Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende secukinumab til behandling af non-radiografisk aksial spondylartrit

Vers. 1.0

Bilagsoversigt

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

Alice Brinch Mørch, MD
Value & Access Manager

Novartis Healthcare A/S
Pharma
Edvard Thomsens Vej 14, 3.
DK-2300 København S

Tlf: +45 28 43 18 25
E-mail:
alice_brinch.moerch@novartis.com

Til Medicinrådet

24. marts 2022

Høringssvar til udkast til Medicinrådets anbefaling vedrørende secukinumab til behandling af non-radiografisk axial spondylartrit

Kære Medicinråd,

Vi har den 22. marts modtaget udkast til Medicinrådets anbefaling vedrørende secukinumab til behandling af non-radiografisk axial spondylartrit.

Novartis vil gerne komplimentere Medicinrådet for et grundigt og gennemarbejdet dokument, og har ingen yderligere kommentarer.

Vi ser frem til Medicinrådets endelige beslutning om ibrugtagning af secukinumab til behandling af non-radiografisk axial spondylartrit i april 2022.

Med venlig hilsen,
Novartis Healthcare A/S

Alice Brinch Mørch
Value and Access Manager, MD

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

30.03.2022

DBS og ECH

Forhandlingsnotat

Dato for behandling i Medicinrådet	20.04.2022
Leverandør	Novartis
Lægemiddel	Cosentyx (secukinumab)
Ansøgt indikation	Behandling af patienter med ikke-radiografisk aksial spondylartrit (nr-axSpA).

Forhandlingsresultat

Amgros har følgende pris på Cosentyx (secukinumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP (DKK)	SAIP (DKK)*	Rabat ift. AIP
Cosentyx (secukinumab)	Sprøjte 75 mg	1 stk	1.977	[redacted]	[redacted]
Cosentyx (secukinumab)	Pen 150 mg	2 stk	7.908	[redacted]	[redacted]
Cosentyx (secukinumab)	Pen 300 mg	1 stk	7.908	[redacted]	[redacted]

*Pris gældende fra d. 01.04.2022

Cosentryx (secukinumab) indgår i det udbud som blev gennemført på baggrund af behandlingsvejledninger for biologiske lægemidler, indenfor reumatologi, dermatologi og gastroenterologi. Denne aftale er gældende fra 01.04.2022.

Konkurrencesituationen

Nedenstående tabel viser et udvalg af lægemidlerne godkendt til sammen indikation. Priserne er gældende fra 01-04.2022 – 01.10.2022. Herefter er der mulighed for prisjustering til en lavere pris.

Tabel 2: Sammenligning af udvalgte nyere lægemidler og deres priser

Lægemiddel	Sammenligningsdosis	Vedligeholdelse sammenligningsdosis	Antal mg/18 måneder	Lægemiddelpris SAIP pr. 18 md. (DKK)
Hyrimoz (adalimumab)	40 mg hver 2 uge	15 mg daglig	1.560 mg	[redacted]
Taltz (ixekizumab)	160 mg (SC) i uge 0	80 mg hver 4. uge	1.640 mg	[redacted]
Cosentyx (secukinumab)	150 mg (SC) i uge 0, 1, 2, 3 og 4	150 mg 1 gang om mdr.	3.150 mg	[redacted]

Konklusion

Det er Amgros's vurdering, at prisen for 18 måneder behandling med Cosentyx (secukinumab) er fordelagtig på nuværende tidspunkt sammenlignet med de andre nyere lægemidler til ikke-radiografisk aksial spondylartrit (nr-axSpA).

Cosentyx (secukinumab) indgår i et dynamisk udbud for biologiske lægemidler, hvor aftalen træder i kraft den 01.04.2022. Der vil dog være mulighed for prisregulering hver 6. måned (første gang den 01.10.2022).

Medicinrådet

Application for the assessment of secukinumab (Cosentyx®) for non-radiographic axial spondyloarthritis (nr-axSpA)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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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	Pia Krogsgaard Villadsen
Title	Head Market Access Denmark
Phone number	+45 21 46 31 96
E-mail	pia.villadsen@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	Interleukin-17-inhibitors
Active substance(s)	Secukinumab
Pharmaceutical form(s)	Solution for injection (injection)

Overview of the pharmaceutical	
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. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence, treatment with secukinumab reduces erythema, induration and desquamation present in plaque psoriasis lesions. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, psoriatic arthritis and axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis (nr-axSpA)); it is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients and in synovial tissue of psoriatic arthritis patients. The frequency of IL-17-producing cells was also significantly higher in the subchondral bone marrow of facet joints from patients with ankylosing spondylitis. Increased numbers of IL-17A-producing lymphocytes have also been found in patients with non-radiographic axial spondyloarthritis. Inhibition of IL-17A was shown to be effective in the treatment of ankylosing spondylitis, thus establishing the key role of this cytokine in axial spondyloarthritis.
Dosage regimen	The recommended dose is 150 mg by subcutaneous (s.c.) injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Secukinumab is also available in strengths of 75 and 300 mg (relevant dosages for other indications).
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Secukinumab is indicated for the treatment of active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).
Other approved therapeutic indications	Adult plaque psoriasis. Paediatric plaque psoriasis. Psoriatic arthritis. Ankylosing spondylitis (AS, radiographic axial spondyloarthritis).
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	None
Packaging – types, sizes/number of units, and concentrations	Cosentyx solution for injection 150 mg/mL, 2 prefilled pens (SensoReady®)
Orphan drug designation	No

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2. Abbreviations

AE	Adverse event
AIP	Apotekernes indkøbspris
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASAS40	Assessment of SpondyloArthritis international Society 40% response
ASAS HI	Assessment of SpondyloArthritis international Society Health Index
ASDAS	Ankylosing Spondylitis Disease Activity score
ASQoL	Ankylosing Spondylitis Quality of Life Scores
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification
axSpA	Axial spondyloarthritis
BAS	Bath Ankylosing Spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% improvement
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacillus Calmette-Guérin
bDMARDs	Disease-modifying biological treatment with antibodies
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
CRP	C-reactive protein
csDMARDs	Conventional synthetic disease-modifying antirheumatic drugs
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double blind
DMARD	Disease-modifying antirheumatic drug
EAIR	Exposure-adjusted incidence rates
ELAM-1	Endothelial leucocyte adhesion molecule-1
EMA	European Medicines Agency
Eow	Every other week
EPAR	European public assessment report
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Level
EU	European Union
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
HSTCL	Hepatosplenic T-cell lymphoma
HSUV	Health state utility values
IBD	Inflammatory bowel disease
IC50	Half-maximal inhibitory concentration
ICAM-1	Intercellular adhesion molecule-1
ICER	Incremental cost-effectiveness ratio
Ig	Immunoglobulin
IL	Interleukin
IL-17A	Interleukin-17A

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ITC	Indirect treatment comparison
IIT	Intention-to-treat
JSEQ	Jenkins Sleep Evaluation Questionnaire
LD	Loading dose
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MMRM	Mixed-effects model of repeated measures
MRI	Magnetic resonance imaging
MTX	Methotrexate
NCT	National Clinical Trial
NL	Without loading dose
NLM	National Library of Medicine
nr-axSpA	Non-radiographic axial spondyloarthritis
NRI	Non-responder imputation
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OL	Open label
PICO	Population, intervention, comparison, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
RCT	Randomised controlled trial
RD	Risk difference
RR	Relative risk
SAE	Serious adverse event
s.c.	Subcutaneous
SE	Standard error
SEM	Standard error of the mean
SJC	Swollen joint count
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TB	Tuberculosis
TJC	Tender joint count
TNF	Tumour necrosis factor
TNFα-i	Tumour necrosis factor alpha inhibitor
ULN	Upper limit normal
US, USA	United States of America
VAS	Visual Analogue Scale
VCAM-1	Vascular cell adhesion molecule-1
WBC	White blood cell

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3. Tables and figures

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4. Summary

Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin (IL)-17A (IL-17A), indicated for the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)[1] . The recommended dose is 150 mg by subcutaneous (s.c.) injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Secukinumab can be self-administered after an initial instruction by a health care professional.

Secukinumab is compared with adalimumab, a tumour necrosis factor (TNF) alpha inhibitor (TNFα-i), which is recommended as the 1st line treatment by the Danish Medicines Council [1], and with ixekizumab, which like secukinumab, is an IL-17 inhibitor. The comparison of efficacy and safety vs. adalimumab is based on the PREVENT and ABILITY-1 phase 3 studies [2, 3]. The comparison of efficacy and safety vs. ixekizumab is based on the PREVENT and COAST-X phase 3 studies [3, 5]. Comparison of the safety profiles is based on the clinical study results as well as the Summary of Product Characteristics (SmPCs) of the three products.

As ixekizumab has recently been evaluated and recommended by the Danish Medicines Council, the protocol from the Medicines Council has been the basis for the choice of relevant outcomes [32].

The PREVENT study provided evidence of relative treatment efficacy and safety of secukinumab vs. placebo in patients with nr-axSpA. An indirect comparison was conducted using evidence of relative treatment efficacy and safety of adalimumab vs. placebo in patients with nr-axSpA from the ABILITY 1 study. Both active treatments (secukinumab and adalimumab) were superior to placebo on all efficacy analyses in each respective study. Following a feasibility assessment on the comparability of the studies, an indirect treatment comparison (ITC) was conducted on the available outcomes of interest to synthesise the evidence identified. For all efficacy and safety outcomes, there were no statistically significant differences between the treatments.

Similarly, an indirect comparison was conducted between the PREVENT study results and the evidence of relative treatment efficacy and safety of ixekizumab vs. placebo in patients with nr-axSpA obtained from the COAST-X study. Both active treatments (secukinumab and ixekizumab) were superior to placebo on all efficacy analyses in each respective study. Following a feasibility assessment on the comparability of the studies, an ITC was conducted on the available outcomes of interest to synthesise the evidence identified. For all efficacy and safety outcomes, there were no statistically significant differences between the treatments.

Based on the indirect and narrative comparisons across the studies, secukinumab is equally efficacious and has a tolerable safety profile when compared with both adalimumab and ixekizumab.

As there were no significant differences in efficacy and safety between secukinumab and the relevant comparators, adalimumab and ixekizumab, the health economic analysis was carried out as a cost minimisation analysis. The total cost, from a Danish perspective and with an 18 months' time horizon, was estimated to be DKK 82 232 for Cosentyx® (secukinumab), DKK 88 582 for adalimumab and DKK 153 157 for ixekizumab. Hence, Cosentyx implied less costs than both adalimumab (Imraldi®) and ixekizumab (Taltz®). Scenario analyses indicated that the conclusion of Cosentyx being associated with cost savings was indifferent to changes in the time horizon, and hence, to treatment length. The budget impact analysis showed that recommending Cosentyx for the treatment of nr-axSpA in Denmark would imply cost savings from a Danish regional perspective equal to DKK –577 507 in year 1 and DKK –3 674 617 in year 5.

Secukinumab provides an additional treatment option for patients with non-radiographic axial spondyloarthritis.

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

5.1 The medical condition and patient population

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that is primarily manifested by pain and stiffness in the spine and the joints between the sacrum and hip bones in the pelvis (sacroiliac joints), especially in the morning or at night. The pain is recurrent and decreases with movement. The disease is characterised by inflammation where tendons, ligaments and joint capsules attach to the bones [8]. The structural damage caused by the disease is progressive and irreversible and leads to increasing restriction of movement of the spine, with increased risk of fracture and subsequent development of osteoporosis [9]. The disease is mostly seen in men and in younger people (<45 years) [8]. The disease is characterised by varying degrees of inflammation detected radiologically or by MRI scan [10].

In addition to back pain, axSpA can also cause extra-axial symptoms characterised by swelling, pain and/or stiffness in peripheral joints, including the shoulder, knee and foot joints. In addition, patients may develop other diseases, such as psoriasis, anterior uveitis or inflammatory bowel disease (Crohn's disease and ulcerative colitis) [8]. Iritis is seen in approximately 30%–40% and inflammatory bowel disease in approximately 6% of patients with axSpA [10].

AxSpA exists in 2 forms: ankylosing spondylitis (AS) and nr-axSpA. Detection of changes by radiographic examination of the sacroiliac joint (pelvic joint) is required for the diagnosis of AS (modified New York criteria for AS) [11]. In nr-axSpA, radiological findings are not mandatory. Patients are diagnosed with nr-axSpA if they meet the Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA [12] but do not meet the modified New York criteria for AS [8, 10]. Nr-axSpA with objective signs of inflammation (MRI detected or elevated CRP) is generally perceived as pre-radiographic AS, and there will typically be MRI detectable signs of inflammation in the spine or sacroiliac joints [10]. Approximately 10% of patients with nr-axSpA develop AS within 2 years and 60% develop AS within 10 years[13].

The cause of spinal injury is not known; however, the disease is probably due to a complex interplay between genetic predisposition (e.g., certain tissue types) and environmental factors. Many of the genes associated with spinal arthritis are also associated with intestinal inflammation, psoriasis and uveitis [8].

Due to the complexity of the disease, the diagnosis is made optimally in a collaboration between rheumatologists, radiologists and possibly other specialists - especially in patients in whom symptoms, clinical findings and/or the radiological description are difficult to interpret. The diagnosis of AS and nr-axSpA is associated with some uncertainty, which is why it is important that the diagnoses are elucidated by MRI/radiographic examination to assess whether patients have AS, nr-axSpA or whether the symptoms are due to other causes [8].

The DANBIO registry collects data on patients with axSpA who are treated at the rheumatology departments in the Danish hospitals. The database thus only covers a fragment of patients with nr-axSpA; however, these are the patients with more severe disease and thus the patients for whom biologic treatment is relevant. The database does not distinguish between patients with AS and nr-axSpA; however, it is estimated by clinicians that approximately 43% of the patients in the registry have nr-axSpA [14].

According to the DANBIO registry, the mean age for new patients in 2019 was 38 years, with a range from 17 to 54 years and a ratio between males and females of 54:46. For all patients, the ratio between the genders was 62:38.

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Table 1 shows the estimated prevalence of nr-axSpA in Denmark over the past 5 years. No data on incidence exists.

Table 1 Prevalence in the past 5 years

Year	2016	2017	2018	2019	2020
Prevalence in Denmark [8]	87 465	87 915	88 365	88 815	89 265

It has not been possible to estimate the number of patients who are eligible for biologic treatment; however, based on historic data from DANBIO, Table 2 shows the estimated number of patients in Denmark with nr-axSpA who are expected to be treated with biologic treatment over the next 5 years. Based on DANBIO reports, a net growth of 134 patients per year is expected [15].

Table 2 Estimated number of patients with nr-axSpA in biologic treatment

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use biologic treatment in the coming years	1 117	1 251	1 385	1 519	1 653

Estimates on the number of patients on secukinumab are provided in the health economic part of this application (see section 8).

5.1.1 Patient populations relevant for this application

The patient population relevant for this application are patients with active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence in adults who have responded inadequately to NSAIDs.

5.2 Current treatment options and choice of comparators

5.2.1 Current treatment options

There is no cure for nr-axSpA. The treatment targets the patient's symptoms, which are described above (section 5.1). It is important that the diagnosis is made as soon as possible, so that information and guidance in training exercises as well as any medical treatment can be started. The treatment goal is to optimise the patient's quality of life and social interaction by controlling symptoms and inflammation, preventing progressive structural damage and preserving the patient's ability to function [16].

The treatment algorithm includes providing information about the disease to patients and relatives as well as training and physiotherapy. The first choice of drug in the treatment of pain and stiffness is conventional medical treatment with NSAIDs. There is no documented effect in the treatment of axSpA with disease-modifying antirheumatic drugs (DMARDs), although such effect is seen in patients with peripheral joint manifestations [8]. If there is significant disease activity despite exercise and NSAID treatment, and other causes of lack of treatment effect are ruled out, disease-modifying biological treatment with antibodies (bDMARDs) can be initiated. Significant disease activity is defined as Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1 or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) overall score ≥40 (range: 0–100) in patients for a continuous 4-week period in which at least two different NSAIDs have had insufficient effect. Experience has shown that biological treatment have a better effect in patients with elevated CRP levels than those with CRP in the normal range [8].

In the current drug recommendation from the Medicines Council for the use of biological treatment of axSpA, patients are divided into AS and nr-axSpA [2]. In addition, there are separate recommendations for patients who have or have had uveitis or inflammatory bowel disease, since a drug that also has indication for these diseases should be selected for these subgroups of patients [8]. IL-17 inhibition is contraindicated in patients with inflammatory bowel disease. The first choice among biological drugs is the TNFα-i adalimumab. There is no clearly defined second choice biological

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therapy. In case of failure of the primary therapy, a drug with a different mechanism of action is considered. In case of secondary failure (decreased response to treatment) or toxicity, the patient can switch to a new treatment with the same mechanism of action.

5.2.2 Choice of comparators

Secukinumab 150 mg administered s.c. with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing is compared to

- Adalimumab 40 mg administered s.c. every other week
- Ixekizumab 160 mg (two 80 mg injections) administered s.c. at week 0, followed by 80 mg every 4 weeks (Q4W).

According to the treatment recommendation for the use of biologic treatments of axSpA, approved by the Danish Medicines Council in January 2021 [2], adalimumab is recommended as the first line treatment of nr-axSpA. Ixekizumab, which like secukinumab, is an IL-17 inhibitor, was recommended for treatment of axSpA, including nr-axSpA, by the Medicines Council in June 2021 [7].

5.2.3 Description of the comparators

The two comparators, adalimumab and ixekizumab, are described in Table 3 below.

Table 3 Description of the comparators

	Humira*	Taltz
Generic name (ATC-code)	Adalimumab (L04AB04)	Ixekizumab (L04AC13)
Mode of action	Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 0.1-0.2 nM).	Ixekizumab is an IgG4 monoclonal antibody that binds with high affinity (< 3 pM) and specificity to interleukin (IL) 17A (both IL-17A and IL-17A/F). Elevated concentrations of IL-17A have been implicated in the pathogenesis of psoriasis by promoting keratinocyte proliferation and activation, as well as in the pathogenesis of psoriatic arthritis and axial spondyloarthritis by driving inflammation leading to erosive bone damage and pathological new bone formation. Neutralisation of IL-17A by ixekizumab inhibits these actions. Ixekizumab does not bind to ligands IL-17B, IL-17C, IL-17D, IL-17E or IL-17F.
Pharmaceutical form	Solution for injection	Solution for injection
Method of administration	Subcutaneous use (s.c.)	S.c. use
Dosing	40 mg s.c. every other week	160 mg s.c. (two 80 mg injections) at week 0, followed by 80 mg s.c. every 4 weeks

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Should the pharmaceutical be administered with other medicines?	No	No
Treatment duration/criteria for end of treatment	Treatment duration is as long as the drug is effective and tolerable. According to the RADS treatment guideline 2017, the treatment should be stopped or changed in case of: • Defined treatment goal is not reached within 4 months • Unacceptable AEs • Critical comorbidity as defined in the summary of products characteristics • Pregnancy/wish to become pregnant	
Necessary monitoring, both during administration and during the treatment period	According to the RADS treatment guideline 2017, the patients should be monitored after 3, 6 and 12 months. Additional monitoring depends on the degree of disease control and is performed at least every 6 months. The following is assessed and documented in DANBIO: • Treatment effect, it is primarily assessed whether BASDAI 50 has been achieved, but also changes in BAS parameters (BASDAI, BASMI and BASFI) and ASDAS. • Documentation of disease status, treatment, effect and any side effects	
Need for diagnostics or other tests (i.e., companion diagnostics)	MRI scanning and/or CRP measurement	MRI scanning and/or CRP measurement
Packaging	Imraldi* 40 mg solution for injection in pre-filled pen (each 0.8 ml single dose pre-filled pen contains 40 mg of adalimumab)	Taltz solution for injection, 80 mg/ml, prefilled pen, syringe (glass)

Source: [17, 18, 10]

*For the purpose of the health economic and budget impact analyses, the lowest priced biosimilar, Imraldi is chosen (pharmacy purchase price).

Abbreviations: AE = adverse event, ATC = Anatomical Therapeutic Chemical Classification, ASDAS = Ankylosing Spondylitis Disease Activity score, BAS = Bath Ankylosing Spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, BASMI = Bath Ankylosing Spondylitis Metrology Index, CRP = C-reactive protein, ELAM-1 = endothelial leucocyte adhesion molecule-1, IC50 = half-maximal inhibitory concentration, ICAM-1 = intercellular adhesion molecule-1, Ig = immunoglobulin, IL = interleukin, MRI = magnetic resonance imaging, RADS = Rådet for Anvendelse af Dyr Sygehusmedicin, s.c. = subcutaneous, TNF = tumour necrosis factor, VCAM-1 = vascular cell adhesion molecule-1.

5.3 The intervention

Secukinumab (Cosentyx) is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine IL-17A. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a key role in the pathogenesis of axSpA (AS and nr-axSpA). Inhibition of IL-17A was shown to be effective in the treatment of AS, thus establishing the key role of this cytokine in axSpA [19].

Secukinumab is administered s.c.; the recommended dose for nr-axSpA is 150 mg s.c. at weeks 0, 1, 2, 3 and 4, followed by 150 mg monthly [19]. Secukinumab is administered without other medicines.

Each unit pack of Cosentyx contains 2 pre-filled pens (SensoReady®), and each pre-filled pen contains 150 mg secukinumab in 1 mL. Shelf life is 18 months (if necessary, Cosentyx may be stored unrefrigerated for a single period of up to 4 days at room temperature, not above 30°C) [1].

The treatment duration with secukinumab is as long as the drug is effective and tolerable. Criteria for treatment discontinuation will follow the Rådet for Anvendelse af Dyr Sygehusmedicin (RADS) treatment guideline [10], i.e., if the defined treatment goal is not reached within 4 months or in case of unacceptable adverse events (AEs), critical comorbidity as defined in the SmPCs, or pregnancy/wish to become pregnant.

The monitoring is in line with other biologic treatments for nr-axSpA, as defined in the RADS treatment guideline, i.e., after 3, 6 and 12 months, and every 6 months thereafter (see Table 3).

No diagnostic tests other than CRP and MRI scan (as for other biological pharmaceuticals for nr-axSpA) are required.

Secukinumab offers an additional choice for an effective and well tolerated biologic treatment of patients with nr-axSpA in Denmark; hence, no change in clinical practice is expected.

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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 and ixekizumab for the treatment of nr-axSpA. The literature searches were performed on 12 October 2021. 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 section 13.1.1.

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 27 in Appendix 13.1).

A total of 46 records were identified through PubMed and CENTRAL. With duplicates removed (n = 15), 31 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 17 excluded records. The 14 records that passed the first screening underwent a more rigorous full-text screening to assess any data of interest according to PICO. Of these, 3 publications corresponding to 3 clinical studies were found relevant, which are further described in section 7. There was no disagreement between the reviewers during the full-text screening and study selection process.

All records excluded after full-text review are presented with reason for exclusion in Table 30 in Appendix 13.1.

The process of study identification and selection is summarised in Figure 3 with a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

In addition, clinicaltrials.gov has been searched for ongoing studies and finalised studies not yet published (see Appendix 13.1), and the relevant EPARs for secukinumab and the comparators have been consulted [19, 20, 21].

6.2 List of relevant studies

The included studies are listed below in Table 4. For detailed information about these studies, please refer to Appendix B in section 13.2.

Table 4 Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study	Used in comparison of
Improvement of signs and symptoms of non-radiographic axial spondyloarthritis in patients treated with secukinumab: primary results of a randomised, placebo-controlled phase III study Deodhar et al., Arthritis & Rheumatology 2021 [3]	PREVENT	NCT02696031	Start date: 29 April 2016 End date: 11 March 2021	Secukinumab vs. adalimumab Secukinumab vs. ixekizumab
Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a	ABILITY-1	NCT00939003	Start date: July 2009 End date: August 2013	Secukinumab vs. adalimumab

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Reference	Trial name	NCT number	Dates of study	Used in comparison of
randomised placebo-controlled trial (ABILITY-1) Sieper et al., Annals of the Rheumatic Diseases 2013 [4]				
Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial Deodhar et al., Lancet 2020 [5]	COAST-X	NCT02757352	Start date: 02 August 2016 End date: 07 May 2019	Secukinumab vs. ixekizumab

Abbreviations: NCT = National Clinical Trial.

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7. Efficacy and safety

7.1 Efficacy and safety of secukinumab compared to adalimumab for patients with nr-axSpA

7.1.1 Relevant studies

Two studies are relevant for the comparison between secukinumab and adalimumab, the PREVENT study and the ABILITY-1 study.

PREVENT [3]
PREVENT (NCT02696031) is a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial, consisting of a 2-year core phase and a 2-year extension phase. Patients were randomly assigned (1:1:1) to receive 150 mg secukinumab administered s.c. Q4W with a loading dose (LD) at week 1, 2 and 3 (LD, N = 185), secukinumab 150 mg s.c. Q4W without a loading dose (NL, N = 184) or placebo (N = 186). Switch to open-label secukinumab or standard of care was permitted after week 20 based on clinical judgement of the disease activity by the investigator and the patient. Starting at week 52, all patients received open-label secukinumab 150 mg s.c. up to week 100. Patients were allocated to treatment via Interactive Response Technology, with stratification by MRI and CRP status at screening (MRI-positive (MRI+) and CRP-positive (CRP+), MRI-positive and CRP-negative (CRP–), or MRI-negative (MRI–) and CRP-positive).

Eligible participants in PREVENT were adults (aged ≥18 years) with active nr-axSpA fulfilling the ASAS classification criteria for axSpA with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS. Patients enrolled had active disease, defined as a BASDAI score ≥4 and a visual analogue scale (VAS) score for total back pain of ≥40 (on a scale of 0–100 mm) despite current or previous NSAID therapy, and increased CRP and/or evidence of sacroiliitis on MRI.

Patients previously treated with a TNFi (no more than 1) could participate if they had an inadequate response or were intolerant. Patients could continue to receive the following medications at a stable dose: sulfasalazine, methotrexate, corticosteroids and NSAIDs.

The primary endpoint was 40% improvement in disease activity according to the ASAS40 criteria at week 16 (European Union (EU)) and week 52 (USA) in TNFi-naïve patients (88.6% in the secukinumab group and 91.9% in the placebo group). For all other endpoints, the population included both TNFi-naive patients and patients who had previously been treated with TNFi.

As the posology for nr-axSpA is 150 mg secukinumab Q4W with loading (150 mg at week 1, 2 and 3), only data from the treatment arm on secukinumab with LD and the placebo arm are presented [1].

ABILITY-1 4
ABILITY-1 (NCT00939003) is a phase 3, randomised, placebo-controlled, double-blind trial. Eligible patients were randomised 1:1 to receive s.c. injections of adalimumab (N = 91, 40 mg every other week) or matching placebo (N = 94) for 12 weeks during the double-blind period. Patients who completed the double-blind period were eligible to receive open-label adalimumab for up to an additional 144 weeks.

Eligible patients in ABILITY-1 were adult patients who fulfilled the ASAS criteria for axSpA, had a BASDAI score of ≥4, total back pain score of ≥4 (10 cm VAS) and inadequate response and intolerance or contraindication to NSAIDs. Patients fulfilling the modified New York criteria for AS were excluded.

Patients could enter the study on concomitant NSAIDs, prednisone (≤10 mg per day), methotrexate (MTX, ≤25 mg per week), sulfasalazine (≤3 g per day) and/or hydroxychloroquine (≤400 mg per day) or azathioprine (≤150 mg per day,

but not concomitant with any other DMARD) if the doses met the pre-specified stability requirements prior to randomisation and remained stable during the first 24 weeks.

The primary endpoint was the percentage of patients achieving ASAS40 at week 12.

Detailed study characteristics for each study are listed in Appendix B in section 13.2. For baseline characteristics of patients included in each study, please see Appendix C in section 13.3.

7.1.1.1 Differences between the studies

The main differences between PREVENT and ABILITY-1 are the number of patients included in the studies (555 in PREVENT vs. 185 in ABILITY-1) and the study duration. In PREVENT, patients were treated for up to 52 weeks and were allowed to switch over to secukinumab after 20 weeks, whereas ABLITITY-1 was a 12-week study. However, reporting of all intention-to-treat (IIT) analyses was done at 16 weeks for PREVENT, and thus, 16-week data for PREVENT have been compared with 12-week data for ABILITY-1. This is justifiable due to stable treatment responses between week 12 and 16 for secukinumab.

With regard to the study populations patients, all patients in ABILITY-1 were TNFi naïve, whereas 90.3% in PREVENT were TNFi naïve. In PREVENT the primary endpoints are ASAS40 response in TNFi-naive patients at week 16 and 52. For all other endpoints, only results for the full analysis set are available. To ensure a common basis for comparison between the two compounds, ASAS40 results from the PREVENT study are based on the TNFi naïve population. Additional differences in study populations are described in Appendix C, section 13.3.1.

7.1.1.2 Validity of the studies

A summary of the risk of bias for each study included in this application is presented in

Table 31 in Appendix A, section 13.1. In conclusion, the risk of bias was low, and thus the validity of the individual studies was high.

7.1.2 Efficacy and safety – results per study

The Danish Medicines Council has recently evaluated ixekizumab for use in nr-axSpA, and all outcomes that were described in the protocol from the Medicines Council for ixekizumab in axial SpA have been included in this application, except for ASDAS <2,1 and SF-36 - physical pain subdomain and physical function subdomain, for which no data were available for secukinumab or adalimumab. Detailed information about the included outcomes is described in Appendix D, section 13.4, and further details about the safety and efficacy outcomes are presented in Appendices D and E, sections 13.4 and 13.5, respectively.

Data presenting the results for PREVENT comparing secukinumab to placebo and results for ABILITY-1 comparing adalimumab to placebo is presented below. Although follow-up data is available until week 52 in PREVENT, emphasis is on week 16 data, as this is the datapoint that will be used for the ITC between secukinumab and adalimumab, as data for adalimumab is available for up to 12 weeks.

7.1.2.1 PREVENT (secukinumab vs. placebo) [3]

The primary endpoint was the proportion of patients achieving ASAS40 in the TNFi-naive patients (i.e., 88.8% of the patients in the secukinumab treated group and 91.9% in the placebo group), and this population is presented for ASAS40. For the remaining outcomes, patients who were previously treated with TNFi are included.

Measures of disease activity

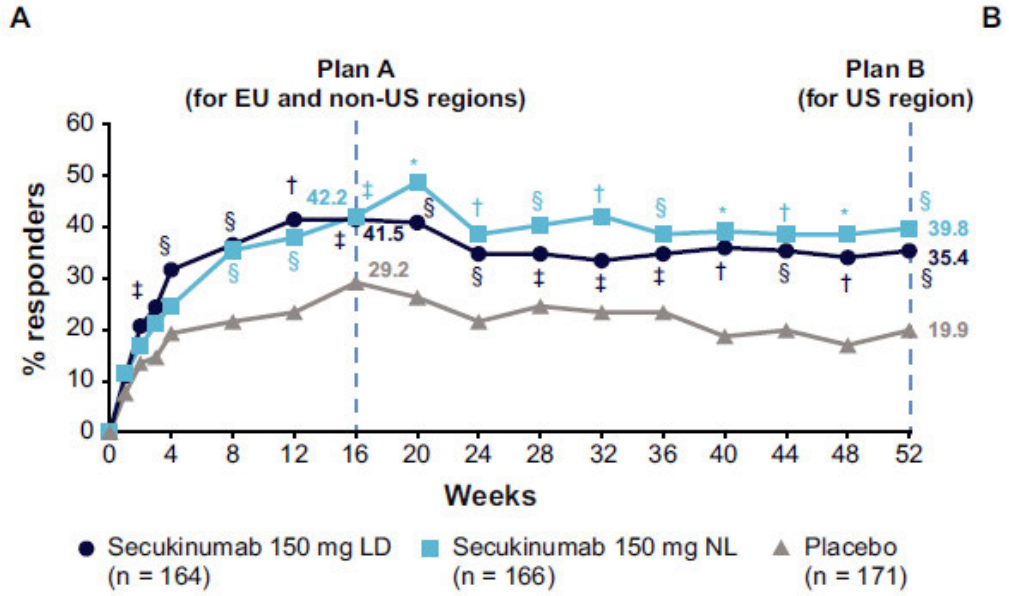
In PREVENT, the ASAS40 and BASDAI50 responder rates were defined as described in Appendix D, section 13.4. The secukinumab treatment group had statistically significant higher responses for all efficacy measures compared to those in the placebo group.

ASAS40

At week 16, the proportion of patients achieving an ASAS40 response was 41.46% (95% confidence interval (CI): 33.98%–49.46%) in the secukinumab group compared to 29.24% (95% CI: 22.80%–36.88%) in the placebo group, resulting in an absolute difference in effect of 12.09% (95% CI: 1.90%–21.96%) and a relative risk of 1.41 (95% CI: 1.05–1.89, p=0.02) [3].

Figure 1 below shows the ASAS40 response rates during the 52-week placebo-controlled phase, showing stable treatment responses until the end of week 52 with no evidence of waning of the treatment effect [3].

Figure 1 ASAS40 response at week 16 and week 52



Abbreviations: ASAS40 = Assessment of SpondyloArthritis international Society 40% response, EU = European Union, LD = loading dose, NL = without loading dose, US = United States.

A post hoc analysis investigating the effect of secukinumab (pooled with and without loading dose) vs. placebo in subgroups with baseline status CRP±, MRI±, human leukocyte antigen (HLA)-B27 (HLA-B27)±, as well as gender, showed that a higher response rate for ASAS40 was found for patients who were CRP+ vs. CRP– or MRI+ vs. MRI– at baseline. While clinically meaningful efficacy was seen in both male and female patients, response rates were higher in males[22].

BASDAI50

At week 16, the proportion of patients achieving a BASDAI50 response was 37.30% (95% CI: 30.48%–44.79%) in the secukinumab group compared to 20.97% (95% CI: 15.66%–27.83%) in the placebo group, resulting in an absolute difference in effect of 16.16% (95% CI: 6.95%–25.00%) and a relative risk of 1.76 (95% CI: 1.26–2.45; p=0.001) [3].

Adverse events

Treatment discontinuations due to adverse events

At week 20, the proportion of patients who discontinued treatment due to AEs was 0% (95% CI: 0.00%–2.94%) (no events) in the secukinumab group compared to 1.61% (95% CI: 0.58%–5.36%) (3 events) in the placebo group, resulting in an absolute difference in effect of –1.59% (95% CI: –4.84%–1.16%) and a relative risk of 0.25 (95% CI: 0.03–2.23, p=0.3717). There was no evidence of any meaningful difference in discontinuations between the treatments [3].

Serious infections

At week 20, the proportion of patients who experienced a serious infection was 0.54% (95% CI: 0.13%–3.81%)

(1 event) in the secukinumab group compared to 0% (95% CI: 0.0%–1.61%) (no events) in the placebo group, resulting in an absolute difference in effect of 0.54% (95% CI: –2.00%–3.32%) and a relative risk of 2.01 (95% CI: 0.18–21.99, p=0.62). There was no evidence of any meaningful difference in the proportion of patients who experienced a serious infection between the treatments [3].

Narrative assessment of adverse events

Overall, secukinumab had an acceptable safety profile when compared with placebo in the PREVENT study. Data are shown for up to week 20. During the double-blind period, 54.3% of patients in the placebo arm and 64.3% in the secukinumab arm experienced any AE. The most common AEs were nasopharyngitis (12.4%, placebo; 14.6%, secukinumab), diarrhoea (3.8%, placebo; 7.6%, secukinumab), headache (3.8%, placebo; 9.2%, secukinumab) and upper respiratory tract infection (3.8%, placebo; 5.9%, secukinumab). There were few serious AEs (SAEs). In the placebo arm, 2.7% of patients experienced an SAE vs. 1.1% in the secukinumab-treated arm [3].

Quality of life

SF-36 - physical component score

Mean change from baseline on SF-36 physical component summary at week 16 was a 5.71 ± 0.68 (SE) point improvement for the secukinumab treatment group and 2.93 ± 0.71 point improvement for the placebo group, representing a mean difference of 2.78 ± 0.98, (95% CI: 0.85–4.70, p=0.005) [3]. The difference is statistically significant.

Discontinuation

At week 24, the proportion of patients who discontinued treatment was 5.41% (95% CI: 2.97%–10.28%) (10 patients) in the secukinumab group compared to 5.91% (95% CI: 3.34%–10.88%) (11 patients) in the placebo group, resulting in an absolute difference in effect of –0.50% (95% CI: –5.63%–4.61%) and a relative risk of 0.92 (95% CI: 0.42–2.04, p=1.00). There was no evidence of any meaningful difference in discontinuations between the treatments [3].

7.1.2.2 ABILITY-1 (adalimumab vs. placebo) [4]

Due to investigator non-compliance identified at a single site, 7 patients (3 placebo, 4 adalimumab) were excluded from all efficacy analyses but were included in safety analyses. Therefore, patient count differs between safety and efficacy reporting. Limited reporting of efficacy estimates was available in the ABILITY-1 publication. Based on the patient count and events reported in the publication, standard methodology was applied to calculate the p-values and 95% CI.

Measures of disease activity

In ABILITY-1, the ASAS40 and BASDAI50 responder rates were defined as described in Appendix D, section 13.4. The adalimumab treatment group had statistically significantly higher responses for all efficacy measures when compared with the placebo treatment group.

ASAS40

At week 12, the proportion of patients achieving an ASAS40 response was 36.3% (95% CI: 26.44%–47.01%) in the adalimumab group compared to 14.89% (95% CI: 8.38–23.73%) in the placebo group, resulting in an absolute difference in effect of 21.37% (95% CI: 8.85%–33.15%) and a relative risk of 2.43 (95% CI: 1.40–4.24, p <0.001) [4].

Based on subgroup interaction analyses, symptom duration, age and baseline CRP status showed significant interactions with treatment on ASAS40 response (p=0.02, p=0.05 and p=0.03, respectively; non-responder imputation (NRI)). There was a greater treatment effect with adalimumab among patients with symptom duration <5 years [4].

BASDAI50

At week 12, the proportion of patients achieving a BASDAI50 response was 35.17% (25.44-45.88%) in the adalimumab group compared to 14.89% (8.39-23.73%) in the placebo group, resulting in an absolute difference in effect of 20.27% (7.83-32.04%) and a relative risk of 2.36 (1.35-4.13), p =0.001 [4].

Adverse events

Treatment discontinuations due to adverse events

At week 12, the proportion of patients who discontinued treatment due to AEs was 2.10% (95% CI: 0.64%–8.77%) (2 events) in the adalimumab group compared to 1.03% (95% CI: 0.25%–7.11%) (1 event) in the placebo group, resulting in an absolute difference in effect of 1.07% (95% CI: –4.37%–6.87%) and a relative risk of 1.53 (95% CI: 0.26–8.96, p=0.6810). There was no evidence of any meaningful difference in discontinuations between the treatments [4].

Serious infections

At week 12, no patients experienced a serious infection in either the adalimumab group or the placebo group [4].

Narrative assessment of adverse events

Overall, adalimumab had an acceptable safety profile when compared with placebo in the ABILITY-1 study. Data are shown up to week 12. During the double-blind period, 58.8% of patients in the placebo arm and 57.9% in the adalimumab arm experienced any AE. The most common AEs were nausea (8.2%), diarrhoea (7.2%) and upper respiratory tract infection (4.1%) among patients in the placebo group and nasopharyngitis (11.6%), nausea (7.4%) and headache (6.3%) in the adalimumab group. There were few SAEs. In the placebo arm, 1.0% experienced an SAE vs. 3.2% in the adalimumab treated arm [4].

Quality of life

SF-36 – physical component score

Mean change from baseline on SF-36 physical component summary at week 12 was a 5.5-point improvement for the adalimumab treatment group and a 2.0-point improvement for the placebo group, representing a mean difference of 3.0, p=0.001. The difference is statistically significant. No CIs or standard error [SE]/standard error of the mean [SEM] are presented; thus, it is not possible to include the outcome in an indirect comparison vs. secukinumab [4].

Discontinuation

At week 12, the proportion of patients who discontinued treatment was 4.40% (95% CI: 1.77%–12.10%) (4 patients) in the adalimumab group compared to 2.13% (95% CI: 0.65%–8.87%) (2 patients) in the placebo group, resulting in an absolute difference in effect of 2.25% (95% CI: –4.19%–9.16%) and a relative risk of 1.72% (95% CI: 0.42%–7.00%, p=0.49). There was no evidence of any meaningful difference in discontinuations between the treatments [4].

7.1.3 Comparative analyses of efficacy and safety

Method of synthesis

No head-to-head comparisons of the efficacy and safety of secukinumab and adalimumab were identified by the systematic literature review. The present comparison is based on the two phase 3 studies, PREVENT (secukinumab vs. placebo) and ABILITY-1 (adalimumab vs. placebo), applying an ITC on the available outcomes of interest to synthesise the evidence identified. In addition, a narrative comparison of the safety profile of secukinumab vs. adalimumab based on the approved SmPCs is presented.

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Results from the comparative analysis

Measures of disease activity

ASAS40

The absolute difference between secukinumab and adalimumab for the proportion of patients achieving ASAS40 was –21.22% points (95% CI: –35.03–4.67), with a relative risk of 0.58 (95% CI: 0.31–1.09, p=0.09). The difference is not statistically significant.

BASDAI50

The absolute difference between secukinumab and adalimumab for the proportion of patients achieving BASDAI50 was –10.29% points (95% CI: –25.33–18.56), with a relative risk of 0.75 (95% CI: 0.39–1.44, p=0.3941). The difference is not statistically significant.

Adverse events

Treatment discontinuations due to adverse events

The absolute difference between secukinumab and adalimumab for the proportion of patients discontinuing treatment due to AEs was –2.67% points (95% CI: –6.88–1.54), with a relative risk of 0.12 (95% CI: 0.01–3.12, p=0.20). The difference is not statistically significant.

Serious infections

The absolute difference between secukinumab and adalimumab for the proportion of patients who experienced a serious infection was 0.52% points (95% CI: –2.83–3.86), with a relative risk of 1.97 (95% CI: 0.05–75.83, p=0.72). Only a few patients experienced this event. The difference is not statistically significant.

Narrative assessment of adverse events

The proportion of patients experiencing an AE and a SAE, respectively, was approximately the same in PREVENT and ABILITY-1, taking into account the longer follow up time in PREVENT (20 weeks) when compared with ABILITY-1 (12 weeks). The details are shown in Table 5.

Table 5 Proportion of patients with an adverse event or a serious adverse event

Study	PREVENT		ABILITY-1	
Treatment arm	Secukinumab N=185	Placebo N=186	Adalimumab N=95	Placebo N=97
Exposure time	20 weeks [3]		12 weeks [4]	
Proportion of patients with at least 1 adverse event, n (%)	119 (64.3)	101 (54.3)	55 (57.9)	57 (58.8)
Proportion of patients with at least 1 serious adverse event, n (%)	2 (1.1)	5 (2.7)	3 (1.0)	1 (3.2)

The most frequently reported AEs for secukinumab were nasopharyngitis (14.6%), diarrhoea (7.6%), headache (9.2%) and upper respiratory tract infection (5.9%) [3]. For adalimumab, the most frequently reported AEs were nasopharyngitis (11.6%), nausea (7.4%) and headache (6.3%).

In the following, the safety profiles are compared based on the SmPCs. 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.

According to the SmPC, 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).

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Serious infections were reported in 1.2% of the patients treated with secukinumab (0.015 per patient-year of follow-up). 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 (CTCAE) 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 [1].

According to the SmPC for adalimumab (Humira) [23], 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. TNF-antagonists, 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 (TB)), hepatitis B virus (HBV) reactivation and various malignancies (including leukaemia, lymphoma and hepatosplenic T-cell lymphoma (HSTCL)) 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 [23].

In general, the SmPC of adalimumab holds data from other indications 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 and reducing the direct comparability.

Details from the SmPCs are presented in Appendix E, section 13.5.

Quality of life

SF-36 - physical component score

Both secukinumab and adalimumab were superior to placebo and provided significant improvements in SF-36-physical component score (2.93 ± 0.71 points for the placebo group and 5.71 ± 0.68 points for the secukinumab treatment group in the PREVENT study, and 2.0 points for the placebo group and 5.5 points for the adalimumab treatment group in the ABILITY-1 study). As SE/SEM was not provided for ABILITY-1, a comparative analysis is not possible. However, the results seem to be similar for the two products.

Discontinuation

The absolute difference between secukinumab and adalimumab for the proportion of patients who discontinued the treatment for any reason was –2.78% points (95% CI: –9.73–4.18), with a relative risk of 0.44 (95% CI: 0.07–2.87, p=0.39). The difference is not statistically significant.

For more details for all comparative analyses, see Appendix F in section 13.6.

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7.1.4 Conclusion for the efficacy and safety of secukinumab vs. adalimumab

The PREVENT study provided evidence of relative treatment efficacy and safety of secukinumab vs. placebo in patients with nr-axSpA. An indirect comparison was conducted using evidence of relative treatment efficacy and safety of adalimumab vs. placebo in patients with nr-axSpA from the ABILITY 1 study. Both active treatments were superior to placebo on all efficacy analyses in the respective studies. Following a feasibility assessment on the comparability of the studies, an indirect treatment comparison using direct modelling, was conducted on the available outcomes of interest to synthesise the evidence identified (Appendix K in Section 13.11). For all efficacy and safety outcomes, there were no statistically significant differences between the active treatments.

7.2 Efficacy and safety of secukinumab compared to ixekizumab for patients with nr-axSpA

7.2.1 Relevant studies

Two studies are relevant for the comparison between secukinumab and ixekizumab, the PREVENT study and the COAST-X study.

PREVENT [3]
PREVENT (NCT02696031) is a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial, consisting of a 2-year core phase and a 2-year extension phase. Patients were randomly assigned (1:1:1) to receive 150 mg secukinumab administered s.c. Q4W with an LD at week 1, 2 and 3 (LD, N = 185), secukinumab 150 mg s.c. Q4W without an LD (NL, N = 184) or placebo (N = 186). Switch to open-label secukinumab or standard of care was permitted after week 20 based on clinical judgement of the disease activity by the investigator and the patient. Starting at week 52, all patients received open-label secukinumab 150 mg s.c. up to week 100. Patients were allocated to treatment via Interactive Response Technology, with stratification by MRI and CRP status at screening (MRI+ and CRP+, MRI+ and CRP–, or MRI– and CRP+).

Eligible participants in PREVENT were adults (aged ≥18 years) with active nr-axSpA fulfilling the ASAS classification criteria for axSpA with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS. Patients enrolled had active disease, defined as a BASDAI score ≥4 and a VAS score for total back pain of ≥40 (on a scale of 0–100 mm) despite current or previous NSAID therapy, and increased CRP and/or evidence of sacroiliitis on MRI.

Patients previously treated with a TNFi (no more than 1) could participate if they had an inadequate response or were intolerant. Patients could continue to receive the following medications at a stable dose: sulfasalazine, methotrexate, corticosteroids and NSAIDs.

The primary endpoint was 40% improvement in disease activity according to the ASAS40 criteria at week 16 (EU) and week 52 (USA) in TNFi-naive patients (88.6% in the secukinumab group and 91.9% in the placebo group). For all other endpoints, the population included both TNFi-naive patients and patients who had previously been treated with TNFi.

As the posology for nr-axSpA is 150 mg secukinumab Q4W with LD (150 mg at week 1, 2 and 3), only data from the treatment arm on secukinumab with an LD and the placebo arm are presented [1].

COAST-X [5]
COAST-X (NCT02757352) is a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial, followed by an optional open-label 2-year extension trial (COAST-Y). Patients were randomly assigned (1:1:1) to receive s.c. 80 mg ixekizumab Q4W (N = 96) or every 2 weeks (Q2W, N = 102), or placebo (N = 105). The starting dose of ixekizumab was either 80 mg or 160 mg at week 0. Changing background medications or switching to open-label ixekizumab Q2W, or both, was allowed after week 16 at the discretion of the investigator. Patients were allocated to

treatment by a computer-generated random sequence, with stratification by country and MRI and CRP status at screening (MRI+ and CRP+, MRI+ and CRP–, or MRI– and CRP+).

Eligible participants in COAST-X were adults (aged ≥18 years) with active axSpA without definite radiographic sacroiliitis (nr-axSpA), with objective signs of inflammation (via MRI or CRP), and an inadequate response or intolerance to NSAIDs.

Exclusion criteria included previous treatment with bDMARDs. Patients could continue background medications, including NSAIDs, conventional synthetic DMARDs (csDMARDs), glucocorticoids and analgesics. Stable doses of background medications were required during the first 16 weeks of the study.

The primary endpoint was 40% improvement in disease activity according to the ASAS40 criteria at week 16 (EU) and week 52 (USA).

As the posology for nr-axSpA is 160 mg (two 80 mg injections) s.c. injection at week 0 followed by 80 mg Q4W, only data from the Q4W with ixekizumab and the placebo arm are presented [17].

Analyses of ixekizumab Q4W compared with placebo were done without regard to the week 0 starting dose of 80 mg or 160 mg [5].

Safety data covering 70.0 patient years in 95 patients in the ixekizumab group and 60.5 total patient years in 104 patients in the placebo group was presented.

Detailed study characteristics for each study are listed in Appendix B, section 13.2. For baseline characteristics of the patients included in each study, please see Appendix C, section 13.3.

7.2.1.1 Differences between the studies

PREVENT and COAST-X

PREVENT and COAST-X were very similar in design and study duration, although more patients were enrolled in PREVENT (n=555) than in COAST-X (n=303). In PREVENT, switch to secukinumab was allowed at week 20, whereas in COAST-X, switch to ixekizumab was permitted at week 16. Thus, the comparison between secukinumab and ixekizumab is based on week 16 data from the IIT population in the two studies.
With regard to the study populations, all patients in COAST-X were TNFi naïve, whereas 90.3% in PREVENT were TNFi naïve. In PREVENT the primary endpoint is ASAS40 response in TNFi-naive patients at week 16 and 52. For all other endpoints, only results for the full analysis set are available. To ensure a common basis for comparison between the two compounds, ASAS40 results from the PREVENT study are based on the TNFi naïve population. Additional differences in study populations are described in Appendix C, section 13.3.1.

7.2.1.2 Validity of the studies

A summary of the risk of bias for each study included in this application is presented in Table 31 in Appendix 13.1. In conclusion, the risk of bias was low, and thus, the validity of the individual studies was high.

7.2.2 Efficacy and safety – results per study

The Danish Medicines Council has recently evaluated ixekizumab for use in nr-axSpA, and all outcomes that were described in the protocol from the Medicines Council for ixekizumab in axial SpA have been included in this application, except for ASDAS <2,1, for which no data were available for secukinumab, and SF-36 - physical pain subdomain and physical function subdomain, for which no data were available for secukinumab or ixekizumab. Detailed information about the included outcomes is described in Appendix D, section 13.4, and further details about the safety and efficacy outcomes are presented in Appendices D and E, sections 13.4 and 13.5, respectively.

Data presenting the results for PREVENT comparing secukinumab to placebo and results for COAST-X comparing ixekizumab to placebo is presented below. Patients in PREVENT could switch treatment after week 20 and those in COAST-X could switch after week 16. Thus, data from week 16 are used for the ITC between secukinumab and ixekizumab.

7.2.2.1 PREVENT [3]

The primary endpoint was the proportion of patients achieving ASAS40 in the TNFi-naive patients (i.e., 88.8% of the patients in the secukinumab treated group and 91.9% in the placebo group), and this population is presented for ASAS40. For the remaining outcomes, patients who were previously treated with TNFi are included.

Measures of disease activity

In PREVENT, the ASAS40 and BASDAI50 responder rates were defined as described in Appendix D, section 13.4. The secukinumab treatment group had statistically significant higher responses for all efficacy measures compared to those in the placebo group.

ASAS40

At week 16, the proportion of patients achieving an ASAS40 response was 41.46% (95% CI: 33.98%–49.46%) in the secukinumab group compared to 29.24% (95% CI: 22.80%–36.88%) in the placebo group, resulting in an absolute difference in effect of 12.09% (95% CI: 1.90%–21.96%) and a relative risk of 1.41 (95% CI: 1.05–1.89, p=0.02) [3].

Figure 1 above shows the ASAS40 response rates during the 52-week placebo-controlled phase, showing stable treatment responses until the end of week 52 with no evidence of waning of the treatment effect [3].

A post hoc analysis investigating the effect of secukinumab (pooled with and without loading dose) vs. placebo in subgroups with baseline status CRP±, MRI±, HLA-B27±, as well as gender, showed that a higher response rate for ASAS40 was found for patients who were CRP+ vs. CRP– or MRI+ vs. MRI– at baseline. While clinically meaningful efficacy was seen in both male and female patients, response rates were higher in males [22].

BASDAI50

At week 16, the proportion of patients achieving a BASDAI50 response was 37.30% (95% CI: 30.48%–44.79%) in the secukinumab group compared to 20.97% (95% CI: 15.66%–27.83%) in the placebo group, resulting in an absolute difference in effect of 16.16% (95% CI: 6.95%–25.00%) and a relative risk of 1.76 (1.26–2.45, p=0.001) [3].

Adverse events

Treatment discontinuations due to adverse events

At week 20, the proportion of patients who discontinued treatment due to AEs was 0% (95% CI: 0.00%–1.62%) (no events) in the secukinumab group compared to 1.61% (95% CI: 0.58%–5.36%) (3 events) in the placebo group, resulting in an absolute difference in effect of –1.59% (95% CI: –4.84%–1.16%) and a relative risk of 0.25 (95% CI: 0.03–2.23, p=0.3717). There was no evidence of any meaningful difference in discontinuations between the treatments [3].

Serious infections

At week 20, the proportion of patients who experienced a serious infection was 0.54% (95% CI: 0.13%–3.81%) (1 event) in the secukinumab group compared to 0% (95% CI: 0.0%–1.61%) (no events) in the placebo group, resulting in an absolute difference in effect of 0.54% (95% CI: –2.00%–3.32%) and a relative risk of 2.01 (95% CI: 0.18–21.99, p=0.6230). There was no evidence of any meaningful difference in the proportion of patients who experienced a serious infection between the treatments [3].

Narrative assessment of adverse events

Overall, secukinumab had an acceptable safety profile when compared with placebo in the PREVENT study. Data are shown for up to week 20. During the double-blind period, 54.3% of patients in the placebo arm and 64.3% in the

secukinumab arm experienced any AE. The most common AEs were nasopharyngitis (12.4%, placebo; 14.6%, secukinumab), diarrhoea (3.8%, placebo; 7.6%, secukinumab), headache (3.8%, placebo; 9.2%, secukinumab) and upper respiratory tract infection (3.8%, placebo; 5.9%, secukinumab). There were few SAEs. In the placebo arm, 2.7% of patients experienced an SAE vs. 1.1% in the secukinumab treated arm [3].

Quality of life

SF-36 - physical component score

Mean change from baseline on SF-36 physical component summary at week 16 was a 5.71 ± 0.68 point improvement for the secukinumab treatment group and 2.93 ± 0.71 point improvement for the placebo group, representing a mean difference of 2.78 ± 0.98, (95% CI: 0.85–4.71, p=0.005) [3]. The difference is statistically significant.

Discontinuation

At week 24, the proportion of patients who discontinued treatment was 5.41% (95% CI: 2.97%–10.28%) (10 patients) in the secukinumab group compared to 5.91% (95% CI: 3.34%–10.88%) (11 patients) in the placebo group, resulting in an absolute difference in effect of –0.50% (95% CI: –5.63%–4.61%) and a relative risk of 0.92 (95% CI: 0.42–2.04, p=1.00). There was no evidence of any meaningful difference in discontinuations between the treatments [3].

7.2.2.2 COAST-X (ixekizumab vs. placebo)

Measures of disease activity

In COAST-X, the ASAS40 and BASDAI50 responder rates were defined as described in Appendix D, section 13.4. The ixekizumab treatment group had statistically significant higher responses for all efficacy measures when compared with the placebo group.

ASAS40

At week 16, the proportion of patients achieving an ASAS40 response was 35.42% (95% CI: 26.29%–46.03%) in the ixekizumab group compared to 19.05% (95% CI: 12.58%–28.42%) in the placebo group, resulting in an absolute difference in effect of 16.09% (95% CI: 3.85%–27.85%) and a relative risk of 1.82 (95% CI: 1.14–2.90, p=0.01) [5].

Figure 2 below shows the ASAS40 response rates during the 52-week placebo-controlled phase, showing stable treatment responses until the end of week 52, with no evidence of waning of the treatment effect [5].

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Figure 2 ASAS40 response at week 52. The figure is from Deodar et al, 2020 [5]

BASDAI50

At week 16, the proportion of patients achieving a BASDAI50 response was 31.25% (95% CI: 22.61%–41.80%) in the ixekizumab group compared to 14.29% (95% CI: 8.80%–23.15%) in the placebo group, resulting in an absolute difference in effect of 16.68% (95% CI: 5.13%–27.89%) and a relative risk of 2.12 (95% CI: 1.24–3.62, p=0.01)[35].

Adverse events

Treatment discontinuations due to adverse events

At week 16, the proportion of patients who discontinued treatment due to AEs was 0.0% (95% CI: 0.0%–3.13%) (0 events) in the ixekizumab group compared to 1.92% (95% CI: 0.59%–8.05%) (2 events) in the placebo group, resulting in an absolute difference in effect of –1.81% (95% CI: –7.04%–3.09%) and a relative risk of 0.36 (95% CI: 0.04–3.41, p=0.62). There was no evidence of any meaningful difference in discontinuations between the treatments [5].

Serious infections

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During the study, the proportion of patients who experienced a serious infection was 0% (95% CI: 0.0%–3.13%) (0 events) in the ixekizumab group compared to 0% (95% CI: 0.0%–2.89%) (0 events) in the placebo group, resulting in an absolute difference in effect of 0.08% (95% CI: –4.21%–4.68%) and a relative risk of 1.08 (95% CI: 0.07–17.06, p=1.00). There was no evidence of any meaningful difference in the proportion of patients who experiences a serious infection between the treatments (Table 44 in ref [20]) and [5].

Narrative assessment of adverse events

Overall, ixekizumab had an acceptable safety profile when compared with placebo in the COAST-X study. Data are shown for up to week 16. During the double-blind period, 50.0% of patients in the placebo arm and 54.2% in the ixekizumab arm experienced any AE. The most common AEs were nasopharyngitis (6.7% for placebo and 13.5% for ixekizumab) and injection site reaction (3.8% for placebo and 10.4% for ixekizumab). There were few serious AEs. In the placebo arm, 0.9% of the patients experienced an SAE vs. none in the ixekizumab treated arm (Table 44 in [20]).

Quality of Life

SF-36 - physical component score

Mean change from baseline on SF-36 physical component summary at week 12 was a 8.06 ± 0.81 point improvement for the ixekizumab treatment group and 5.21 ± 0.80 point improvement for the placebo group, representing a mean difference of 2.85 ± 1.14 (p=0.012) [5]. The difference is statistically significant.

Discontinuation

At week 16, the proportion of patients who discontinued treatment was 1.04% (95% CI: 0.25%–7.18%) (1 patient) in the ixekizumab group compared to 7.62% (95% CI: 3.92%–15.37%) (8 patients) in the in the placebo group, resulting in an absolute difference in effect of –6.37% (95% CI: –13.34%–0.06%) and a relative risk of 0.24 (95% CI: 0.05–1.10, p=0.06). There was no evidence of any meaningful difference in discontinuations between the treatments [5].

7.2.3 Comparative analyses of efficacy and safety

Method of synthesis

No head-to-head comparisons of the efficacy and safety of secukinumab and ixekizumab were identified by the systematic literature review. The present comparison is based on the two phase 3 studies, PREVENT (secukinumab vs. placebo) and COAST-X (ixekizumab vs. placebo), applying an ITC on the available outcomes of interest to synthesise the evidence identified. In addition, a narrative comparison of the safety profile of secukinumab vs. ixekizumab based on the approved SmPCs will be presented.

Results from the comparative analysis

Measures of disease activity

ASAS40

The absolute difference between secukinumab and ixekizumab for the proportion of patients achieving ASAS40 was –4.15% points (95% CI: –20.00%–11.71%), with a relative risk of 0.76 (95% CI: 0.44–1.34, p=0.35). The difference is not statistically significant.

BASDAI50

The absolute difference between secukinumab and ixekizumab for the proportion of patients achieving BASDAI50 was –0.64% points (95% CI: –15.25–13.98), with a relative risk of 0.81 (95% CI: 0.43–1.56, p=0.53). The difference is not statistically significant.

Adverse events

Treatment discontinuations due to adverse events

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The absolute difference between secukinumab and ixekizumab for the proportion of patients discontinuing treatment due to AEs was 0.22% points (95% CI: –4.17–4.61), with a relative risk of 0.70 (0.03–15.97, p=0.82). Only a few patients experienced the event. The difference is not statistically significant.

Serious infections

The absolute difference between secukinumab and ixekizumab for the proportion of patients who experienced a serious infection was 0.46% points (95% CI: –2.80%–3.72%), with a relative risk of 1.86 (95% CI: 0.05–71.58, p=0.74). Only a few patients experienced this event. The difference is not statistically significant.

Narrative assessment of adverse events

The proportion of patients experiencing an AE and an SAE, respectively, was approximately the same in PREVENT and COAST-X, taking into account the longer follow-up time in PREVENT (20 weeks) when compared with COAST-X (16 weeks). In addition, more patients in PREVENT were exposed to the study drug, increasing the probability of a rare event, such as an SAE occurring in either treatment arm. Moreover, for safety endpoints, the populations differed, with approximately 10% of the patients having been previously treated with TNFi, which may possibly make them more prone to experiencing AEs. Patients in PREVENT and COAST-X were treated for 52 weeks; however, they could switch to open-label secukinumab and ixekizumab at 16 and 20 weeks, respectively, which is the reason why these timepoints are chosen for this analysis [3, 5].

Details on the incidence of AEs and SAE are shown in Table 6 below.

Table 6 Proportion of patients with an adverse event or a serious adverse event

Study	PREVENT		COAST-X	
Treatment arm	Secukinumab N=185	Placebo N=186	Ixekizumab N=96	Placebo N=104
Exposure time	20 weeks [3]		16 weeks (Table 44 in [20])	
Proportion of patients with at least 1 adverse event, n (%)	119 (64.3)	101 (54.3)	52 (54.2)	52 (50.0)
Proportion of patients with at least 1 serious adverse event, n (%)	2 (1.1)	5 (2.7)	0	1 (0.9)

Most frequently reported AE for secukinumab at 20 weeks were nasopharyngitis (14.6%), diarrhoea (7.6%), headache (9.2%) and upper respiratory tract infection (5.9%) [3]. For ixekizumab, the most frequently reported AEs at 16 weeks were nasopharyngitis (13.5%) and injection site reaction (10.4%) (Table 44 in [20]).

In the following, the safety profiles are compared based on the SmPCs. As the SmPCs of both 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.

According to the SmPC for secukinumab, 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 and rhinitis).

Serious infections were reported in 1.2% of the patients treated with secukinumab (0.015 per patient-year of follow-up). In psoriasis phase 3 clinical studies, neutropenia was more frequently observed with secukinumab than with placebo; however, most cases were mild, transient and reversible. Neutropenia <1.0–0.5 × 10^9/L (CTCAE grade 3) was reported in 18 out of 3,430 (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 [1].

According to the SmPC of ixekizumab, the most frequently reported adverse reactions were injection site reactions (erythema and pain) and upper respiratory tract infections (most frequently, nasopharyngitis).

Serious infections were reported in 1.6% of the patients treated with ixekizumab (1.5 per 100 patient years). In plaque psoriasis studies, 9% of the patients receiving ixekizumab developed neutropenia. In most cases, the blood neutrophil count was ≥1,000 cells/mm^3. Such levels of neutropenia may persist, fluctuate or be transient. Moreover, 0.1% of the patients receiving ixekizumab developed a neutrophil count <1,000 cells/mm^3. In general, neutropenia did not require discontinuation of ixekizumab. In total, 3% of the patients exposed to ixekizumab had a shift from a normal baseline platelet value to <150,000 platelet cells/mm^3 to ≥75,000 cells/mm^3. Thrombocytopaenia may persist, fluctuate or be transient. The frequency of neutropenia and thrombocytopaenia in psoriatic arthritis and axial spondyloarthritis clinical studies is similar to that observed in the plaque psoriasis studies [17].

The safety profiles of secukinumab and ixekizumab seem similar, except for the occurrence of injection site reactions, which are not reported for secukinumab but seen in 15.5% of patients treated with ixekizumab [1, 17].

Details from the SmPCs are presented in Appendix E in section 13.5.

Quality of life

SF-36 - physical component score

The absolute difference in change from baseline for secukinumab vs. ixekizumab for the SF-36-physical component score was –0.07 points (95% CI: –3.02–2.88, p=0.96). The difference is not statistically significant.

Discontinuation

The absolute difference between secukinumab and ixekizumab for the proportion of patients who discontinued the treatment for any reason was 6.07% points (95% CI: –1.14%–13.28%), with a relative risk of 6.69 (95% CI: 0.73–61.67, p=0.09). The difference is not statistically significant.

For more details for all comparative analyses, see Appendix F in section 13.6.

7.2.4 Conclusion for the efficacy and safety of secukinumab vs. ixekizumab

The PREVENT study provided evidence of relative treatment efficacy and safety of secukinumab vs. placebo in patients with nr-axSpA. An indirect comparison was conducted using evidence of relative treatment efficacy and safety of ixekizumab vs. placebo in patients with nr-axSpA from the COAST-X study. Both active treatments were superior to placebo on all efficacy analyses in the respective studies. Following a feasibility assessment on the comparability of studies, an indirect treatment comparison using direct modelling (except for SF-36, where Bucher's method was used) was conducted on the available outcomes of interest to synthesise the evidence identified. For all efficacy and safety outcomes, there were no significant differences between secukinumab and ixekizumab.

8. Health economic analysis

Secukinumab (Cosentyx) is evaluated in comparison with adalimumab (Imraldi) and ixekizumab (Taltz). Please find the rationale in section 5.2.2. Findings suggest there are no statistical differences in efficacy and safety between secukinumab, adalimumab and ixekizumab (see section 7: Efficacy and Safety). Consequently, in accordance with the guidelines from the Danish Medicines Council [24], a cost minimisation analysis has been conducted.

8.1 Model

The cost minimisation analysis was conducted as a simple cost-per-patient analysis for secukinumab compared to adalimumab and ixekizumab.

The model was developed in Microsoft Excel 365 as a simple cohort model. In order to allow the model to align with the treatment regimens, weekly model cycles have been used in the model. As there are no differences in efficacy between the interventions, no mortality is modelled.

A model time horizon of 18 months is applied. This was applied in the Medicine Council's assessment of ixekizumab 36], based on correspondence to an average treatment length in nr-axSpA. However, the model includes the possibility to vary the time horizon to longer or shorter durations.

A discount rate of 3.5% was applied to the costs, as defined by the Danish Ministry of Finance and in the guidelines from the Medicines Council [24].

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

Not applicable. As the comparison is between interventions that are assumed to be equivalent in terms of efficacy and safety, no relative efficacy parameters have been included in the model. In addition, no efficacy parameters are included with the objective of model parsimony.

8.2.1 Presentation of input data used in the model and how they were obtained

Not applicable. Please find the rationale in section 8.2.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The intended patient population for this analysis are patients with active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence in adults who have responded inadequately to NSAIDs.

As the model is a cost minimisation model and all interventions are fixed-dose, no patient characteristics are relevant for the model, as these would not have an impact on the results.

8.2.2.2 Intervention

The intervention is secukinumab (Cosentyx). The posology of the intervention is listed in Table 7.

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Table 7 Intervention: secukinumab

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	150 mg s.c. at weeks 0, 1, 2, 3 and 4, followed by 150 mg monthly	150 mg s.c. at weeks 0, 1, 2, 3 and 4, followed by 150 mg monthly	150 mg s.c. at weeks 0, 1, 2, 3 and 4, followed by 150 mg monthly [1]
Length of treatment (time on treatment) (mean/median)	18 months	18 months	18 months [10]

Abbreviations: s.c. = subcutaneous.

8.2.2.3 Comparators

The comparators are adalimumab (Imraldi) and ixekizumab (Taltz). Both comparators are administrated s.c. The posology of both comparators is listed in Table 8 and Table 9.

Table 8 Comparator: adalimumab

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	40 mg administered every other week as a single dose via s.c. injection	40 mg administered every other week as a single dose via s.c. injection	40 mg administered every other week as a single dose via s.c. injection
Length of treatment	18 months	18 months	18 months [10]

Abbreviations: s.c. = subcutaneous.

Table 9 Comparator: ixekizumab

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	160 mg (two 80 mg injections) by s.c. injection at week 0, followed by 80 mg every 4 weeks	160 mg (two 80 mg injections) by s.c. injection at week 0, followed by 80 mg every 4 weeks	160 mg (two 80 mg injections) by s.c. injection at week 0, followed by 80 mg every 4 weeks
Length of treatment	18 months	18 months	18 months [10]

Abbreviations: s.c. = subcutaneous.

In addition to the comparators in the cost minimisation model (adalimumab and ixekizumab), the budget impact model includes all biological drugs used in clinical practice for the treatment of nr-axSpA (irrespective of whether the drug is approved or not), in accordance with the budget impact estimations in the Medicine Council's assessment of ixekizumab [36] (see section 9 Budget impact analysis).

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8.2.2.4 Relative efficacy outcomes

Not applicable. Please find the rationale in section 8.2.

8.2.2.5 Adverse reaction outcomes

Not applicable. Please find the rationale in section 8.2.

8.3 Extrapolation of relative efficacy

Not applicable. Please find the rationale in section 8.2.

8.3.1 Time to event data – summarised

Not applicable. Please find the rationale in section 8.2.

8.4 Documentation of health-related quality of life (HRQoL)

Not applicable. Please find the rationale in section 8.2.

8.4.1 Overview of health state utility values (HSUV)

Not applicable. Please find the rationale in section 8.2.

8.4.2 Health state utility values used in the health economic model

Not applicable. Please find the rationale in section 8.2.

8.5 Resource use and costs

8.5.1 Drug costs

The drugs costs of the intervention and the comparators are applied as pharmacy purchase prices (apotekernes indkøbspris, AIP). Prices are derived from Medicinpriser.dk (reference accessed:2021-10-08) and listed in Table 10 below. The product and pack with the lowest cost per mg for adalimumab is chosen (Imraldi).

Table 10 Drug costs used in the cost minimisation model (DKK)

Drug	Strength	Price (AIP)	Pack size	Price per unit (AIP)	Price per mg (AIP)
Secukinumab (Cosentyx)	150 mg	7 908.00	2	3 954.00	26.36
Adalimumab (Imraldi)	40 mg	4 594.44	2	2 297.22	57.43
Ixekizumab (Taltz)	80 mg	7 376.35	1	7 376.35	92.20

Abbreviations: AIP = apotekernes indkøbspris.

The applied dosing schedules are derived from the products' SmPCs, in line with guidance from the Medicines Council [24]. The dosing schedules applied in the cost minimisation analysis are presented in Table 11 below.

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Table 11 Applied dosing schedules in cost minimisation model

Drug	Dosing	Reference
Secukinumab (Cosentyx)	150 mg by s.c. injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing	SmPC
Adalimumab (Imraldi)	40 mg administered every other week as a single dose via s.c. injection	SmPC
Ixekizumab (Taltz)	160 mg (two 80 mg injections) by s.c. injection at week 0, followed by 80 mg every 4 weeks	SmPC

Abbreviations: s.c. = subcutaneous, SmPC = summary of product characteristics.

8.5.2 Healthcare resource use costs

Since all three treatment options in the cost minimisation analysis are administrated s.c. by the patient or relatives, costs related to administration, monitoring and patient-related costs are not expected to differ between the treatment options. Hence, these costs will not affect the results and are therefore not included in the model base case. However, the model also contains the option of results being presented including administration and monitoring costs. For explanation of administration and monitoring costs, see section 9: Budget impact analysis.

8.5.3 Adverse event costs

No costs for AEs are included, since no findings suggest that there are differences in AEs between the treatment options (see section 7: Efficacy and safety).

8.6 Results

8.6.1 Base case overview

Table 12 Base case overview

Base case overview	
Intervention	Secukinumab (Cosentyx)
Comparator	Adalimumab (Imraldi) Ixekizumab (Taltz)
Type of analysis	Cost minimisation analysis
Type of model	Cost minimisation model (cost-per-patient analysis)
Time horizon	18 months
Treatment length	18 months
Discount rate	3.5%
Included costs	Pharmaceutical costs (The model also contains a scenario of results presented including administration and monitoring costs. However, this scenario does not affect the results since these costs are the

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	same in all three arms. For explanation of administration and monitoring costs, see section 9: Budget Impact Analysis)
Including of wastage	No
Dosage of pharmaceutical	According to SmPC: Secukinumab: 150 mg by s.c. injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Adalimumab: 40 mg administered every other week as a single dose via s.c. injection. Ixekizumab: 160 mg (two 80 mg injections) by s.c injection at week 0, followed by 80 mg every 4 weeks.

Abbreviations: s.c. = subcutaneous, SmPC = summary of product characteristics.

8.6.2 Base case results

Table 13 and Table 14 present the total cost for secukinumab, adalimumab and ixekizumab arms. The total cost was estimated to be DKK 82 232 for secukinumab, DKK 88 582 for adalimumab and DKK 153 157 for ixekizumab. Hence, the incremental cost of secukinumab vs. adalimumab was estimated to be DKK –6 350 (i.e., secukinumab has lower total cost) and vs. ixekizumab DKK –70 926 (i.e., secukinumab has lower total cost).

All costs estimated are over a time horizon of 18 months and at AIP prices and discounted at 3.5%.

Table 13 Results cost minimisation model (DKK), 18 months' time horizon, discounted (3.5%)

	Secukinumab (Cosentyx)	Adalimumab (Imraldi)	Ixekizumab (Taltz)
Drug costs	82 232	88 582	153 157

Table 14 Ranked costs (DKK), 18 months' time horizon, discounted (3.5%)

	Cost	Incremental cost vs Cosentyx
Secukinumab (Cosentyx)	82 232	
Adalimumab (Imraldi)	88 582	6 350
Ixekizumab (Taltz)	153 157	70 926

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Scenario analyses have been conducted for the time horizon (Table 15). The scenario analyses indicate that the results were not sensitive to the changes in time horizon.

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Table 15 Scenario analyses cost minimisation model (DKK) for secukinumab, discounted by 3.5%

	Change	Reason / Rational / Source	Incremental cost vs Adalimumab (Imraldi) (DKK)	Incremental cost Ixekizumab (Taltz) (DKK)
Base case	-	-	–6 350	–70 926
Time horizon (base case = 18 months)	12 months	To test different treatment lengths	–418	–43 959
	36 months	To test different treatment lengths	–23 745	–135 989
	60 months	To test different treatment lengths	–45 522	–221 900

8.7.2 Probabilistic sensitivity analyses

Not applicable. Since the health economic analysis consists of a cost minimisation analysis, no incremental cost-effectiveness ratios (ICERs) are estimated. Consequently, a probabilistic sensitivity analysis (PSA) is not meaningful to conduct.

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9. Budget impact analysis

The budget impact model was developed to estimate the expected budget impact of recommending secukinumab for nr-axSpA in Denmark. The budget impact analysis has been embedded in the cost minimisation model, but the results are presented separately. In addition to the comparators in the cost minimisation model (adalimumab and ixekizumab), the budget impact model includes all the biological drugs used in clinical practice for the treatment of nr-axSpA (irrespective of whether the drug is approved or not), in accordance with the budget impact estimations in the Medicine Council's assessment of ixekizumab[36].

The costs included in the budget impact model are undiscounted, in line with the guidelines from the Medicines Council [24].

The analysis compares the costs for the Danish regions per year over five years in the scenario where secukinumab is recommended for the treatment of nr-axSpA and the scenario where secukinumab is not recommended for the treatment of nr-axSpA. The total budget impact per year is the difference between the two scenarios.

9.1 Number of patients

The total number of patients is 1 117, derived from the DANBIO sponsor report, September 2021. The total number of patients is assumed to increase by 134 per year, based on data from DANBIO sponsor reports from September 2020 and September 2021.

Table 16 Total number of patients over the next five-year period (total population)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	1 117	1 251	1 385	1 519	1 653

9.2 Market share

For the scenario of secukinumab recommended for the treatment of nr-axSpA, the assumed market shares are based on the market shares of Medicine Council's assessment of ixekizumab (scenario of ixekizumab recommended), and internal selling estimations in terms of an increase in shares of secukinumab and which product it will take market shares from.

Table 17 Market shares in scenario of secukinumab recommended in nr-axSpA

	Scenario 1: Secukinumab is recommended				
	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab	5.7%	6.7%	7.7%	8.6%	9.3%
Adalimumab	36.3%	36.3%	36.3%	36.3%	36.3%
Ixekizumab	1.6%	1.5%	1.5%	1.5%	1.5%
Etanercept	18.2%	18.2%	18.2%	18.2%	18.2%
Golimumab	11.9%	11.6%	11.2%	10.9%	10.6%
Certolizumab pegol	3.7%	3.4%	3.0%	2.7%	2.4%
Tofacitinib	0.2%	0.2%	0.2%	0.2%	0.2%
Infliximab	22.4%	22.2%	21.9%	21.7%	21.5%

Source: Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt Vers. 1.0 - scenario of Ixekizumab recommended [36] (sales data collected from DANBIO) + Internal estimations

For the scenario of secukinumab being not recommended for treatment of nr-axSpA, the assumed market shares are taken from Medicine Council's assessment of ixekizumab [36].

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Table 18 Market shares in scenario of secukinumab not recommended in nr-axSpA

	Scenario 2: Secukinumab is not recommended				
	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab	4.5%	4.5%	4.5%	4.5%	4.5%
Adalimumab	36.3%	36.3%	36.3%	36.3%	36.3%
Ixekizumab	1.9%	2.1%	2.3%	2.5%	2.7%
Etanercept	18.2%	18.2%	18.2%	18.2%	18.2%
Golimumab	12.2%	12.1%	12.0%	11.9%	11.8%
Certolizumab pegol	4.0%	3.9%	3.8%	3.7%	3.6%
Tofacitinib	0.2%	0.2%	0.2%	0.2%	0.2%
Infliximab	22.7%	22.7%	22.7%	22.7%	22.7%

Source: Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt Vers. 1.0 - scenario of Ixekizumab recommended [36] (sales data collected from DANBIO)

9.3 Cost input

9.3.1 Drug costs

Prices are derived from Medicinpriser.dk (accessed:2021-10-08) and listed in Table 19 below. The pack with the lowest cost per mg is chosen.

Table 19 Drug costs used in the budget impact model (DKK)

Drug	Strength	Price (AIP)	Pack size	Price per unit (AIP)	Price per mg (AIP)
Secukinumab (Cosentyx)	150 mg	7 908.00	2	3 954.00	26.36
Adalimumab (Imraldi)	40 mg	4 594.44	2	2 297.22	57.43
Ixekizumab (Taltz)	80 mg	7 376.35	1	7 376.35	92.20
Etanercept (Benepali)	50 mg	6 177.78	4	1 544.45	30.89
Golimumab (Simponi)	50 mg	8 766.00	1	8 766.00	175.32
Certolizumab pegol (Cimzia)	200 mg	7 296.74	2	3 648.37	18.24
Tofacitinib (Xeljanz)	5 mg	5 383.42	56	96.13	19.23
Infliximab (Flixabi)	100 mg	7 139.93	3	2 379.98	23.80

Abbreviations: AIP = apotekernes indkøbspris.

The dosing schedules are derived primarily from the products' SmPCs, in line with guidance from The Medicines Council [24]. The SmPCs of infliximab and tofacitinib do not include dosing instructions for nr-axSpA since infliximab and tofacitinib are not approved for nr-axSpa. Hence assumed dosing is taken from Medicinrådet 2020 - Klinisk sammenligningsgrundlag for biologisk targeterede syntetiske DMARDS til kronisk leddegigt [25] (dosage for rheumatoid arthritis was used) and RAD2017 - Baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandlinger af aksiale spondylartropatier (aSPA) [10]. The dosing schedules applied in the budget impact model are presented in Table 20 below.

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Table 20 Applied dosing schedules in budget impact model

Drug	Dosing	Reference
Secukinumab (Cosentyx)	150 mg by s.c. injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing	SmPC - Cosentyx-secukinumab
Adalimumab (Imraldi)	40 mg administered every other week as a single dose via s.c. injection	SmPC - Imraldi-adalimumab
Ixekizumab (Taltz)	160 mg (two 80 mg injections) by s.c. injection at week 0, followed by 80 mg every 4 weeks	SmPC - Taltz-ixekizumab
Etanercept (Benepali)	25 mg by s.c. injection administered twice weekly, or 50 mg administered once weekly	SmPC-Enbrel-etanercept
Golimumab (Simponi)	50 mg by s.c. injection given once a month, on the same date each month.	SmPC-Simponi-golimumab
Certolizumab pegol (Cimzia)	400 mg (given as 2 s.c. injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.	SmPC-Cimzia- certolizumab pegol
Tofacitinib (Xeljanz)	5 mg given orally twice per day	Medicinrådet 2020
Infliximab (Flixabi)	Intravenous 5 mg per kg bodyweight week 0, 2, 6 followed by every 6 weeks	RADS 2017

Abbreviations: RADS = Rådet for Anvendelse af Dyr Sygehusmedicin, s.c. = subcutaneous, SmPC = summary of product characteristics.

Infliximab is administrated intravenously based on body weight. An average body weight of 73.9 kg is applied. This was defined in the RADS treatment recommendation of rheumatoid arthritis [10]. Rheumatoid arthritis patients are assumed to be equivalent to patients with nr-axSpA in terms of body weight.

9.3.2 Cost for healthcare resource use

According to the guidelines from the Medicines Council, the budget impact analysis should include the total additional costs for the regions in connection with use of the new pharmaceutical, including both costs of pharmaceuticals and other treatment-related costs for the regional sector [24]. Therefore, in addition to drug costs, the budget impact analysis also includes costs related to administration and monitoring.

No patient cost and transportation cost have been included, in line with the guidelines by the Medicines Council.

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Administration costs

Costs for drug administration are derived from *Medicinrådet: Udvidet sammenligningsgrundlag for biologiske og targeterede syntetiske DMARDS til kronisk leddegigt* [25], in line with the Medicines Council's assessment of ixekizumab[36]. Costs are specified below in Table 21 below.

Table 21 Drug administration costs budget impact model (for 18 months)

	Labour time (min)	Unit cost per minute (DKK)	Total cost (DKK)	Reference
Secukinumab, adalimumab, ixekizumab, etanercept, golimumab, certolizumab pegol				
Labour costs for physician	200	12.8	2 560	Medicinrådet 2020
Labour costs for nurse	242	8.7	2 105	Medicinrådet 2020
Tools			78	Medicinrådet 2020
Total			4 743	
Tofacitinib				
Labour costs for physician	216	12.8	2 765	Medicinrådet 2020
Labour costs for nurse	212	8.7	1 844	Medicinrådet 2020
Tools				Medicinrådet 2020
Total			4 609	
Infliximab				
Labour costs for physician	200	12.8	2 560	Medicinrådet 2020
Labour costs for nurse	1 517	8.7	13 198	Medicinrådet 2020
Tools			1 014	Medicinrådet 2020
Total			16 772	

Administration costs are applied every 18 months in the budget impact model.

Monitoring costs

Costs for drug monitoring are derived from *Medicinrådet: Udvidet sammenligningsgrundlag for biologiske og targeterede syntetiske DMARDS til kronisk leddegigt* [25], in line with the Medicine Council's assessment of ixekizumab[36]. Costs are specified below in Table 22 below.

Table 22 Drug monitoring costs budget impact model (for 18 months)

	Total cost (DKK)	Reference
Secukinumab, Adalimumab, Ixekizumab, Etanercept, Golimumab, Certolizumab pegol		
Blood tests	1 420	Medicinrådet 2020
Tofacitinib		
Blood tests	1 437	Medicinrådet 2020
Infliximab		
Blood tests	1 420	Medicinrådet 2020

Monitoring costs are applied every 18 months in the budget impact model.

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9.4 Results of the Budget Impact Analysis

The number of patients on different treatment for nr-axSpA in scenario of secukinumab recommended and in scenario of secukinumab not recommended, based on the assumptions on market shares and total number of patients, are shown in Table 23 and Table 24 below.

Number of patients

Table 23 Number of patients expected to be treated over the next five-year period – if secukinumab is recommended for treatment of nr-axSpA

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab	64	84	106	130	154
Adalimumab	406	455	503	552	601
Ixekizumab	18	19	20	22	24
Etanercept	203	227	251	276	300
Golimumab	133	145	156	166	175
Certolizumab pegol	41	42	42	41	40
Tofacitinib	2	3	3	3	3
Infliximab	250	277	304	330	355
Total number of patients	1 117	1 251	1 385	1 519	1 653

Table 24 Number of patients expected to be treated over the next five-year period - if secukinumab is not recommended for treatment of nr-axSpA

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab	50	57	63	69	75
Adalimumab	406	455	503	552	601
Ixekizumab	22	26	31	37	44
Etanercept	203	227	252	276	300
Golimumab	136	152	166	181	195
Certolizumab pegol	45	49	53	56	59
Tofacitinib	2	3	3	3	3
Infliximab	253	284	314	345	375
Total number of patients	1 117	1 251	1 385	1 519	1 653

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Budget impact

The estimated budget impact of recommending secukinumab for the treatment of nr-axSpA in Denmark at AIP is DKK –577 507 in year 1 and DKK –3 674 617 year 5 (i.e., recommending secukinumab nr-AxSpa implies lower total costs for Danish regions) as shown in Table 25.

Table 25 Expected budget impact of recommending the pharmaceutical for the current indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Secukinumab is recommended	93 118 868	100 358 150	108 231 739	120 169 338	130 139 181
Minus: **Secukinumab is NOT recommended**	93 696 375	101 594 319	110 202 391	122 986 520	133 813 797
Budget impact of the recommendation	–577 507	–1 236 169	–1 970 652	–2 817 182	–3 674 617

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10. Discussion on the submitted documentation

This application for secukinumab for patients with nr-axSpA is based on comparisons of secukinumab vs. adalimumab and ixekizumab, respectively.

Adalimumab has been chosen as a comparator as it is the first line of choice according to the treatment recommendation from the Danish Medicines Council. Ixekizumab has recently been recommended for standard treatment of nr-axSpA by the Danish Medicines Council, and as ixekizumab is an IL-17 inhibitor like secukinumab, it is a relevant comparator.

The chosen outcomes are based on the outcomes defined in the protocol from the Danish Medicines Council for the assessment of ixekizumab and are thus considered to be critical or important outcomes.

The time horizon chosen is similar for both comparisons, i.e., 12 and 16 weeks, to be consistent with the time horizon previously applied by RADS and the Medicines Council for assessments within nr-axSpA. For both secukinumab and ixekizumab, data are available for 52 weeks. However, in the PREVENT and COAST-X studies, switch to open active treatment was allowed from different timepoints (i.e., after 20 and 16 weeks, respectively) and for both treatments, the effect on ASAS40 was maintained over 52 weeks.

In PREVENT, approximately 10% of the patients had previously been treated with a TNFα-i. However, for the primary endpoint, i.e., the proportion of patients achieving ASAS40, only patients who were TNFα-i naive were included in the analysis.

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

The total cost, from a Danish perspective, based on pharmacy purchase prices and with an 18 months' time horizon, was estimated to be DKK 82 232 for Cosentyx, DKK 88 582 for adalimumab and DKK 153 157 for ixekizumab. Hence, secukinumab implied lower costs than both adalimumab (Imraldi) and ixekizumab (Taltz). Scenario analyses indicated that the conclusion of secukinumab being associated with cost savings was indifferent to changes in the time horizon, and hence, to treatment length. The budget impact analysis showed that recommending secukinumab for the treatment of nr-axSpA in Denmark would imply cost savings from a Danish perspective that is equal to DKK –577 507 in year 1 and DKK –3 674 617 in year 5.

In conclusion, secukinumab provides an additional treatment option for patients with non-radiographic axial spondyloarthritis.

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11. List of experts

None.

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12. References

1. Cosentyx (secukinumab) (summary of product characteristics). Dublin, Ireland: Novartis Europharm Limited 2019 (cited 2021 October 21). Available from: https://www.ema.europa.eu/en/documents/product-information/cosentyx-epar-product-information_en.pdf.

2. Medicinrådet. Lægemiddelrekommandation for anvendelse af biologisk behandling af aksiale spondylartropatier (aksial SPA). Version 3.7 2021 (cited 2021 October 21). Available from: https://medicinraadet.dk/media/5ngju5ik/l%C3%A6gemiddelrekom-_for_anvendelse_af_biologisk_behandling_af_aksiale_spondylartropatier_-aksial_spa-vers-_3-7_adlegacy.pdf.

3. Deodhar A, Blanco R, Dokoupilová E, Hall S, Kameda H, Kivitz AJ, et al. Improvement of Signs and Symptoms of Nonradiographic Axial Spondyloarthritis in Patients Treated With Secukinumab: Primary Results of a Randomized, Placebo-Controlled Phase III Study. Arthritis Rheumatol. 2021;73(1):110-20.

4. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;72(6):815-22.

5. Deodhar A, van der Heijde D, Gensler LS, Kim TH, Maksymowych WP, Østergaard M, et al. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. Lancet. 2020;395(10217):53-64.

6. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683-91.

7. Medicinrådet. Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt. Version 1.1 Dokument nr. 116573, 11.06.21 Available from: https://medicinraadet.dk/media/i0jpaprq/medicinrdets_anbefaling_vedr-_ixekizumab_til_rygs%C3%B8jlegigt-vers-_1-1_adlegacy.pdf.
.

8. Loft AG, Schlemmer A, Hendricks O, Horn HC, Pedersen SJ, Pelck R, et al. Behandlingsvejledning for non-radiografisk inflammatorisk aksial spondylartritis (axSpA) og ankyloserende spondylitis (AS) hos voksne. 2017 (cited 2021 October 22). Available from: https://danskreumatologi.dk/nbv/sygdomme/aksial-spondyloartritis/.

9. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369(9570):1379-90.

10. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). Baggrundsnotat for biologiske og syntetiske targeterede lægemidler til behandlinger af aksiale spondylartropatier (aSPA). 2017 (cited 2021 October 22). Available from: https://rads.dk/media/4362/bgn-aspa-31-237690.pdf.

11. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-8.

12. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.

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13. Boonen A, Sieper J, van der Heijde D, Dougados M, Bukowski JF, Valluri S, et al. The burden of non-radiographic axial spondyloarthritis. Semin Arthritis Rheum. 2015;44(5):556-62.

14. Medicinrådet. Medicinrådets vurdering vedrørende ixekizumab til behandling af rygsøjlegigt. Ver 1.0 2021 (cited 2021 November 8). Available from: https://medicinraadet.dk/media/d3loiewt/medicinr%C3%A5dets_vurdering_vedr-_ixekizumab_til_rygs%C3%B8jlegigt-vers-_1-0_adlegacy.pdf.

15. DANBIO. National Årsrapport 2019 2019 (cited 2021 November 4). Available from: https://danbio-online.dk/formidling/dokumentmappe/danbio-arsrapport-2019_endeligversion.pdf.

16. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77(1):3-17.

17. Taltz (ixekizumab) (summary of product characteristics). Cork, Ireland: Eli Lilly and Company (Ireland) Limited 2020 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/documents/product-information/taltz-epar-product-information_en.pdf.

18. Imraldi (adalimumab) (summary of product characteristics). Delft, The Netherlands: Samsung Bioepis NL B.V. 2017 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/documents/product-information/imraldi-epar-product-information_en.pdf.

19. European Medicines Agency (EMA). European Public Assessment Report. Cosentyx (secukinumab) 2021 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/cosentyx.

20. European Medicines Agency (EMA). European Public Assessment Report. Taltz (ixekizumab) 2020 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/taltz.

21. European Medicines Agency (EMA). European Public Assessment Report. Humira (adalimumab) 2021 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/documents/variation-report/humira-h-c-481-ii-0085-epar-assessment-report-variation_en.pdf.

22. Braun J, Blanco R, Marzo-Ortega H, Gensler LS, van den Bosch F, Hall S, et al. Secukinumab in non-radiographic axial spondyloarthritis: subgroup analysis based on key baseline characteristics from a randomized phase III study, PREVENT. Arthritis Res Ther. 2021;23(1):231.

23. Humira (adalimumab) (summary of product characteristics). Ludwigshafen, Germany: AbbVie Deutschland GmbH & Co. KG 2008 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf.

24. Medicinrådet. Medicinrådets metodevejledning for vurdering af nye lægemidler 2020 (cited 2021 November 4). Available from: https://medicinraadet.dk/media/5nvplk03/efter-1-januar-2021_medicinr%C3%A5dets-metodevejledning-for-vurdering-af-nye-l%C3%A6gemidler-vers-1-0_adlegacy.pdf.

25. Medicinrådet. Udvidet sammenligningsgrundlag for biologiske og targeterede syntetiske DMARDS til kronisk leddegigt 2020 (cited 2021 October 22). Available from: https://medicinraadet.dk/media/xgrad4yi/udvidet-sammenligningsgrundlag-fra-amgros-kronisk-leddegigt_adlegacy.pdf.

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26. Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheum. 2013;65(5):1213-23.

27. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76(6):978-91.

28. Glintborg B, Lindström U, Aaltonen K, Kristianslund EK, Gudbjornsson B, Chatzidionysiou K, et al. Biological treatment in ankylosing spondylitis in the Nordic countries during 2010-2016: a collaboration between five biological registries. Scand J Rheumatol. 2018;47(6):465-74.

29. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21(12):2281-5.

30. van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, Braun J, et al. ASsessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. Arthritis Rheum. 2005;52(2):386-94.

31. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis 2018 (cited 2021 October 22). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-axial-spondyloarthritis-revision-1_en.pdf.

32. Medicinrådet. Medicinrådets protokol for vurdering af ixekizumab til behandling af rygsøjlegigt 2020 (cited 2021 October 22). Available from: https://medicinraadet.dk/media/wfna3eit/medicinr%C3%A5dets_protokol_for_vurdering_af_ixekizumab_til_rygs%C3%B8jlegigt-vers-_1-0_adlegacy.pdf.

33. Ward MM, Guthrie LC, Alba MI. Clinically important changes in short form 36 health survey scales for use in rheumatoid arthritis clinical trials: the impact of low responsiveness. Arthritis Care Res (Hoboken). 2014;66(12):1783-9.

34. Agresti A, Caffo B. Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures. The American Statistician. 2000;54(4):280-8.

35. Medicinrådet. Bilag til Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt. Bilag 5 Ansøgers endelige ansøgning, Vers. 1.0 Dokument nr. 114224 25.5.2021 (cited 2021 October 21). Bilag til Medicinrådets anbefaling vedr. ixekizumab til rygsøjlegigt-vers. 1.0 (medicinraadet.dk)

36. Medicinrådet. Bilag til Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt. Bilag 1 Medicinrådets sundhedsøkonomiske afrapportering vedr. Ixekizumab, Vers. 1.0 Dokument nr. 114224 25.5.2021 (cited 2021 October 21). Bilag til Medicinrådets anbefaling vedr. ixekizumab til rygsøjlegigt-vers. 1.0 (medicinraadet.dk)

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13. Appendices

13.1 Appendix A – Literature search for efficacy and safety of intervention and comparators

The objective of the literature search was to identify published randomised controlled trials (RCTs) of the efficacy and safety of secukinumab and the comparators adalimumab and ixekizumab for the treatment of nr-axSpA.

Literature searches were performed on 12 October 2021 in PubMed (NLM) and CENTRAL (Wiley).

Table 26 Databases included in the search

Database	Platform	Relevant period for the search	Date of search completion
PubMed	NLM (https://pubmed.ncbi.nlm.nih.gov/)	1946-October 2021	12 October 2021
CENTRAL	Wiley (https://www.cochranelibrary.com/advanced-search)	Until October 2021	12 October 2021

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials; NLM = National Library of Medicine.

In addition, clinicaltrials.gov and the EU Clinical Trials Register were searched for ongoing and unpublished RCTs with secukinumab or the comparators adalimumab and ixekizumab for the treatment of nr-axSpA. The clinicaltrials.gov search was performed 10 October 2021 while the EU Clinical Trials Register search was done on 12 October 2021.

13.1.1 Search strategy

The search strategy developed to meet the objective of the literature search was defined by the inclusion and exclusion criteria in Table 27.

Table 27 Literature search inclusion and exclusion criteria

Inclusion criteria
• Population: non-radiographic axial spondyloarthritis • Intervention(s): secukinumab • Comparator(s): adalimumab; ixekizumab • Outcomes: ASAS40; BASDAI-50; treatment discontinuations due to adverse events; treatment discontinuations due to lack of efficacy or serious infections; SF-36 physical functioning subdomain, physical pain domain, and physical component summary • Settings (if applicable): Peer-reviewed publication • Study design: Randomised controlled trial (RCT) • Language restrictions: English, Danish • Other search limits or restrictions applied: see exclusion criteria
Exclusion criteria
• Population: radiographic axial spondyloarthritis or other indications • Interventions: If not listed in the inclusion criteria above • Comparators: If not listed in the inclusion criteria above • Outcomes: Any other outcomes than those listed in the inclusion criteria above

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- Settings (if applicable): Not applicable
- 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: ASAS40 = Assessment of SpondyloArthritis international Society 40% response; BASDAI-50 = Bath Ankylosing Spondylitis Disease Activity Index 50% improvement

Searches for RCTs were performed in MEDLINE vis PubMED and CENTRAL via Cochrane Library. The search strings and results are shown with screen shots in Table 28 and Table 29 below.

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PUBMED search, 12 October 2021

Table 28 Literature search – PubMed

History and Search Details

Download Delete

Search	Actions	Details	Query	Results	Time
#16	•••	›	Search: **#12 NOT #15** Sort by: **Most Recent**	29	16:35:52
#15	•••	›	Search: **#13 OR #14** Sort by: **Most Recent**	9,775,611	16:35:38
#14	•••	›	Search: **Case report[ti] OR case reports[ti] OR comment[pt] OR editorial[pt] OR guideline[pt] OR letter[pt] OR review[pt]** Sort by: **Most Recent**	5,106,962	16:35:26
#13	•••	›	Search: **Animals[Mesh terms] NOT humans[Mesh terms]** Sort by: **Most Recent**	4,896,632	16:35:19
#12	•••	›	Search: **#10 AND #11** Sort by: **Most Recent**	48	16:35:10
#11	•••	›	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**	1,651,935	16:34:56
#10	•••	›	Search: **#8 OR #9** Sort by: **Most Recent**	105	16:34:45
#9	•••	›	Search: **#3 AND #7** Sort by: **Most Recent**	85	16:34:18
#8	•••	›	Search: **#3 AND #4** Sort by: **Most Recent**	38	16:34:01
#7	•••	›	Search: **#5 OR #6** Sort by: **Most Recent**	10,191	16:33:48
#6	•••	›	Search: **adalimumab OR Humira*** Sort by: **Most Recent**	9,620	16:33:29
#5	•••	›	Search: **Ixekizumab OR Taltz** Sort by: **Most Recent**	745	16:33:22
#4	•••	›	Search: **secukinumab OR Cosentyx** Sort by: **Most Recent**	1,474	16:33:07
#3	•••	›	Search: **#1 AND #2** Sort by: **Most Recent**	1,119	16:32:57
#2	•••	›	Search: **Non-radiographic* OR Nonradiographic* OR pre-radiographic* OR preradiographic* OR without radiograph* OR absence of radiograph*** Sort by: **Most Recent**	578,623	16:32:41
#1	•••	›	Search: **Axial spondyloarthritis OR axSpA OR axial SpA OR axial spondylarthritis OR axial spondylarthropath* OR axial spondyloarthropath*** Sort by: **Most Recent**	3,527	16:32:28

Showing 1 to 16 of 16 entries

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CENTRAL search, 01 October 2021

Table 29 Literature search - CENTRAL

Search | Search manager | Medical terms (MeSH) | PICO search BETA

Save this search | View saved searches | ? Search help

View fewer lines | Print

#1	Spondylarthritis(MeSH) (Word variations have been searched)	Limits	10134
#2	axial:ti,ab,kw (Word variations have been searched)	Limits	4092
#3	#1 and #2	Limits	533
#4	axial NEXT (spondyloarthritis OR spondylarthritis OR spondylarthropath* OR spondyloarthropath* OR SpA) OR axSpA (Word variations have been searched)	Limits	731
#5	#3 OR #4	Limits	749
#6	Non-radiographic* OR Nonradiographic* OR pre-radiographic* OR preradiographic* (Word variations have been searched)	Limits	335
#7	#5 AND #6	Limits	302
#8	secukinumab OR Cosentyx (Word variations have been searched)	Limits	987
#9	Ixekizumab OR Taltz (Word variations have been searched)	Limits	555
#10	adalimumab OR Humira* (Word variations have been searched)	Limits	3568
#11	#9 OR #10	Limits	3980
#12	#7 AND #8	Limits	23
#13	#7 AND #11	Limits	93
#14	#12 OR #13	Limits	114
#15	("conference abstract" OR review OR protocol):ti,ab,pt	Limits	319289
#16	NCT*:au	Limits	214753
#17	(EUCTR* OR clintrial.gov OR trialsearch):so	Limits	159645
#18	#15 OR #16 OR #17	Limits	657623
#19	#14 NOT #18	Limits	17

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials

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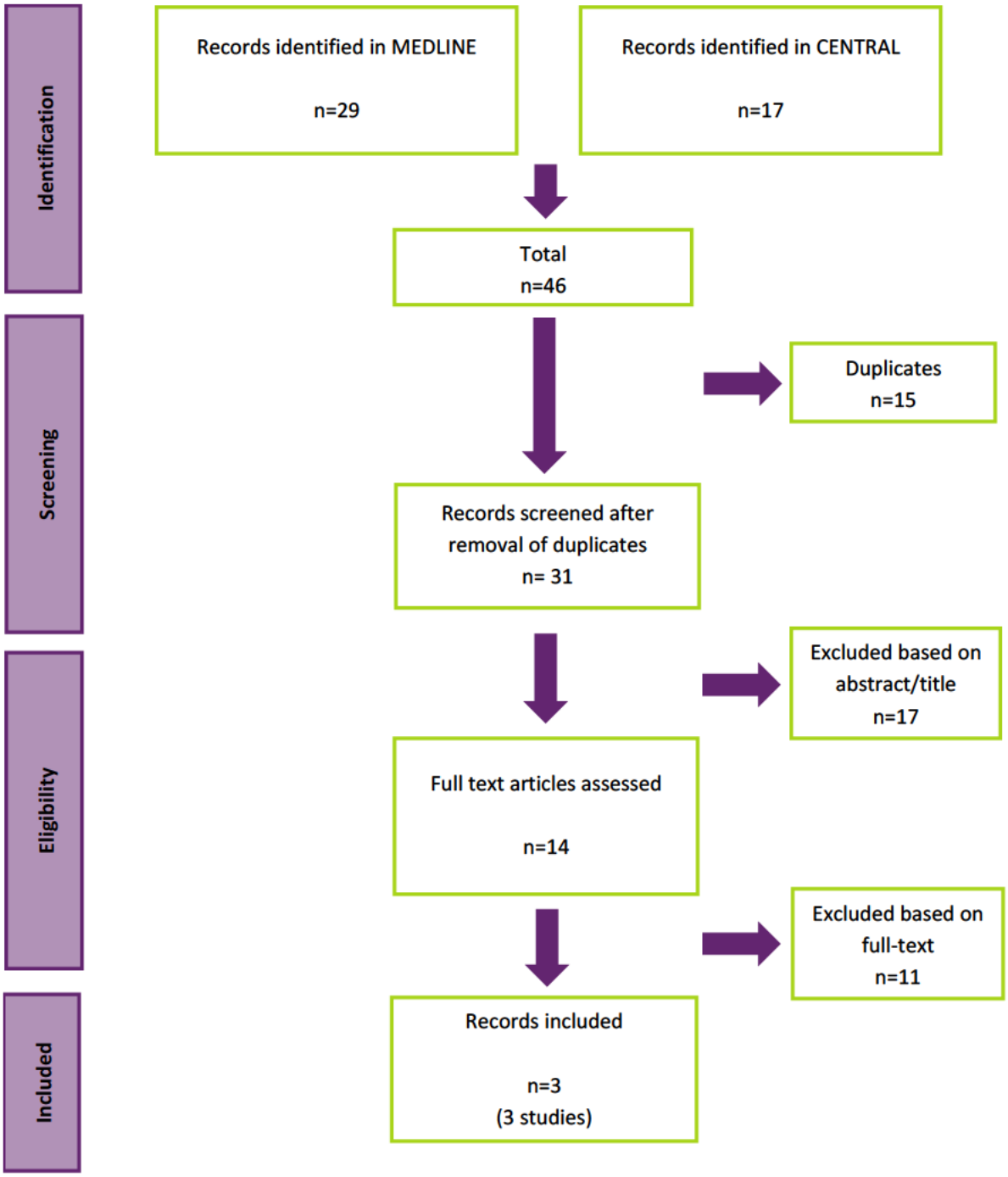
The outcome of the search is shown in the PRISMA flow in Figure 3 below.

Figure 3 PRISMA flow diagram



Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials

For a list of included studies and publications, see Table 4.

Table 30 shows a list of studies that were excluded upon full-text screening.

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Table 30 Studies excluded based on full-text screening

Full reference	Reason for exclusion
Adalimumab: in non-radiographic axial spondyloarthritis. Burness CB, Deeks ED. Drugs. 2012 Dec 24;72(18):2385-95.	A secondary report (review) of the already-included ABILITY-1 trial with no new data relevant for this application
ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis. van der Heijde D, Joshi A, Pangan AL, Chen N, Betts K, Mittal M, Bao Y. Rheumatology (Oxford). 2016 Jan;55(1):80-8.	Subgroup analysis with outcomes (e.g., Health Assessment Questionnaire (HAQ) for spondyloarthropathies, physical component summary score, work productivity, activity impairment etc.) not relevant for this application (responder versus non-responder analysis)
Clinical and MRI remission in patients with nonradiographic axial spondyloarthritis who received long-term open-label adalimumab treatment: 3-year results of the ABILITY-1 trial. van der Heijde D, Sieper J, Maksymowych WP, Lambert RG, Chen S, Hojnik M, Anderson JK, Pangan AL. Arthritis Res Ther. 2018 Mar 27;20(1):61.	Long-term data on the total population and subgroups based on baseline C-reactive protein level and magnetic resonance imaging scores
Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, Braun J, Sieper J. Arthritis Rheum. 2008 Jul;58(7):1981-91.	Patients had unclear biologic exposure and was therefore not considered comparable to the target population in this application. For this reason, the Medicines Council did not include the study in their assessment of ixekizumab in nr-axSpA. To ensure the the Medicines Council´s assessment of secukinumab is done on the same basis as for ixekizumab, the study has been excluded.
Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Ann Rheum Dis. 2015 Jun;74(6):1241-8.	Meta-analysis of 20 studies, including the ones included in this application; no new data reported
Ixekizumab improves functioning and health in the treatment of active non-radiographic axial spondyloarthritis: 52-week results, COAST-X trial. Walsh JA, Magrey MN, Baraliakos X, Inui K, Weng MY, Lubrano E, van der Heijde D, Boonen A, Gensler LS, Strand V, Braun J, Hunter T, Li X, Zhu B, León L, Marcelino Sandoval Calderon D, Kiltz U. Arthritis Care Res (Hoboken). 2020 Oct 12.	52-week results of the COAST-X trial with outcomes reported (e.g., Medical Outcomes Study 36-Item Short Form Health Survey 36-item (SF-36), Assessment of SpondyloArthritis international Society Health Index (ASAS HI), and European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) health-utility) that are not relevant for this application
Ixekizumab improves sleep and work productivity in patients with non-radiographic axial spondyloarthritis: results from the COAST-X trial at 52 weeks. Deodhar A, Mease P, Marzo-Ortega H, Hunter T, Sandoval D, Kronbergs A, Lauzon S, Leung A, Navarro-Compán V. BMC Rheumatol. 2021 Sep 25;5(1):50.	Reported outcomes (e.g., sleep, work productivity, and activity impairment) not relevant for this application
Ixekizumab improves patient-reported outcomes in non-radiographic axial spondyloarthritis: results from the Coast-X trial. Deodhar A, Mease P, Rahman P, Navarro-Compán V, Marzo-Ortega H, Hunter T, Sandoval D, Kronbergs A, Leon L, Shan M, Leung A, De Vlam K, Strand V. Rheumatol Ther. 2021 Mar;8(1):135-150.	Reported outcomes (e.g., patient global disease activity, spinal pain, function, stiffness) not relevant for this application

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New treatment targets for axial spondyloarthritis. Sieper J. Rheumatology (Oxford). 2016 Dec;55(suppl 2):ii38-ii42.	Review article with no additional relevant information
Risk of serious infections in biological treatment of patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Wang S, He Q, Shuai Z. Clin Rheumatol. 2018 Feb;37(2):439-450.	Meta-analysis with the endpoint risk of serious infections, which is already captured in the primary publications
Secukinumab in non-radiographic axial spondyloarthritis: subgroup analysis based on key baseline characteristics from a randomized phase III study, PREVENT. Braun J, Blanco R, Marzo-Ortega H, Gensler LS, van den Bosch F, Hall S, Kameda H, Poddubnyy D, van de Sande M, Wiksten AS, Porter BO, Shete A, Richards HB, Haemmerle S, Deodhar A. Arthritis Res Ther. 2021 Sep 4;23(1):231.	Post hoc subgroup analysis based on C-reactive protein levels, magnetic resonance imaging scores, human leukocyte antigen (HLA)-B27 status, and sex

Ongoing studies and studies that have not yet been published

A search of clinicaltrials.gov with the search term "non-radiographic" and "nonradiographic" on 10 October 2021 revealed 25 results. One of these is an ongoing study with secukinumab vs. placebo in Chinese patients with nr-axSpA (NCT04732117). There were no other ongoing studies or studies that have not yet been published, neither for secukinumab sc. or the comparators

A similar search of the EU Clinical Trials Register was undertaken on October 12. It revealed nine studies (five with secukinumab, three with adalimumab, and one with ixekizumab). Four of the secukinumab studies are ongoing and the remaining completed one is the PREVENT trial already discussed in this application. None of the ongoing studies were found to be relevant for this application. Moreover, no relevant study was found with adalimumab or ixekizumab.

13.1.2 Risk of bias for included studies

Risk of bias for included studies is evaluated in Table 31 below.

Table 31 Risk of bias for included studies

Trial name/ ID	PREVENT	ABILITY-1	COAST-X
Was randomisation carried out appropriately	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	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

13.1.3 Quality assessment

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

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13.1.4 Unpublished data

Not relevant.

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13.2 Appendix B Main characteristics of included studies

Table 32 Main characteristics for the PREVENT study

Trial name: PREVENT	NCT number: NCT02696031
Objective	To evaluate the efficacy, safety, and tolerability of secukinumab 150 mg, with or without loading doses, in patients with active non radiographic axial spondyloarthritis (nr-axSpA)
Publications – title, author, journal, year	Improvement of Signs and Symptoms of Nonradiographic Axial Spondyloarthritis in Patients Treated with Secukinumab: Primary Results of a Randomized, Placebo-Controlled Phase III Study. Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120 [3]. Secukinumab in non-radiographic axial spondyloarthritis: subgroup analysis based on key baseline characteristics from a randomised phase III study, PREVENT. Braun J, et al. Arthritis Res Ther Vol. 23, No. 1, Sep 2021, pp 231 [22].
Study type and design	PREVENT was a 2-year phase 3 study with an extension of up to 2 years. The study was double-blind, randomised, placebo-controlled and conducted in 24 countries at 130 sites. Patients were randomised (1:1:1) to receive subcutaneous secukinumab 150 mg with a loading dose (LD group), secukinumab 150 mg without a loading dose (non–loading dose (NL) group), or placebo weekly and then every 4 weeks starting at week 4. The NL group received placebo at weeks 1, 2, and 3 to maintain blinding. Switch to open label secukinumab or standard of care was permitted after week 20. The study had 2 independent analysis plans, as per European Union (EU) and non-United States (plan A; week 16) and US (plan B; week 52) regulatory requirements.
Sample size (n)	555 patients
Main inclusion and exclusion criteria	Inclusion and exclusion criteria according to clinicaltrials.gov. Inclusion criteria: • Male or non-pregnant, non-nursing female patients at least 18 years of age • Diagnosis of axial spondyloarthritis according to Ankylosing SpondyloArthritis International Society (ASAS) axial spondyloarthritis criteria • Objective signs of inflammation (magnetic resonance imaging (MRI) or abnormal C-reactive protein (CRP)) • Active axial spondyloarthritis as assessed by total Bath Ankylosing Spondylitis Disease Activity Index ≥ 4 cm • Spinal pain as measured by Bath Ankylosing Spondylitis Disease Activity Index question #2 ≥ 4 cm (0-10 cm) at baseline • Total back pain as measured by visual analogue scale (VAS) ≥ 40 mm (0–100 mm) at baseline • Patients should have been on at least 2 different non-steroidal anti-inflammatory drugs with an inadequate response • Patients who have been on a tumour necrosis factor (TNF) α inhibitor (not more than one) must have experienced an inadequate response Exclusion Criteria: • Patients with radiographic evidence for sacroiliitis, grade ≥ 2 bilaterally or grade ≥ 3 unilaterally • Inability or unwillingness to undergo MRI • Chest X-ray or MRI with evidence of ongoing infectious or malignant process • Patients taking high potency opioid analgesics

Trial name: PREVENT	NCT number: NCT02696031
	• Previous exposure to secukinumab or any other biologic drug directly targeting interleukin-17 (IL-17) or IL-17 receptor • Pregnant or nursing (lactating) women
Intervention	A total of 185 subjects received secukinumab 150 mg with loading dose as a subcutaneous injection at baseline, week 1, 2 and 3, followed by every 4 weeks starting at week 4. At total of 184 subjects received secukinumab 150 mg without loading dose as a subcutaneous injection at baseline, followed by every 4 weeks starting at week 4. Placebo was given week 1, 2 and 3.
Comparator(s)	A total of 186 subjects received matching placebo as a subcutaneous injection at baseline, week 1, 2 and 3, followed by every 4 weeks starting at week 4.
Follow-up time	52 weeks. Analyses on the intention-to-treat (IIT) population was made at week 16 (for EU) and week 52 (for US).
Is the study used in the health economic model?	No. For rationale see section 8.2.
Primary, secondary and exploratory endpoints	Primary outcomes: 1. The Proportion of TNF Naive Participants Who Achieved an ASAS 40 Response (Assessment of SpondyloArthritis International Society Criteria) Time Frame: Week 16 2. The Proportion of TNF Naive Participants Who Achieved an ASAS 40 Response Time Frame: Week 52 ASAS40 response is defined as an improvement of ≥40% and ≥2 units on a scale of 10 in at least three of the four ASAS main domains and no worsening at all in the remaining domain. Secondary outcomes: 1. The Proportion of Participants Who Achieved an ASAS 5/6 Time Frame: Week 16 (The ASAS 5/6 improvement criteria is an improvement of ≥20% in at least five of all six domains) 2. Change in BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) Over Time, Time Frame: Week 16 (The BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem, captured as a continuous VAS), which is used to answer 6 questions pertaining to the 5 major symptoms of AS) 3. Change in SF-36 (Short Form-36 Physical Component Summary) Physical Component Summary Over Time Frame: Week 16 (The SF-36 (Short Form-36 Physical Component Summary) is an instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions) 4. The Proportion of Patients to Achieve a BASDAI 50 Response Time Frame: Week 16 and 52 (The BASDAI 50 is defined as an improvement of at least 50% in the BASDAI compared to baseline) 5. Change in Sacroiliac Joint Oedema Time Frame: Week 16 and 52 (MRI assessment of the Sacroiliac Joint. The comparison of SIJ oedema score at Week 52 between secukinumab 150 mg NL vs. placebo (H19) and between secukinumab 150 mg Load vs. placebo (H32) using FAS2 were not tested at week 16, since the Week 52 MRI reading campaign was not performed until all patients had completed Week 52) 6. Change in High Sensitivity CRP Over Time, Time Frame: Week 16 (High sensitivity CRP is measured as a marker of inflammation from blood samples during the study)

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Trial name: PREVENT	NCT number: NCT02696031

7. Change in BASFI (Bath Ankylosing Spondylitis Functional Index) Over Time Frame: Week 16
(The BASFI (Bath Ankylosing Spondylitis Functional Index) is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS)
8. The Proportion of Participants Who Achieved an ASAS 20 Response Time Frame: Week 16
(ASAS 20 response is defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain)
9. Change in ASQoL (Ankylosing Spondylitis Quality of Life Scores) Over Time - Week 16 Time Frame: Week 16
(The ASQoL (Ankylosing Spondylitis Quality of Life scores) is an instrument to measure health-related quality of life among patients with Ankylosing spondyloarthritis)
10. The Proportion of Patients Who Achieved an Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP Inactive Disease Time Frame: Week 52
(The Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP inactive disease criteria are defined as a value below 1.3 of a composite)
11. Change in ASQoL (Ankylosing Spondylitis Quality of Life Scores) Over Time - Week 52 Time Frame: Week 52
(The ASQoL (Ankylosing Spondylitis Quality of Life scores) is an instrument to measure health-related quality of life among patients with Ankylosing spondyloarthritis)

Change in Sacroiliac Joint Oedema - Week 52 Time Frame: Week 52
(MRI assessment of the Sacroiliac Joint. The comparison of SIJ oedema score at Week 52 between secukinumab 150 mg No Load vs. placebo (H19) and between secukinumab 150 mg Load vs. placebo (H32) using FAS2 were not tested at week 16, since the Week 52 MRI reading campaign was not performed until all patients had completed Week 52)

Method of analysis

Efficacy analyses were performed on the full analysis set, which comprised all patients who were randomised and had study treatment assigned.

Primary and secondary end points were analysed according to a predefined statistical hierarchy. End points are shown in the order of the testing strategy. The family-wise Type I error rate was set to 5% and was controlled with the applied sequential testing strategy. All end points are shown with unadjusted P values with statistical significance only claimed for end points within the predefined hierarchy which met significance based on adjusted P values corrected for multiplicity of testing. For all exploratory end points unadjusted P values are shown. The primary analysis in the TNFi-naive population was conducted via logistic regression with treatment group and stratification (CRP level or MRI) as factors and weight as a covariate.

Missing values were imputed as nonresponders (by nonresponder imputation (NRI)) for binary variables and via a mixed-effects model repeated measures (MMRM; valid under the missing at random assumption) for continuous variables up to week 20. MMRM analysis included treatment group, CRP level or MRI stratification group, TNFi therapy status, and analysis visit as factors and baseline score of the respective end point and weight as continuous covariates. Treatment-by–analysis visit and baseline score–by–analysis visit were included as interaction terms in the model. An unstructured covariance structure was assumed for the model. The significance of treatment effect for the secukinumab regimens was determined from the pairwise comparisons performed between secukinumab regimens and placebo at week 16. For the change in hsCRP level, the log(e) ratio of the post-baseline value to the baseline value was used to normalise the distribution of the hsCRP level at each assessment time point.

Safety analyses included all patients who received ≥1 dose of study medication. AEs are reported as exposure-adjusted incidence rates (EAIR) per 100 patient-years over the entire treatment period, which refers to the cumulative treatment period (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose plus 84 days). Patients switching to standard of care were counted in their previous treatment until the end of the washout phase.

Trial name: PREVENT	NCT number: NCT02696031
Subgroup analyses	Subgroup analysis were pre-specified: The primary endpoint was evaluated within stratification factor levels (CRP+/MRI+, CRP+/MRI-, and CRP-/MRI+). Secondary endpoints were evaluated within TNF-alpha inhibitor status (TNF-alpha naive and TNF-IR) and within stratification factor levels (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+). Post hoc subgroup analysis, where the two secukinumab arms (with and without loading dose) NL) are pooled, has been published [22]
Other relevant information	NA

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Table 33 Main characteristics for the ABILITY-1 study

Trial name: ABILITY-1	NCT number: NCT00939003
Objective	To evaluate the efficacy and safety of adalimumab 40 mg given every other week (eow) subcutaneously compared to placebo for 12 weeks followed by open-label (OL) safety and efficacy assessments in subjects with active axial SpA not fulfilling the modified New York criteria for AS who had an inadequate response to, or intolerance to 1 or more non-steroidal anti-inflammatory drug (NSAIDs) or had a contraindication for NSAIDs.
Publications – title, author, journal, year	Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822 [4].
Study type and design	The pivotal randomised, double-blind, placebo-controlled design of study M10-791 was chosen to demonstrate the efficacy of adalimumab in subjects with active axial spondyloarthritis (SpA) not fulfilling the modified New York criteria for ankylosing spondylitis (AS) who had an inadequate response or intolerance to 1 or more NSAIDs or had a contraindication for NSAIDs. Study M10-791 includes a 12-week, double-blind (DB), placebo-controlled period and a 92-week OL treatment period. The 40 mg adalimumab dose was chosen in accordance with the AS and PsA dosage recommendations in the European Union (EU) summary of product characteristics (SmPC). Moreover, the adalimumab clinical trial safety database across multiple disease indications is also largely comprised of data recorded with the 40 mg every other week (eow) dose, which is also the approved maintenance dose for adult patients across all other indications.
Sample size (n)	179 patients
Main inclusion and exclusion criteria	Main inclusion criteria: 1.Subject was ≥18 years of age. 2.Subject must have had an inadequate response to NSAIDs, intolerance to ≥1 NSAID, or had a contraindication for NSAIDs as defined by the investigator. 3.Subject must have had chronic back pain (of at least 3 months duration) with onset at age <45 years. 4.MRI evidence of active inflammatory lesions of sacroiliac joints (past or present) with definite bone marrow oedema/osteitis, suggestive of sacroiliitis associated with SpA plus ≥1 of the clinical criteria listed below: OR Positive human leukocyte antigen-B27 (HLA-B27) plus ≥2 of the clinical criteria listed below other than HLA-B27 positivity: • Inflammatory back pain defined as the presence at screening of at least 4 out of the following 5 parameters: 1) age at onset < 40 years, 2) insidious onset, 3) improvement with exercise, 4) no improvement with rest, 5) night pain with improvement upon getting up; • Arthritis (past or present); • Heel enthesitis (past or present); • Anterior uveitis confirmed by an ophthalmologist (past or present); • Dactylitis (past or present); • Crohn's disease (CD) or ulcerative colitis (past or present);

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Trial name: ABILITY-1	NCT number: NCT00939003
	• Good prior response to an NSAID – back pain was not present anymore or much better 24 to 48 hours after a full dose of an NSAID; • Family history of SpA; • Positive HLA-B27; • Elevated C-reactive protein (CRP). 5. Subjects must have Baseline disease activity as defined by having a Total Back Pain VAS score ≥ 40 mm and BASDAI ≥ 4 at both the Screening and Baseline visits. Main exclusion criteria: 1. Past or present diagnosis of AS, psoriasis, psoriatic arthritis, or history of inflammatory arthritis other than axial SpA (e.g., rheumatoid arthritis, gout, lupus, or polyarticular or systemic juvenile idiopathic arthritis). 2. Prior exposure to any biologic therapy with a potential therapeutic impact on SpA, including anti-TNF therapy. 3. Use of second-line antirheumatic therapy, except methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine, or azathioprine, within 28 days prior to baseline. 4. Subject had been treated with intra-articular joint injection(s) or spinal/paraspinal injection(s) of corticosteroids in the preceding 28 days prior to the baseline visit 5. Subject with extra-articular manifestations (e.g., inflammatory bowel disease (IBD), uveitis, etc.) that were not clinically stable for at least 30 days prior to study entry.
Intervention	91 patients were provided with a sterile subcutaneous (s.c.) injection solution in 1-ml pre-filled syringes containing adalimumab 40 mg/0.8 mL, to be self-administered s.c. eow at approximately the same time of day. The day of the first dose of study drug was designated as Day 1.
Comparator(s)	94 patients were provided with a sterile s.c. injection solution in 1-ml pre-filled syringes containing placebo for adalimumab, to be self-administered s.c. eow at approximately the same time of day. The day of the first dose of study drug was designated as Day 1.
Follow-up time	12 weeks.
Is the study used in the health economic model?	No. For rationale see section 8.2.
Primary, secondary and exploratory endpoints	**Primary endpoints:** The primary efficacy variable for this study was the proportion of subjects who achieved ASAS40 response at the Week 12 visit. A subject was to be categorised as an ASAS40 responder at the Week 12 visit if the subject achieved: Improvement of ≥ 40% and absolute improvement of ≥ 20 units (on a scale of 0 to 100) from baseline in ≥ 3 of the following 4 domains with no deterioration at all in the potential remaining domain: • Patient's Global Assessment – Represented by the Patient's Global Assessment of Disease Activity VAS score (0 to 100 scale) • Pain – Represented by the total back pain VAS score (0 to 100 scale) • Function – Represented by the BASFI score (10 VAS scales on functional items, like putting on socks, bending for a pen, doing a full day's activities (0 to 100 scale). Mean of the ten scores is calculated.)

- Inflammation – Represented by the mean of the two morning stiffness-related BASDAI VAS scores (i.e., the average of items 5 and 6 of the BASDAI, severity and duration of morning stiffness.)

Secondary endpoints:

The ranked secondary efficacy variables that were to be analysed at Week 12 included:

1. ASAS20 response (improvement of ≥20% and absolute improvement of ≥10 units from Baseline in ≥3 of the 4 domains identified above in ASAS40, with no deterioration in the remaining domain (defined as a worsening of ≥20% and a net worsening of ≥10 units))

2. BASDAI 50 (50% improvement from Baseline in BASDAI. 6 VAS-scales scoring fatigue, spinal pain, peripheral arthritis, enthesitis, intensity and duration of morning stiffness. The mean of the 2 last items is calculated and added to the mean of questions 1-4. The result is divided by 5.)

3. Mean change in SF-36v2 physical component

4. ASAS partial remission (absolute score of <20 units for each of the 4 domains identified above in ASAS40)

5. ASAS5/6 response (20% improvement in 5 out of the following 6 domains: BASFI, total back pain, PTGA-Disease Activity, inflammation (represented by questions 5 and 6 of the BASDAI), lateral lumbar flexion from BASMI, and acute phase reactant (pooled CRP))

6. Mean change in HAQ-S

7. Mean change in hs-CRP

8. Mean change in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI score for sacroiliac joints

9. Mean change in SPARCC MRI score for the spine

Other variables that were to be analysed at various timepoints included:

- ASAS50 response (improvement of ≥ 50% and absolute improvement of ≥ 20 units from Baseline in ≥ 3 of the 4 domains identified above in ASAS40, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units))

- ASAS70 response (improvement of ≥ 70% and absolute improvement of ≥ 30 units from Baseline in ≥3 of the 4 domains identified above in ASAS40, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units))

- AS disease activity score (ASDAS) (a composite score of BASDAI questions 2, 3, and 6; PTGA-Disease Activity; and pooled CRP)

- Swollen joint index (66 joints)

- Tender joint index (68 joints)

- BASDAI

- Inflammation (mean of BASDAI questions 5 and 6)

- BASMI (the results from 5 mobility assessments are transformed into values form 0-10 with the aid of a linear function sheet.)

- Chest expansion

- MASES (Maastricht Ankylosing Spondylitis Enthesitis Score, 13 sites are scored as 0 or 1)

- Plantar fascia enthesitis

- Dactylitis

- Physician's Global Assessment of Disease Activity (VAS)

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Trial name: ABILITY-1	NCT number: NCT00939003
	● Nocturnal pain VAS ● Total back pain VAS ● Patient's Global Assessment of Disease Activity (VAS) ● Patient's Global Assessment of Pain (VAS) ● Short Form-36v2 Health Survey questionnaire ● WPAI-SHP ● PASS ● MOS Sleep Scale ● EQ-5D ● BASFI ● Levels of biomarkers (serum MMP-3, urine CTX-II, and VEGFA)
Method of analysis	Efficacy variables were analysed for all randomised patients who received at least one dose of blinded study medication but excluding seven patients from one site due to investigator noncompliance. The safety population consisted of all patients who received at least one dose of study medication. For categorical variables, patients with missing data at week 12 were considered to be non-responders using non-responder imputation (NRI). Last observation carried forward imputed values were used for continuous variables. Analysis of covariance (ANCOVA) adjusting for the baseline score was used to compare change from baseline at week 12 between adalimumab and placebo treatment groups. VAS data were collected on 0–100 mm scales and reported as 0–10 cm data for consistency. To evaluate the impact of baseline demographics and disease conditions on the primary efficacy endpoint, ASAS40 response at week 12 was summarised by subgroups of sex (male, female), race (white, non-white), age (<40, ≥40 years), weight (<70, ≥70 kg), symptom duration (<5, ≥5 years), baseline C-reactive protein (CRP) (normal, elevated), concomitant baseline NSAID use (yes, no) or DMARD use (yes, no), history of inflammatory bowel disease (yes, no) or uveitis (yes, no), baseline HLA-B27 status (positive, negative), past or current MRI evidence of inflammation of the SI joints according to the local radiologist/rheumatologist (positive, negative) and baseline SPARCC SI joint score (<2, ≥2). For subgroup analyses, a logistic model was used to assess treatment and subgroup interaction, with a significant interaction defined as p≤0.10. AEs were summarised as the number and percentage of patients experiencing AEs using Medical Dictionary for Regulatory Activities (MedDRA, V.13.1) system organ classes and preferred terms.
Subgroup analyses	To evaluate the impact of baseline demographics and disease conditions on the primary efficacy endpoint, ASAS40 response at week 12 was summarised by subgroups of sex (male, female), race (white, non-white), age (<40, ≥40 years), weight (<70, ≥70 kg), symptom duration (<5, ≥5 years), baseline C-reactive protein (CRP) (normal, elevated), concomitant baseline NSAID use (yes, no) or DMARD use (yes, no), history of inflammatory bowel disease (yes, no) or uveitis (yes, no), baseline HLA-B27 status (positive, negative), past or current MRI evidence of inflammation of the SI joints according to the local radiologist/rheumatologist (positive, negative) and baseline SPARCC SI joint score (<2, ≥2). For the pre-specified subgroup analyses, a logistic model was used to assess treatment and subgroup interaction, with a significant interaction defined as p≤0.10.
Other relevant information	NA

Table 34 Main characteristics for the COAST-X study

Trial name: COAST-X	NCT number: NCT02757352
Objective	To compare ixekizumab 80 mg every 2 weeks (Q2W) and 80 mg every 4 weeks (Q4W) versus placebo in the treatment of patients with active radiographic axial spondyloarthritis (rad-axSpA) at Week 16, as measured by the proportion of patients achieving an Assessment of Spondyloarthritis International Society 40 (ASAS40) response.
Publications – title, author, journal, year	Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial Deodhar, Lancet vol. 395, 2020 pp. 53–64 [5].
Study type and design	COAST-X was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial, followed by an optional 2-year extension trial (COAST-Y). The study was done over 52 weeks by 109 investigators at 107 sites in 15 countries in Europe, Asia, North America, and South America. At week 0, patients were randomly assigned to receive placebo (placebo group), 80 mg subcutaneous ixekizumab every 4 weeks (Q4W; ixekizumab Q4W group) or ixekizumab every 2 weeks (Q2W; ixekizumab Q2W group; appendix p 32). From week 16, adjustment of non-biologic background medication for axial spondyloarthritis was allowed, or patients were able to switch to open-label ixekizumab Q2W treatment or subsequent TNF inhibitor treatment as part of the study if their disease activity required escalation of treatment, at investigator discretion, with no specific predefined rescue criteria. Patients who had switched to open-label treatment continued to be followed up during the study.
Sample size (n)	303 patients
Main inclusion and exclusion criteria	**Key Inclusion criteria** The study population included patients aged 18 years or older who met the following criteria: 1. Have sacroiliitis present on MRI (according to ASAS/OMERACT criteria and based on central reading) and at least 1 spondyloarthropathy (SpA) feature OR were positive for human leukocyte antigen B27 (HLA-B27) and having at least 2 additional SpA features 2. Have a history of back pain for at least 3 months with age at onset <45 years 3. Have active nr-axSpA, defined as BASDAI ≥4 and total back pain ≥4 on a numeric rating scale (NRS) 4. Have objective signs of inflammation, by sacroiliitis on MRI or elevated C-reactive protein (CRP) 5. Have an inadequate response, as determined by the investigator, to 2 or more NSAIDs for a total duration of at least 4 weeks OR had a history of intolerance to NSAIDs, and 6. Have a history of prior therapy for axSpA of at least 12 weeks **Main Exclusion criteria** *Medical conditions:* 1. Fulfilment of the modified New York (mNY) criteria (van der Linden et al. 1984) with sacroiliitis defined radiographically, based on central reading: sacroiliitis grade ≥2 bilaterally or grades 3 to 4 unilaterally 2. A history of other systemic inflammatory diseases or chronic pain conditions 3. Active Crohn's disease or active ulcerative colitis 4. Active anterior uveitis (an acute episode) within 4 weeks prior to baseline.

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Other medical conditions

1. Current or history of lymphoproliferative disease or malignant disease within 5 years prior to baseline

2. A history of fluid overload, myocardial infarction, uncompensated heart failure, or evidence of new-onset ischemic heart disease within 12 weeks prior to baseline

3. Significant, uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders

4. A recent history of suicide attempt, score of 3 on Item 12 (Thoughts of Death or Suicide) of the Quick Inventory of Depressive Symptomatology–Self Report 16 items (QIDS-SR16), or at risk for suicide.

Infections

1. A serious infection, hospitalisation, or intravenous antibiotics for an infection, within a prespecified period prior to baseline

2. The presence or history of a known immunodeficiency or of being immunocompromised

3. Herpes zoster or other varicella zoster virus infection within 12 weeks prior to baseline

4. Any other active or recent infection within 4 weeks prior to baseline that may pose an unacceptable risk to the patient if enrolled in the study

A known allergy or hypersensitivity to any biologic therapy

1. Surgical treatment to a joint to be assessed in the study within 8 weeks prior to baseline or during the first 16 weeks of the study Major surgery within 8 weeks prior to baseline

Prior or concurrent therapy or clinical trial experience

1. NSAIDs or cyclooxygenase-2 (COX-2) inhibitors, unless dose is stable for at least 2 weeks prior to baseline

2. csDMARDs or any other immunosuppressive agents within 4 weeks prior to baseline (exceptions include methotrexate, sulfasalazine, and hydroxychloroquine)

3. Oral corticosteroids >10 mg/day

4. Concurrent or prior use of biologic or other immunomodulatory agents, including investigational therapies

5. Current or recent participation in clinical trial involving a study drug Parenteral glucocorticoid administration within 6 weeks prior to baseline or anticipated administration during Period 2 of the study

6. A live vaccination or participated in a vaccine clinical study within 12 weeks prior to baseline or intended to have a live vaccination during the course of the study or within 12 weeks of completing treatment in the study, or

7. A vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline, or intended to have a vaccination of BCG during the course of the study or within 12 months of completing treatment in the study Vaccinations Diagnostic assessments

8. Evidence or suspicion of active or latent TB (note: patients with latent TB may be rescreened after appropriate treatment)

9. Positive for HIV (human immunodeficiency virus), hepatitis B virus (HBV), or hepatitis C virus

10. Electrocardiogram (ECG) abnormalities

11. Any of the following at screening: o neutrophil count <1500 cells/µL, lymphocyte count <800 cells/µL, platelet count <100,000 cells/µL, aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times the upper limit of normal (>2.5x upper limit of normal (ULN)), total white blood

Trial name: COAST-X	NCT number: NCT02757352
	cell (WBC) count <3000 cells/µL, haemoglobin <8.5 g/dL (85.0 g/L) for male patients or <8.0 g/dL (80 g/L) for female patients, or other clinical laboratory test results at screening that are outside the normal reference range for the population and are considered clinically significant.
Intervention	The Blinded Treatment Dosing Period (Period 2) involved a comparison of ixekizumab at 2 treatment regimens (80 mg Q2W and 80 mg Q4W) with placebo. Each ixekizumab treatment group included patients receiving an 80-mg or a 160-mg starting dose at Week 0. All doses were administered via s.c. injection. To maintain blinding, all patients received 2 injections at baseline (Week 0). During the remainder of Period 2, all patients received 1 injection Q2W. Beginning at Week 16 and up to Week 44, any patient, regardless of their original treatment group, could be identified by an investigator based on clinical judgment as an inadequate responder. At such time, changes in background therapy, biologic rescue therapy (open-label ixekizumab 80 mg Q2W), or both, could be offered at the discretion of the investigator, while remaining blinded to the original randomisation treatment assignment.
Comparator(s)	Placebo
Follow-up time	52 weeks. Analyses on IIT population was made at week 16 and week 52.
Is the study used in the health economic model?	No. For rationale see section 8.2.
Primary, secondary and exploratory endpoints	**Primary endpoint** Proportion of patients achieving an ASAS40 response at weeks 16 and 52. An ASAS40 response is defined as an improvement of 40% or more and an absolute improvement from baseline of 2 or more units (range 0–10) in at least three of the following four domains: 1. patient global score (patient global assessment of disease activity), 2. spinal pain score (spinal pain numerical rating score), 3. function score (Bath Ankylosing Spondylitis Functional Index (BASFI), and 4. inflammation score (mean of BASDAI question 5 (intensity of morning stiffness) and question 6 (duration of morning stiffness)), without any worsening in the one remaining domain. **Secondary endpoints:** • To compare ixekizumab 80 mg Q2W and 80 mg Q4W versus placebo in the treatment of patients with active rad-axSpA during the 16-week placebo-controlled period, as assessed by: 1. proportion of patients who achieve ASAS20, ASAS40, ASAS5/6, partial remission by ASAS criteria, BASDAI50, clinical-important improvement (ASDAS change from baseline≥1.1), major improvement (change of ASDAS change from baseline ≥2.0), ASDAS <2.1, or inactive disease. 2. change from baseline in the individual components of the ASAS criteria, BASDAI, ASDAS, BASFI, measure of high sensitivity C-reactive protein (hs-CRP), mobility (BASMI linear and individual components, chest expansion, occiput-to-wall distance), MRI of the SIJ (SPARCC), MRI of the spine (Ankylosing Spondylitis Spinal Magnetic Resonance Imaging activity–Berlin Score (ASSpiMRI-Berlin)), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), SPARCC Enthesitis Score, Fatigue NRS score, ASAS HI score, Jenkins Sleep Evaluation Questionnaire (JSEQ), Work Productivity Activity Impairment— Spondyloarthritis (WPAI-SpA) scores, SF-36 (both PCS and mental component summary (MCS) scores), Quick Inventory of Depressive Symptomatology–

Self Report 16 items (QIDS-SR16) score, and European Quality of Life-5 Dimensions 5-level (EQ-5D-5L)

3. incidence and severity of peripheral arthritis by tender joint count (TJC) and swollen joint count (SJC) scores of 46/44 joints
4. incidence rate of anterior uveitis flares

• to determine if the effect of either ixekizumab regimen is maintained through Week 52 for

1. all endpoints assessed at Week 16 (above) and during the 16-week placebo-controlled period (above)
2. Nonsteroidal anti-inflammatory drug (NSAID) intake, as assessed by ASAS-NSAID score and Percentage of patients taking NSAIDs.

• to explore the effect of the starting dose (160 mg versus 80 mg at Week 0) as assessed by the onset of action and treatment response (e.g., ASAS, ASDAS, CRP, and BASFI) during the 16-week placebo-controlled period

Method of analysis

Efficacy analyses for the blinded treatment dosing period were done on the intention-to-treat population, defined as all patients randomly assigned to treatment. Analyses of the ixekizumab Q4W and ixekizumab Q2W treatment groups were done regardless of the starting dose.

The composite strategy, which was applied to categorical efficacy and health outcome variables, indicated that any intercurrent events—e.g., discontinuing treatment or switching to open-label treatment—were to be assigned unfavourable values (i.e., non-responder). Thus, patients were considered non-responders at timepoints when they did not meet the clinical response criteria or when they had missing clinical response data. Patients who discontinued the masked study treatment to which they were originally assigned and switched to open-label ixekizumab Q2W were considered non-responders after switching.

We repeated our analysis of ASAS40 in the per-protocol population, defined as all patients who were compliant with therapy and did not have significant protocol deviations. For patients who switched to open-label ixekizumab Q2W, the requirements for per-protocol population only applied during the treatment period before they took open-label ixekizumab.

The primary analysis method for categorical outcome variables was logistic regression with treatment, geographical region, and MRI and CRP status at screening included in the model. Because the mixed-effects model of repeated measures (MMRM) is a robust method even when the data are not missing at random, the primary analysis method for most continuous outcomes was the MMRM with treatment, geographical region, MRI and CRP status at screening, baseline value, visit, baseline value or visit interaction, and treatment or visit interaction as fixed factors. The MMRM model for CRP included treatment, geographical region, MRI and CRP status at screening, visit, and treatment or visit interaction as fixed factors.

The primary analysis method for MRI sacroiliac joints SPARCC scores was ANCOVA with observed case analysis. The ANCOVA included treatment, geographical region, MRI and CRP status at screening, and baseline MRI score. The assumptions for the MMRM model and ANCOVA were assessed via residual plots and no serious violations were found. We used a graphical multiple testing strategy for primary and major secondary endpoints to control the overall familywise type I error rate at a two-sided α level of 0·05. Two testing schemes were executed independently, with one focused on the 16-week data (12 group comparisons) and the other on the 52-week data (14 group comparisons; appendix pp 33–34). We ordered the comparisons by relative importance to the disease and the magnitude of the estimated effect size. We optimised the α allocations in a simulation study. We started with testing the first outcomes at the top of the hierarchy (appendix pp 33–34). If the null hypothesis of an outcome was not rejected, then the α allocated to this endpoint was considered spent and could not be

Trial name: COAST-X	NCT number: NCT02757352
	passed to other outcomes below. Thus, testing would end at that outcome for that group. If the null hypothesis was rejected, then the testing continued for the remaining outcomes.
Subgroup analyses	Results for ixekizumab and placebo on the primary endpoint ASAS40 response for the subgroups with baseline MRI+/CRP-, MRI-/CRP+ and MRI+/CRP+ was shown in Figure 4 in the supplementary material of the publication, however, no information on method of analysis or results from this is presented, and the study was not powered for evaluating the subgroups.
Other relevant information	NA

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

Table 35 Baseline characteristics by study

Study	PREVENT [3]		ABILITY-1 [4]		COAST-X [5]	
Treatment arm	Secukinumab with loading (n=185)	Placebo (n=186)	Adalimumab (n=91)	Placebo (n=94)	Ixekizumab Q4W group (n=96)	Placebo (n=105)
Age, mean ± SD years	39.10 ± 11.45	39.30 ± 11.47	37.6 ± 11.3	38.4 ± 10.4	40.9 ± 14.5	39.9 ± 12·4
Sex, no. (%) men	80 (43.2)	91 (48.9)	44 (48)	40 (43)	50 (52)	44 (42)
Race, no. (%) white	176 (95.1)	167 (89.8)	91 (100)	91 (97)	80 (83)	76 (73)
Time since diagnosis, mean ± SD years	2.75 ± 4.63	2.96 ± 5.01	2.7 ± 4.2	3.0 ± 3.8		
Symptom duration, mean ± SD years	8.72 ± 9.27	8.39 ± 8.34	10.1 ± 9.0	10.1 ± 8.8	11.3 ± 10.7	10.1 ± 8.3
HLA–B27 positive, no. (%)	136 (73.5)	129 (69.4)	75 (82)	70 (74)	77 (74)	73 (72)
Elevated CRP* (>5 mg/litre), no. (%)	104 (56.2)	105 (56.5)	36 (40)	36 (38)	55 (57)	57 (54)
CRP*, mean ± SD mg/later	13.17 ± 27.21	10.76 ± 21.34			12.4 ± 18.0	14.3 ± 24.4
Historic or current SI joint inflammation on MRI, no (%)	132 (71.4)	139 (74.7)			66 (79)	78 (75)
TNFi-naive, no. (%)	164 (88.6)	171 (91.9)	91 (100)	94 (100)	96 (100)	105 (100)
Total back pain (0–100-mm VAS), mean ± SD	73.30 ± 13.02	70.90 ± 12.52	69 ± 18	70 ± 17		
BASDAI score, mean ± SD	7.08 ± 1.33	6.76 ± 1.24	6.4 ± 1.5	6.5 ± 1.6	7.0 ± 1.5	7.2 ± 1.5
BASFI score, mean ± SD	6.24 ± 2.04	5.89 ± 1.90	4.5 ± 1.9	4.9 ± 2.3	6.4 ± 2.1	6.7 ± 2.0
ASDAS-CRP score, mean ± SD	3.70 ± 0.87	3.49 ± 0.81	3.2 ± 0.8	3.4 ± 0.8	3.8 ± 0.8	3.8 ± 0.9
Concomitant NSAIDs, no. (%)	154 (83.2)	156 (83.9)	72 (79)	74 (79)	81 (84)	96 (91)
Concomitant DMARDs**, no. (%)			17 (19)	16 (17)		
Concomitant MTX, no. (%)	17 (9.2)	23 (12.4)			17 (18)	17 (16)
Concomitant sulfasalazine no. (%)	29 (15.7)	29 (15.6)			23 (24)	21 (20)

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Study	PREVENT [3]		ABILITY-1 [4]		COAST-X [5]	
Treatment arm	**Secukinumab with loading**	**Placebo**	**Adalimumab**	**Placebo**	**Ixekizumab Q4W group**	**Placebo**
	(n=185)	**(n=186)**	**(n=91)**	**(n=94)**	**(n=96)**	**(n=105)**
Concomitant steroids no. (%)	14 (7.6)	17 (9.1)			8 (8)	14 (13)

*** High sensitivity CRP was used in PREVENT**

**** Includes MTX and sulfasalazine**

13.3.1 Comparability of patients across studies

Generally, the populations are very similar in the three included studies. However, there are some differences. Approximately 10% of patients in PREVENT were not TNFi naive, meaning they were TNFi inadequate-responders (TNF-IR). For patients with psoriatic arthritis it has been shown that TNFi inadequate-responders are generally less responsive to secukinumab than TNFi naive patients [26], why one could expect lower response rates in the PREVENT study compared to ABILITY-1 and COAST-X. This does, however, not impact ASAS40 results, as the ASAS40 results from PREVENT are based on TNFi naive patients, only.

There was evidence of more active disease in PREVENT compared to ABILITY-1 evidenced by higher CRP values, and slightly higher baseline activity (BASDAI, BASFI and ASDAS). This would, however, only be in favour of the comparator and lead to conservative estimates in the comparison.

In PREVENT and COAST-X concomitant steroids were allowed, which was not the case in ABILITY-1, however, low dose steroids do generally not impact axial symptoms [27]. Use of concomitant MTX and sulfasalazine seemed to be similar in PREVENT and ABILITY-1, although for the ABILITY-1 study there is no information regarding split between the two treatments. A higher proportion of patients in COAST-X were treated concomitantly with MTX and sulfasalazine compared to PREVENT. The impact on the outcomes is not clear.

13.3.2 Comparability of the study populations with Danish patients eligible for treatment

There is no specific data on Danish biologic naive nr-axSpA patients since patients are not registered with ICD-10 codes in DANBIO. The Danish AS population consist of fewer females (29%) and have a higher proportion of HLA-B27 positive patients (83%), reflecting the AS population. CRP-levels are comparable, as is the proportion of patients on csDMARDs. Fewer patients in Denmark are on steroid treatment (1%). The BASDAI and BASFI scores are slightly lower in the Danish population (5.9 and 5.1 respectively) [28]. Overall, study populations in the 3 studies reflect the Danish biologic naive AS population, and the study results can be applied to the Danish nr-axSpA population.

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13.4 Appendix D Efficacy and safety results per study

13.4.1 Outcome measures

The Medicines council has recently evaluated ixekizumab for use in nr-axSpA, and all outcomes that were described in the protocol from the Medicines Council for ixekizumab in axial SpA have been included in this application, except for ASDAS <2,1 and SF-36 - physical pain subdomain and physical function subdomain, for which no data were available for secukinumab or adalimumab. In Table 36 below, the definition, validity and clinical relevance is described. The methods of analysis are described in the result tables below and in Appendix K in section 13.11.

Table 36 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
ASAS40 (Assessment of SpondyloArthritis international Society)	Proportion of patients achieving ASAS40. An ASAS40 response was defined as a ≥40% improvement and an absolute improvement from baseline of ≥2 units (range 0–10) in ≥3 of the following four domains: Patient Global Assessment of Disease Activity (0–10 cm VAS), pain (total back pain, 0–10 cm VAS), function (Bath Ankylosing Spondylitis Functional Index (BASFI), 0–10 cm VAS [29] and inflammation/morning stiffness (mean score of items 5 and 6 of the BASDAI (0–10 cm VAS)) without any worsening in the remaining domain [30].	See clinical relevance.	The ASAS Response Criteria (ASAS 20, ASAS 40) have been extensively used in clinical trials, and with a higher magnitude of the clinical response are expected for biological medicinal products, CHMP states that the ASAS 40 response criteria would be the preferred primary endpoint [31]. The Medicines Council considers the minimal important difference to be 15% points [32].

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Outcome measure	Definition	Validity	Clinical relevance
BASDAI50 **(Bath Ankylosing Spondylitis Disease Activity Index)**	Proportion of patients achieving BASDAI50 BASDAI is a composite index that includes the assessment by the patients of their symptoms on six parameters: fatigue, back pain, joint pain, enteritis, duration and severity of morning stiffness and fatigue. Each parameter is scored on a scale from 0-10) BASDAI50 signifies an improvement of ≥50% [32].	See clinical relevance.	BASDAI50 It is a widely used measure of disease activity and its changes with treatment should be assessed. The percentage of patients with clinical response as measured by an improvement of at least a 50% from the baseline score in BASDAI is considered useful to judge the clinical benefit of a treatment [31]. The Medicines Council considers the minimal important difference to be 15% points [32].
Withdrawal due to AE	Proportion of patients withdrawing from treatment due to an adverse event (AE).		Generally used safety outcome. The Medicines Council considers the minimal important difference to be 5% points [32].
Serious infection	Proportion of patients experiencing a serious infection.		Generally used safety outcome for studies with biologic treatments. The Medicines Council considers the minimal important difference to be 5% points [32].

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Outcome measure	Definition	Validity	Clinical relevance
Average change from baseline for SF-36 physical component summary	Average change from baseline for SF-36 physical component summary. SF-36 (short form 36) is a questionnaire based on 36 questions and measures health-related quality of life and functional ability. The questionnaire is divided into 8 health-related domains (subdomains): physical function, physical limitations, mental limitations, social function, physical pain, mental health, energy and general health. In addition, two summarised scores can also be calculated: physical component summary and mental component summary. The score is measured on a scale from 0-100, where high scores represent better quality of life [32].		Generally used QoL measure. The Medicines Council considers the minimal important difference to be 7.1 point for the physical domain [32, 33].
Withdrawal from treatment	Proportion of patients withdrawing from treatment		Generally used outcome. The Medicines Council considers the minimal important difference to be 10% points [32].

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13.4.2 Results per study

Table 37 Results of the PREVENT study

Study name:	PREVENT study: A Randomized, Double-blind, Parallel-group Study Comparing the Efficacy and Safety of Secukinumab versus Placebo in Patients with nr-axSpa.
NCT number:	NCT02696031

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion who experienced response to ASAS40 at week 16	secukinumab	164	41.463 (33.980-49.459)	12.0865	1.901-21.955	0.0231	1.4100	1.052-1.889	0.0231	See table footnote and statistical appendix K	Table 47, EPAR Cosentyx
	placebo	171	29.240 (22.803-36.875)								
Proportion who experienced response to BASDAI50 at week 16	secukinumab	185	37.297 (30.479-44.792)	16.1566	6.954-25.003	0.0007	1.7594	1.263-2.451	0.0007	See table footnote and statistical appendix K	Table 2, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	20.968 (15.657-27.826)								
Proportion of patients who	secukinumab	185	0.000 (0.0-1.622)	-1.5929	-4.837-1.163	0.3717	0.2513	0.028-2.228	0.3717	See table footnote and	Table 3, Deodhar A, et al. Arthritis & Rheumatology
	placebo	186	1.613 (0.583-5.358)								

Study name:	PREVENT study: A Randomized, Double-blind, Parallel-group Study Comparing the Efficacy and Safety of Secukinumab versus Placebo in Patients with nr-axSpa.
NCT number:	NCT02696031

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
discontinued due to adverse events at week 20										statistical appendix K	Vol. 73, No. 1, January 2021, pp 110–120
Proportion of patients who experienced severe infections at week 20	secukinumab	185	0.541 (0.130-3.810)	0.5376	-2.003-3.318	0.6229	2.0107	0.184-21.986	0.6229	See table footnote and statistical appendix K	Table 2, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	0.000 (0.0 - 1.613)								
Proportion of patients who discontinued treatment at week 24	secukinumab	185	5.405 (2.973-10.281)	-0.5006	-5.630-4.610	1.0000	0.9216	0.417-2.036	1.0000	See table footnote and statistical appendix K	Figure 1, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	5.914 (3.341-10.884)								
	secukinumab	185	5.710 ± 0.680		0.853-4.707	0.005			0.005		

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Study name:	PREVENT study: A Randomized, Double-blind, Parallel-group Study Comparing the Efficacy and Safety of Secukinumab versus Placebo in Patients with nr-axSpa.
NCT number:	NCT02696031

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Average change from baseline on SF-36, Physical component summary (least square mean ± standard error) at week 16	placebo	186	2.930 ± 0.710	2.780 ± 0.983			not applicable (NA)	not applicable (NA)		See table footnote and statistical appendix K	Table 2, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120

Results are based on the Intention-to -treat population for the efficacy outcomes, and the safety set for the safety outcomes. For ASAS40 only patients who were TNFi-treatment naïve (90.3%) were included in the analysis. This was the primary endpoint in the study. In the ABILITY-1 and COAST-X studies only TNFi-treatment naïve patients were included in the trial (see Section 7.1.1.1 and 7.2.1.1).
The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.

To deal with occasional zero event situations, the procedure of Agresti and Caffo (“Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures”, The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.
In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts.

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Table 38 Results of the ABILITY-1 study

Study name:	**ABILITY-1 study: A randomized, double-blind, parallel-group study comparing the efficacy and safety of adalimumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT00939003**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion who experienced response to ASAS40 at week 12	adalimumab	91	36.264 (26.439-47.010)	21.3701	8.847-33.150	< 0.001	2.4349	1.398-4.240	< 0.001	See table footnote and statistical appendix K	Table 7, EPAR Humira
	placebo	94	14.894 (8.389-23.725)								
Proportion who experienced response to BASDAI50 at week 12	adalimumab	91	35.165 (25.442-45.882)	20.2712	7.826-32.035	0.001	2.3611	1.351-4.125	0.001	See table footnote and statistical appendix K	Table 7, EPAR Humira
	placebo	94	14.894 (8.389-23.725)								
Proportion of patients who discontinued due to adverse	adalimumab	95	2.105 (0.642-8.773)	1.0726	-4.371-6.870	0.6811	1.5309	0.262-8.962	0.6811	See table footnote and statistical appendix K	Table 3, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	97	1.031 (0.246-7.108)								

Study name:	ABILITY-1 study: A randomized, double-blind, parallel-group study comparing the efficacy and safety of adalimumab versus placebo in patients with nr-axSpa.
NCT number:	NCT00939003

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
events at week 12											
Proportion of patients who experienced severe infections at week 12	adalimumab	95	0.000 (0.0-3.158)	0.0208	-4.550-4.675	1.0000	1.0206	0.065-16.087	1.0000	See table footnote and statistical appendix K	Table 3, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	97	0.000 (0.0-3.093)								
Proportion of patients who discontinued treatment at week 12	adalimumab	91	4.396 (1.768-12.102)	2.2513	-4.185-9.163	0.4926	1.7204	0.423-6.995	0.4926	See table footnote and statistical appendix K	Figure 1, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	94	2.128 (0.649-8.862)								

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Study name:	**ABILITY-1 study: A randomized, double-blind, parallel-group study comparing the efficacy and safety of adalimumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT00939003**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Average change from baseline on SF-36, Physical component summary (least square mean ± standard error) at week 12	adalimumab	91	5.5	3.0	not applicable (NA)	0.001	not applicable (NA)	not applicable (NA)	0.001	See table footnote and statistical appendix K	Table 2, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	94	2.0								

Results are based on the Full Analysis Set for the efficacy outcomes, and the safety set for the safety outcomes. The FAS was used for efficacy outcomes as the page 9 of the adalimumab EPAR states that the MAH determined that 7 subjects enrolled at a specific site should be excluded from the efficacy analyses. [21] The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.

To deal with occasional zero event situations, the procedure of Agresti and Caffo ("Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures", The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.

In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts.

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Table 39 Results of the COAST-X study

Study name:	**COAST-X: A randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT02757352**

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion who experienced response to ASAS40 at week 16	ixekizumab	96	35.417 (26.287-46.030)	16.0881	3.851-27.852	0.0120	1.8197	1.141-2.901	0.0120	See table footnote and statistical appendix K	Table 2, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	105	19.048 (12.579-28.422)								
Proportion who experienced response to BASDAI50 at week 16	ixekizumab	96	31.250 (22.606-41.804)	16.6794	5.129-27.892	0.0049	2.1154	1.236-3.621	0.0049	See table footnote and statistical appendix K	Bilag til Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt, page 42 in Bilag 5
	placebo	105	14.286 (8.795-23.145)								

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Study name:	COAST-X: A randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab versus placebo in patients with nr-axSpa.
NCT number:	NCT02757352

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients who discontinued due to adverse events at week 16	ixekizumab	96	0.0 (0.0-3.125)	- 1.8098	-7.040-3.093	1.0000	0.3605	0.038-3.409	0.622453	See table footnote and statistical appendix K	Figure 1, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	104	1.923 (0.587-8.049)								
Proportion of patients who experienced severe infections at week 16	ixekizumab	96	0.000 (0.000-3.125)	0.0770	-4.214-4.678	0.6088	1.0816	0.069-17.058	1.0000	See table footnote and statistical appendix K	Table 4, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64 and Table 44 in [20]..
	placebo	104	0.000 (0.0-2.885)								
Proportion of patients who discontinued treatment	ixekizumab	96	1.042 (0.248-7.178)	-6.3704	-13.335-0.062	0.0612	0.2426	0.054-1.096	0.0612	See table footnote and statistical appendix K	Figure 1, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	105	7.619 (3.918-15.367)								

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Study name:	**COAST-X: A randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT02757352**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Average change from baseline on SF-36, Physical component summary (least square mean ± standard error) at week 16	ixekizumab	96	8.060 ± 0.810	2.850 ± 1.138	0.619-5.081	0.012	not applicable (NA)	not applicable (NA)	not applicable (NA)	See table footnote and statistical appendix K	Table 3, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	105	5.210 ± 0.800								

Results are based on the Intention-to -treat population for the efficacy outcomes, and the safety set for the safety outcomes.

According to Deodhar 2020, one patient in the ixekizumab Q4W experienced a serious infection, but the number was 0 according to the EPAR, the event must have occurred after week 16

The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.

To deal with occasional zero event situations, the procedure of Agresti and Caffo ("Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures", The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.

In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts.

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13.5 Appendix E Safety data for intervention and comparators

Data for proportion of patients who experience a serious infection, who withdraw from treatment due to an SAE and who withdraw from treatment for any cause are accounted for in the comparative analysis (see Appendix 13.4 and 13.6).

Proportion of patients with at least one AE and one SAE is shown in Table 40. In order to compare across treatments, data for the COAST-X study derive from the EPAR, where 16-week data are available.

Table 40 Proportion of patients with at least one adverse event and one serious adverse event

Study	PREVENT		ABILITY-1		COAST-X	
Treatment arm	Secukinumab N=185	Placebo N=186	Adalimumab N=95	Placebo N=97	Ixekizumab N=96	Placebo N=104
Exposure time	20 weeks [3]		12 weeks [4])		16 weeks (Table 44 in [20])	
Proportion of patients with at least one Adverse Event, n (%)	119 (64.3)	101 (54.3)	55 (57.9)	57 (58.8)	52 (54.2)	52 (50.0)
Proportion of patients with at least one Serious Adverse Event, n (%)	2 (1.1)	5 (2.7)	3 (1.0)	1 (3.2)	0	1 (0.9)

There are no published data on proportion of patients with adverse drug reactions. However, AEs considered related to the drugs are shown in Table 41, based on the approved SmPCs and across all approved indications [1, 17, 18, 23].

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Table 41 Safety information for secukinumab, adalimumab and ixekizumab from the SmPCs

	Secukinumab	Adalimumab	Ixekizumab
Mechanism of action	IL-17 inhibitor	TNF-α inhibitor	IL-17 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)	• Serious hypersensitivity to the active substance or to any of the excipients • Clinically important active infections (e.g., active tuberculosis)
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.	The most frequently reported adverse reactions were injection site reactions (15.5 %) and upper respiratory tract infections (16.4 %) (most frequently nasopharyngitis).
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	• Upper respiratory tract infection • Injection site reactions

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	Secukinumab	Adalimumab	Ixekizumab
Common (≥ 1/100 to < 1/10)	• Oral herpes, Tinea pedis • Headache • Rhinorrhoea • Diarrhoea, Common Nausea • Fatigue	• Systemic infections, intestinal infections, skin and soft tissue infections, ear infections, oral infections, 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	• Tinea infection, Herpes simplex • Oropharyngeal pain • Nausea

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	Secukinumab	Adalimumab	Ixekizumab
		• Worsening or new onset of psoriasis, urticaria, bruising, dermatitis, onychoclasis, hyperhidrosis, alopecia1, pruritus • Muscle spasms • Renal impairment, haematuria • Chest pain, oedema, pyrexia • Coagulation and bleeding disorders, blood lactate dehydrogenase increased • Impaired healing	
Uncommon (≥ 1/1,000 to < 1/100)	• Oral candidiasis, Otitis externa • Neutropenia • Conjunctivitis • Inflammatory bowel disease • Urticaria	• 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	• Influenza, Rhinitis, Oral candidiasis, Conjunctivitis, Cellulitis • Neutropenia, Thrombocytopenia • Angioedema • Inflammatory bowel disease • Urticaria, Rash, Eczema

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	Secukinumab	Adalimumab	Ixekizumab
		• 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 • 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	

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13.6 Appendix F Comparative analysis of efficacy and safety

Table 42 Results: Secukinumab vs. adalimumab for patients with nr-axSpA

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		
Proportion of patients who experienced response to ASAS40	PREVENT ABLITY-1	-21.22	-35.03-4.67	0.0919	0.58	0.31-1.09	0.0919	See table footnote and statistical appendix K	No
Proportion of patients who experienced response to BASDAI50	PREVENT ABLITY-1	-10.29	-25.33-18.56	0.3941	0.75	0.39-1.44	0.3941	See table footnote and statistical appendix K	No
Proportion of patients who discontinued due to adverse events	PREVENT ABLITY-1	-2.667	-6.877-1.543	0.2039	0.123	0.005-3.116	0.2039	See table footnote and statistical appendix K	No
Proportion of patients who experienced serious side effects	PREVENT ABLITY-1	-3.734	-8.636-1.168	0.1513	0.131	0.008-2.101	0.1513	See table footnote and statistical appendix K	No

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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		
Proportion of patients who experienced severe infections	PREVENT ABLITY-1	0.517	-2.826-3.860	0.7158	1.970	0.051-75.831	0.7158	See table footnote and statistical appendix K	No
Proportion of patients who discontinued treatment	PREVENT ABLITY-1	-2.777	-9.731-4.178	0.3922	0.442	0.068-2.865	0.3922	See table footnote and statistical appendix K	No

The indirect comparisons of secukinumab and the two other active treatments were performed using generalized linear models for the observed proportions with treatment and study as factors and using a log link function for relative risks and the identity link for absolute risks. This was done in order to avoid the approximative normality assumptions needed for the Bucher method.
For the continuous SF36 outcome, the indirect comparison of secukinumab and ixekizumab was however done by Bucher's method [6].

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Table 43 Meta-analysis of studies comparing secukinumab to ixekizumab for patients with Non-radiographic Spondyloarthritis

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		
Proportion of patients who experienced response to ASAS40	PREVENT COAST-X	-4.145	-19.997-11.706	0.3447	0.763	0.435-1.338	0.3447	See table footnote and statistical appendix K	No
Proportion of patients who experienced response to BASDAI50	PREVENT COAST-X	-0.635	-15.248-13.979	0.5318	0.813	0.425-1.555	0.5318	See table footnote and statistical appendix K	No
Proportion of patients who discontinued due to adverse events	PREVENT COAST-X	0.217	-4.173-4.607	0.8213	0.697	0.030-15.972	0.8213	See table footnote and statistical appendix K	No
Proportion of patients who experienced serious side effects	PREVENT COAST-X	-2.729	-7.122;1.665	0.2529	0.186	0.010-3.329	0.2529	See table footnote and statistical appendix K	No

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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		
Proportion of patients who experienced severe infections	PREVENT COAST-X	0.461	-2.795-3.716	0.7392	1.859	0.048-71.583	0.7392	See table footnote and statistical appendix K	No
Average change from baseline on SF-36, the physical component summary	PREVENT COAST-X	-0.070	-3.018-2.878	0.9629				See table footnote and statistical appendix K	No
Proportion of patients who discontinued treatment	PREVENT COAST-X	6.069	-1.141-13.279	0.0938	6.685	0.725-61.673	0.0938	See table footnote and statistical appendix K	No

RD% = risk difference in %, RD 95%CI = 95% confidence interval for the risk difference in %, RR = relative risk, RR 95%CI = 95% confidence interval for the relative risk.

The indirect comparisons of secukinumab and the two other active treatments were performed using generalized linear models for the observed proportions with treatment and study as factors and using a log link function for relative risks and the identity link for absolute risks. This was done in order to avoid the approximative normality assumptions needed for the Bucher method.
For the continuous SF36 outcome, the indirect comparison of secukinumab and ixekizumab was however done by Bucher's method [6].

13.7 Appendix G Extrapolation

Not applicable. Please find the rationale in section 8.2.

13.8 Appendix H Literature search for HRQoL data

Not applicable. Please find the rationale in section 8.2.

13.9 Appendix I Mapping of HRQoL data

Not applicable. Please find the rationale in section 8.2.

13.10 Appendix J Probabilistic sensitivity analyses

Not applicable. Please find the rationale in section 8.2.

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13.11 Appendix K Statistical methods

The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.
To deal with occasional zero event situations, the procedure of Agresti and Caffo ("Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures", The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.
In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts.

The indirect comparisons of secukinumab and the two other active treatments were performed using generalized linear models for the observed proportions with treatment and study as factors and using a log link function for relative risks and the identity link for absolute risks. This was done in order to avoid the approximative normality assumptions needed for the Bucher method. For the continuous SF36 outcome, the indirect comparison of secukinumab and ixekizumab was however done by Bucher's method ref. [6].

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Addendum to:
Application for the assessment of secukinumab (Cosentyx®) for non-radiographic axial spondyloarthritis (nr-axSpA)

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13.4 Appendix D Efficacy and safety results per study

Table 1 Results of the PREVENT study

Study name:	**PREVENT study: A Randomized, Double-blind, Parallel-group Study Comparing the Efficacy and Safety of Secukinumab versus Placebo in Patients with nr-axSpa.**
NCT number:	**NCT02696031**

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion who experienced response to ASAS40 at week 16	secukinumab	164	41.463 (33.980-49.459)	12.0865	1.901-21.955	0.0231	1.4100	1.052-1.889	0.0231	See table footnote and statistical appendix K	Table 47, EPAR Cosentyx
	placebo	171	29.240 (22.803-36.875)								
Proportion who experienced response to BASDAI50 at week 16	secukinumab	185	37.297 (30.479-44.792)	16.1566	6.954-25.003	0.0007	1.7594	1.263-2.451	0.0007	See table footnote and statistical appendix K	Table 3, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	20.968 (15.657-27.826)								

Study name:	**PREVENT study: A Randomized, Double-blind, Parallel-group Study Comparing the Efficacy and Safety of Secukinumab versus Placebo in Patients with nr-axSpa.**
NCT number:	**NCT02696031**

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients who discontinued due to adverse events at week 20	secukinumab	185	0.000 (0.0-1.622)	-1.5929	-4.837-1.163	0.3717	0.2513	0.028-2.228	0.3717	See table footnote and statistical appendix K	Table 3, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	1.613 (0.583-5.358)								
Proportion of patients who experienced severe infections at week 20	secukinumab	185	0.541 (0.130-3.810)	0.5376	-2.003-3.318	0.6229	2.0107	0.184-21.986	0.6229	See table footnote and statistical appendix K	Table 2, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	0.000 (0.0 - 1.613)								
Proportion of patients who discontinued	secukinumab	185	5.405 (2.973-10.281)	-0.5006	-5.630-4.610	1.0000	0.9216	0.417-2.036	1.0000	See table footnote and statistical appendix K	Figure 1, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1,
	placebo	186	5.914 (3.341-10.884)								

Study name:	PREVENT study: A Randomized, Double-blind, Parallel-group Study Comparing the Efficacy and Safety of Secukinumab versus Placebo in Patients with nr-axSpa.
NCT number:	NCT02696031

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
treatment at week 24											January 2021, pp 110–120
Average change from baseline on SF-36, Physical component summary at week 16	secukinumab	185	5.710 ± 0.680*	2.780 ± 0.983*	0.853-4.707	0.005	not applicable (NA)	NA	NA	See table footnote and statistical appendix K	Table 2, Deodhar A, et al. Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 110–120
	placebo	186	2.930 ± 0.710*								

* Least square mean ± standard error

Results are based on the Intention-to -treat population for the efficacy outcomes, and the safety set for the safety outcomes. For ASAS40 only patients who were TNFi-treatment naïve (90.3%) were included in the analysis. This was the primary endpoint in the study. In the ABILITY-1 and COAST-X studies only TNFi-treatment naïve patients were included in the trial (see Section 7.1.1.1 and 7.2.1.1).

The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.

To deal with occasional zero event situations, the procedure of Agresti and Caffo ("Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures", The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.

In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts.

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Table 2 Results of the ABILITY-1 study

Study name:	**ABILITY-1 study: A randomized, double-blind, parallel-group study comparing the efficacy and safety of adalimumab versus placebo in patients with nr-axSpa.**										
NCT number:	**NCT00939003**										
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion who experienced response to ASAS40 at week 12	adalimumab	91	36.264 (26.439-47.010)	21.3701	8.847-33.150	0.001	2.4349	1.398-4.240	0.001	See table footnote and statistical appendix K	Table 7, EPAR Humira
	placebo	94	14.894 (8.389-23.725)								
Proportion who experienced response to BASDAI50 at week 12	adalimumab	91	35.165 (25.442-45.882)	20.2712	7.826-32.035	0.002	2.3611	1.351-4.125	0.002	See table footnote and statistical appendix K	Table 8, EPAR Humira
	placebo	94	14.894 (8.389-23.725)								
Proportion of patients who discontinued due to adverse	adalimumab	95	2.105 (0.642-8.773)	1.0726	-4.371-6.870	0.6811	1.5309	0.262-8.962	0.6811	See table footnote and statistical appendix K	Table 3, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	97	1.031 (0.246-7.108)								

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Study name:	ABILITY-1 study: A randomized, double-blind, parallel-group study comparing the efficacy and safety of adalimumab versus placebo in patients with nr-axSpa.
NCT number:	NCT00939003

				Estimated absolute difference in effect			Estimated relative difference in effect			Method used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
events at week 12											
Proportion of patients who experienced severe infections at week 12	adalimumab	95	0.000 (0.0-3.158)	0.0208	-4.550-4.675	1.0000	1.0206	0.065-16.087	1.0000	See table footnote and statistical appendix K	Table 3, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	97	0.000 (0.0-3.093)								
Proportion of patients who discontinued treatment at week 12	adalimumab	91	4.396 (1.768-12.102)	2.2513	-4.185-9.163	0.4926	1.7204	0.423-6.995	0.4926	See table footnote and statistical appendix K	Figure 1, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	94	2.128 (0.649-8.862)								

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Study name:	**ABILITY-1 study: A randomized, double-blind, parallel-group study comparing the efficacy and safety of adalimumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT00939003**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Average change from baseline on SF-36, Physical component summary at week 12	adalimumab	91	5.5	3.0	not applicable (NA)	0.001	NA	NA	NA	See table footnote and statistical appendix K	Table 2, Sieper et al, Ann Rheum Dis Vol. 72, 2013, pp 815-822
	placebo	94	2.0								

Results are based on the Full Analysis Set for the efficacy outcomes, and the safety set for the safety outcomes. The FAS was used for efficacy outcomes as the page 9 of the adalimumab EPAR states that the MAH determined that 7 subjects enrolled at a specific site should be excluded from the efficacy analyses. [21] The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.

To deal with occasional zero event situations, the procedure of Agresti and Caffo ("Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures", The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.

In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts

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Table 3 Results of the COAST-X study

Study name:	**COAST-X: A randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT02757352**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion who experienced response to ASAS40 at week 16	ixekizumab	96	35.417 (26.287-46.030)	16.0881	3.851-27.852	0.0120	1.8197	1.141-2.901	0.0120	See table footnote and statistical appendix K	Table 2, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	105	19.048 (12.579-28.422)								
Proportion who experienced response to BASDAI50 at week 16	ixekizumab	96	31.250 (22.606-41.804)	16.6794	5.129-27.892	0.0049	2.1154	1.236-3.621	0.0049	See table footnote and statistical appendix K	Bilag til Medicinrådets anbefaling vedrørende ixekizumab til behandling af rygsøjlegigt, page 42 in Bilag 5
	placebo	105	14.286 (8.795-23.145)								

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Study name:	**COAST-X: A randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT02757352**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients who discontinued due to adverse events at week 16	ixekizumab	96	0.0 (0.0-3.125)	- 1.8098	-7.040-3.093	0.622453	0.3605	0.038-3.409	0.622453	See table footnote and statistical appendix K	Figure 1, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	104	1.923 (0.587-8.049)								
Proportion of patients who experienced severe infections at week 16	ixekizumab	96	0.000 (0.000-3.125)	0.0770	-4.214-4.678	1.0000	1.0816	0.069-17.058	1.0000	See table footnote and statistical appendix K	Table 4, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64 and Table 44 in [20].
	placebo	104	0.000 (0.0-2.885)								
Proportion of patients who discontinued treatment	ixekizumab	96	1.042 (0.248-7.178)	-6.3704	-13.335-0.062	0.0612	0.2426	0.054-1.096	0.0612	See table footnote and statistical appendix K	Figure 1, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	105	7.619 (3.918-15.367)								

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Study name:	**COAST-X: A randomized, double-blind, parallel-group study comparing the efficacy and safety of ixekizumab versus placebo in patients with nr-axSpa.**
NCT number:	**NCT02757352**

				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Method used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Average change from baseline on SF-36, Physical component summary at week 16	ixekizumab	96	8.060 ± 0.810	2.850 ± 1.138	0.619-5.081	0.012	NA	NA	NA	See table footnote and statistical appendix K	Table 3, Deodhar et al., Lancet vol. 395, 2020 pp. 53–64.
	placebo	105	5.210 ± 0.800								

*Least square mean ± standard error

Results are based on the Intention-to -treat population for the efficacy outcomes, and the safety set for the safety outcomes.

According to Deodhar 2020, one patient in the ixekizumab Q4W experienced a serious infection, but the number was 0 according to the EPAR, the event must have occured after week 16

The 'single study' derivation of proportions and 95% CIs were found as exact Clopper-Pearson intervals, whereas CIs for risk differences were derived directly as Newcombe intervals.

To deal with occasional zero event situations, the procedure of Agresti and Caffo ("Simple and Effective Confidence Intervals for Proportions and Differences of Proportions Result from Adding Two Successes and Two Failures", The American Statistician, Vol. 54, No. 4, pp. 280-288. [34]), was followed. Note however that the upper 95% confidence limit for single proportions (0/N) were derived by the approximative 3/N rule.

In order to use the same way of calculating relative and absolute risks differences, the Agresti/Caffo method was used throughout, also in cases without zero counts.

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13.6 Appendix F Comparative analysis of efficacy and safety

Table 4 Results: Secukinumab vs. adalimumab for patients with nr-axSpA

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	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients who experienced response to ASAS40	PREVENT ABLITY-1	-21.22	-35.03-4.67	0.0919	0.58	0.31-1.09	0.0919	See table footnote and statistical appendix K	No
Proportion of patients who experienced response to BASDAI50	PREVENT ABLITY-1	-10.29	-25.33-18.56	0.3941	0.75	0.39-1.44	0.3941	See table footnote and statistical appendix K	No
Proportion of patients who discontinued due to adverse events	PREVENT ABLITY-1	-2.667	-6.877-1.543	0.2039	0.123	0.005-3.116	0.2039	See table footnote and statistical appendix K	No
Proportion of patients who experienced serious side effects	PREVENT ABLITY-1	-3.734	-8.636-1.168	0.1513	0.131	0.008-2.101	0.1513	See table footnote and statistical appendix K	No

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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	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients who experienced severe infections	PREVENT ABLITY-1	0.517	-2.826-3.860	0.7158	1.970	0.051-75.831	0.7158	See table footnote and statistical appendix K	No
Proportion of patients who discontinued treatment	PREVENT ABLITY-1	-2.777	-9.731-4.178	0.3922	0.442	0.068-2.865	0.3922	See table footnote and statistical appendix K	No

The indirect comparisons of secukinumab versus adalimumab were performed using a generalized linear model for the observed proportions with treatment and study as factors and using a log link function for calculation of relative risks (RR). This was done in order to avoid the approximative normality assumptions needed for the Bucher method. For the risk difference (RD), the proportion of subjects with the event in question, in the adalimumab arm, was used as baseline and the standard expression RD = baseline*(RR -1) subsequently applied. The 95% CI was derived likewise, using the lower and upper limits for the RR.

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Table 5 Results: Secukinumab vs. ixekizumab for patients with nr-axSpA

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	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients who experienced response to ASAS40	PREVENT COAST-X	-4.145	-19.997-11.706	0.3447	0.763	0.435-1.338	0.3447	See table footnote and statistical appendix K	No
Proportion of patients who experienced response to BASDAI50	PREVENT COAST-X	-0.635	-15.248-13.979	0.5318	0.813	0.425-1.555	0.5318	See table footnote and statistical appendix K	No
Proportion of patients who discontinued due to adverse events	PREVENT COAST-X	0.217	-4.173-4.607	0.8213	0.697	0.030-15.972	0.8213	See table footnote and statistical appendix K	No

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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	95% CI	*P* value	Difference	95% CI	*P* value		
Proportion of patients who experienced serious side effects	PREVENT COAST-X	-2.729	-7.122;1.665	0.2529	0.186	0.010-3.329	0.2529	See table footnote and statistical appendix K	No
Proportion of patients who experienced severe infections	PREVENT COAST-X	0.461	-2.795-3.716	0.7392	1.859	0.048-71.583	0.7392	See table footnote and statistical appendix K	No
Average change from baseline on SF-36, the physical component summary	PREVENT COAST-X	-0.070	-3.018-2.878	0.9629				See table footnote and statistical appendix K	No
Proportion of patients who discontinued treatment	PREVENT COAST-X	6.069	-1.141-13.279	0.0938	6.685	0.725-61.673	0.0938	See table footnote and statistical appendix K	No

The indirect comparisons of secukinumab versus ixekizumab were performed using a generalized linear model for the observed proportions with treatment and study as factors and using a log link function for calculation of relative risks (RR). This was done in order to avoid the approximative normality assumptions needed for the Bucher method. For the risk difference (RD), the proportion of subjects with the event in question, in the active comparator treatment arm, was used as baseline and the standard expression RD = baseline*(RR -1) subsequently applied. The 95% CI was derived likewise, using the lower and upper limits for the RR. For the continuous SF36 outcome, the indirect comparison of secukinumab and ixekizumab was done by Bucher's method [6].

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Addendum to 13.11 Appendix K Statistical methods

For the indirect comparisons of binary endpoints, an alternative way of deriving the absolute risk-difference was also used. Here, the proportion of subjects with the event in question, in the active comparator treatment arm, was used as baseline and the standard expression:
risk difference = baseline*(relative risk -1)
subsequently applied. The 95% CI was likewise derived by using the lower and upper limits for the relative risk.

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