	• Hypersensitivity to the active substance or to any of the excipients • Active tuberculosis or other severe infections such as sepsis, and opportunistic infections • Moderate to severe heart failure (NYHA class III/IV)
Undesirable effects:	The most frequently reported adverse drug reactions (ADRs) for secukinumab are upper respiratory tract infections (most frequently nasopharyngitis, rhinitis).	The most commonly reported adverse reactions for adalimumab are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.
Very common (≥ 1/10)	Upper respiratory tract infections	• Respiratory tract infections • Leukopenia, Anaemia • Lipids increased • Headache • Abdominal pain, nausea and vomiting • Elevated liver enzymes • Rash • Musculoskeletal pain • Injection site reaction
Common (≥ 1/100 to < 1/10)	• Oral herpes, Tinea pedis • Headache	• Systemic infections, intestinal infections, skin and soft tissue infections, ear infections, oral infections,

	Secukinumab	Adalimumab
	• Rhinorrhoea • Diarrhoea • Nausea • Fatigue	reproductive tract infections, urinary tract infections, fungal infections, joint infections. • Skin cancer excluding melanoma, benign neoplasm • Leucocytosis, thrombocytopenia • Hypersensitivity, allergies • Hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphatemia, dehydration • Mood alterations, anxiety, insomnia • Paraesthesias, migraine, nerve root compression • Visual impairment, conjunctivitis, blepharitis, eye swelling • Vertigo • Tachycardia • Hypertension, flushing, haematoma • Asthma, dyspnoea, cough • GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome • Worsening or new onset of psoriasis, urticaria, bruising, dermatitis, onychoclasis, hyperhidrosis, alopecia, pruritus • Muscle spasms • Renal impairment, haematuria • Chest pain, oedema, pyrexia

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Secukinumab	Adalimumab
		• Coagulation and bleeding disorders, autoantibody test positive, blood lactate dehydrogenase increased • Impaired healing
Uncommon (≥ 1/1,000 to < 1/100)	• Oral candidiasis, Otitis externa, lower respiratory tract infection • Neutropenia • Conjunctivitis • Inflammatory bowel disease • Urticaria, dyshidrotic eczema	• Neurological infections, opportunistic infections and tuberculosis, bacterial infections, eye infections, diverticulitis • Lymphoma, solid organ neoplasm, melanoma • Idiopathic thrombocytopenic purpura • Sarcoidosis, vasculitis • Cerebrovascular accident, tremor, neuropathy • Diplopia • Deafness, tinnitus • Myocardial infarction, arrhythmia, congestive heart failure • Aortic aneurysm, vascular arterial occlusion, thrombophlebitis • Pulmonary embolism, interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis, pleural effusion • Pancreatitis, dysphagia, face oedema • Cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased • Night sweats, scar • Rhabdomyolysis, systemic lupus erythematosus

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Secukinumab	Adalimumab
		• Nocturia • Erectile dysfunction • Inflammation
Not known (cannot be estimated from the available data).	• Mucosal and cutaneous candidiasis	• Hepatosplenic T-cell lymphoma, Merkel cell carcinoma, Kaposi's sarcoma • Liver failure • Worsening of symptoms of dermatomyositis • Weight increased

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix F Comparative analysis of efficacy and safety

The comparative analyses consisted of both meta-analyses and Bucher's method. The methods used and the results of the comparative analyses are presented in section 7.1.3.

Meta-analyses

Table 35 Meta-analysis of studies comparing secukinumab to placebo for patients with moderate to severe HS

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 16 weeks – Secukinumab Q4W vs placebo	SUNSHINE SUNRISE	NA	NA	NA	RR: 1.35	1.12, 1.64	0.002	A random effects meta-analysis using inverse variance weights. .	No
HiSCR50 12 weeks – Secukinumab Q4W vs placebo	SUNSHINE SUNRISE	NA	NA	NA	RR: 1.69	1.14, 2.50	0.010	A random effects meta-analysis using inverse variance weights.	No
DLQI response 16 weeks – Secukinumab Q4W vs placebo	SUNSHINE SUNRISE	NA	NA	NA	RR: 1.57	1.26, 1.95	<0.001	A random effects meta-analysis using inverse variance weights.	No
SAEs 16 weeks – Secukinumab Q4W vs placebo	SUNSHINE SUNRISE	NA	NA	NA	RR: 0.84	0.34, 2.03	0.693	A random effects meta-analysis using inverse variance weights.	No

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		
Discontinuation 16 weeks – Secukinumab Q4W vs placebo	SUNSHINE SUNRISE	NA	NA	NA	RR: 0.94	0.49, 1.81	0.844	A random effects meta-analysis using inverse variance weights.	No

Note: Q4W: treatment given every 4 weeks. MD: Mean difference. RR: relative risk.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 36 Meta-analysis of studies comparing adalimumab to placebo for patients with moderate to severe HS

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 12 weeks – adalimumab Q1W vs placebo	PIONEER I PIONEER II	NA	NA	NA	RR: 1.88	1.43, 2.47	<0.001	A random effects meta-analysis using inverse variance weights.	No
DLQI response 12 weeks – Adalimumab Q1W vs placebo	PIONEER I PIONEER II	NA	NA	NA	RR: 1.47	1.21, 1.78	<0.001	A random effects meta-analysis using inverse variance weights.	No
SAEs 12 weeks – Adalimumab Q1W vs placebo	PIONEER I PIONEER II	NA	NA	NA	RR: 0.63	0.20, 1.92	0.415	A random effects meta-analysis using inverse variance weights.	No
Discontinuation 12 weeks – Adalimumab Q1W vs placebo	PIONEER I PIONEER II	NA	NA	NA	RR: 0.33	0.44, 1.61	0.601	A random effects meta-analysis using inverse variance weights.	No

Note: Q1W: treatment given every week. RR: relative risk.

Indirect treatment comparison

Table 37 Indirect treatment comparison of studies comparing secukinumab to adalimumab for patients with moderate to severe HS

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 – Secukinumab Q4W 16 weeks vs adalimumab Q1W 12 weeks	SUNSHINE SUNRISE PIONEER I PIONEER II	NA	NA	NA	RR: 0.72	0.52, 1.01	0.055	Bucher's method for the indirect treatment comparison was used. The inputs were based on random effects meta-analysis presented in Table 35 and Table 36	No
HiSCR50 – Secukinumab Q4W 12 weeks vs adalimumab Q1W 12 weeks	SUNSHINE SUNRISE PIONEER I PIONEER II	NA	NA	NA	RR: 0.90	0.56, 1.45	0.66	Bucher's method for the indirect treatment comparison was used. The inputs were based on random effects meta-analysis presented in Table 35 and Table 36	No
DLQI response – Secukinumab Q4W 16 weeks vs adalimumab Q1W 12 weeks	SUNSHINE SUNRISE PIONEER I PIONEER II	NA	NA	NA	RR: 1.07	0.80, 1.43	0.65	Bucher's method for the indirect treatment comparison was used. The inputs were based on random effects meta-analysis presented in Table 35 and Table 36	No
SAEs – Secukinumab Q4W 16 weeks vs adalimumab Q1W 12 weeks	SUNSHINE SUNRISE PIONEER I PIONEER II	NA	NA	NA	RR: 1.34	0.32, 5.58	0.69	Bucher's method for the indirect treatment comparison was used. The inputs were based on random effects meta-analysis presented in Table 35 and Table 36	No

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		
Discontinuation – Secukinumab Q4W 16 weeks vs adalimumab Q1W 12 weeks	SUNSHINE SUNRISE PIONEER I PIONEER II	NA	NA	NA	RR: 1.11	0.44, 2.81	0.819	Bucher's method for the indirect treatment comparison was used. The inputs were based on random effects meta-analysis presented in Table 35 and Table 36	No

Note: Q1W: treatment given every week. Q4W: treatment given every 4 weeks. MD: mean difference. RR: relative risk.

Appendix G Extrapolation

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix H – Literature search for HRQoL data

N/A

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix I Mapping of HRQoL data

N/A

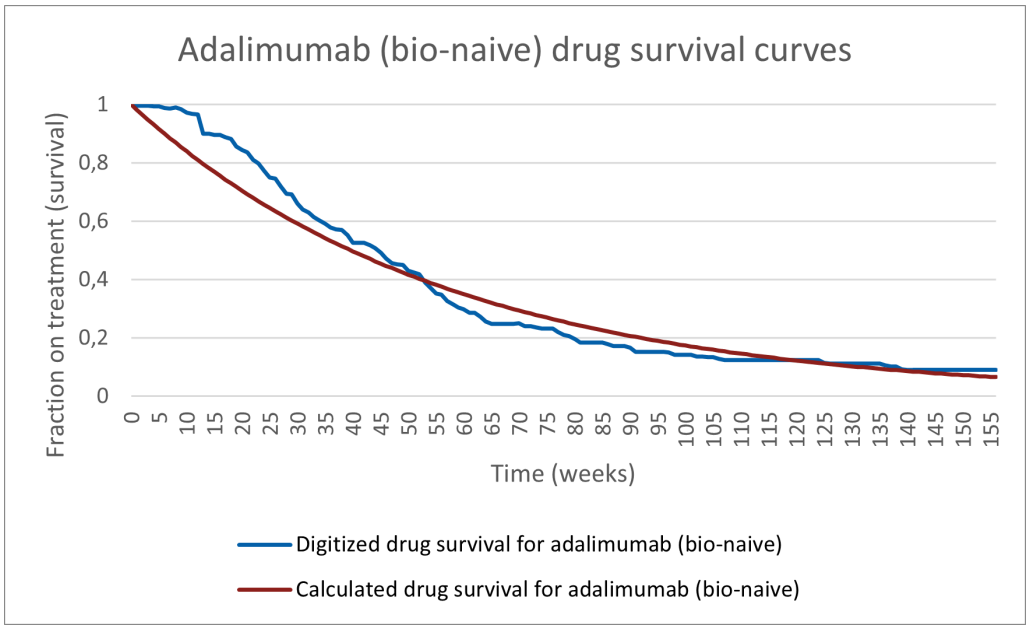
Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

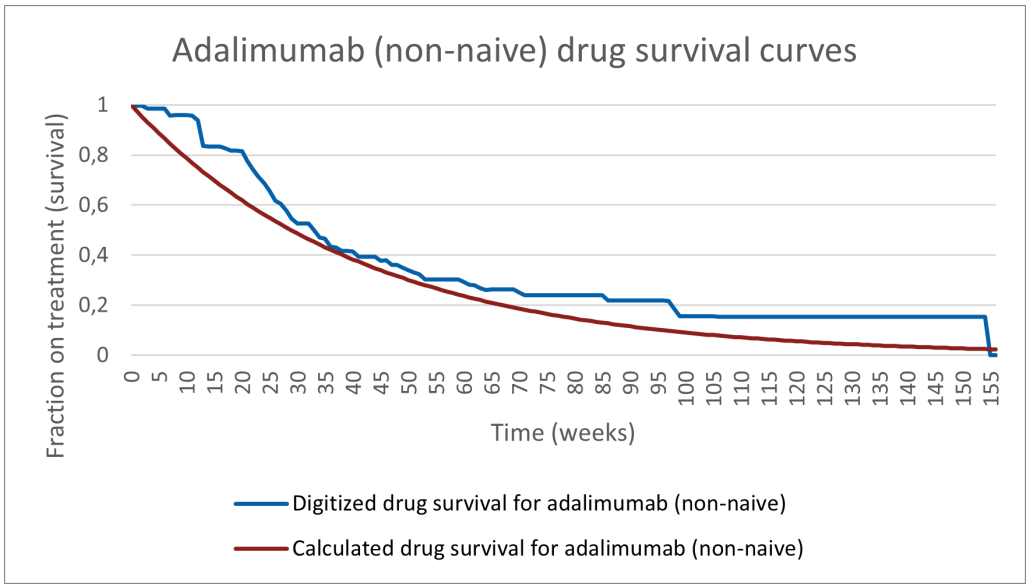
Appendix J Probabilistic sensitivity analyses

N/A

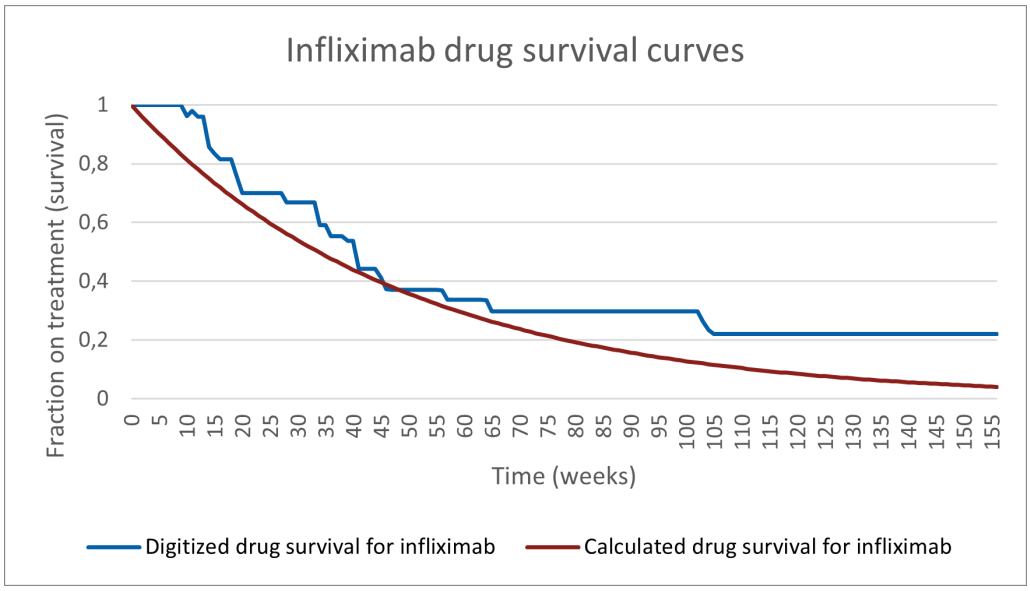
Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

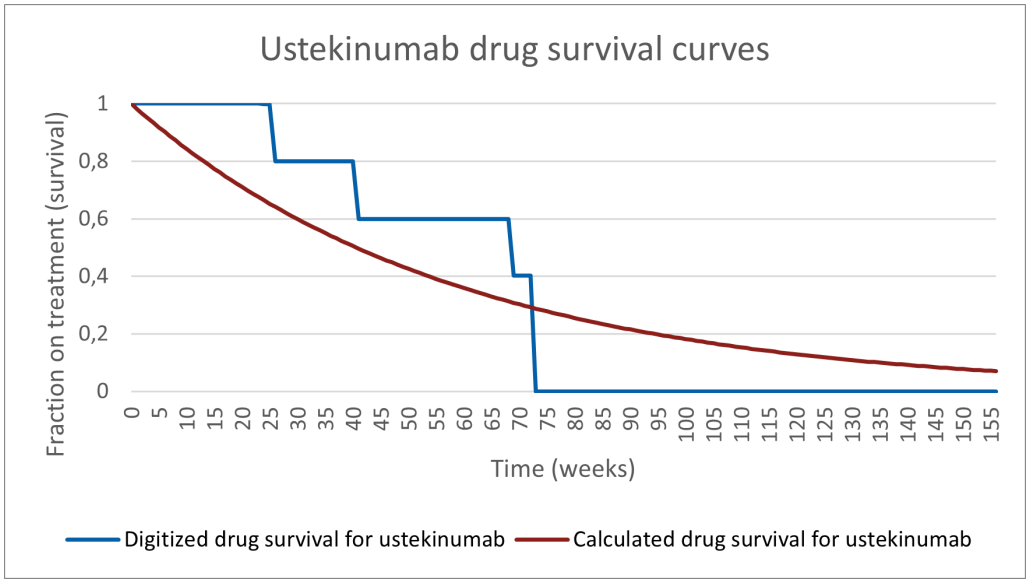
Appendix K Drug survival curves





Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk





Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk