Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende upadacitinib til behandling af non-radiografisk aksial spondylartritis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. upadacitinib til non-radiografisk aksial spondylartritis
2. Forhandlingsnotat fra Amgros vedr. upadacitinib til non-radiografisk aksial spondylartritis
3. Ansøgers endelige ansøgning vedr. upadacitinib til non-radiografisk aksial spondylartritis

AbbVies svar på Medicinrådets vurdering af Rinvoq til nr-AxSpa

AbbVie har ansøgt Medicinrådet om evaluering af upadicitinib som et klinisk ækvivalent behandlingsalternativ til eksisterende standardbehandlinger for nr-AxSpa, dvs. TNF-hæmmere, samt IL-17 hæmmerne ixekizumab og secukinumab. Upadicitinib er en JAK hæmmer og repræsenterer derfor en ny effektiv og veltolereret behandlingsmulighed til patienter med nr-AxSpa i Danmark. Desuden er upadicitinibanbefalet til inflammatoriske tarmsygdomme, som er en relativt hyppigt forekommende komorbiditet til nr-AxSpa og påvirker op mod 9% af patienter i Danmark [1]. Både ixekizumab og secukinumab er kontraindiceret hos patienter med IBD, da tilfælde af ny sygdom eller eksacerbationer er blevet rapporteret under behandling med disse lægemidler.

Behandlingserfarne patienter
I vurderingen af upadicitinib er der lagt stor vægt på data for b/tsDMARD-erfarne[2] patienter, hvilket umiddelbart giver mening da b/tsDMARD-naive patienter i Danmark i dag får biosimilære TNF-hæmmere fordi disse er billigst. Vi har desuden bemærket at manglen på data for b/tsDMARD-erfarne lader til at have været udslagsgivende i vurderingen af bimekizumab som ikke endte med en anbefaling[3].

AbbVie vil derfor bemærke at de lægemidler der i dag gives til b/tsDMARD-erfarne patienter ikke er anbefalet på baggrund af data i denne population. TNF-hæmmere som blev anbefalet før Medicinrådets tid var kun undersøgt i den b/tsDMARD-naive population og IL17-hæmmerne (ixekizumab og secukinumab) havde ingen eller meget begrænsede data for populationen. I PREVENT studiet, som var datagrundlag for anbefalingen af secukinumab, var ca. 10% af patienterne b/tsDMARD-erfarne, mens et eksklusionskriterie for deltagelse i COAST-X studiet (datagrundlag for anbefaling af ixekizumab) var tidligere bDMARD behandling. Ikke desto mindre skrev Medicinrådet i deres anbefaling:

Der foreligger også evidens for ixekizumabs effekt hos behandlingserfarne patienter, hvor Medicinrådet vurderer, at der ikke er noget, der taler for, at balancen mellem effekt og bivirkninger af ixekizumab hos biologisk behandlingserfarne patienter adskiller sig fra balancen hos biologisk behandlingsnaive patienter.

Til sammeligning er 33% af patienterne i datagrundlaget for upadicitinib behandlingserfarne (SELECT-AXIS-2 studie 2). SELECT-AXIS-2 (studie 2) er ikke planlagt til at have statistisk styrke til at vise forskel på upadicitinib og placebo blandt b/tsDMARD-erfarne patienter. AbbVie har dog gennemført et studie med tilstrækkelig statistisk styrke blandt b/tsDMARD-erfarne patienter med ankyloserende spondylitis (AS) (SELECT-AXIS 2 studie 1). På trods af det ikke er den samme indikation, bekræfter disse resultater, at upadicitinib er effektivt efter b/tsDMARD-eksponering i en lignende gruppe patienter. Upadacitinib 15 mg blev sammenlignet med placebo blandt b/tsDMARD-behandlede patienter med AS og i dette studie viste upadacitinib statistisk signifikant bedre resultater end placebo for ASAS40 (45% vs 18%; p<0,0001), BASDAI50 (43% vs 17%; p<0,0001) og ASDAS>2,1 (44% vs 10% p<0,0001), for patienter med AS refraktær over for biologisk terapi[4].

Når AbbVie læser anbefalingen af bimekizumab og vurderingen af upadicitinib, så lader det til, at Medicinrådet har ændret vurderingspraksis for lægemidler til nr-AxSpa, og de lægemidler der anvendes på

[1] https://pubmed.ncbi.nlm.nih.gov/27909080/
[2] b/tsDMARD: biologic/targeted synthetic disease-modifying antirheumatic drug
[3] https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/b/bimekizumab-bimzelx-aksial-spondylartrit-axspa
[4] https://pubmed.ncbi.nlm.nih.gov/35788492/

nuværende tidspunkt er anbefalet på baggrund af dårligere data end der nu accepteres. Dette finder AbbVie problematisk af konkurrencemæssige årsager og af hensyn til patienterne.

Sikkerhed
Medicinrådet indikerer at man vil fortolke EMA's vurdering af sikkerhed som man har gjort indenfor kronisk leddegigt. EMA's anbefaling er at JAK-hæmmere ikke anvendes til patienter med visse risikofaktorer, medmindre der ikke findes anden mulig behandling. Indenfor kronisk leddegigt har Medicinrådet valgt at nedgradere alle JAK-hæmmere for alle patienter, uden individuel vurdering af patienten. AbbVie vil gerne udfordre følgende:

Medicinrådets fortolkning af EMA's anbefaling:
EMA anbefaler at man skal vurdere patientens risikofaktorer. Patienter uden risikofaktorer kan behandles med JAK-hæmmere mens patienter med risikofaktorer kun skal behandles med JAK-hæmmere hvis andre muligheder er udtømt. Denne del har Medicinrådet udbredt til alle patienter uden individuel hensyntagen. AbbVie mener at Medicinrådet bør stole på at lægerne kan træffe et informeret valg på baggrund af en individuel patientvurdering.

JAK - klasseeffekt
Alle JAK-hæmmere er ikke ens. For eksempel er der ganske betydelige forskelle, når det kommer til farmakokinetikken for de forskellige JAK-hæmmere, der er tilgængelige på markedet. Lægemidlernes metabolisme er forskellig, deres halveringstid varierer og deres kemiske sammensætninger er ikke identisk. Disse forskelle kan føre til til forskelle i effektivitet og sikkerhedsprofiler for de forskellige JAK-hæmmere. Effekt- og sikkerhedsdata fra randomiserede kliniske forsøg i JAK-hæmmerklassen har også vist sig at være forskellige, skønt der ikke kan drages en endelig konklusion, da randomiserede direkte sammenligninger ikke er foretaget.

Medicinrådet har en formodning om en klasseeffekt for JAK-hæmmere, der giver øget risiko for blandt andet alvorlige kardiovaskulære hændelser og venøs tromboembolisme (VTE). Denne formodning er primært baseret på sikkerhedsdata for tofacitinib (ORAL surveillance studiet) og der er ikke fundet lignende sikkerhedssignaler for upadicitinib. Et nyligt publiceret studie blandt mere end 4000 patienter behandlet i kliniske forsøg fandt at upadicitinib er sammenlignelig med andre behandlinger (adalimumab og methotrexat) hvad angår forekomst af disse bivirkninger[5].

Tilsvarende fandt et studie blandt patienter i risikogruppen for kardiovaskulære hændelser (≥50 år ≥1 kardiovaskulære risikofaktorer) at patienter behandlet med upadicitinib 15 mg/dag havde sammenlignelig risiko for alvorlige kardiovaskulære hændelser og VTE som patienter behandlet med adalimumab eller methotrexat[6].

Samlet set er der nu sikkerhedsdata på mange tusinde patienter i kliniske trials, og der følges løbende op. Senest er der publiceret en opsamling på upadicitinib patienter indenfor kronisk leddegigt, psoriasisartrit, rygsøjlegigt og atopisk dermatit der samler data på næsten 7000 patienter og mere end 15000 patientår. Studiet finder at upadicitinib generelt er veltolereret og der ikke er nye sikkerhedssignaler [7].

Samlet set er upadicitinib et veltolereret og effektivt lægemiddel og tilbyder en ny behandlingsmulighed til en gruppe af patienter der nu kun kan behandles med TNF- og IL17-hæmmere. AbbVie opfordrer derfor til at Medicinrådet følger den vurderingspraksis der hidtil har været anvendt på området og ikke vurderer nye lægemidler til indikationen efter strengere kriterier end de lægemidler der tidligere er anbefalet.

[5] https://pubmed.ncbi.nlm.nih.gov/37945286/
[6] https://pubmed.ncbi.nlm.nih.gov/37308218/
[7] https://pubmed.ncbi.nlm.nih.gov/36754548

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21.03.2024
BMC/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.04.2024
Leverandør	Abbvie
Lægemiddel	Rinvoq (upadacitinib)
Ansøgt indikation	Indiceret til behandling af aktiv non-radiografisk aksial spondylartritis hos voksne patienter med objektive tegn på inflammation, som kan ses ved forhøjet C-reaktion protein (CRP) og/eller magnetisk resonans billeddannelse (MR), som har responderet utilstrækkeligt på non-steroide antiinflammatoriske lægemidler (NSAID'er).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Rinvoq (upadacitinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Rinvoq	15 mg	28 stk.	6.020,26	[redacted]	[redacted]
Rinvoq	30 mg	28 stk.	12.040,51	[redacted]	[redacted]
Rinvoq	45 mg	28 stk.	18.467,03	[redacted]	[redacted]

Aftaleforhold

Rinvoq er en del af det dynamiske udbud på de lægemidler, der indgår i behandlingsvejledninger indenfor reumatologi, gastroenterologi og dermatologi. Alle lægemidlerne indenfor disse terapiområder har mulighed for at justere deres pris ved den kommende prisregulering per 31.03.2024 og herefter vil der blive udarbejdet nye lægemiddelrekommandationer.

Konkurrencesituationen

I Medicinrådets vurderingsrapport er Rinvoq sammenlignet med adalimumab og Cosentyx (secukinumab). I tabel 2 nedenfor vises de årlige lægemiddeludgifter for de sammenlignede lægemidler i Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 18 måneder (SAIP, DKK)
Rinvoq (upadacitinib)	15 mg	28 stk.	15 mg én gang dagligt, PO	[redacted]	[redacted]
Amgevita (adalimumab)	40 mg	2 stk.	40 mg hver 2. uge, SC	[redacted]	[redacted]
Cosentyx (secukinumab)	150 mg	2 stk.	150 mg i uge 0, 1, 2, 3 og 4 derefter 150 mg én gang om måneden, SC	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke ansøgt	
Sverige	Ikke ansøgt	
England	Anbefalet	Link til anbefaling

Konklusion

Leverandøren har mulighed for at sætte prisen ned ved næste prisregulering.

abbvie

Application for the assessment of Rinvoq for non-radiographic axial spondyloarthritis (nr-axSpA)

Instructions for companies

This is the template for submission of evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new pharmaceutical or new indication for an existing pharmaceutical. The template is not exhaustive; companies must adhere to the current version of the guidelines alongside using this template when preparing their submission.

Headings and subheadings are not to be removed. Additional subheadings can be added when appropriate. All sections in the template must be filled in. If a section is not applicable, state “not applicable” and explain why. Examples of texts and tables are provided in the template. These can be edited or removed. The company can provide different table layouts to accommodate data, as long as the required information is provided.
The submission should be as brief and informative as possible. The main body of submission must not be longer than 100 pages, excluding the appendices. Submissions in Danish and English are accepted.

In addition to this template, the company must submit a health economic model in Excel, with full access to the programming code. All the information requested in this template and described in the guidelines must be presented in the application. The model can be accompanied by a technical document. The information in the technical document will, however, not be considered as part of the application. Hence, all relevant information for the application must also be described in the application (including appendices) itself. This can be done by copying the relevant information from the technical document into the application, and by presenting it as described in this template and in the guidelines. Companies are encouraged to provide the European Public Assessment Report (EPAR) including the scientific discussion as an Appendix to the submission (draft versions will be accepted).
When making an evidence submission, companies must ensure that all confidential information is highlighted in yellow and provide the expected date of publication. If confidential appendices are provided, these must be watermarked as “confidential”.

Version 1.0

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Rinvoq
Generic name	Upadacitinib
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG
ATC code	L04AA44
Pharmacotherapeutic group	Janus kinase inhibitor (JAK)
Active substance(s)	Upadacitinib
Pharmaceutical form(s)	Prolonged-release tablet
Mechanism of action	Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2
Dosage regimen	The recommended dose of upadacitinib is 15 mg once daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	RINVOQ is indicated for the treatment of active non-radiographic axial spondylarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

Overview of the pharmaceutical	
Other approved therapeutic indications	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Atopic Dermatitis, Ulcerative Colitis and Crohn's disease.
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Monotherapy
Packaging – types, sizes/number of units, and concentrations	Each pack contains 28, 15mg or 30 mg prolonged-release tablets
Orphan drug designation	No

2. Abbreviations

AS	Ankylosing Spondylitis
AE	Adverse Events
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
axSpA	axial SpA
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
b/tsDMARD	biological/targeted systemic disease-modifying antirheumatic drugs
CPK	Creatine phosphokinase
CRP	C-reactive protein
csDMARD	conventional synthetic Disease-Modifying Anti Rheumatic Drugs
DMARD	Disease Modifying Anti-Rheumatic Drugs
DMC	Danish Medicines Council
EBC	Extended Basis of Comparison
FAS	Full Analysis Set
HAQ-S	Healthy Assessment Questionnaire for Spondyloarthropathies
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
hsCRP	high-sensitivity C-Reactive Protein
IBD	Inflammatory Bowel Disease
IL	Interleukin
IL-17i	IL-17A inhibitor
JAK	Janus Kinases
JAKi	JAK-inhibitor
MACE	Major Adverse Cardiac Event
MRI	Magnetic Resonance Imaging
NA	Not Applicable
nr-axSpA	non-radiographic axSpA
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PsA	Psoriatic Arthritis
QD	Once Daily
QoL	Quality of Life
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TNF	Tumor Necrosis Factor
TNFi	TNF-inhibitor
VAS	Visual analogue Scale
VTE	Venous Thromboembolic Events

3. Tables and Figurees

4. Summary

Non-radiographic spondylarthritis (nr-axSpA) is a disease subgroup of Spondylarthritis (SpA). The disease subgroups within SpA are classified based on the principal location of joint involvement – axial or peripheral. Axial spondyloarthropathies predominantly affect the spine (axial) and sacroiliac joint (connects the two pelvic bones), and include non-radiographic axSpA (nr-axSpA) and radiographic axSpA (AS). Clinical characteristics that are common in include articular features, such as inflammatory arthritis, dactylitis and enthesitis and extra-articular features such as uveitis, psoriasis and inflammatory bowel disease.

Physical impairment affects patients' ability to carry out daily activities, such as walking and working, which have direct negative effect on social participation, psychological wellbeing, and quality of life (QoL). The early age of onset, typically in the patient's thirties, is a critical factor affecting QoL, as SpA manifests at a crucial age of educational, professional, and social development. Axial SpA has a large negative impact on the patients' ability to work. Fifty percent of people with axial SpA experience work instability, and 15% reduce or change their work because of axial SpA. Both physical and psychosocial factors have an important role, such that loss of employment is associated with being older, longer disease duration, lower educational achievement, co-morbidity, greater physical impairment, pain, fatigue, stiffness, anxiety, depression and lower self-esteem.

The treatment algorithm for nr-axSpA in Denmark includes primary treatment where patients receive non-pharmacological treatment such as training, physiotherapy and rehabilitation. Pain and stiffness are treated with traditional NSAID. For patients who despite the primary treatment have high disease activity, treatment with b/tsDMARDs, such as TNF-inhibitors or IL-inhibitors can be initiated. The treatment of nr-axSpA revolves around having effective treatments that prevent disease progression, eliminate pain, and improve patient QoL.

There is a need for additional treatment options as described in EMA:s assessment report for upadacitinib in nr-axSpA:

"Overall, available treatment options remain limited, particularly for nr-axSpA as compared to other rheumatic diseases such as RA or PsA. In axSpA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and long-term corticosteroids are not efficacious and therefore not recommended for treatment of axial symptoms. Once patients have an inadequate response to NSAIDs, and more advanced systemic therapies are required, available biologics are all administered either subcutaneous (SQ) or intravenous. To date, there have been no oral targeted therapies approved for the treatment of nr axSpA."

Upadacitinib is the first JAKi treatment approved for nr-axSpA, with a fast onset of action, offering an entirely new mode-of-action and can be an additional effective tool for treating patients with nr-axSpA. Upadacitinib is administered as an oral tablet, once daily. Upadacitinib is approved for patients who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs), and will be a treatment option to the biological DMARDs currently included in the treatment algorithm. First line DMARD treatment in Danish clinical practice are TNF-inhibitors, followed by IL- inhibitors. In this application, upadacitinib will be compared to a TNF-inhibitor (adalimumab, the most common first line treatment) and an IL-inhibitor (secukinumab, which also has a proportion of b/tsDMARD experienced patients included in its pivotal trials).

All JAK -inhibitors, including upadacitinib, has been part of a safety review by EMA, following safety signals for the JAK-inhibitor tofacitinib Upadacitinib's safety profile is broadly studied across 19 Phase III clinical trials with over 10,500 upadacitinib patients and over 23,000 PY of exposure across rheumatology, dermatology, and gastroenterology. The safety profile is generally consistent across different patient types studied in all approved indications with three different dosing strengths (15mg, 30mg, and 45mg). Upadacitinib is also approved for use in adolescents with AD.

Overall rates of MACE, malignancies (excluding NMSC) and VTE with upadacitinib were not increased relative to real-world background rates across indications. Upadacitinib is the only JAKi with long-term follow-up compared to adalimumab in head-to-head studies for RA and PsA. Available data do not suggest that the observed rates of MACE, malignancies (excluding NMSC), and VTE are increased as compared to adalimumab in up to 4.5 years of data.

Furthermore, in a sub-analysis of SELECT-COMPARE (RA patients 50 years and older with at least 1 CV risk factor) upadacitinib did not demonstrate an increased risk of MACE, malignancies (excluding NMSC) and VTE to adalimumab.

A literature search identified 3 studies of relevance for this application, but no study directly comparing upadacitinib and adalimumab or secukinumab in nr-axSpA. In an indirect treatment comparison none of the analyses showed any statistically significant difference for the outcomes used in previous evaluations in AS and nr-AxSpA by the Medicines Council (ASAS40, BASDAI50 or ASDAS>2.1) when upadacitinib was compared with adalimumab and secukinumab. Results from the analysis suggest that upadacitinib has the same clinical efficacy as adalimumab and secukinumab. The results from the comparative analysis on safety also gives similar outcomes for upadacitinib and the comparators and, the number of events are low for all treatments.

Upadacitinib and secukinumab trials included approximately 30% and 10% respectively of patients previously treated with b/tsDMARDs, a subgroup of patients that are relevant to this application considering current clinical practice. The clinical efficacy of secukinumab for patients previously treated with b/tsDMARDs is not known as no results from the clinical trial for this subset of patients has been published. In addition, both studies included a small number of b/tsDMARD experienced patients and were thus not powered to detect any statistically significant differences of the treatment efficacy versus placebo. Therefore, the indirect treatment comparison was carried out for the full study populations only

The clinical efficacy of the treatment options that are currently available for patients previously treated with b/tsDMARDs is not known. Based on the evidence submitted in this application, upadacitinib has similar efficacy as secukinumab based on an indirect treatment comparison between two studies that includes both b/tsDMARD naïve and b/tsDMARD experienced patients. As mentioned before, as the proportion of previously treated patients in the SELECT-AXIS 2 study is higher, this results in a conservative estimate of the relative efficacy of upadacitinib compared to secukinumab. Given the result of the indirect treatment comparison, where no differences in efficacy or safety for upadacitinib compared to adalimumab or secukinumab was found, the most appropriate model for the health economic analysis is a cost-minimization analysis. This analysis show that upadacitinib has incremental cost of 34 000 DKK over 18 months compared to adalimumab, and 38 000 DKK compared to secukinumab.

The budget impact of recommending upadacitinib was also analyzed, in the perspective of the regional hospital budgets. Based on the tender ranking available for PsO, upadacitinib is not expected to take market shares from adalimumab, but from certolizumab, golimumab, secukinumab and ixekizumab. Budget impact analysis show that recommendation of upadacitinib for use in Denmark would be cost saving for the regional hospitals. With an assumption of the market share to gradually increase to 5% of the patients in 5 years for patients initiating b/tsDMARD treatment, the total budget impact if upadacitinib is recommended is –204 403 DKK over 5 years

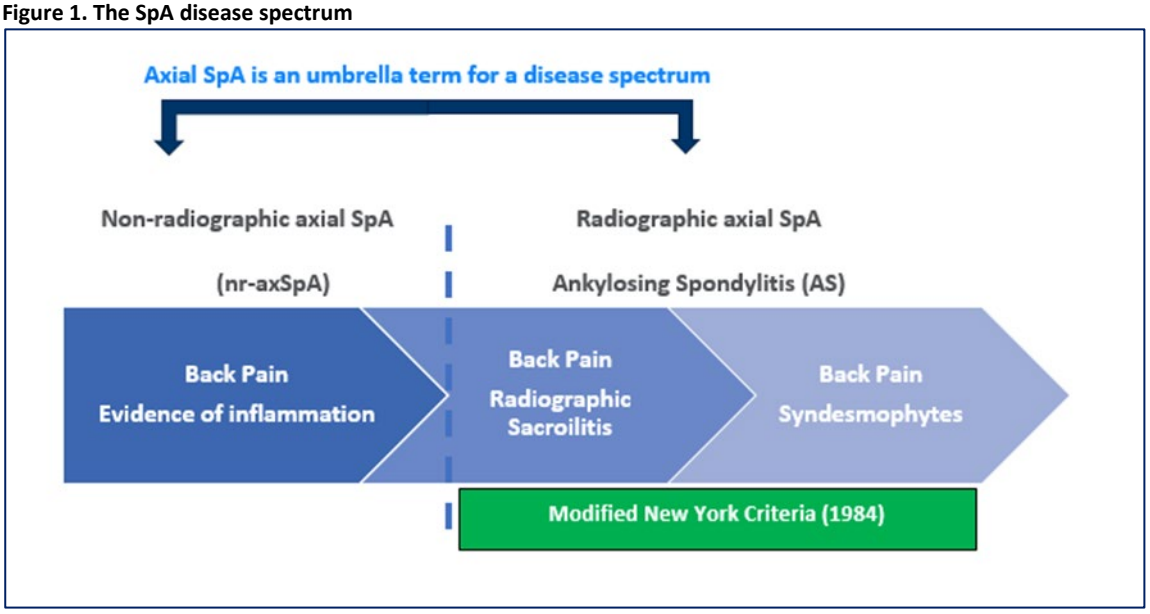
5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Spondyloarthritis (SpA) is a clinically heterogenous group of overlapping inflammatory rheumatic diseases with similar genetic and clinical features, that can occur simultaneously or sequentially in the patient. (1,2) Clinical characteristics that are common in the SpA subgroups include articular features, such as inflammatory axial and peripheral arthritis, dactylitis (inflammation in finger or toe) and enthesitis (inflammation where the tendons meet the bone), and extra-articular features such as uveitis (inflammation in the middle layer of the eye wall), psoriasis (inflammation of the skin), and inflammatory bowel disease (IBD). However, symptoms among SpA subgroups are variable, including psychological comorbidities such as symptom-driven depression and anxiety, as well as physical comorbidities such as osteoporosis.(3) The disease subgroups within SpA are classified based on the principal location of joint involvement – axial or peripheral.(4) Axial spondyloarthropathies predominantly affect the spine (axial) and sacroiliac joint (connects the two pelvic bones), and include non-radiographic axSpA (nr-axSpA) and radiographic axSpA. Radiographic axSpA is also known as ankylosing spondylitis(AS). (5)

Patients with nr-axSpA have not developed radiographically visible structural damage. (5,6) Thus, patients usually first experience nr-axSpA before later progressing to AS, se schematic presentation in Figure 1. The SpA disease spectrum. The proportion of patients who progress and the duration of progression can vary widely, however on average 12% of patients with nr-axSpA progress to AS over a 2-year period. (7)

Figure 1. The SpA disease spectrum



Source: Based on (8)*; Modified New York Criteria: the most widely used tool for the classification and diagnosis.*

In most patients with nr-AxSpA the first symptom is inflammatory back pain. However, this is not sufficient to diagnose the disease. (9) Physical examination to evaluate spinal and sacroiliac joint involvement is essential for initial diagnosis. These evaluations can be also used to identify disease activity, which is defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a Patient's Assessment of total back pain score ≥ 4 based on a 0 – 10 Numeric Rating Scale (NRS). For nr-axSpA, MRI is considered to be an integral tool to aid in early recognition of inflammation of the axial skeleton, since it can detect active inflammatory changes at the sacroiliac joints with or without structural damage. MRI scan of the SI joints is therefore vital for recognizing nr-AxSpA at the stage when X-ray of the SI joints looks normal. (9,10)

Both diseases within the axial SpA spectrum, nr-axSpA and AS, pose a similar burden in terms of disease activity, physical function and health related QoL impairment.(5) Physical impairment affects patients' ability to carry out daily activities, such as walking and working, which have direct negative effect on social participation, psychological wellbeing, and quality of life (QoL). (4,11) The early age of onset, typically in the patient's thirties, is a critical factor affecting QoL, as SpA manifests at a crucial age of educational, professional, and social development. (12) Axial SpA has a large negative impact on the patients' ability to work. Fifty percent of people with axial SpA experience work instability, and 15% reduce or change their work because of axial SpA. Both physical and psychosocial factors have an important role, such that loss of employment is associated with being older, longer disease duration, lower educational achievement, co-morbidity, greater physical impairment, pain, fatigue, stiffness, anxiety, depression and lower self-esteem. (12)

5.1.1 Patient population expected to use Rinvoq in Denmark

In the protocol for assessing the clinical added value of upadacitinib in AS published by the Medicines Council, the prevalence of AS in Denmark is estimated to 0,5 %. In DANBIO (Danish Rheumatologic Database), approximately 2 270 patients were registered as being treated with biological therapy for SpA by the end of 2019. Data extracts from DANBIO also showed that approximately 57% of patients have AS, resulting in 43 % (976 patients) with nr-axSpA being treated with b/tsDMARDs in Denmark. In addition 320 patients were registered as starting treatment per year, of

which 138 have nr-axSpA (13). Rinvoq is expected to be used as an alternative to the biological treatments already used in Danish clinical practice.

The estimated number of patients that will be treated with upadacitinib is expected to be low, as shown in Table 1. That estimation is based on the treatment recommendation in Denmark for similar indications, such as RA.(14) The majority of patients, both treatment naïve and treatment experienced (switch) patients are expected to be treated primarily with TNF-inhibitors, in line with the treatment recommendations.

Table 1. Estimated number of patients eligible for treatment with upadacitinib in Denmark

	2023	2024	2025	2026	2027
Number of nr-ax SpA patients treated with b/tsDMARDS in Denmark	976	1114	1252	1390	1528
Number of patients in Denmark who are expected to use the upadacitinib	10	23	38	49	69
Number of new b/tsDMARDS patients per year	138	138	138	138	138
Number of new b/tsDMARDS patients who are expected to use the upadacitinib	1	6	8	10	12

5.1.2 Patient populations relevant for this application

Upadacitinib is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

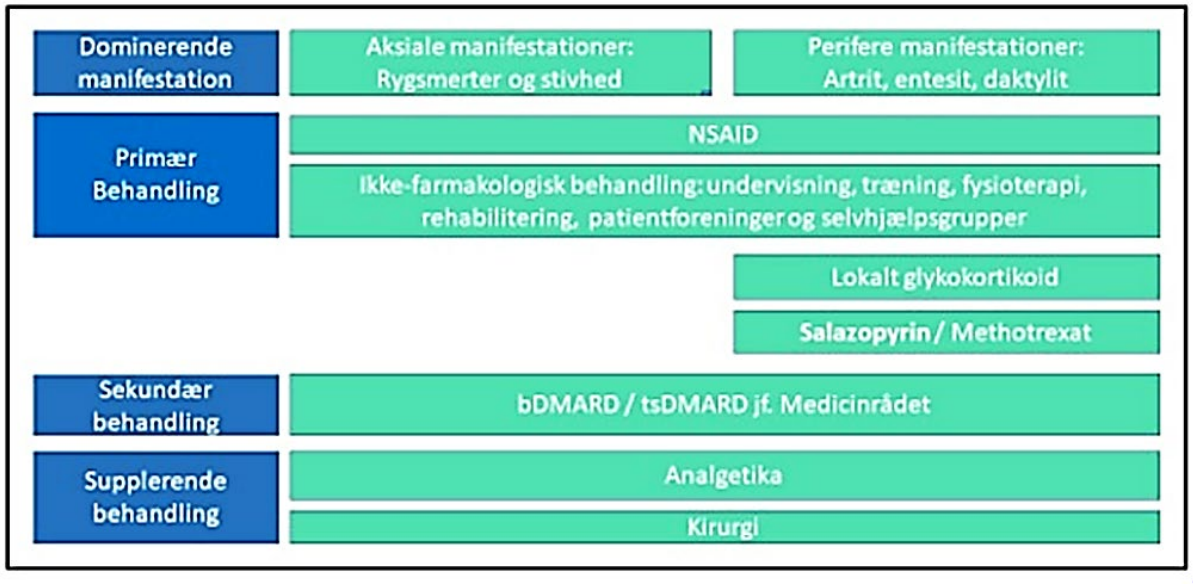
5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Nr-axSpA is a chronic condition with a variable disease course where patients must deal with a multitude of varying symptoms and widespread effects over the course of their disease. Treatment in nr-axSpA aims to optimize the long-term quality of life in patients through the control of their symptoms, and preventing further structural damage and toxicities, maintaining physical function, and minimizing any possible comorbidities. (15)

The Danish rheumatology association has published a treatment guideline (16), including the treatment algorithm shown in Figure 2.

Figure 2. Treatment algorithm for SpA (16)



The treatment algorithm includes primary treatment where patients receive non-pharmacological treatment such as training, physiotherapy and rehabilitation. Pain and stiffness are treated with traditional NSAID. For patients who despite the primary treatment have high disease activity, treatment with b/tsDMARDS can be initiated. High disease activity is defined as persistent (>4 weeks) Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥ 2.1 or Bath Ankylosing Spondylitis Disease Activity Index) BASDAI score ≥ 40. The decision to start biological treatment is based on a conference decision between specialists in rheumatology, where any contraindications and comorbidities are taken into account.

There is no current drug recommendation or treatment guideline from the Medicines Council for the use of biological treatment of nr-axSpA. In the previous drug recommendation, treatment with the TNF-inhibitor adalimumab was the primary choice for both treatment naïve patients and patients needing to switch treatment. Patients who does not respond to treatment with a TNF-inhibitor might benefit from switching mode of action, to an IL-17 inhibitor (ixekizumab and secukinumab). Patients with nr-axSpA have an increased risk of also having other inflammatory diseases.(17) At diagnosis, information about concurrent inflammatory bowel disease (IBD), uveitis and psoriasis should also be noted and will impact choice of treatment. For instance, IL-inhibitors are contraindicated for patients with IBD, which as described above is a common extra articular feature of nr-axSpA. (18,19) Nr-axSpA is a chronic disease with no cure, and patients are expected to need life-long treatment and there is a need for a variety of treatment options, including different modes of action.

The need for additional treatment options is described in EMA:s assessment report for upadacitinib in nr-axSpA (20):

Overall, available treatment options remain limited, particularly for nr-axSpA as compared to other rheumatic diseases such as RA or PsA. In axSpA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and long-term corticosteroids are not efficacious and therefore not recommended for treatment of axial symptoms. Once patients have an inadequate response to NSAIDs, and more advanced systemic therapies are required, available biologics are all administered either subcutaneous (SQ) or intravenous. To date, there have been no oral targeted therapies approved for the treatment of nr axSpA.

5.2.2 Choice of comparator(s)

Rinvoq is indicated for the treatment of patients with active non-radiographic axial spondylitis who have responded inadequately to NSAIDs. Patients in Danish clinical practice who have high disease activity despite being treated with NSAID are treated with either an TNF-inhibitor or a IL-17 inhibitor. Adalimumab has until recently been recommended by the Medicines Council as the first choice of TNF-inhibitor in the treatment of nr-axSpA. (21) Both ixekizumab and secukinumab has recently been approved by the Medicines Council for nr-axSpA, (22). As for upadacitinib, the clinical studies of secukinumab include patients previously treated with b/tsDMARDs, which is a relevant population in the Danish clinical setting. Upadacitinib will therefore be compared to adalimumab and secukinumab in this application. Please note that although b/tsDMARD experienced patients are included in the clinical studies for secukinumab, no data for this population has been published and the clinical efficacy of secukinumab in b/tsDMARD experienced patients is not known. Both adalimumab and secukinumab will therefore be analyzed as comparators for the full nr-axSpA population, regardless of previous treatment.

Rinvoq (15 mg daily) will be compared to:

- Adalimumab (40 mg subcutaneously every other week)
- Secukinumab (150 mg week 0, 1 ,2 , 3 and 4, followed by 150 mg monthly)

5.2.3 Description of the comparator(s)

Information about the comparators is summarized in table below. Adalimumab and secukinumab are both administered as subcutaneous injections. After training by a medical professional, patients usually administer the drugs at home.

Treatment efficacy should be evaluated after 3-4 months, according to the Danish Rheumatologists Associations treatment guideline for axial SpA (16). In the RADS guideline 2017, the patients should be monitored after 3, 6 and 12 months.(23)

Generic name(s) (ATC-code)	Adalimumab (LO4AB04)	Secukinumab (L04AC10)
Mode of action	TNF-inhibitor	IL-17-inhibitor
Pharmaceutical form	Solution for injection	Solution for injection
Method of administration	Subcutaneus (s.c.) injection	Subcutaneus (s.c.) injection
Dosing	40 mg every other week	150 mg week 0, 1 ,2 , 3 and 4, followed by 150 mg monthly
Should the pharmaceutical be administered with other medicines?	No	No
Treatment duration/criteria for end of treatment	Until loss of either efficacy or tolerability Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.	Until loss of either efficacy or tolerability Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks
Necessary monitoring, both during administration and during the treatment period	No	No
Need for diagnostics or other tests (i.e. companion diagnostics)	MRI-scanning CRP	MRI-scanning CRP
Packaging	Humira, 1 x 40 mg, pre-filled pen	Cosentyx, 2 x 150 mg, pre-filled pen

5.3 The intervention

Generic name(s) (ATC-code)	Upadacitinib (L0AA44)
Mode of action	Reversible Janus kinase (JAK) inhibitor
Pharmaceutical form	Depot tablet
Posology	15 mg
Method of administration	Per oral administration
Dosing	15 mg daily
Should the pharmaceutical be administered with other medicines?	No
Treatment duration/criteria for end of treatment	Until loss of either efficacy or tolerability. Consideration should be given to discontinuing treatment in patients who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.
Necessary monitoring, both during administration and during the treatment period	Laboratory monitoring for Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC), Hemoglobin (Hb), Hepatic transaminases and Lipids. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib Patients should be monitored for the development of signs and symptoms of TB (tuberculosis), including patients who tested negative for latent TB infection prior to initiating therapy. Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with upadacitinib.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Packaging	28 tablets

Upadacitinib is expected to be a treatment alternative to b/tsDMARDs. Nr-ax SpA is a chronic disease with no cure, and patients are expected to need lifelong treatment, including therapy switches due to lack or loss of efficacy and/or adverse events. Upadacitinib offers an additional mode of action and route of administration to already approved TNF inhibitors and IL- inhibitors, but is not expected to change the treatment algorithm.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

To identify clinical trials investigating the clinical efficacy and safety of upadacitinib, adalimumab or secukinumab in adult patients with non-radiographic ankylosing spondylitis a literature search was performed in Medline and Central. The search strategy used the PICOs in Table 2.

Table 2. PICOS for systemic literature search.

Criteria	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with nr-AxSpA, NSAID-IR and either b/tsDMARD-naïve or b/tsDMARD-IR Mixed populations of adult NSAID-IR, b/tsDMARD-naïve and -b/tsDMARD-IR nr-AxSpA patients	Children (<18 years) Mixed populations (e.g., adults and children) if data for target population are not reported separately Patients with AS only
Intervention	Upadacitinib, adalimumab, or secukinumab.	Other active comparators
Comparators	PBO Active intervention (i.e., head-to-head trials) including adalimumab and secukinumab.	No comparator (i.e., single-arm trials) Non-pharmacologic therapies (e.g., physiotherapy) Conventional management strategies with or without PBO and/or background medication.
Outcomes	Efficacy outcomes (ASAS40 and BASDAI 50, safety outcomes and HRQoL) at Week 12 to 16	
Study design	RCTs (phases 3+) Randomized crossover/cluster trials, provided randomized phase is at least 12 weeks Head-to-head comparisons	RCTs (phase 1 and 2). Long-term follow-up studies with maintained randomization (e.g., open-label follow-up studies with continuation of treatment in randomized treatment arms) Single-arm trials Open-label trials

Table 1

After duplicates had been removed, 56 titles and abstracts were screened for eligibility, and 7 articles were assessed in full -text. 4 articles were excluded, see Table 3 in Appendix A, primarily due to the reported outcomes not identified in the PICOS. The three publications included in this assessment are presented in Table 3.

6.2 List of relevant studies

Table 3. Relevant studies included in the assessment

Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of:	Reference
ABILITY-1	NCT00939003	July, 2009 – August, 2013	Upadacitinib vs. adalimumab	(24)
PREVENT	NCT02696031	April, 2016 – March, 2021	Upadacitinib vs. secukinumab	(25)
SELECT-AXIS 2	NCT04169373	November, 2019 – May, 2025	Upadacitinib vs. adalimumab, and secukinumab	(26)

For detailed information about included studies, please refer to Appendix B.

7. Efficacy and safety

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

7.1.1 Relevant studies.

The relevant studies are described shortly below. For detailed study characteristics please refer to Appendix B. For baseline characteristics of patients included in each study please refer to Appendix C.

SELECT-AXIS 2 (26)

SELECT-AXIS 2 is a randomized, placebo-controlled, double-blind, multicenter phase III trial that includes 2 independent studies for subjects with active axSpA including b/tsDMARD-IR AS (Study 1) and nr-axSpA (Study 2). Study 2 (nr-axSpA), which is relevant for this application, is comprised of a 35-day screening period; a 52-week randomized, double-blind, parallel-group, placebo-controlled period, followed by a 52 week open-label, long-term extension period. Subjects were randomized in a 1:1 ratio to upadacitinib 15 mg once daily (QD) (N = 156) or placebo QD (N = 157). Subjects in the placebo group were switched to upadacitinib 15 mg QD at Week 52 in the open-label extension period. The study design is presented in Figure 3.

Figure 3. Study design of Study 2 (nr-axSpA) in SELECT-AXIS 2

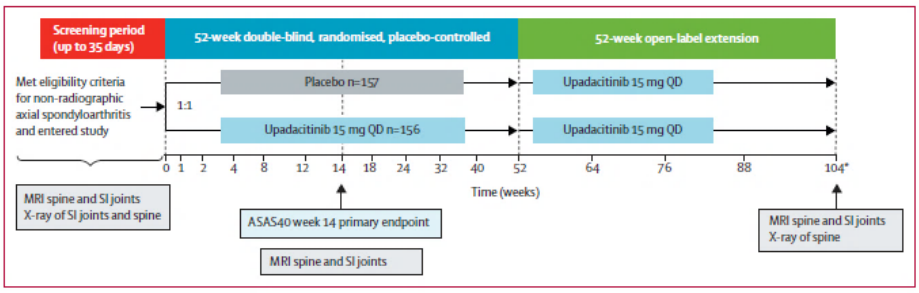


Figure 1: **SELECT-AXIS 2 non-radiographic axial spondyloarthritis study design**
ASAS40=Assessment of SpondyloArthritis international Society 40 response. QD=once daily. SI=sacroiliac. *Patients in remission at week 104 could enter a remission-withdrawal period until flare or week 152.

SELECT-AXIS 2 included patients with a clinical diagnosis of nr-axSpA fulfilling the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS. Patients also had to have:

- **Objective signs of active inflammation (OSI)** consistent with axSpA on magnetic resonance imaging (MRI) of sacroiliac (SI) joints or based on high sensitivity C-reactive protein (hsCRP) > the upper limit of normal (ULN).
- **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4** at the Screening and Baseline Visits.
- **Total Back Pain score ≥ 4** based on a 0 - 10 numerical rating scale at the Screening and Baseline Visits.
- **An inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs)** over an at least 4-week period in total at maximum recommended or tolerated doses, or has an intolerance to or contraindication for NSAIDs as defined by the Investigator.

Prior treatment with at most one b/tsDMARD (either TNF inhibitor or IL-17i) was allowed for at least 20% but no more than 35% of enrolled patients who had to discontinue the prior b/tsDMARD due to either lack of efficacy (after ≥ 12 weeks at an adequate dose) or intolerance (regardless of treatment duration). Prior b/tsDMARD therapy was washed out before study start. Stable doses of background medications could be continued, including conventional synthetic DMARDs, oral corticosteroids, and NSAIDs.

The primary endpoint of the study is ASAS40 response at week 14. Secondary outcome measures include BASDAI 50, ASDAS<2.1, Patient's Assessment of Total Back Pain; Patient's Assessment of Nocturnal Back Pain, and ASQoL.

ABILITY-1

ABILITY-1 is a randomized placebo-controlled double blind phase III trial, evaluating the efficacy and safety of 40 mg adalimumab given subcutaneously every other week. Patients were randomized to receive either adalimumab (N= 91) or matching placebo (N=94) for 12 weeks during the double blind period. After finishing the double-blind period patients were eligible to receive open-label adalimumab for up to an additional 144 weeks.

ABILITY-1 included patients ≥18 years of age and fulfilled ASAS classification criteria for axial SpA without meeting modified New York criteria for AS. Patients also had to have:

- **Active disease, exhibited by a total back pain score of ≥4** on a 0–10 cm visual analogue scale (VAS) (≥40 on a 0–100 mm VAS)
- **Magnetic resonance imaging (MRI) indicating active sacroiliitis or positive human leukocyte antigen-B27 (HLA-B27)** blood test in addition to meeting spondyloarthritis clinical criteria.
- **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4.**
- They must also have **responded inadequately or been intolerant to one or more NSAIDs, or had a contraindication to NSAIDs** based on the clinical judgment of the investigator.

Patients could enter the study on concomitant NSAIDs (prednisone, methotrexate, sulfasalazine and/or hydroxychloroquine or azathioprine), but not concomitant with any other DMARD if the doses met pre-specified stability requirements prior to randomization and remained stable during the first 24 weeks of the study. Prior TNF-inhibitor therapy was not allowed.

The primary efficacy endpoint was the proportion of patients who achieved an ASAS40 response at week 12. Secondary outcome measures include ASAS20, BASDAI 50, ASAS partial remission, SF-36, and HAQ-S.

Comparison between SELECT-AXIS 2 and ABILITY-1

SELECT-AXIS 2 and ABILITY-1 have very similar study design as multicenter, double-blind, placebo- controlled phase 3 studies. The length of the double blind periods differ as in ABILITY-1 patients in the placebo group were switched to active treatment after 12 weeks, and followed in the 144 open label phase. SELECT-AXIS 2 had a 52-week double blind phase, followed by 52 weeks open label. Since data from 12 weeks is available from SELECT-AXIS 2, comparison between treatments will be done with data from the same timepoints.

A summary of the baseline patient characteristics is available in Appendix C. Though similar, there are difference between the studies regarding the included patients. A proportion of patients in the SELECT-AXIS 2 trial are b/tsDMARD experienced, which is not the case in ABILITY-1 as this study was the first RCT of a TNF-inhibitor for nr-AxSpa. As b/tsDMARD-naïve patients are expected to have a better response to treatment, including the full study population from SELECT-AXIS 2 will likely result in a conservative estimate of the incremental treatment efficacy. While patients objective signs of inflammation (OSI) was an inclusion criteria in SELECT-AXIS 2, ABILITY-1 includes a mix of patients with or without OSI. Data for the patient population with OSI is available from ABILITY-1, and will be used in the comparative analysis as the approved indication for upadacitinib is for patients with OSI.

7.1.2 Efficacy and safety – results per study

The primary endpoint in all studies included in this application is the proportion of patients who achieve ASAS40 response. In addition to ASAS40, previous evaluations by the Medicines council for treatments for nr-axSpA has included efficacy comparisons based on the outcomes BASDAI 50 and ASDAS Low Disease Activity (LDA) defined as ASDAS<2.1. Data for these three endpoints will be presented.

Health related quality of life was measured with Ankylosing Spondylitis Quality of Life (ASQoL) in the SELECT-AXIS 2 trial, and with HAQ-S and SF-36 in the ABILITY-1 trial. Data for these endpoints will be presented.

SELECT-AXIS 2 (study 2)

All efficacy analysis presented are conducted in the full analysis set (FAS), which comprises all randomized patients who received at least one dose of study treatment.

Disease activity (ASAS40, BASDAI50 and ASDAS<2.1)
SELECT-AXIS 2 met the primary endpoint of the study, as 45 % of patients treated with upadacitinib compared with 23% in the placebo group reported ASAS40 at week 14, a difference of 22% (95% CI 12%–32%; p<0,0001). A higher proportion of patients in the upadacitinib group had ASAS40 compared with the placebo group from week 2 onwards.

42 % of the patients treated with upadacitinib reached BASDAI 50, compared with 22 % of the patients treated with placebo, a difference of 20% (95% CI 10 %–30 %; p<0,0001). Similarly, a statistically significant higher proportion of patients treated with upadacitinib also achieved ASDAS Low disease activity (ASDAS>2.1), 42% compared to 18% in the placebo group, a difference of 24% (95% CI 14 %–33 %; p<0,0001).
As mentioned in the comparison between the studies, ABILITY-1 has efficacy at 12 weeks as primary endpoint. Data from the same timepoint is available from SELECT-AXIS 2 as well, and will be used in the indirect treatment comparison in order to get the comparison done with as similar data as possible. The proportion of patients reaching ASAS40 at 12 weeks was 46% and 23% for upadacitinib and placebo respectively, a difference of 23% (95% CI 13%–33). 41% in the upadacitinib group reached BASDAI50, compared with 19% in the placebo group, a difference of 22% (95% CI 12%–32%). ASDAS>2.1 was not reported in the ABILITY-1 study, and therefore no data on ASDAS>2.1 for upadacitinib at 12 weeks is included in the analysis.

Disease activity (ASAS40, BASDAI50 and ASDAS<2.1) – subgroup analysis for b/tsDMARD experienced patients
About a third of the patients in the SELECT-AXIS 2 trial had previously been treated with a b/tsDMARD, 49 of 156 patients in the upadacitinib group and 54 of 157 patients in the placebo group. A subgroup-analysis for these patients has been carried out.

33% of patients treated with upadacitinib compared with 24% in the placebo group reported ASAS40 at week 14, a difference of 9% (95% CI -8,4 - 25,7) (26). Similar results were seen for BASDAI 50; 33 % of the patients treated with upadacitinib reached BASDAI 50, compared with 24 % of the patients treated with placebo, a difference of 8,3 % (95% CI -9,2%; 24,8%). For ASDAS Low disease activity (ASDAS>2.1) 31% in the upadacitinib group compared to 17% in the placebo group, a difference of 14% (95% CI -2,1 – 29,4 %) (Abbvie, Confidential data on file)

These results should be interpreted with caution, bearing in mind that the study was planned for a full analysis set of at least 304 patients, randomized 1:1, to achieve at least 90% power for the ASAS40 response rate of upadacitinib versus placebo (26), and power calculations show that the study was underpowered to detect any statistically significant differences between upadacitinib and placebo in the b/tsDMARD subgroup of patients.

AbbVie has conducted a properly powered study in b/tsDMARD experienced AS patients, SELECT-AXIS 2 (Study 1). While not the same indication, these results support the claim that upadicitinib is effective after b/tsDMARD exposure in a similar group of patients. Upadacitinib 15 mg was compared with placebo in b/tsDMARD experienced patients with AS in the SELECT-AXIS 2 (Study 1), mentioned above, with a planned sample size of at least 386 b/tsDMARD experienced patients to provide ≥90% power for testing the superiority of upadacitinib to placebo for the primary endpoint of ASAS40 at week 14.(27) In that study, upadacitinib demonstrated statistically significant better results compared to placebo for ASAS40 (45% vs 18%; p<0.0001), BASDAI50 (43% vs 17%; p<0.0001), and ASDAS>2.1 (44% vs 10% p<0.0001), for patients with AS refractory to biological therapy (27).

In patients **not** previously treated with biological treatments, upadicitinib has shown similar results in AS and nr-AxSpA. For example the absolute response rates for ASAS40 for upadicitinib when compared to placebo was 22% (95% CI 12%–32%) in nr-axSpA in the SELECT-AXIS 2 trial, and 26% (95% CI 13% - 40%) in AS in the SELECT-AXIS 1 trial. (26,27) Considering that these two indications are part of the same disease spectrum, it is a reasonable assumption that the response rates are similar also for the b/tsDMARD experienced population.

Health related Quality of Life

Health related Quality of life was measured with the tool ASQoL in SELECT-AXIS 2. Patients treated with upadacitinib demonstrated a statistically significant improvement of health related quality of life compared with placebo (-5,38 versus -3,15; a difference of -2,23 (95% CI: -3,26; -1,21).

Safety

An overview of treatment-emergent adverse events reported during the double blind period of the SELECT AXIS 2 trial are presented in Table 4. In addition, a total of 7 of 157 (4,4%) in the placebo group and 11 of 156 (7,0%) in the upadacitinib discontinued the study during the double blind period. (26) Overall, upadacitinib was well tolerated. The study was conducted during the COVID-19 pandemic. The rates of treatment- emergent adverse events, including serious and COVID-19-related events, were similar between treatment groups

Table 4. Safety outcomes up to week 14 reported in the SELECT AXIS 2 trial.

	Placebo group (n=157)		Upadacitinib group (n=156)	
Any adverse event	72	45,9%	75	48,1%
Serious adverse events	2	1,3%	4	2,6%
Discontinuation of study drug due to adverse event	2	1,3%	4	2,6%
COVID-19-related adverse event	10	6,4%	8	5,1%
Death	0	0,0%	0	0,0%
Infection	36	22,9%	36	23,1%
Serious infection	1	0,6%	2	1,3%
Opportunistic infection	0	0,0%	0	0,0%
Active tuberculosis	0	0,0%	0	0,0%
Herpes zoster	1	0,6%	2	1,3%
Malignancy	1	0,6%	0	0,0%
Malignancy other than NMSC	0	0,0%	0	0,0%
Non-melanoma skin cancer	1	0,6%	0	0,0%
Lymphoma	0	0,0%	0	0,0%
Hepatic disorder	5	3,2%	4	2,6%
Anaemia	0	0,0%	1	0,6%
Neutropenia	0	0,0%	5	3,2%
Lymphopenia	0	0,0%	0	0,0%
Renal dysfunction	0	0,0%	0	0,0%
Gastrointestinal perforation (adjudicated)	0	0,0%	0	0,0%
Major adverse cardiovascular events (adjudicated)	0	0,0%	0	0,0%
Venous thromboembolic events (adjudicated)	0	0,0%	0	0,0%
Uveitis	0	0,0%	1	0,6%
Inflammatory bowel disease	0	0,0%	0	0,0%
Psoriasis	0	0,0%	0	0,0%

Upadacitinib is approved for several other indications, and thus the total safety population is considerably larger than the population from SELECT-AXIS 2 alone. In accordance with section 4.2 in the Medicines Council's guideline, data from the full safety population is therefore included -based on the SmPC.

According to the SmPC the most commonly reported adverse reactions (≥2% of patients in at least one of the indications with the highest rate among indications presented) with upadacitinib 15 mg in the placebo-controlled clinical trials for rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, were upper respiratory tract infections (19.5%), blood creatine phosphokinase (CPK) increased (8.6%), alanine transaminase increased (4.3%), bronchitis (3.9%), nausea (3.5%), neutropaenia (2.8%), cough (2.2%), aspartate transaminase increased (2.2%), and hypercholesterolaemia (2.2%). The safety profile of upadacitinib with long-term treatment was generally similar to the safety profile during the placebo-controlled period across indications.(28)

The most common serious adverse reactions for patients treated with upadacitinib are serious infections. The most frequent serious infection included pneumonia and cellulitis. Cases of bacterial meningitis have been reported in patients receiving upadacitinib. Among opportunistic infections, tuberculosis, herpes zoster, oral/oesophageal

candidiasis, and cryptococcosis were reported with upadacitinib. Upadacitinib should not be initiated in patients with an active, serious infection, including localized infection, and should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib.(28)

All JAK -inhibitors, including upadacitinib, has been part of a safety review by EMA, following safety signals for the JAK-inhibitor tofacitinib. EMA has issued the following recommendations:

JAK-inhibitors should be used in the following patients only if no suitable treatment alternatives are available:

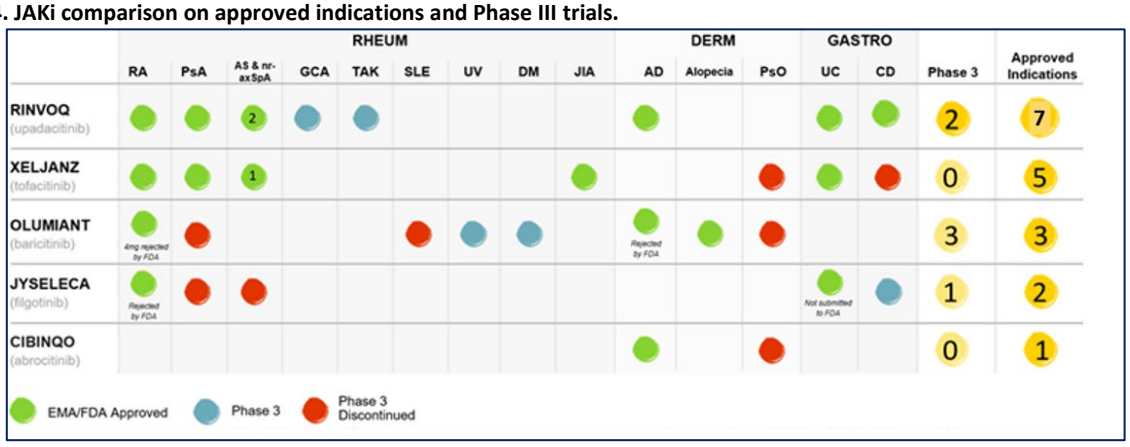
- those aged 65 years or above
- those at increased risk of major cardiovascular problems (such as heart attack or stroke)
- those who smoke or have done so for a long time in the past and those at increased risk of cancer.

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

Given the interest around benefit/risk of JAK inhibitors it is important to acknowledge that not all JAKi are the same and given the differences in pharmacology, each JAKi should be assessed based on its individual clinical profile. Upadacitinib has a unique chemical structure leading to preferential inhibition of JAK1 or JAK1/3 and differing metabolic and elimination profiles as compared to other JAKi.

Upadacitinib is approved in more indications than any other JAKi (Figure 4), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondylarthritis (nr-axSpA), atopic dermatitis (AD), ulcerative colitis (UC), and Crohn's Disease(CD). These diagnoses are all chronic conditions with long-term and disabling disease manifestations, and despite the availability of innovative therapies, many patients fail to achieve remission and sustain disease control. Upadacitinib is under evaluation for additional approvals in immunological diseases; unlike other JAKis, upadacitinib has never failed a clinical trial and has all its indications and dosages approved by both EMA and FDA.

Figure 4. JAKi comparison on approved indications and Phase III trials.



Upadacitinib's safety profile is broadly studied across 19 Phase III clinical trials with over 10,500 upadacitinib patients and over 23,000 PY of exposure across rheumatology, dermatology, and gastroenterology. The safety profile is generally consistent across different patient types studied in all approved indications with three different dosing strengths (15mg, 30mg, and 45mg). Upadacitinib is also approved for use in adolescents with AD.

Overall rates of MACE, malignancies (excluding NMSC) and VTE with upadacitinib were not increased relative to real-world background rates across indications (29). Upadacitinib is the only JAKi with long-term follow-up compared to adalimumab in head-to-head studies for RA and PsA. Available data do not suggest that the observed rates of MACE, malignancies (excluding NMSC), and VTE are increased as compared to adalimumab in up to 4.5 years of data. Furthermore, in a sub-analysis of SELECT-COMPARE (RA patients 50 years and older with at least 1 CV risk factor)

upadacitinib did not demonstrate an increased risk of MACE, malignancies (excluding NMSC) and VTE to adalimumab.(30)

ABILITY-1

Efficacy outcomes were analyzed for the full analysis set (FAS) consisting of all randomized patients receiving at least one dose of study medication. Seven patients (tree placebo, four adalimumab) from one site were excluded from analysis of efficacy outcomes due to investigator non-compliance, but they are included in the safety analysis.

Disease activity (ASAS40, BASDAI50 and ASDAS<2.1)

A significantly greater proportion of patients treated with adalimumab achieved the primary endpoint of ASAS40 response at week 12 compared with patients treated with placebo (36% versus 15%, p<0.001). A greater proportion of patients treated with adalimumab also achieved BASDAI50 compared with patients treated with placebo (35 % versus 15 %, p<0.001). ASDAS>2.1 was not reported in the ABILITY-1 trial.

For the population in ABILITY-1 showing OSI, which were 69 (78%) of patients in the placebo group and 73 (76 %) of patients in the adalimumab group, the treatment difference is slightly higher in favor of adalimumab. 41 % of patients treated with adalimumab achieved ASAS 40 compared with 14 % of patients treated with placebo, a treatment difference of 27% (95% CI: 13% -41%, p=0,001). The proportion of patients with BASDAI 50 were 39% and 14 % for adalimumab and placebo respectively, a treatment difference of 25 % (95% CI: 11% -39%, p=0,002).

Health related Quality of Life

Health related Quality of Life was measured with the HAQ-S and SF-36 (physical component) in the ABILITY-1 trial. Adalimumab showed a numerically higher change from baseline for HAQ-S compared to placebo, -0,3 versus -0,1 (p=0,025), and for SF-36 the difference was also statistically significant 5,5 versus 2,0 (p=0,001).

Safety

An overview of adverse events in the double-blind period of the ABILITY-1 trial is shown in Table 5. Totally 2 of 94 (2,1%) patients compared to (4,4%) discontinued the study.

Table 5. Adverse events reported during the 12-week double blind period in ABILITY-1.

	Placebo (N=97), n (%)	Adalimumab (N=95), n (%)
Any AE	57 (58,8)	55 (57,9)
Serious AE	1 (1,0)	3 (3,2)
AE leading to discontinuation of study drug	1 (1,0)	2 (2,1)
Infectious AE	28 (28,9)	28 (29,5)
Serious infection	0	0
Malignancy	0	0
Hepatic-related AE	4 (4,1)	4 (4,2)

As for upadacitinib, the total safety population of adalimumab is much larger than the study population of the ABILITY-1 trial, as adalimumab has nine approved indications and safety data from the full safety population based on the SmPC will be presented for adalimumab.

The most commonly reported adverse reactions for adalimumab are infections such as nasopharyngitis, upper respiratory tract infection and sinusitis (1,51 per patient year), injection site reactions (12,9% of patients), headache and musculoskeletal pain.

Serious adverse reactions have been reported for adalimumab (0.04 per patient year). Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukemia, lymphoma and HSTCL) have also been reported with use of adalimumab. The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 8,5 per 1,000 patient years. The observed rate

of non-melanoma skin cancers is approximately 9,6 per 1,000 patient years, and the observed rate of lymphomas is approximately 1,3 per 1,000 patient years.

Treatment with adalimumab is contraindicated for patients with active tuberculosis, opportunistic infections and sepsis, and for patients with moderate to severe heart failure.

Treatment with adalimumab should not be initiated in patients with active infections including chronic or localized infections until infections are controlled, and patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation.

7.1.3 Comparative analyses of efficacy and safety

Comparative analyses of efficacy on disease activity

No direct comparison between upadacitinib and adalimumab was identified in the literature for the indication non-radiographic SpA. Therefore, an indirect treatment comparison has been carried out, comparing the efficacy of upadacitinib and adalimumab on disease activity.

Method of synthesis

The analysis includes studies identified in the literature search described above. The comparison is done with efficacy data from week 12, as this is the last timepoint where placebo-controlled data is available from all studies. All relevant data used in the analysis is presented in the tables in Appendix D.

Indirect treatment effect estimates and their 95% confidence intervals were produced by using the method described by Rücker (31), and Rücker and Schwarzer (32). When only indirect comparisons are envisioned (there is no closed loop in the evidence network), such as in our scenario, the method described by Rücker and Schwarzer correspond to the method of adjusted indirect comparison as described by Bucher.

Results from the comparative analysis

The results of the indirect treatment comparison is shown in Table 6, demonstrate no difference in treatment effect. The point estimates favor adalimumab but the confidence intervals overlap showing no difference in effect between adalimumab and upadacitinib.

Table 6. Results of indirect treatment comparison between adalimumab and upadacitinib

Endpoint	OR (95% CI)	RR (95% CI)
ASAS40	0,67 (0,26, 1,74)	0,68 (0,33, 1,40)
BASDAI50	0,73 (0,28, 1,92)	0,75 (0,36, 1,59)

Comparative analyses of efficacy on HRQoL

No common measurements of HRQoL was used in SELECT-AXIS 2 (reports on ASQoL) and ABILITY-1 (reports on HAQ-S and SF-36). No comparative analysis of HRQoL is possible to perform. Both upadacitinib and adalimumab demonstrates statistically significant differences from placebo.

Comparative analyses of safety

An overview of the safety outcomes reported for adalimumab and upadacitinib in ABILITY-1 and SELECT AXIS -2 is presented in the Table 7 and show low rates of adverse events not significantly different from placebo, for either of the drugs. The absolute difference for upadacitinib and adalimumab compared to placebo is similar.

Table 7. Comparison of safety outcomes in SELECT-AXIS 2 and ABILITY-1.

	Placebo (n=157)	Upadacitinib (n=156)	Relative difference (%-points, 95% CI)	Placebo (n=97)	Adalimumab (n=95)	Relative difference (%-points, 95% CI)
Any adverse event n (%)	72 (46 %)	75 (48%)	**2,2 (-8,8 - 13)**	57 (59%)	55 (58%)	**-0,9 (-15 - 13)**
Serious adverse events n (%)	2 (1%)	4 (3%)	**1,2 (-1,7 - 4,3)**	1 (1%)	3 (3%)	**2,1 (-1,9 - 6,2)**
Discontinuation due to adverse event n (%)	2 (1%)	4 (3%)	**1,2 (-1,7 - 4,3)**	1 (1%)	2 (2%)	**1,1 (-2,4 - 4,6)**
Serious infection n (%)	1 (0,6%)	2 (1,3 %)	**0,6 (-1,5 - 2,8)**	0 (0%)	0 (0%)	**0**

In addition to the outcomes from ABILITY-1 and SELECT-AXIS 2, there are differences in contraindications and warnings between upadacitinib andadalimumab . The safety of upadacitinib has recently been re-investigated by EMA, along with the whole JAKi-class of drugs. As a result of this investigation, treatment with upadacitinib is not recommended for patients at risk for VTE, cancer or major cardiovascular problems, if there are other treatment alternatives available. Upadacitinib is also contraindicated for patients with severe hepatic impairment. Adalimumab is contraindicated for patients with moderate to severe heart failure. Both treatments are contraindicated for patients with active tuberculosis. Neither treatment should be initiated in patients with active infections including chronic or localised infections until infections are controlled. Assuming these precautions are taken into account prior to starting treatment with either upadacitinib or adalimumab, there does not seem to be any major differences concerning safety between the two treatments

Upadacitinib is the only JAKi with long-term follow-up compared to adalimumab in head-to-head studies for RA and PsA. Available data do not suggest that the observed rates of MACE, malignancies (excluding NMSC), and VTE are increased as compared to adalimumab in up to 4.5 years of data. Furthermore, in a sub-analysis of SELECT-COMPARE (RA patients 50 years and older with at least 1 CV risk factor) upadacitinib did not demonstrate an increased risk of MACE, malignancies (excluding NMSC) and VTE to adalimumab.(30)

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

7.2.1 Relevant studies

SELECT-AXIS 2 (26)

SELECT-AXIS 2 is a randomized, placebo-controlled, double-blind, multicenter phase III trial that includes 2 independent studies for subjects with active axSpA including b/tsDMARD-IR AS (Study 1) and nr-axSpA (Study 2). Study 2 (nr-axSpA), which is relevant for this application, is comprised of a 35-day screening period; a 52-week randomized, double-blind, parallel-group, placebo-controlled period, followed by a 52 week open-label, long-term extension period. Subjects were randomized in a 1:1 ratio to upadacitinib 15 mg once daily (QD) (N = 156) or placebo QD (N = 157). Subjects in the placebo group were switched to upadacitinib 15 mg QD at Week 52 in the open-label extension period. The study design is presented in Figure 5 below.

Figure 5. Study design of the SELECT-AXIS 2 trial.

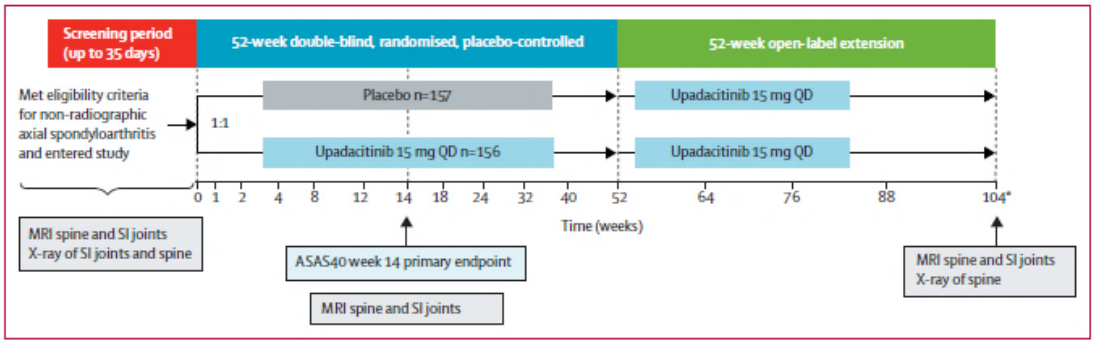


Figure 1: **SELECT-AXIS 2 non-radiographic axial spondyloarthritis study design**
ASAS40=Assessment of SpondyloArthritis international Society 40 response. QD=once daily. SI=sacroiliac. *Patients in remission at week 104 could enter a remission-withdrawal period until flare or week 152.

SELECT-AXIS 2 included patients with a clinical diagnosis of nr-axSpA fulfilling the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS. Patients also had to have:

- **Objective signs of active inflammation (OSI)** consistent with axSpA on magnetic resonance imaging (MRI) of sacroiliac (SI) joints or based on high sensitivity C-reactive protein (hsCRP) > the upper limit of normal (ULN).
- **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4** at the Screening and Baseline Visits.
- **Total Back Pain score ≥ 4** based on a 0 - 10 numerical rating scale at the Screening and Baseline Visits.
- **An inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs)** over an at least 4-week period in total at maximum recommended or tolerated doses, or has an intolerance to or contraindication for NSAIDs as defined by the Investigator.

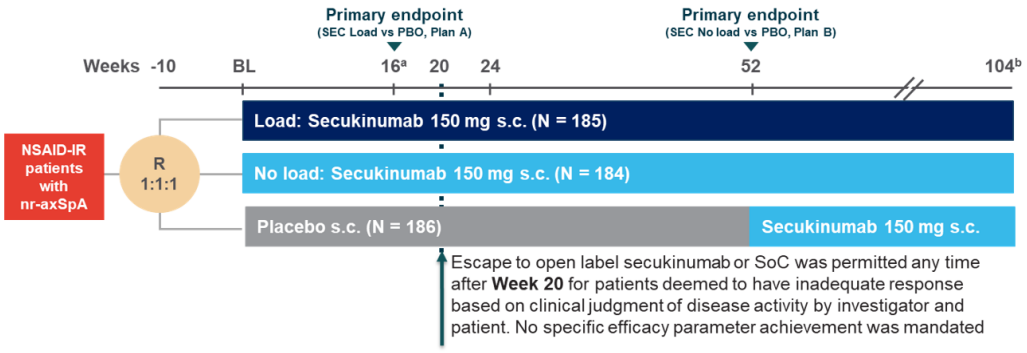
Prior treatment with at most one b/tsDMARD (either TNF inhibitor or IL-17i) was allowed for at least 20% but no more than 35% of enrolled patients who had to discontinue the prior b/tsDMARD due to either lack of efficacy (after ≥ 12 weeks at an adequate dose) or intolerance (regardless of treatment duration). Prior b/tsDMARD therapy was washed out before study start. Stable doses of background medications could be continued, including conventional synthetic DMARDs, oral corticosteroids, and NSAIDs.

The primary endpoint of the study is ASAS40 response at week 14. Secondary outcome measures include BASDAI 50, ASDAS<2.1, Patient's Assessment of Total Back Pain; Patient's Assessment of Nocturnal Back Pain, and ASQoL.

PREVENT (25)

PREVENT is a randomized, double-blind, placebo-controlled phase III study evaluating secukinumab in patients with non- radiographic axial SpA. Patients were randomised (1:1:1) to receive subcutaneous secukinumab 150 mg with a loading dose (150 mg loading dose [LD] group, N=185), 150 mg without a loading dose (150 mg non–loading dose [NL] group, N=184), or matching placebo (N=186) at baseline and weeks 1, 2, and 3, followed by every 4 weeks starting at week 4. At week 20, patients with inadequate response could switch to open label secukinumab 150 mg or standard of care. After 52 weeks, patients in the placebo group could switch to secukinumab 150 mg, and continue in the open label extension until 104 weeks. The study design is shown in Figure 1 below.

Figure 5. Study design of the PREVENT trial.



PREVENT included patients with a clinical diagnosis of non- radiographic axial SpA who were age ≥18 years meeting the ASAS classification criteria for axial SpA, but not radiographic evidence for sacroiliitis. Patients must also have:

- **Objective signs of inflammation** (MRI with SI joint inflammation and/or high-sensitivity CRP greater than the upper limit of normal.
- 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 ≥ 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 previously treated with a TNFi (no more than 1) could participate if they had an inadequate response or were intolerant, but not patients previously treated with an IL-inhibitor. Patients could continue to receive the following medications at a stable dose: sulfasalazine (≤3 gm/day), methotrexate (≤25 mg/week), corticosteroids (≤10 mg/day prednisone or equivalent), and NSAIDs

The primary outcome of the study was ASAS 40 at week 16 (plan A) for LD versus placebo, and a ASAS40 at week 52 (plan B) for NL versus placebo. Secondary objectives comprised week 16 end points (plan A) and a combination of week 16 and week 52 end points (plan B). These were assessed in the overall population and included ASAS40 response, BASDAI50 response, SF-36 physical component summary, and ASQoL.

Comparison between SELECT-AXIS 2 and PREVENT.

SELECT-AXIS-2 and PREVENT have similar study design as they are both multicenter, double-blind, placebo- controlled phase 3 studies. Both studies are placebo controlled for 52 weeks, followed by open label extension studies. PREVENT have three study arms, investigating secukinumab in with or without a loading-dose, versus placebo.

A description and comparison of the baseline patient characteristics is available in Appendix C. Though similar in many regards, there are differences between the studies regarding the included patients that could impact the outcome of an indirect comparison. A larger proportion of patients in the SELECT-AXIS 2 trial (31,41% and 34,39% in the two study arms) are b/tsDMARD experienced, compared to the patients in the PREVENT trial (8,06%, 11,35% and 9,78% in the

three treatment arms respectively). As b/tsDMARD-naïve patients are expected to have a better response to treatment, this will likely result in a conservative estimate of the incremental treatment efficacy when comparing upadacitinib and secukinumab in an indirect treatment comparison based on these two studies.

7.2.2 Efficacy and safety – results per study

SELECT-AXIS 2

All efficacy analysis presented are conducted in the full analysis set (FAS), which comprises all randomized patients who received at least one dose of study treatment.

Disease activity (ASAS40, BASDAI50 and ASDAS<2.1)

SELECT-AXIS 2 met the primary endpoint of the study, as 45 % of patients treated with upadacitinib compared with 23% in the placebo group reported ASAS40 at week 14, a difference of 22% (95% CI 12%–32%; p<0,0001). A higher proportion of patients in the upadacitinib group had ASAS40 compared with the placebo group from week 2 onwards.

42 % of the patients treated with upadacitinib reached BASDAI 50, compared with 22 % of the patients treated with placebo, a difference of 20% (95% CI 10 %–30 %; p<0,0001). Similarly, a statistically significant higher proportion of patients treated with upadacitinib also achieved ASDAS Low disease activity (ASDAS>2.1), 42% compared to 18% in the placebo group, a difference of 24% (95% CI 14 %–33 %; p<0,0001).

Disease activity (ASAS40, BASDAI50 and ASDAS<2.1) – subgroup analysis for b/tsDMARD experienced patients

About a third of the patients in the SELECT-AXIS 2 trial had previously been treated with a b/tsDMARD, 49 of 156 patients in the upadacitinib group and 54 of 157 patients in the placebo group. A subgroup-analysis for these patients has been carried out.

33% of patients treated with upadacitinib compared with 24% in the placebo group reported ASAS40 at week 14, a difference of 9% (95% CI -8,4 - 25,7) (26). Similar results were seen for BASDAI 50; 33 % of the patients treated with upadacitinib reached BASDAI 50, compared with 24 % of the patients treated with placebo, a difference of 8,3 % (95% CI -9,2%; 24,8%). For ASDAS Low disease activity (ASDAS>2.1) 31% in the upadacitinib group compared to 17% in the placebo group, a difference of 14% (95% CI -2,1 – 29,4 %). (Abbvie, Data on file)

These results should be interpreted with caution, bearing in mind that the study was planned for a full analysis set of at least 304 patients, randomized 1:1, to achieve at least 90% power for the ASAS40 response rate of upadacitinib versus placebo (26), and power calculations show that the study was underpowered to detect any statistically significant differences between upadacitinib and placebo in the b/tsDMARD subgroup of patients.

AbbVie has conducted a properly powered study in b/tsDMARD experienced AS patients, SELECT-AXIS 2 (Study 1). While not the same indication, these results support the claim that upadicitinib is effective after b/tsDMARD exposure in a similar group of patients. Upadacitinib 15 mg was compared with placebo in b/tsDMARD experienced patients with AS in the SELECT-AXIS 2 (Study 1), mentioned above, with a planned sample size of at least 386 b/tsDMARD experienced patients to provide ≥90% power for testing the superiority of upadacitinib to placebo for the primary endpoint of ASAS40 at week 14.(27) In that study, upadacitinib demonstrated statistically significant better results compared to placebo for ASAS40 (45% vs 18%; p<0.0001), BASDAI50 (43% vs 17%; p<0.0001), and ASDAS>2.1 (44% vs 10% p<0.0001), for patients with AS refractory to biological therapy (27).

In patients **not** previously treated with biological treatments, upadicitinib has shown similar results in AS and nr-AxSpA. For example the absolute response rates for ASAS40 for upadicitinib when compared to placebo was 22% (95% CI 12%–32%) in nr-axSpA in the SELECT-AXIS 2 trial, and 26% (95% CI 13% - 40%) in AS in the SELECT-AXIS 1 trial. (26,27) Considering that these two indications are part of the same disease spectrum, it is a reasonable assumption that the response rates are similar also for the b/tsDMARD experienced population.

Health related Quality of Life

Health related Quality of life was measured with the tool ASQoL in SELECT AXIS 2. Patients treated with upadacitinib demonstrated a statistically significant improvement of health related quality of life compared with placebo (-5,38 versus -3,15; a difference of -2,23 (95% CI: -3,26; -1,21).

Safety

An overview of treatment-emergent adverse events reported during the double blind period of the SELECT AXIS 2 trial are presented in . In addition, a total of 7 of 157 (4,4%) in the placebo group and 11 of 156 (7,0%) in the upadacitinib discontinued the study during the double blind period. (26) Overall, upadacitinib was well tolerated. The study was conducted during the COVID-19 pandemic. The rates of treatment- emergent adverse events, including serious and COVID-19-related events, were similar between treatment groups.

Table 8. Safety outcomes up to week 14 reported in the SELECT AXIS 2 trial.

	Placebo group (n=157)		Upadacitinib group (n=156)	
Any adverse event	72	45,9%	75	48,1%
Serious adverse events	2	1,3%	4	2,6%
Discontinuation of study drug due to adverse event	2	1,3%	4	2,6%
COVID-19-related adverse event	10	6,4%	8	5,1%
Death	0	0,0%	0	0,0%
Infection	36	22,9%	36	23,1%
Serious infection	1	0,6%	2	1,3%
Opportunistic infection	0	0,0%	0	0,0%
Active tuberculosis	0	0,0%	0	0,0%
Herpes zoster	1	0,6%	2	1,3%
Malignancy	1	0,6%	0	0,0%
Malignancy other than NMSC	0	0,0%	0	0,0%
Non-melanoma skin cancer	1	0,6%	0	0,0%
Lymphoma	0	0,0%	0	0,0%
Hepatic disorder	5	3,2%	4	2,6%
Anaemia	0	0,0%	1	0,6%
Neutropenia	0	0,0%	5	3,2%
Lymphopenia	0	0,0%	0	0,0%
Renal dysfunction	0	0,0%	0	0,0%
Gastrointestinal perforation (adjudicated)	0	0,0%	0	0,0%
Major adverse cardiovascular events (adjudicated)	0	0,0%	0	0,0%
Venous thromboembolic events (adjudicated)	0	0,0%	0	0,0%
Uveitis	0	0,0%	1	0,6%
Inflammatory bowel disease	0	0,0%	0	0,0%
Psoriasis	0	0,0%	0	0,0%

Upadacitinib is approved for several other indications, and thus the total safety population is considerably larger than the population from alone. In accordance with section 4.2 in the Medicines Council's guideline, data from the full safety population is therefore included -based on the SmPC.

According to the SmPC the most commonly reported adverse reactions (≥2% of patients in at least one of the indications with the highest rate among indications presented) with upadacitinib 15 mg in the placebo-controlled clinical trials for rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, were upper respiratory tract infections (19.5%), blood creatine phosphokinase (CPK) increased (8.6%), alanine transaminase increased (4.3%), bronchitis (3.9%), nausea (3.5%), neutropenia (2.8%), cough (2.2%), aspartate transaminase increased (2.2%), and hypercholesterolemia (2.2%). The safety profile of upadacitinib with long-term treatment was generally similar to the safety profile during the placebo-controlled period across indications(28).

The most common serious adverse reactions for patients treated with upadacitinib are serious infections. The most frequent serious infection included pneumonia and cellulitis. Cases of bacterial meningitis have been reported in patients receiving upadacitinib. Among opportunistic infections, tuberculosis, herpes zoster, oral/esophageal

candidiasis, and cryptococcosis were reported with upadacitinib. Upadacitinib should not be initiated in patients with an active, serious infection, including localized infection, and should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib.(28)

All JAK -inhibitors, including upadacitinib, has been part of a safety review by EMA, following safety signals for the JAK-inhibitor tofacitinib. EMA has issued the following recommendations:

JAK-inhibitors should be used in the following patients only if no suitable treatment alternatives are available:

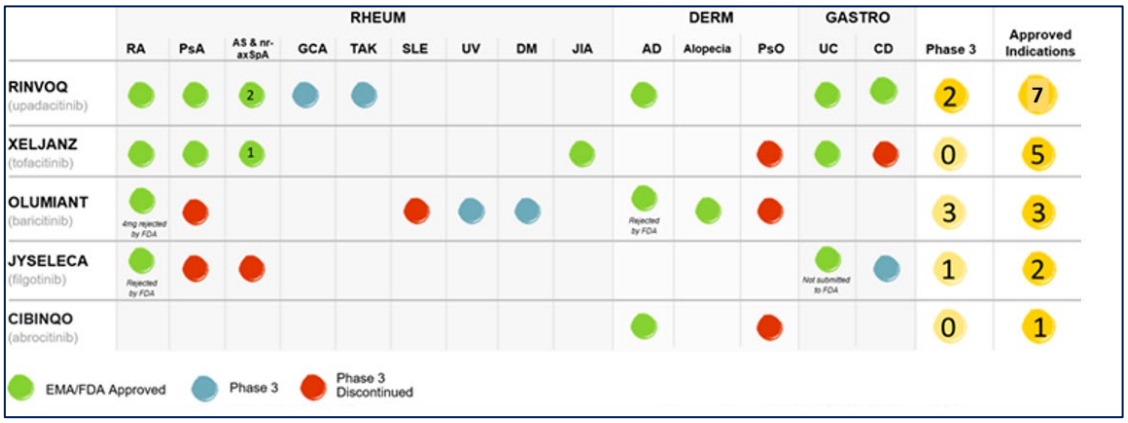
- those aged 65 years or above
- those at increased risk of major cardiovascular problems (such as heart attack or stroke)
- those who smoke or have done so for a long time in the past and those at increased risk of cancer.

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

Given the interest around benefit/risk of JAK inhibitors it is important to acknowledge that not all JAKi are the same and given the differences in pharmacology, each JAKi should be assessed based on its individual clinical profile. Upadacitinib has a unique chemical structure leading to preferential inhibition of JAK1 or JAK1/3 and differing metabolic and elimination profiles as compared to other JAKi.

Upadacitinib is approved in more indications than any other JAKi (Figure 7), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), atopic dermatitis (AD), ulcerative colitis (UC), and Crohns disease CD. These diagnoses are all chronic conditions with long-term and disabling disease manifestations, and despite the availability of innovative therapies, many patients fail to achieve remission and sustain disease control. Upadacitinib is under evaluation for additional approvals in immunological diseases; unlike other JAKis, upadacitinib has never failed a clinical trial and has all its indications and dosages approved by both EMA and FDA.

Figure 6. JAKi comparison on approved indications and Phase III trials.



Upadacitinib's safety profile is broadly studied across 19 Phase III clinical trials with over 10,500 upadacitinib patients and over 23,000 PY of exposure across rheumatology, dermatology, and gastroenterology. The safety profile is generally consistent across different patient types studied in all approved indications with three different dosing strengths (15mg, 30mg, and 45mg). Upadacitinib is also approved for use in adolescents with AD.

Overall rates of MACE, malignancies (excluding NMSC) and VTE with upadacitinib were not increased relative to real-world background rates across indications (29). Upadacitinib is the only JAKi with long-term follow-up compared to adalimumab in head-to-head studies for RA and PsA. Available data do not suggest that the observed rates of MACE, malignancies (excluding NMSC), and VTE are increased as compared to adalimumab in up to 4.5 years of data.

Furthermore, in a sub-analysis of SELECT-COMPARE (RA patients 50 years and older with at least 1 CV risk factor) upadacitinib did not demonstrate an increased risk of MACE, malignancies (excluding NMSC) and VTE to adalimumab.(30)

PREVENT (25)

The PREVENT trial has three study arms, including placebo and secukinumab 150 mg at week 0, 1, 2 and 3 followed by every 4 weeks starting at week 4. The NL group received placebo at weeks 1, 2 and 3 to maintain blinding. The approved dosing of secukinumab is 150 mg at week 0, 1, 2 and 4 followed by monthly injections (that is with a loading dose, LD). Results from the LD-study arm compared with placebo will be presented, as this is the relevant dosing for the comparison with upadacitinib in this application. Efficacy analysis were performed on the full analysis set, which comprise all randomized patients who had study treatment assigned.

Disease activity (ASAS40, BASDAI50 and ASDAS<2.1)

41,5% of patients treated with secukinumab 150 mg LD compared with 29,2% in the placebo group reported ASAS40 at week 16 (P=0,0197). The proportion of BASDAI50 responders was significantly higher in patients treated with 150 mg LD (37.3%) versus placebo (21.0%; P = 0.0001). ASDAS<2.1 was not reported in the PREVENT trial.

Health related Quality of Life

Health related quality of life was measured with the SF-36 (physical component summary) in PREVENT. The mean change from baseline was 2,93±0,71 in the placebo group compared with 5,71 ± 0,68 in the patients treated with secukinumab 150 mg LD. This corresponds to a statistically significant difference between the treatment groups (p=0,0006). In addition, the PREVENT study reports on ASQoL. The change from baseline was −3.45 ± 0.41 in the secukinumab 150 mg LD group, compared to −1.84 ± 0.42 in the placebo group (P=0,0008).

Safety

The safety outcomes reported in the PREVENT trial are presented in . In total, 29 patients of 185 (15,7%) patients in the secukinumab 150mg LD group and 26 of 186 (14%) in the placebo group discontinued the study during the 52 week placebo controlled phase of the study.

Table 9. Safety outcomes in the PREVENT trial.

	Secukinumab 150 mg with loading (n = 185)	Secukinumab 150 mg without loading (n = 184)	Any secukinumab (n = 369)†	Placebo (n = 186)
Up to week 20 (safety set)	119 (64,3)	107(58,2)	226 (61,2)	101 (54,3)
Any AE, no. (%)	2 (1,1)	4(2,2)	6 (1,6)	5 (2,7)
Any serious AE, no. (%)	0 (0)	3(1,6)	3 (0,8)	3 (1,6)
Discontinuation due to any AE, no. (%)	0 (0)	0(0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Most common AEs, no. (%)‡				
Nasopharyngitis	27 (14,6)	19 (10,3)	46 (12,5)	23 (12,4)
Diarrhea	14 (7,6)	9 (4,9)	23 (6,2)	7 (3,8)
Headache	17 (9,2)	5 (2,7)	22 (6,0)	7 (3,8)
Upper respiratory tract infection	11 (5,9)	11 (6,0)	22 (6,0)	7 (3,8)
Selected AEs, no. (%)				
Serious infections	1 (0,5)	1 (0,5)	2 (0,5)	0 (0)
IBD (preferred term)	0 (0)	1 (0,5)	1 (0,3)	0 (0)
MACE	0 (0)	0 (0)	0 (0)	1 (0,5)
Uveitis	2 (1,1)	0 (0)	2 (0,5)	1 (0,5)
Entire treatment period (safety set)§				
Any AE, no. (%)	162 (87,6)	156 (84,8)	431 (79,4)	121 (65,1)
Any serious AE, no. (%)	20 (10,8)	12 (6,5)	39 (7,2)	8 (4,3)
Discontinuation due to any AE, no. (%)	7 (3,8)	13 (7,1)	24 (4,4)	3 (1,6)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Most common AEs, no. (EAIR/100 patient-years)¶				
Nasopharyngitis	56 (25,4)	43 (17,6)	122 (19,4)	32 (32,5)
Upper respiratory tract infection	25 (9,6)	24 (9,0)	59 (8,4)	13 (12,4)
Diarrhea	23 (8,8)	20 (7,4)	50 (7,1)	10 (9,5)
Headache	26 (10,1)	12 (4,3)	46 (6,5)	9 (8,6)
Selected AEs, no. (EAIR/100 patient-years)				
Serious infections	5 (1,8)	5 (1,7)	12 (1,6)	1 (0,9)
IBD	3 (1,1)	1 (0,3)	7 (0,9)	0 (0)
MACE	0 (0)	0 (0)	0 (0)	1 (0,9)
Uveitis	5 (1,8)	2 (0,7)	9 (1,2)	2 (1,8)
Malignancies	0 (0)	0 (0)	3 (0,4)	0 (0)
Suicide attempt	0 (0)	1 (0,3)	1 (0,1)	0 (0)

* IBD = inflammatory bowel disease; MACE = major adverse cardiovascular event. † The "any secukinumab" group (n = 369 for up to week 20 and n = 543 for the entire treatment period) included patients originally randomized to receive secukinumab and patients originally randomized to receive placebo who switched to open-label secukinumab 150 mg. ‡ Adverse events (AEs) with a frequency of >5% up to week 20, presented in descending order in the "any secukinumab" group. Events are listed according to preferred term in the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1. § The entire treatment period includes safety data up to the cutoff date July 1, 2019 and includes at least 52 weeks of exposure for all patients and up to 104 weeks of exposure for some patients. The cumulative exposure was 286.1 patient-years for the secukinumab 150 mg with loading group, 291.3 patient-years for the secukinumab 150 mg without loading group, 757.9 patient-years for the "any secukinumab" group, and 109.3 patient-years for the placebo group. ¶ AEs that occurred with an exposure-adjusted incidence rate (EAIR) of >5.0 cases per 100 patient-years in the "any secukinumab" group over the entire treatment period. Events are listed according to preferred term in the MedDRA, version 21.1.

As upadacitinib, secukinumab has several approved indications in addition to nr-axSpA which results in a significantly larger safety population than the population included in the PREVENT trial, and the safety profile for secukinumab will also be described using the SmPC.

According to the SmPC, the most frequently reported adverse reactions was upper respiratory tract infections (17.1 %) (most frequently nasopharyngitis, rhinitis). Over the entire treatment period infections were reported in 47,5 % of patients treated with secukinumab (0,9 per patient-year of follow-up). Serious infections were reported in 1.2 % of patients treated with secukinumab (0,015 per patient-year). Secukinumab is contraindicated for patients with active infections, and should be used with caution in patients with chronic infection or a history of recurrent infection. Common adverse events, occurring in ≥1/100 to <1/10 of the patients, includes oral herpes, headache, rhinorrhea, diarrhea, nausea and fatigue. Though uncommon, neutropenia and hypersensitivity reactions has been reported for patients treated with secukinumab. Neutropenia was in most cases mild, transient and reversible.

Cases of new or exacerbations of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, have been reported with secukinumab. Secukinumab is not recommended in patients with inflammatory bowel disease.

7.2.3 Comparative analyses

Comparative analyses of efficacy on disease activity

No direct comparison between upadacitinib and secukinumab was identified in the literature. Therefore, an indirect treatment comparison has been carried out, comparing the efficacy of upadacitinib and secukinumab on disease activity. The analysis is carried out using results from the full analysis set population in the clinical trials.

As described above, patients previously treated with b/tsDMARD is a population of interest as TNF-inhibitors are recommended as first line treatment. An indirect treatment comparison in this population is not possible as no data is available for secukinumab. In addition, both included a relatively small number of b/tsDMARD experienced patients and thus were s underpowered to detect a statistically significant difference of the treatment efficacy versus placebo.

Method of synthesis

The analysis includes studies identified in the literature search described above. The comparison is done with efficacy data from week 14 for upadacitinib and week 16 for secukinumab, as this is the last timepoint where placebo-controlled data is available from all studies. All relevant data used in the analysis is presented in the tables in Appendix D, along with the forest plots.

Indirect treatment effect estimates and their 95% confidence intervals obtained from random-effects models, were produced by using the method described by Rücker (31), and Rücker and Schwarzer (32). When only indirect comparisons are envisioned (there is no closed loop in the evidence network), such as in our scenario, the method described by Rücker and Schwarzer correspond to the method of adjusted indirect comparison as described by Bucher.

Results from the comparative analysis

The results of the indirect treatment comparison is shown in . Regardless of outcome measure, the confidence intervals overlap 1 (which is the efficacy of secukinumab). No statistically significant difference in effect between secukinumab and upadacitinib was found in the indirect treatment comparison.

Table 9. Results of the indirect treatment comparison of upadacitinib versus secukinumab

Endpoint	OR (95% CI)	RR (95% CI)
ASAS40	1,65 (0,86; 3,18)	1,41 (0,90; 2,20)
BASDAI50	1,14 (0,58; 2,24)	1,07 (0,66; 1,73)

Comparative analyses of efficacy on HRQoL

Both SELECT AXIS 2 and PREVENT report outcome on health related quality of life measured with the ASQoL – tool. Patients treated with upadacitinib demonstrated a statistically significant improvement of health related quality of life compared with placebo (-5,38 versus -3,15; a difference of -2,23 (95% CI: -3,26; -1,21). Patients treated with secukinumab 150 mg LD also demonstrated statistically significant improvement of health related quality of life compared with placebo with a change from baseline of −3,45 ± 0,41 in the secukinumab 150 mg LD group, compared to −1,84 ± 0,42 in the placebo group (P=0,0008), an absolute difference of - 1,61.

Comparative analyses of safety

An overview of the safety outcomes reported for secukinumab and upadacitinib in PREVENT and SELECT AXIS -2 is presented in and show low rates of adverse events not significantly different from placebo, though secukinumab demonstrates a higher rate of any adverse events compared to placebo. The absolute difference for upadacitinib and

secukinumab compared to placebo is similar, except for *any adverse event* where the difference is higher for secukinumab relative to placebo compared for upadacitinib versus placebo.

According to the SmPC, the safety profile of upadacitinib with long-term treatment was generally similar to the safety profile during the placebo-controlled period across indications. Study data on adverse events from the placebo-controlled phase is therefore used for the comparison between upadacitinib and secukinumab.

Table 10. Adverse events reported in SELECT-AXIS 2 (26) and PREVENT

	Placebo (n=157)	Upadacitinib (n=156)	Absolute difference (% point, 95 % CI)	Placebo (n=186)	Secukinumab 150 mg LD (n=185)	Absolute difference (% point, 95 % CI)
Any adverse event	72 (46 %)	75 (48%)	**2,2% (-8,8; 13)**	101 (54,3 %)	119 (64,3%)	**10,0% (7,8; 19,9)**
Serious adverse events	2 (1%)	4(3%)	**1,2 % (-1,7; 4,3)**	5 (2,7%)	2 (1,1%)	**-1,6% (-4,4; 1,15)**
Discontinuation due to adverse event	2 (1%)	4 (3%)	**1,2 % (-1,7; 4,3)**	3 (1,6%)	0 (0%)	**-1,6 (-3,4; 19,9)**
Serious infection	1 (1%)	2 (1%)	**0,6 % (-1,5; 2,8)**	0 (0%)	1 (0,5%)	**0,54 (-0,52; 1,6)**

In addition to the outcomes from PREVENT and SELECT-AXIS 2, there are differences in contraindications and warnings between upadacitinib and secukinumab. Treatment with upadacitinib is not recommended for patients at risk for VTE, cancer or major cardiovascular problems, if there are other treatment alternatives available. Secukinumab should not be used in patients with inflammatory bowel disease. Assuming these precautions are taken into account prior to starting treatment with either upadacitinib or secukinumab, the safety profile is generally similar.

8. Health economic analysis

8.1 Model

For the indication nr-axSpA, upadacitinib is compared with adalimumab and secukinumab. As demonstrated above, upadacitinib has comparable efficacy on disease activity and generally similar safety profile. The most appropriate model for health economic analysis is a cost-minimization model.

The model has been developed in Excel as a cost-per-patient analysis including drug costs, monitoring costs and patient costs. As upadacitinib, adalimumab and secukinumab have different modes of action, the safety profiles differ. Costs for adverse events have been included in the model to account for these differences. The model time horizon is 18 months, which is the time-horizon used in previous evaluations of upadacitinib, and secukinumab in nr-axSpA.

All costs are discounted with a rate of 3,5% in accordance with the Medicines Council guideline.

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

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

The health economic analysis is carried out with a cost-minimization analysis, as the indirect treatment comparison did not identify any statistically significant differences in clinical efficacy or safety. There is no input data on clinical efficacy in the model. Costs for adverse events are included in the model, using adverse event rates from the clinical studies. These are further described in section 8.2.2.5 below.

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

8.2.2.1 Patient population

The patient population in the analysis are patients with active non-radiographic axial spondylarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs), in line with the approved indication of upadacitinib in nr-axSpA.

No costs in the cost-minimization analysis vary based on patient characteristics, therefore no patient characteristics are included in the model.

8.2.2.2 Intervention

The intervention upadacitinib is described in Table 12. The expected use in Danish clinical practice is the same in the clinical documentation and SmPC, and the model.

Table 11. The intervention – upadacitinib.

Intervention	Clinical documentation: SELECT AXIS - 2	Used in the model	Expected Danish clinical practice (including source if known)
Posology	15 mg per orally, daily	15 mg per orally, daily	15 mg per orally, daily
Length of treatment	No stopping rules was included in SELECT-AXIS 2.	18 months, per previous evaluations in AS and nr-axSpA	18 months
Criteria for discontinuation	Until loss of either efficacy or tolerability.	No discontinuation, all patients are assumed to stay on treatment for 18 months.	Until loss of either efficacy or tolerability.

Upadacitinib (and comparators, see below) are expected to be used until loss of either efficacy or tolerability. In clinical practice the treatment length is assumed to be 18 months, which is also used in the model. The model assumes that all patients stay on treatment throughout the model life-time.

8.2.2.3 Comparators

In Danish clinical practice patients with active nr-axSpA who have responded inadequately to treatment with NSAID is expected to be treated primarily with adalimumab (Table 13), and secondarily with IL-inhibitors such as secukinumab (Table 14). Upadacitinib is compared with both adalimumab and secukinumab in this application.

The same assumptions are made for the comparators as for upadacitinib – the use will be according to clinical documentation and the SmPC and the treatment length will be according to Danish clinical practice and previous evaluations within the indication.

Table 12. The comparator – adalimumab.

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	40 mg subcutaneously every other week	40 mg subcutaneously every other week	40 mg subcutaneously every other week
Length of treatment	No stopping rules was included in ABILITY 1	18 months, per previous evaluations in AS and nr-axSpA	18 months
The comparator's position in the Danish clinical practice	First line b/tsDMARD. There is no ranking in place for nr-axSpA, the assumption is made based on the ranking for RA and PsO where adalimumab is first of the b/tsDMARDs.		

Table 13. The comparator –secukinumab.

Comparator	Clinical documentation PREVENT	Used in the model	Expected Danish clinical practice (including source)
Posology	150 mg week 0, 1 ,2 , 3 and 4, followed by 150 mg monthly	150 mg week 0, 1 ,2 , 3 and 4, followed by 150 mg monthly	150 mg week 0, 1 ,2 , 3 and 4, followed by 150 mg monthly
Length of treatment	No stopping rules was included in COAST - X	18 months, per previous evaluations in AS and nr-axSpA	18 months
The comparator's position in the Danish clinical practice	Second line b/tsDMARD, for patients not reaching adequate treatment response on adalimumab. There is no ranking in place for nr-axSpA.		

8.2.2.4 Relative efficacy outcomes

The modelling is done assuming that there is no difference in treatment efficacy, based on the results of the indirect treatment comparison. No efficacy outcomes are included in the model.

8.2.2.5 Adverse reaction outcomes

As upadacitinib has a different mode of action than the comparators (a JAK-inhibitor versus TNF-inhibitor and IL-inhibitor) there could be differences in the adverse event profiles affecting costs for adverse events, even though no major differences in the safety outcomes could be identified. Adverse events are included as costs in the model, based on the adverse event rates (Table 15) from placebo-controlled phases of the clinical trials as according to the SmPC, the safety profile of upadacitinib with long-term treatment was generally similar to the safety profile during the placebo-controlled period across indications

All adverse events reported in the publications for any of the active substances in the clinical studies are included in the analysis. If rates for specific adverse events are not included in the publications of the studies, rates has been sourced from the site of the clinical trial on clinicaltrials.gov.

Table 14. Adverse events outcomes included in the cost-minimization analysis.

	Upadacitinib 15 mg	Secukinumab 150 mg LD	Adalimumab 40mg
Anaemia	0,64%	0,18%	0,00%
Depression	0,00%	0,00%	2,11%
Diarrhea	0,00%	7,60%	4,21%
Headache	5,77%	9,20%	6,32%
Hepatic disorder	2,56%	0,55%	4,21%
Herpes zoster	1,28%	0,00%	2,11%
Infection	23,08%	21,73%	29,47%
Injection site reactions	0,00%	0,00%	4,21%
Nasopharyngitis	0,00%	14,60%	11,58%
Nausea	0,00%	0,00%	6,32%
Neutropenia, all grades	3,21%	0,00%	0,00%
Serious infection	1,28%	0,50%	0,00%
Upper respiratory tract infection	0,00%	5,90%	3,16%
Uveitis	0,64%	1,10%	0,00%

8.3 Extrapolation of relative efficacy

No extrapolations of relative efficacy is included in the model as treatments are assumed to be equally efficacious.

8.3.1 Time to event data – summarized

No time to event data is used in the model.

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

No health-related quality of life data is included in the model, as treatments are assumed to be equally efficacious with no difference in HRQoL outcomes.

8.4.1 Overview of health state utility values (HSUV)

Not applicable, see 8.4.

8.5 Resource use and costs

The cost-minimization analysis includes drug costs, monitoring costs, patient costs and costs for adverse events.

8.5.1 Drug costs

The drug prices used in the model are presented in Table 16 below. All prices are the pharmacy purchase price (PPP).

Table 15. Drug prices used in the model.

Drug	Strength per unit	Pack size (units)	Price (PPP) per pack	Source
Upadacitinib (Rinvoq)	15 mg	28	6 155,68 DKK	Medicinpriser.dk Accessed 26.01.2024
Adalimumab (Imraldi)*	40 mg	2	4367,57 DKK	
Secukinumab (Cosentyx)	150 mg	2	7 710,60 DKK	

*The product with the lowest price for adalimumab was chosen, as biosimilars are available.

The drug costs were calculated based on the dosing as described in the SmPC, see Table 17.

Table 16. Dosing used in the model for calculation of drug costs.

Drug	Dosing	Source
Upadacitinib (Rinvoq)	The recommended dose of upadacitinib is 15 mg once daily.	SmPC
Adalimumab (Amgevita)*	The recommended dose of adalimumab is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.	SmPC
Secukinumab (Cosentyx)	The recommended dose of secukinumab is 150 mg week 0, 1 ,2 , 3 and 4, followed by 150 mg monthly.	SmPC

8.5.2 Monitoring and administration costs

For the monitoring and administrations cost an overall cost based on Medicine Council's Extended Basis for Comparison (hereafter the EBC) from treatment area RA was used. (23)

AbbVie considers that these costs are relevant since they are based on input from all five Danish regions regarding costs and resource use associated with treatment of biologic treatments given subcutaneous and orally. Adalimumab is represented in the EBC in RA from the Medicine council. Costs are assumed to be independent of immunological indication, and costs for treatment for AS assumed to be equal to costs for RA.

Costs for hospital monitoring for tofacitinib is assumed to be applicable also for upadacitinib, as both drugs are JAK-inhibitors with the same administration method. Costs for secukinumab are assumed to be similar to the costs for golimumab as the number of administrations are similar over 18 months (18 for golimumab versus 21 for secikunumab). As the number of doses is slightly higher for secukinumab any differences will likely result in a conservative estimate of the costs for secukinumab. Compared to tofacitinib in RA, upadacitinib is given orally only once a day without the need for methotrexate which can impact the doctor time and blood test to be lower than estimated in the EBC. However, this is the best estimate of the monitoring and administration costs that we currently have and is a conservative estimate for hospital costs related to upadacitinib.

The costs have been projected using the consumer price index without energy (PRIS114), available on the Statistics Denmark website, as described in the Medicines Council's methods guide. The final costs used in the analysis are presented in Table 18.

Table 17. Monitoring costs over 18 months from the EBC, projected to 2023.

	Worked time		Diagnostics	Other costs		
(DKK)	Doctor	Nurse	Bloodsamples etc	Roomcost	Utensils	Sum
Upadacitinib	3050	2052	1592	72	0	6766
Adalimumab	2825	2342	1574	80	86	6908
Secukinumab	2825	2342	1574	80	86	6908

8.5.3 Patient costs and transportation costs

As for monitoring costs patient time and transportation costs related to start of treatment and treatment monitoring are estimated based on the Medicines Council EBC (23) and shown in Table 19.

Table 18. Patient costs and transportation costs related to treatment from the EBC, projected to 2023.

(DKK)	Patient time cost	Transportation costs
Upadacitinib	1423	1 829
Adalimumab	2 499	1 819
Secukinumab	1 930	1 819

The costs have been projected using the consumer price index without energy (PRIS114), available on the Statistics Denmark website, as described in the Medicines Council's methods guide. At the time of analysis, December 2023 was the latest available index.

In addition, patient costs and transportation costs for treating adverse events are included in the analysis. These costs are assumed for each treatment visit resulting from adverse events, see Table 20.

Table 19. Patient costs and transportation costs related to adverse events.

Description		Cost (DKK) per visit	Source
Transportation			
	Distance (km)	40	Værdisætning-af-enhedsomkostninger-vers-1.7
	Cost per km (DKK)	3,73	
	Transportation cost per visit (DKK)	**149,2**	Calculated (3,73DKK x 40km)
Patient cost			
	Transportation (h)	1	Assumption
	Visit, total (h)	0,5	Assumption
	Mean hourly wage (DKK)	**203**	Værdisætning-af-enhedsomkostninger-vers-1.7
	Patient cost per visit	**304,5**	Calculated (203DKK x 1,5h)

8.5.4 Adverse event costs

Adverse event costs have been included in the cost-minimization model to capture any difference in adverse events profile between the treatment. Unit costs and number of visits for each adverse event is described in Table 21, and are based om the following assumptions:

- The majority of the adverse events are assumed to be treated by general practitioners.
- Depression are assumed to be treated by private specialists.

- Serious infections are by definition severe adverse events infections that are causing hospitalizations, and the cost for serious infections reflect that.
- The number of consultations and follow-up visits has been estimated based on whether a condition is considered chronic or not, or if a follow-up visit is deemed needed.
- Adverse events are assumed to occur once in the first year of treatment. Costs for depression are also limited to the first year.
- As costs for monitoring at start and follow up of treatment has been included, see Table 18, all adverse events that are related to laboratory findings are assumed to already be covered.
- The number of visits are used to calculate the patient- and transportation costs that are included in the model. Patient time costs for hospitalization is also included, see Table 20.

Table 20. Adverse event costs.

Adverse event	Treated needed	Unit cost	Description and source	Number of patient visits	Additional patient time (hours)	Assumption
Anaemia	Yes	307,22	2 visit to general practitioner, á 153,61. PLO Honorartabel 2023	2	0	
Depression	Yes	4 002,97	Specialist treatment Psykiatri Takstkort 20A, 1 konsultation and 3 Konsultation i et primært medicinsk behandlingsforløb og støttende samtale	4	0	
Diarrhea	No					
Headache	No					
Hepatic disorder	No					
Herpes zoster	Yes	153,61	1 visit to general practitioner, á 153,61. PLO Honorartabel 2023	1	0	
Infection	Yes	153,61	1 visit to general practitioner, á 153,61. PLO Honorartabel 2023	1	0	
Injection site reactions	Yes	153,61	1 visit to general practitioner, á 153,61. PLO Honorartabel 2023	1	0	
Nasopharyngitis	No					
Nausea	No					
Neutropenia, all grades	Yes*					
Serious infection	Yes	41 862,00	18MA08 Andre infektioner eller parasitære sygdomme	1	112	7 days inpatient care
Upper respiratory tract infection	No					
Uveitis	Yes	153,61	1 visit to general practitioner, á 153,61. PLO Honorartabel 2023	1	0	

*Assumed to be elevated liver enzymes, which is the most common reported hepatic disorder for all three treatments included in the analysis.

**Assumed to be monitored and treated at start of treatment and include in the costs in Table 18. Monitoring costs over 18 months from the EBC, projected to 2023.

8.6 Results

8.6.1 Base case overview

A base case overview of the analysis is presented in Table 22.

Table 21. Base case overview

Comparators	Adalimumab and secukinumab
Type of model	Cost-minimization analysis
Time horizon	18 months
Measurement and valuation of health effects	Not applicable as treatment efficacy and safety is assumed to be equal to comparators.
Included costs	Pharmaceutical costs Hospital costs Costs of adverse events Patient costs
Dosage of pharmaceutical	Based on SmPC, not dependent on patient characteristics.

8.6.2 Base case results

The base case results of the cost-minimization analysis is shown in Table 23.

Table 22. Base case results

	Upadacitinib	Adalimumab	Secukinumab
Drug cost	118 683	84 208	80 179
Monitoring cost	6 690	6 830	6 830
Adverse event costs	577	139	245
Patient and transportation costs	3 632	4 471	3 970
Total cost	**129 581**	**95 648**	**91 224**
Incremental cost		**33 934**	**38 357**

8.7 Sensitivity analyses

Costs for adverse events are the costs in the analysis where assumptions have been made to calculate the costs, and are also the costs that vary most between treatments. A sensitivity analysis has been performed where the adverse event rates for upadacitinib has been doubled while the adverse events rates for the comparators are as in the base case. The results, as presented in Table 24, show that adverse event costs have limited impact on the results of the cost-minimization analysis. The result is expected since costs for adverse events make up a small proportion of the total costs.

Table 23. Sensitivity analysis, incremental cost versus upadacitinib.

	Adalimumab	Secukinumab
Doubled rate of AE's for upadacitinib	**34 511**	38 934
24 months treatment length	45 163	54 666

9. Budget impact analysis

A budget impact analysis analyzing the budget impact of introducing upadacitinib for patients with nr-axSpA has been carried out. In line with the Medicine Council guideline the budget impact analysis has been done with the perspective of the regional hospitals, and include undiscounted costs for the pharmaceuticals and hospital costs.

The budget impact analysis is based on the same costs and assumptions on treatment length as are used in the cost-minimization analysis, please refer to the following tables for details:

- Table 16. Drug prices used in the model.
- Table 17. Dosing used in the model for calculation of drug costs.
- Table 18. Monitoring costs over 18 months from the EBC, projected to 2023.

The budget impact analysis is done on yearly costs, over a total period of 5 years.

9.1 Number of patients

In DANBIO (Danish Rheumatologic Database), approximately 2 270 patients registered as being treated with biological therapy for SpA by the end of 2019. Data extracts from DANBIO also show that approximately 57% of patients have AS, resulting in 43 % (976 patients) with nr-axSpA being treated with b/tsDMARDs in Denmark. In addition 320 patients were registered as starting treatment per year, of which 138 have nr-axSpA (13). The number of treated patients is expected to increase with 138 per year, see Table 25. As described above, upadacitinib is expected to have the same place in the treatment sequence as b/tsDMARD, but is not expected to have a large market share as TNFi is recommended for first line treatment. The budget calculations are based on the number of new patients that start treatment with b/tsDMARD each year

Table 24. Number of patients with nr-axSpA treated with b/tsDMARD and upadacitinib.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of treated patients	138	276	276	276	276
Expected marketshare upadacitinib	1%	2%	3%	4%	5%
Number of patients treated with upadacitinib	1	6	8	10	12

In the evaluation of and ixekizumab for AS and nr-AxSpA, the Medicines Council did a budget impact analysis including all treatments on the market for AS/nr-axSpA. The DANBIO register were used to inform the analysis with data on present market shares, in Q3 2020, and includes both AS and nr-AxSpA. (33) Since then, ixekizumab has been approved for AS and nr-AxSpA and secukinumab for nr-axSpA and is assumed to have taken market shares. The market shares are assumed not to change over the 5 year period of the budget analysis in the scenario where upadacitinib is not recommended. For this analysis the market shares for the nr-axSpA

population is assumed to be identical to the market shares for the whole AS/nr-axSpA population, Table 26.

Table 25. Market share assumptions for b/tsDMARD and tsDMARDs for patients with nr-AxSpA if upadacitinib is not recommended.

	Q3 2020[33]	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	36,2%	36,2%	36,2%	36,2%	36,2%	36,2%
Upadacitinib	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%
Infliximab	22,7%	21,2%	21,2%	21,2%	21,2%	21,2%
Etanercept	18,2%	16,7%	16,7%	16,7%	16,7%	16,7%
Secukinumab	4,6%	7,6%	7,6%	7,6%	7,6%	7,6%
Certolizumab pegol	4,6%	2,6%	2,6%	2,6%	2,6%	2,6%
Golimumab	12,9%	7,9%	7,9%	7,9%	7,9%	7,9%
Tofacitinib	0,2%	0,2%	0,2%	0,2%	0,2%	0,2%
Ixekizumab	0,7%	7,7%	7,7%	7,7%	7,7%	7,7%

All pharmaceuticals included in the budget impact analysis, including upadacitinib, are tendered and their use is directed towards the least costly alternatives. Therefore, if recommended by the Medicines Council, upadacitinib is not expected to take market shares from adalimumab (or any other treatment alternatives with a lower cost), but to take market shares from ixekizumab and secukinumab. Additionally, market shares might also be taken from golimumab and certolizumab. The total number of patients who will be treated with upadacitinib is expected to be small, and an equal proportion of market shares is expected to be taken from each of the treatments. The expected market uptake with these assumptions is shown in Table 27.

Table 26. Market shares assumptions in the scenario where upadacitinib is recommended.

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	36,2%	36,2%	36,2%	36,2%	36,2%
Upadacitinib	1,0%	2,0%	3,0%	3,5%	4,5%
Infliximab	21,2%	21,2%	21,2%	21,2%	21,2%
Etanercept	16,7%	16,7%	16,7%	16,7%	16,7%
Secukinumab	7,4%	7,1%	6,9%	6,7%	6,5%
Certolizumab pegol	2,4%	2,1%	1,9%	1,7%	1,5%
Golimumab	7,7%	7,4%	7,2%	7,0%	6,8%
Tofacitinib	0,2%	0,2%	0,2%	0,2%	0,2%
Ixekizumab	7,5%	7,2%	7,0%	6,8%	6,6%

9.2 Expenditure per patient

The expenditure per patient for the pharmaceuticals included in the budget impact analysis is shown in Table 28. The budget impact analysis is done in the perspective of the regional hospitals, and includes costs of the pharmaceuticals and hospital costs for monitoring and administration of the respective drugs.

Table 27. Expenditure per patient, 18 months of treatment.

	Drug costs (DKK)		Monitoring and administration costs (DKK)	
Product	**First year (month 0-12)**	**Following year (month 13-18)**	**First year (month 0-12)**	**Following year (month 13-18)**
Adalimumab	56 778	28 389	4 605	2 303
Upadacitinib	80 024	40 012	4 511	2 255
Infliximab	22 625	9 050	13 753	6 877
Etanercept	76 346	38 173	4 605	2 303
Secukinumab	57 830	23 132	4 605	2 303
Certolizumab pegol	100 579	45 087	4 605	2 303
Golimumab	99 998	49 999	4 605	2 303
Tofacitinib	66 529	33 264	4 511	2 255
Ixekizumab	98 170	49 085	4 184	2 092

9.3 Budget impact

The budget impact of introducing upadacitinib for patients with nr-axSpA is presented in Table 29, and show that the costs for the regional hospitals will be lower if upadacitinib is recommended for patients with nr-axSpA. These calculations are based on the expected number of new nr-AxSpA b/tsDMARD-treated patients, and do not include already treated patients. Increasing the patient numbers in the calculations would result in further lower cost in proportion to the patient numbers.

Table 28. Budget impact of recommending upadacitinib for patients with nr-axSpA.

	Year 1	Year 2	Year 3	Year 4	Year 5
If not recommended	9 241 067 kr.	13 707 614 kr.	13 689 813 kr.	13 683 473 kr.	13 669 513 kr.
If recommended	9 253 747 kr.	13 735 534 kr.	13 735 534 kr.	13 735 534 kr.	13 735 534 kr.
Incremental cost	**-12 680 kr.**	**-27 920 kr.**	**-45 721 kr.**	**- 52 061 kr.**	**- 66 021 kr.**
				Total budget impact after 5 years-	**- 204 403 kr.**

10. Discussion on the submitted documentation

The efficacy and safety of upadacitinib is well documented within several indications. For patients with nr-axSpA, upadacitinib has been compared with placebo in the randomized clinical trial SELECT-AXIS 2. The study population is patients with an inadequate response to NSAIDs and with active disease, and thus corresponds well to the patients expected to be treated with upadacitinib in Danish clinical practice. In addition about 30 % of the study population has previously been treated with b/tsDMARDs and since TNF-inhibitors are the first line treatment for patients with inadequate response to NSAIDs this makes the SELECT-AXIS 2 population relevant for Danish clinical practice.

As no study comparing upadacitinib and the relevant comparators adalimumab and secukinumab could be identified, indirect comparisons were carried out, as described in the Medicines Councils' methods guide. The studies included in the indirect treatment comparisons (ITCs), ABILITY-1 for adalimumab and PREVENT for secukinumab, are both randomized placebo-controlled clinical trials with similar study designs as SELECT-AXIS 2. The patient populations are also similar, however the proportion of patients previously treated with b/tsDMARD differ. A larger proportion (about 30 %) of patients in the SELECT-AXIS 2 trial are b/tsDMARD experienced, than in the PREVENT trial (about 10 %), while no b/tsDMARD experienced patients are included in the ABILITY-1 trial. As b/tsDMARD-naïve patients are expected to have a better response to treatment, this difference between the studies will result in a conservative estimate for upadacitinib in the indirect treatment comparison.

Both upadacitinib and secukinumab are expected to be used primarily for patients who have already been treated with a TNF-inhibitor, and will be b/tsDMARD experienced. Although b/tsDMARD experienced patients are included in the PREVENT trial population, no results from this subgroup in the PREVENT trial has been published. The clinical efficacy of the treatment options that are currently available for patients previously treated with b/tsDMARDs is not known. Based on the evidence submitted in this application, upadacitinib has similar efficacy as secukinumab based on an indirect treatment comparison between two studies that includes both b/tsDMARD naïve and b/tsDMARD experienced patients. As mentioned before, as the proportion of previously treated patients in the SELECT-AXIS 2 study is higher, this results in a conservative estimate of the relative efficacy of upadacitinib compared to secukinumab.

Following the result of the ITC, which demonstrate no difference in efficacy or overall safety for upadacitinib compared to adalimumab and secukinumab the health economic analysis consists of a cost-minimization analysis. The model includes the same source of hospital- and patient costs that has been used by the Medicines council in previous evaluations. Even though no difference between the treatments on overall safety was found in the ITC, the mode of action of the three treatments are different. This could result in different adverse event profiles and adverse event costs are included in the model to analyze if this has any impact on the outcome of the cost-minimization analysis. The result show that adverse events costs make up a very small proportion of the total costs, and the scenario analysis where the adverse event rate for upadacitinib was doubled still demonstrate consistent cost-effective results for upadacitinib with very similar results as in the base case.

11. List of experts

No experts were consulted during this application submission.

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Appendix A - Literature search for efficacy and safety of intervention and comparators

Objective of the literature search: To identify clinical trials investigating the clinical efficacy and safety of upadacitinib, adalimumab, ixekizumab or secukinumab in adult patients with non-radiographic ankylosing spondylitis according to the PICOS in
Databases: The literature search was performed in Medline and Central.

Table 1. Bibliographic databases included in the literature search.

Database	Platform	Relevant period for the search	Date of search completion
Medline	https://pubmed.ncbi.nlm.nih.gov	To search date	01.12.2023
Central	https://www.cochranelibrary.com/	To search date	01.12.2023

Search strategy and results

The PICOS in Table 2 was used to inform the search strategy. No language restriction was included in the search strategy, but studies in other languages than English, Danish, Swedish, and Norwegian were to be excluded at review. The final search strategies and results are presented in Table 3 and Figure 1.

Table 2. PICOS for systematic literature search and indirect treatment comparison.

Criteria	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with nr-AxSpA, NSAID-IR and either bDMARD-naïve or bDMARD-IR Mixed populations of adult NSAID-IR, bDMARD-naïve and -bDMARD-IR nr-AxSpA patients	Children (<18 years) Mixed populations (e.g., adults and children) if data for target population are not reported separately Patients with AS only
Intervention	Upadacitinib, adalimumab or secukinumab	Other active comparators
Comparators	PBO Active intervention (i.e., head-to-head trials) including adalimumab, or secukinumab	No comparator (i.e., single-arm trials) Non-pharmacologic therapies (e.g., physiotherapy) Conventional management strategies with or without PBO and/or background medication.
Outcomes	Efficacy outcomes (ASAS40 and BASDAI 50, safety outcomes and HRQoL) at Week 12 to 16	
Study design	RCTs (phases 3+) Randomized crossover/cluster trials, provided randomized phase is at least 12 weeks Head-to-head comparisons	RCTs (phase 1). Long-term follow-up studies with maintained randomization (e.g., open-label follow-up studies with continuation of treatment in randomized treatment arms) Single-arm trials Open-label trials

Table 3. Search strategy and search results, PubMed.

Search	Actions	Details	Query	Results	Time
#15	•••	›	Search: **#4 AND #10 AND #11 NOT #14**	19	11:28:17
#14	•••	›	Search: **#12 OR #13**	9,167,103	11:28:05
#13	•••	›	Search: **animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]**	1,680,162	11:27:34
#12	•••	›	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]**	7,546,322	11:27:18
#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[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh])**	1,512,208	11:26:46
#10	•••	›	Search: **#5 OR #6 OR #7 OR #8 OR #9**	13,626	11:26:30
#9	•••	›	Search: **secukinumab[tiab] OR cosentyx*[tiab]**	2,007	11:23:11
#8	•••	›	Search: **adalimumab[tiab] OR humira*[tiab] OR D2E7[tiab] OR amjevita*[tiab] OR cyltezo*[tiab]**	9,706	11:22:55
#7	•••	›	Search: **adalimumab[mh]**	7,110	11:22:39
#6	•••	›	Search: **upadacitinib[tiab] OR ABT-494[tiab] OR rinvoq*[tiab]**	753	11:22:29
#5	•••	›	Search: **upadacitinib[nm]**	307	11:22:16
#4	•••	›	Search: **#1 OR #2 OR #3**	882	11:22:01
#3	•••	›	Search: **non-radiographic* OR nonradiographic* OR preradiographic* OR pre-radiographic***	882	11:21:52
#2	•••	›	Search: **Non-Radiographic Axial Spondyloarthritis [tiab]**	236	11:21:44
#1	•••	›	Search: **Non-Radiographic Axial Spondyloarthritis [Mesh]**	43	11:21:28

Advanced Search

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

Save this search | View/Share saved searches | ? Search help

View fewer lines | Print search history

#1	(Non-Radiographic Axial Spondyloarthritis):kw (Word variations have been searched)	S	Limits	67
#2	(Non-Radiographic Axial Spondyloarthritis):ti,ab,kw (Word variations have been searched)	S	Limits	336
#3	non-radiogtaphic*:ti,ab OR nonradiographic:ti,ab		Limits	394
#4	#1 or #2 or #3		Limits	407
#5	(upadacitinib or ABT-494 or rinvoq*):ti,ab,kw		Limits	749
#6	(adalimumab or humira* or D2E7 OR amjevita* OR cyltezo*):ti,ab,kw		Limits	3958
#7	(secukinumab or cosentyx*):ti,ab,kw		Limits	1125
#8	#5 OR #6 OR #7		Limits	5592
#9	#4 and #8		Limits	135
#10	("conference abstract" or review or protocol):pt,ab,kw		Limits	302518
#11	(clinicaltrials.gov or trialsearch or EUCTR*):so	S	Limits	492440
#12	NCT*:au		Limits	256880
#13	#10 or #11 or #12		Limits	723269
#14	#9 not #13		Limits	59
#15	#14 not pubmed:an		Limits	47

Clear all | Highlight orphan lines

Figure 1. Search strategy and search results for CENTRAL.

Systematic selection of studies

The systematic selection of studies identified in the literature review is depicted in the PRISMA- flow diagram in Figure 2. The publications that were excluded from the analysis, and the reason for exclusion are presented in Table 4. The studies that are included in the analysis are listed and further described in Table 5.

Figure 2 PRISMA flow - diagram

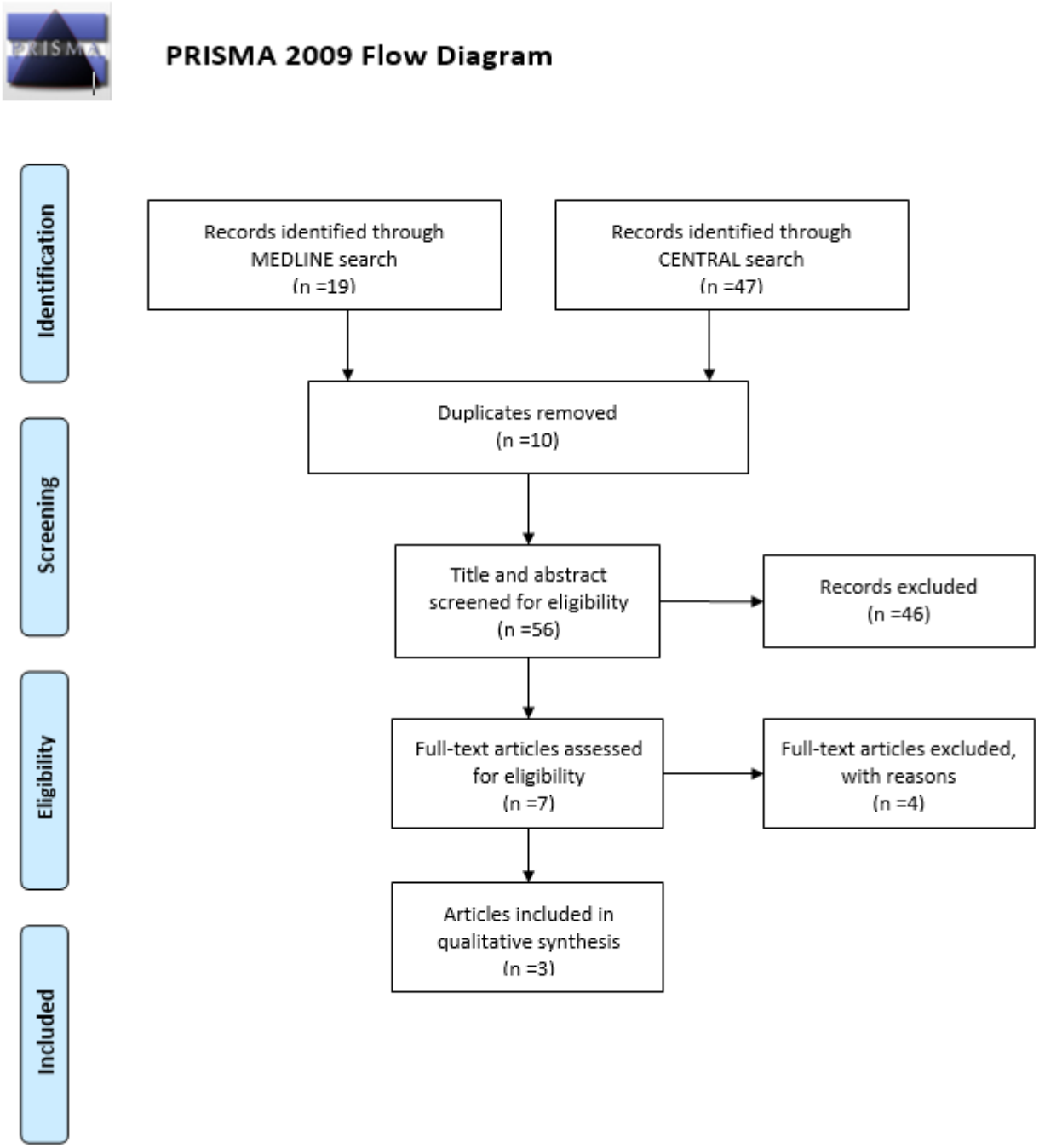

Table 4. List of publications excluded from the analysis.

Publication, full reference	Reason for exclusion
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 Sep 4;23(1):231.	Wrong population, subgroup analysis
Kiltz U, Kishimoto M, Walsh JA, Sampaio-Barros P, Mittal M, Saffore CD, et al. Effect of Upadacitinib on Quality of Life and Work Productivity in Active Non-radiographic Axial Spondyloarthritis: Results From Randomized Phase 3 Trial SELECT-AXIS 2. Rheumatol Ther. 2023 May 16	Wrong outcome
van der Heijde D, Joshi A, Pangan AL, Chen N, Betts K, Mittal M, et al. 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. Rheumatology (Oxford). 2016 Jan;55(1):80–8.	Wrong outcome measure
van der Heijde D, Sieper J, Maksymowych WP, Lambert RG, Chen S, Hojnik M, et al. 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. Arthritis Res Ther. 2018 Mar 27;20(1):61	Wrong follow up-time

Quality assessment

The search strategies for the databases used a range of key words for identifying the correct study type, population, intervention, and comparators. Similar search strategies have been suggested by the Medicines Council in protocols for previous application, for example for Rinvoq in AS.

Unpublished data

Unpublished data from the SELECT-AXIS 2 trial is included in the comparison of upadacitinib versus adalimumab. The data in question is outcomes at week 12, to match the follow-up time in the ABILITY-1 trial. In addition, unpublished data for the bDMARD experienced population in the SELECT-AXIS 2 trial is included in the submission. The unpublished data is patient baseline characteristics and results for BASDAI50 and ASDAS>2.1. Previously unpublished data for the baseline characteristics of the OSI+ population of the ABILITY-1 trial is also presented. The data is presented Appendix C and D.

Table 5. Overview of study design for studies included in the technology assessment.

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
ABILITY-1	To evaluate the efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis (nr-axSpA).	Phase III randomized, double-blind, placebo controlled.	192 participants	Patients were randomized to adalimumab (N=91) or placebo (N=94).	ASAS40 at week 12	ASDAS20 and BASDAI was assessed at week 12
PREVENT	To evaluate efficacy, safety and tolerability of secukinumab compared to placebo in patients with nr-axSpA at Week 16 as well as Week 52.	2-year phase III, randomized, double-blind, placebo-controlled study.	555 participants	Group 1 (n=185), (secukinumab 150 mg Load). Group 2 (n=184), (secukinumab 150 mg No Load). Group 3 (n=186), (placebo): placebo (1 mL).	ASAS40 at week 16 and 52	ASAS20, BASDAI, and ASQoL at week 16 and 52.
SELECT-AXIS 2	To assess the safety and efficacy of Upadacitinib, a Janus kinase inhibitor, in a multicenter, randomized, double-blind, placebo controlled, phase III trial in patients with non-radiographic axial spondylarthritis with objective signs of inflammation based on MRI or elevated C-reactive protein and an inadequate response to nonsteroidal anti-inflammatory drugs.	Randomized, double-blind, placebo-controlled, multicenter trial that comprises a 35-day screening period; a 52-week, randomized, double-blind, parallel-group, placebo-controlled period; and a 52-week open-label extension period.	734 participants	Study 1: Upadacitinib 15 mg (N=211) Study 1: Placebo (N=209) Study 2: Upadacitinib 15 mg (N=156) Study : Placebo (N=158)	ASAS40 at week 14 and 52	ASDAS, SPARCC, BASDAI, ASAS20, BASDI, ASAS, ASQoL, BASMI, MASES, MRI SPARCC,

Appendix B - Main characteristics of included studies.

Trial name: ABILITY-1	NCT number: NCT00939003
Objective	The overall objective of the study was to evaluate the efficacy and safety of 40 mg adalimumab given subcutaneously every other week, followed by an open-label (OL) safety and efficacy assessments in patients with active non-radiographic axial spondyloarthritis (nr-axSpA), not fulfilling the modified New York criteria for AS who had an inadequate response to, or intolerance to NSAIDs.
Publications – title, author, journal, year	Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomized placebo-controlled trial (ABILITY-1), Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, Arora V, Pangan AL). Ann Rheum Dis. 2013 Jun;72(6):815-22. doi: 10.1136/annrheumdis-2012-201766. Epub 2012 Jul 7. 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. doi: 10.1186/s13075-018-1556-5. Spinal inflammation in the absence of sacroiliac joint inflammation on magnetic resonance imaging in patients with active nonradiographic axial spondyloarthritis, van der Heijde D, Sieper J, Maksymowych WP, Brown MA, Lambert RG, Rathmann SS, Pangan AL. Arthritis Rheumatol. 2014 Mar;66(3):667-73. doi: 10.1002/art.38283.
Study type and design	ABILITY-1 (NCT00939003) was initiated in August 2009 and is a pivotal randomized, double-blind, placebo-controlled trial and includes subjects with active axial spondylarthritis (SpA) not fulfilling the 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. The study includes a 12-week, double-blind (DB), placebo-controlled period and a 92-week open label treatment period. Patients were randomized to adalimumab (N=91) or placebo (N=94). Eligible patients were randomized 1:1 to receive subcutaneous injections of adalimumab (40 mg every other week) or matching placebo for 12 weeks during the double-blind period. Efficacy and safety were assessed at weeks 2, 4, 8 and 12. The primary endpoint was the percentage of patients achieving ASAS40 at week 12. Efficacy assessments included BASDAI and Ankylosing Spondylitis Disease Activity Score (ASDAS). The double-blind period was followed by a 92-week open label treatment period.
Sample size (n)	192

Trial name: ABILITY-1	NCT number: NCT00939003
Main inclusion and exclusion criteria	Main inclusion Criteria: • Subject was 18 years and older • All sexes were eligible for study • Adult patients with inadequate response to >/= 1 non-steroidal anti-inflammatory drugs (NSAIDs) • Chronic back pain with onset < 45 years of age • Magnetic resonance imaging (MRI) indicating active sacroiliitis or positive human leukocyte antigen-B27 (HLA-B27) blood test in addition to meeting spondyloarthritis clinical criteria • Negative purified protein derivative (PPD) test and chest x-ray performed at Baseline visit must be negative • Ability to administer subcutaneous injections • General good health otherwise Main exclusion Criteria: • Prior anti-tumor necrosis factor (TNF) therapy • Psoriasis or psoriatic arthritis • Fulfillment of modified New York criteria for ankylosing spondylitis • Recent infection requiring treatment • Significant medical events or conditions that may put patients at risk for participation • Females who are pregnant or breast-feeding or considering becoming pregnant during the study • History of cancer, except successfully treated skin cancer • Recent history of drug or alcohol abuse
Intervention	A total of 95 subjects received adalimumab 40 mg subcutaneously every other week for 12 weeks during the double-blind period and then received adalimumab 40 mg subcutaneously every other week for up to 144 weeks during the open-label period. The day of the first dose of study drug was designated as Day 1.
Comparator(s)	94 patients were provided with a sterile subcutaneous injection solution in 1-ml pre-filled syringes containing placebo for adalimumab to be subcutaneously self-administered every other week at approximately the same time of the day. The day of the first dose of study drug was designated as Day 1.
Follow-up time	Efficacy and safety were assessed at weeks 2, 4, 8 and 12.
Is the study used in the health economic model?	No

Trial name: ABILITY-1	NCT number: NCT00939003
Primary, secondary and exploratory endpoints	**Primary endpoints:** Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 40 Response [Time Frame: Baseline and Week 12] **Secondary endpoints:** Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response [Time Frame: Baseline and Week 12] Number of Participants Achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response [Time Frame: Baseline and Week 12] Change From Baseline in Short Form-36 (SF-36) Physical Component Summary Score [Time Frame: Baseline and Week 12] Number of Participants Achieving ASAS Partial Remission [Time Frame: Week 12] Number of Participants Achieving an ASAS5/6 Response [Time Frame: Baseline and Week 12] Change From Baseline in Disability Index of Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S) [Time Frame: Baseline and Week 12] Change From Baseline in High-Sensitivity C-Reactive Protein (hsCRP) [Time Frame: Baseline and Week 12] Change From Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Score for Sacroiliac Joints [Time Frame: Baseline and Week 12] Change From Baseline in SPARCC MRI Score for the Spine [Time Frame: Baseline and Week 12] **Other endpoints:** Number of Participants Reporting Adverse Events [Time Frame: Through Week 12] Number of Participants With Blood Hematology or Chemistry Values Common Toxicity Criteria Grade ≥ 3 [Time Frame: Through Week 12] Number of Participants Achieving an ASAS20 Response During the Open-label Period [Time Frame: Baseline and Weeks 52, 104, and 156] Number of Participants Achieving an ASAS40 Response During the Open-label Period [Time Frame: Baseline and Weeks 52, 104, and 156] Number of Participants Achieving a BASDAI50 Response During the Open-label Period [Time Frame: Baseline and Weeks 52, 104, and 156]

Trial name: ABILITY-1	NCT number: NCT00939003
Method of analysis	Efficacy variables were analyzed for all randomized 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. A target sample size of 194 patients (97 placebo and 97 adalimumab) was calculated to provide approximately 90% statistical power to detect a 20% difference in ASAS40 response rates between the treatment groups, based on a two-sided $\chi 2$ test with a significance level of 0.05. For categorical variables, patients with missing data at week 12 were 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. AEs were summarized 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 summarized 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.
Other relevant information	N/A

Trial name: PREVENT	NCT number: NCT02696031
Objective	The purpose of this study was to demonstrate the clinical efficacy, safety and tolerability of secukinumab 150 mg, with or without loading doses, compared to placebo in patients with non-radiographic axial spondyloarhritis (nr-axSpA) at Week 16 as well as Week 52.
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, Blanco R, Dokoupilova E, Hall S, Kameda H, Kivitz AJ, Poddubnyy D, van de Sande M, Wiksten AS, Porter BO, Richards HB, Haemmerle S, Braun J. Arthritis Rheumatol. 2021. ▪ 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. ▪ Effect of Secukinumab on Traditional Cardiovascular Risk Factors and Inflammatory Biomarkers: Post Hoc Analyses of Pooled Data Across Three Indications. Merola JF, McInnes IB, Deodhar AA, Dey AK, Adamstein NH, Quebe-Fehling E, Aassi M, Peine M, Mehta NN. Rheumatol Ther. 2022.
Study type and design	PREVENT is a randomized, double-blind, placebo-controlled 2-year phase III study with an extension of up to 2 years in patients with non-radiographic axial SpA, conducted in 24 countries at 130 sites. Approximately 555 patients were randomized to one of three treatment groups (secukinumab 150 mg Load, secukinumab 150 mg No Load or placebo in a ratio of 1:1:1. The study had 2 independent analysis plans per European Union and non-US regulatory requirements (plan A [week 16]) and US regulatory requirements (plan B [week 52]). The study was initiated on April 29, 2016 (first patient's first visit) and is being conducted across 130 sites in 24 countries.
Sample size (n)	555

Trial name: PREVENT	NCT number: NCT02696031
Main inclusion and exclusion criteria	**Main inclusion criteria** • 18 years and older (Adult, Older Adult) • All sexes eligble for study • 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) • 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 ≥ 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 Tumor Necrosis Factor (TNF) α inhibitor (not more than one) must have experienced an inadequate response. **Main 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. • 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	Group 1 (n=185), (secukinumab 150 mg Load): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. prefilled syringe (PFS) at baseline (BSL), Weeks 1, 2 and 3, followed by administration every four weeks starting at Week 4. Group 2 (n=184), (secukinumab 150 mg No Load): secukinumab 150 mg (1 mL, 150 mg/mL) s.c. PFS at BSL, placebo at Weeks 1, 2 and 3, followed by secukinumab 150 mg PFS administration every four weeks starting at Week 4.
Comparator(s)	Group 3 (n=186), (placebo): placebo (1 mL) s.c. PFS at BSL, Weeks 1, 2, 3, followed by administration every four weeks starting at Week 4 Based on the clinical judgment of disease activity by the investigator and the patient, background medications, such as NSAIDs and DMARDs, may have been modified or added to treat signs and symptoms of nr-axSpA from Week 16 on.
Follow-up time	The follow up time was 52 weeks. Analysis on the intention-to-treat (IIT) population was made at week 16 (for EU) and weeks 51 (for US)
Is the study used in the health economic model?	No

Trial name: PREVENT	NCT number: NCT02696031
Primary, secondary and exploratory endpoints	▪ **Endpoints included in this application:** ▪ The Number and Percentage of TNF Naive Participants Who Achieved an Assessment of Spondylo Arthritis International Society (ASAS) 40 Response at Week 16 [Time Frame: Week 16]. ▪ The Number and Percentage of TNF Naive Participants Who Achieved an Assessment of SpondyloArthritis International Society (ASAS) 40 Response at Week 52 [Time Frame: Week 52]. ▪ **Other endpoints:** ▪ The Number and Percentage of Participants Who Achieved an Assessment of SpondyloArthritis International Society (ASAS) 40 Response [Time Frame: Week 16 and week 52]. ▪ The Number and Percentage of Participants Who Achieved an Assessment of SpondyloArthritis International Society (ASAS) 20 Response [Time Frame: Week 16] ▪ The Number and Percentage of Participants Who Achieved an Assessment of SpondyloArthritis International Society (ASAS) 5/6 Response [Time Frame: Week 16] ▪ The Number and Percentage of Participants Who Achieved an Assessment of SpondyloArthritis International Society Partial Remission (ASAS PR) [Time Frame: Week 16] ▪ Change in Bath Ankylosing Spondylitis Functional Index (BASFI) [Time Frame: Baseline and Week 16] ▪ The Number and Percentage of Patients to Achieve a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response [Time Frame: Week 16 and 52] ▪ Change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [Time Frame: Baseline and Week 16] ▪ Change in Ankylosing Spondylitis Quality of Life (ASQoL) Scores at Week 16 [Time Frame: Baseline and Week 16] ▪ Change in Ankylosing Spondylitis Quality of Life (ASQoL) Scores at Week 52 [Time Frame: Baseline and Week 52] ▪ The Number and Percentage of Patients Who Achieved an Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) Inactive Disease [Time Frame: Week 52] ▪ Change in High Sensitivity C-reactive Protein [Time Frame: Baseline and Week 16] ▪ Change in Short Form-36 Physical Component Summary (SF-36 PCS) [Time Frame: Baseline and Week 16] ▪ Change in Sacroiliac Joint Edema [Time Frame: Baseline Week 16, Week 52]

Trial name: PREVENT	NCT number: NCT02696031
Method of analysis	The sample sizes for analysis plans A and B were calculated so as to have 91% and 97% power, respectively, for the primary end point, with a 5% Type I error rate for comparison between secukinumab 150 mg and placebo. The assumed ASAS40 response rates (primary end point) for the corresponding plans were 47.1% and 43.0%, respectively, for secukinumab 150 mg compared with 27.9% and 21.7%, respectively, for placebo. Based on this estimation, at least 185 patients were needed to have 90% power to show superiority versus placebo. Efficacy analyses were performed on the full analysis set, which comprised all patients who were randomized and had study treatment assigned. Primary and secondary end points were analyzed according to a predefined statistical hierarchy 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
Subgroup analyses	Subgroup analysis were pre-specified: The primary endpoint within stratification factor levels (CRP+/MRI+, CRP+/MRI-, and CRP-/MRI+).
Other relevant information	N/A

Trial name: SELECT-AXIS 2	NCT number: NCT04169373
Objective	The objective of the study was to assess the safety and efficacy of upadacitinib, a Janus kinase inhibitor, in a multicenter, randomized, double-blind, placebo controlled, phase III trial in patients with non-radiographic axial spondylarthritis (nr-axSpA) with objective signs of inflammation based on MRI or elevated C-reactive protein and an inadequate response to nonsteroidal anti-inflammatory drugs, measured by assessment of Spondyl Arthritis international Society 40 (ASAS40) response at week 14.
Publications – title, author, journal, year	Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomized, double-blind, placebo-controlled, phase 3 trial. Deodhar A, Van den Bosch F, Poddubnyy D, Maksymowych WP, van der Heijde D, Kim TH, Kishimoto M, Blanco R, Duan Y, Li Y, Pangan AL, Wung P, Song IH. Lancet. 2022 Efficacy and safety of upadacitinib for active ankylosing spondylitis refractory to biological therapy: a double-blind, randomized, placebo-controlled phase 3 trial. van der Heijde D, Baraliakos X, Sieper J, Deodhar A, Inman RD, Kameda H, Zeng X, Sui Y, Bu X, Pangan AL, Wung P, Song IH. Ann Rheum Dis. 2022
Study type and design	The SELECT-AXIS 2 non-radiographic axial spondyloarthritis study was a multicentre, randomized, doubleblind, placebo-controlled, phase 3 trial at 113 sites across 23 countries. Eligible adults had active non-radiographic axial spondyloarthritis with objective signs of inflammation based on MRI or elevated C-reactive protein and an inadequate response to nonsteroidal anti-inflammatory drugs. Patients were randomly assigned (1:1) to receive oral upadacitinib 15 mg once daily or placebo using interactive response technology. Random treatment assignment was stratified by MRI inflammation in the sacroiliac joints and screening high-sensitivity C-reactive protein status (MRI-positive and C-reactive protein-positive, MRI-positive and C-reactive protein-negative, and MRI-negative and C-reactive protein-positive) and previous exposure to biologic disease-modifying antirheumatic drugs (yes vs no). Treatment assignment was masked from patients, investigators, study site personnel, and the study sponsor. The primary endpoint was the proportion of patients with an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14. Analyses were performed on the full analysis set of patients, who underwent random allocation and received at least one dose of study drug.
Sample size (n)	734

Trial name: SELECT-AXIS 2	NCT number: NCT04169373

Main inclusion and exclusion criteria

Main Inclusion criteria:

Study 2:

- Must have a clinical diagnosis of nr-axSpA fulfilling the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS
- Must have objective signs of active inflammation consistent with axSpA on magnetic resonance imaging (MRI) of sacroiliac (SI) joints or based on high sensitivity C-reactive protein (hsCRP) > the upper limit of normal (ULN).
- Prior treatment with at most one bDMARD (either TNF inhibitor or IL-17i) is allowed for at least 20% but no more than 35% of enrolled patients who had to discontinue the prior bDMARD due to either lack of efficacy (after ≥ 12 weeks at an adequate dose) or intolerance (regardless of treatment duration).

- Must have a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 at the Screening and Baseline Visits.
- Must have a Total Back Pain score ≥ 4 based on a 0 - 10 numerical rating scale at the Screening and Baseline Visits.
- Has had an inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs) over an at least 4-week period in total at maximum recommended or tolerated doses, or has an intolerance to or contraindication for NSAIDs as defined by the Investigator.

Main exclusion criteria:

- Must not have been exposed to any Janus kinase (JAK) inhibitor (including but not limited to upadacitinib [Rinvoq®], tofacitinib [Xeljanz®], baricitinib [Olumiant®], filgotinib, ruxolitinib [Jakafi®], abrocitinib [PF-04965842], and peficitinib [Smyraf®]).
- Prior bDMARD therapy must be washed out.
- Participant must not have a history of an allergic reaction or significant sensitivity to constituents of the study drug.

Intervention

Experimental: Study 1: Upadacitinib 15 mg

Participants receive 15 mg upadacitinib orally once a day for 104 weeks. Participants who flare after 104 weeks will receive open-label upadacitinib once daily from the time of flare for 24 weeks (re-treatment).

Experimental: Study 2: Upadacitinib 15 mg

Participants receive 15 mg upadacitinib orally once a day for 104 weeks. Participants who flare after 104 weeks will receive open-label upadacitinib once daily from the time of flare for 24 weeks (re-treatment).

Trial name: SELECT-AXIS 2	NCT number: NCT04169373
Comparator(s)	Placebo Comparator: Study 1: Placebo Participants receive matching placebo for 14 weeks and then switch to receive 15 mg upadacitinib orally once a day for 90 weeks. Participants who flare after 104 weeks will receive open-label upadacitinib once daily from the time of flare for 24 weeks (re-treatment). Placebo Comparator: Study 2: Placebo Participants receive matching placebo for 52 weeks and then switch to receive 15 mg upadacitinib orally once a day for 52 weeks. Participants who flare after 104 weeks will receive open-label upadacitinib once daily from the time of flare for 24 weeks (re-treatment).
Follow-up time	The primary endpoint was the proportion of patients with an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14
Is the study used in the health economic model?	No

Primary, secondary and exploratory endpoints	**Endpoints included in this application:** 1. Study 1: Percentage of Participants Achieving Assessment of SpondyloArthritis International Society (ASAS) 40 Response at Week 14 [Time Frame: Baseline and Week 14] **Other endpoints:** 1. Study 1: Change From Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 14 [Time Frame: Baseline and Week 14] 2. Study 1: Change From Baseline in Magnetic Resonance Imaging (MRI) Spondyloarthritis Research Consortium of Canada (SPARCC) Score for the Spine at Week 14 [Time Frame: Baseline and Week 14] 3. Study 1: Percentage of Participants With Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at Week 14 [Time Frame: Baseline and Week 14] 4. Study 1: Percentage of Participants With an ASAS20 Response at Week 14 [Time Frame: Baseline and Week 14] 5. Study 1: Percentage of Participants With ASDAS Inactive Disease at Week 14 [Time Frame: Week 14] 6. Study 1: Change From Baseline in Patient's Assessment of Total Back Pain at Week 14 [Time Frame: Baseline and Week 14] 7. Study 1: Change From Baseline in Patient's Assessment of Nocturnal Back Pain at Week 14 [Time Frame: Baseline and Week 14] 8. Study 1: Percentage of Participants With ASDAS Low Disease Activity at Week 14 [Time Frame: Week 14] 9. Study 1: Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14 [Time Frame: Baseline and Week 14] 10. Study 1: Percentage of Participants With ASAS Partial Remission at Week 14 [Time Frame: Week 14] 11. Study 1: Change From Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) Score at Week 14 [Time Frame: Baseline and Week 14] 12. Study 1: Change From Baseline in ASAS Health Index at Week 14 [Time Frame: Baseline and Week 14] 13. Study 1: Change From Baseline in Linear Bath Ankylosing Spondylitis Metrology Index (BASMI[Lin]) at Week 14 [Time Frame: Baseline and Week 14] 14. Study 1: Change From Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Week 14 [Time Frame: Baseline and Week 14] 15. Study 1: Change From Baseline in MRI SPARCC Score for Sacroiliac Joints at Week 14 [Time Frame: Baseline and Week 14] 16. Study 2: Change From Baseline in ASDAS at Week 14 [Time Frame: Baseline and Week 14] 17. Study 2: Change From Baseline in MRI SPARCC Score for SI Joints at Week 14 [Time Frame: Baseline and Week 14] 18. Study 2: Percentage of Participants With BASDAI 50 Response at Week 14 [Time Frame: Baseline and Week 14] 19. Study 2: Percentage of Participants With ASDAS Inactive Disease at Week 14 [Time Frame: Week 14] 20. Study 2: Change From Baseline in Patient's Assessment of Total Back Pain at Week 14 [Time Frame: Baseline and Week 14] 21. Study 2: Change From Baseline in Patient's Assessment of Nocturnal Back Pain at Week 14 [Time Frame: Baseline and Week 14]

Trial name: SELECT-AXIS 2	NCT number: NCT04169373

22. Study 2: Percentage of Participants With ASDAS Low Disease Activity at Week 14 [Time Frame: Week 14]
23. Study 2: Percentage of Participants With ASAS Partial Remission at Week 14 [Time Frame: Week 14]
24. Study 2: Change From Baseline in BASFI at Week 14 [Time Frame: Baseline and Week 14]
25. Study 2: Change From Baseline in ASQoL at Week 14 [Time Frame: Baseline and Week 14]
26. Study 2: Change From Baseline in ASAS Health Index at Week 14 [Time Frame: Baseline and Week 14]
27. Study 2: Percentage of Participants Achieving an ASAS20 Response at Week 14 [Time Frame: Baseline and Week 14]
28. Study 2: Change From Baseline in BASMI(Lin) at Week 14 [Time Frame: Baseline and Week 14]
29. Study 2: Change From Baseline in MASES at Week 14 [Time Frame: Baseline and Week 14]
30. Study 2: Change From Baseline in MRI SPARCC Score for the Spine at Week 14 [Time Frame: Baseline and Week 14]
31. Study 2: Percentage of Participants Achieving an ASAS40 Response at Week 52 [Time Frame: Baseline and Week 52]
32. Study 2: Percentage of Participants Rescued Between Week 24 and Week 52 [Time Frame: Week 24 through Week 52]
33. Study 2: Percentage of Participants With ASDAS Major Improvement at Week 52 [Time Frame: Baseline and Week 52]
34. Study 2: Percentage of Participants With ASDAS Inactive Disease at Week 52 [Time Frame: Week 52]
35. Study 2: Percentage of Participants With ASDAS Low Disease Activity at Week 52 [Time Frame: Week 52]

Method of analysis

Efficacy analyses were conducted in the full analysis set, which comprised all randomly assigned patients who received at least one dose of study treatment. A sample size of 304 patients (with a 1:1 randomization ratio) was planned to achieve at least 90% power for the ASAS40 response rate of upadacitinib versus placebo (assuming 42% and 17% response rates, respectively) using a two-sided χ^2 test at a 0·05 significance level. Additionally, the sample size provided at least 80% power for evaluating most multiplicity-controlled secondary endpoints.

A per-protocol analysis of the primary endpoint was performed, excluding patients with major protocol deviations. The primary endpoint was also assessed in patients who were bDMARD-naive versus those who had an inadequate response to bDMARDs and who had previous exposure to a TNF inhibitor versus previous exposure to an IL-17 inhibitor.

Safety evaluations were based on the safety analysis set, which included all patients who received at least one dose of study treatment. Binary endpoints were analysed using the Cochran-Mantel-Haenszel test stratified by the main stratification factor of positivity for MRI inflammation in the sacroiliac joints and screening high-sensitivity C-reactive protein status (MRI-positive and C-reactive protein-positive, MRI-positive and C-reactive protein-negative, and MRI-negative and C-reactive protein-positive). Non-responder imputation incorporating multiple imputation was used for handling missing data and intercurrent events.

Trial name: SELECT-AXIS 2	NCT number: NCT04169373
Subgroup analyses	Assessment of MASES was performed in the subgroup of patients with pre-existing enthesitis, defined as MASES greater than 0 at baseline. Additional efficacy outcomes without multiplicity adjustment included ASDAS major improvement and clinically important improvement (appendix p 2),[27] changes from baseline in individual ASAS and ASDAS components,[25] and SPARCC MRI spine inflammation score. Post-hoc subgroup analyses were conducted for the primary endpoint by previous bDMARD exposure (naive *vs* inadequate response), the type of previous bDMARD used (TNF inhibitor *vs* IL-17 inhibitor), and baseline MRI sacroiliitis and screening high-sensitivity C-reactive protein status (MRI-positive and high-sensitivity C-reactive protein-positive *vs* MRI-positive and high-sensitivity C-reactive protein-negative *vs* MRI-negative and high-sensitivity C-reactive protein-positive).
Other relevant information	N/A

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

The baseline characteristics of patients in studies used for the comparative analysis are presented in the tables below. In the SELECT-AXIS 2 trial, approximately a third of the patients had previous exposure to bDMARD; baseline patient characteristics for these patients are also presented in the tables.

Table 6. Baseline patient characteristics, continuous data.

Study	Arm	N randomized	Age (years)	CRP* (mg/L)	Diagnosis duration (years)	Symptoms duration (years)	BASDAI (0-10)	BASFI (0-10)	Total Back Pain (0-10)
ABILITY-1	PBO	94	38.40 (10.4))	7.60 (10.2)	3.00 (3.8)	10.10 (8.8))	6.50 (1.6))	4.90 (2.3)	7.00 (1.7)
ABILITY-1	ADA40	91	37.60 (11.3))	6.80 (11.8)	2.70 (4.2)	10.10 (9.0)	6.40 (1.5)	4.50 (1.9)	6.90 (1.8)
ABILITY-1 OSI+	*PBO*	*73*	*38.30 (10.49)*	*9.3 (10.94)*	*3.10 (3.83)*	*10.37 (9.17)*	*6.38 (1.50)*	*4.82 (23.1)*	*6.7 (1.7)*
ABILITY-1 OSI+	*ADA40*	*69*	*38.30 (11.70)*	*8.6 (13.07)*	*2.52 (3.96)*	*10.71 (9.62)*	*6.43 (1.55)*	*4.47 (20.6)*	*7.0 (1.9)*
PREVENT	PBO	186	39.30 (0.84)	10.76 (1.56)	2.96 (0.37)	8.39 (0.61)	6.76 (0.09)	5.89 (0.14)	7.09 (0.09)
PREVENT	SEC150	185	39.10 (0.84)	13.17 (2.00)	2.75 (0.34)	8.72 (0.68)	7.08 (0.10)	6.24 (0.15)	7.33 (0.10)
PREVENT	SEC150 (no LD)	184	39.80 (0.86)	9.67 (1.17)	2.12 (0.22)	8.57 (0.64)	6.93 (0.11)	5.92 (0.15)	7.20 (0.11)
SELECT-AXIS-2	PBO	157	42.50 (12.4)	10.5 (13.5)	4.4 (5.8)	9.20 (8.1)	6.9 (1.2)	6.0 (2.1)	7.30 (1.4)
SELECT-AXIS-2	UPA15	156	41.60 (12.0)	13.6 (24.8)	4.5 (5.5)	9.00 (7.9)	6.8 (1.3)	5.9 (2.1)	7.20 (1.6)
SELECT-AXIS-2 bDMARD-IR	*PBO*	*54*	*45.0 (11.21)*	*7.16 (9.03)*	*5.19 (4.67)*	*9.67 (7.29)*	*7.12 (1.28)*	*6.44 (1.98)*	*7.6 (1.40)*
SELECT-AXIS-2 bDMARD-IR	*UPA15*	*49*	*44.8 (10.72)*	*5.59 (4.83))*	*6.37 (6.48)*	*11.44 (7.91)*	*6.87 (1.19)*	*6.19 (2.08)*	*7.4 (1.48)*

All data is presented as Mean (SD). *hsCRP at screening

Table 7. Baseline patient characteristics, binary data.

Study	Arm	N randomized	bDMARD-experienced (%)	Male (%)	HLA-B27 (%)	SI MRI+ (%)	CRP+ (%)	OSI+ (%)	Concomitant NSAID (%)	Concomitant csDMARD (%)	Concomitant glucocorticoid (%)
ABILITY-1	PBO	94	0.00%	42.55%	74.47%	45.75%	38.3%	77.66%	78.72%	17.02%	7.4%
ABILITY-1	ADA40	91	0.00%	48.35%	82.42%	50.55%	39.6%	75.82%	79.12%	18.68%	9.9%
ABILITY-1 OSI+	*PBO*	*73*	*0.00%*	*45.2%*	*79.5%*	*43.8%*	*50.7%*	*100%*	*76.7%*	*15.1%*	*5.5%*
ABILITY-1 OSI+	*ADA40*	*69*	*0.00%*	*46.4%*	*81.2%*	*58.0%*	*42.0%*	*100%*	*79.7%*	*20.3%*	*8.7%*
PREVENT	PBO	186	8.06%	48.93%	69.36%	74.73%	56.45%	100.00%	83.87%	27.96%	9.14%
PREVENT	SEC150	185	11.35%	43.24%	73.51%	71.35%	56.22%	100.00%	83.24%	24.86%	7.57%
PREVENT	SEC150 (no LD)	184	9.78%	45.65%	63.59%	72.83%	58.15%	100.00%	83.15%	21.20%	9.24%
SELECT-AXIS-2	PBO	157	34.39%	40.13%	59.24%	42.04%	54%	100.00%	71.98%	31.85%	10.83%
SELECT-AXIS-2	UPA15	156	31.41%	42.95%	57.69%	44.87%	64%	100.00%	77.56%	26.28%	11.54%
SELECT-AXIS-2 bDMARD-IR	*PBO*	*54*	*100%*	*42.6*	*48.1%*	*37.0%*	*63.0%*	*100%*	*NA*	*NA*	*NA*
SELECT-AXIS-2 bDMARD-IR	*UPA15*	*49*	*100%*	*26.5*	*56.5%*	*36.7%*	*63.3%*	*100%*	*NA*	*NA*	*NA*

CRP+(%): Proportion of patients with hsCRP>5mg/l at screening for PREVENT and SELECT-AXIS-2 and Upper Limit of Normal (ULN) for ABILITY-1

Comparability of patients across studies

The analysis of comparability across studies is carried out in patient baseline characteristics from the full study population of the respective studies.

Demographics

The overall mean age of patients in the study falls within a relatively narrow range of 37.6 to 42.5, as does the overall mean proportion of male patients, with a range of 40.1% to 52.08%.

Disease characteristics:

The baseline duration of nr-AxSpA (years) at inclusion were similar between the three studies, for both time from first symptom and time from diagnosis. Patients in ABILITY-1 and PREVENT had slightly shorter time from diagnosis, but similar time from first symptom. The mean proportion HLA- B27 positive patients in the RCTs was within a relatively narrow range of 57.7% to 82.42%. The proportion CRP+ – one of two types of OSI – of included RCTs had a range between studies of 31.87%to 63.46%. Of note, much of the difference can be explained by the threshold for elevated CRP used across the RCTs. Specifically, ABILITY-1, used the upper limit of normal (ULN), and PREVENT and SELECT-AXIS-2 used greater than 5 mg/L. The proportion MRI+ – one of two types of OSI – of included RCTs had a range between studies of 42.0% to 74.29%. Two of the included RCTs enrolled only nr-AxSpA patients with OSI; only ABILITY-1 allowed enrollment of patients without it. The proportion of patients without OSI is 77% in ABILITY-1.

Clinical scores:

The overall baseline BASDAI score (range 6.40 – 7.30), BASFI score (range 4.50 – 6.70) and Total Back Pain Score (6.90 – 7.40) in the included RCTs were all within a relatively narrow range.

Treatments:

The proportion with prior biologic use of included RCTs had a range of 0% to 34.4%. ABILITY-1 included no patients with prior biologic use, while SELECT-AXIS-2 included about one-third and PREVENT that included about 10%. of patients with prior biologic use. The proportion of concomitant NSAID had a range of 71.98% to 93.14%., while the proportion of concomitant csDMARD use of included RCTs differed between 17.02% and 41.67%. Finally, the proportion of concomitant glucocorticoid was between 8.33% and 19.6%. Only SELECT-AXIS-2 reported on this characteristic.

In summary, there appears to be some small cross-study heterogeneity with respect to baseline patient characteristics among the included RCTs. The demographics of the populations, in terms of age and gender, appear to be similar. The disease characteristics of the populations are likewise similar with respect to nr-AxSpA with OSI (all RCTs had >75% with OSI, with most having 100%), though the OSI make-up (CRP+ and/or MRI+) of patients differ across the RCTs (e.g., SELECT-AXIS-2 had approximately 50% CRP+ and 50% MRI+ patients, while other RCTs had more MRI+ patients). The baseline clinical scores of the populations, in terms of BASDAI, BASFI, and Total Back Pain scores, appear to be similar with minimal cross-study heterogeneity.

Finally, the baseline treatments of the populations, in terms of prior biologic use, concomitant NSAID use, concomitant csDMARD use, and concomitant glucocorticoid use, appear to be likewise similar, with the exception that there were more bDMARD-exposed patients in PREVENT and SELECT-AXIS-2. This difference is likely to result in a conservative estimate of the efficacy of upadacitinib compared to adalimumab, and secukinumab, as patients with prior biological treatments show a slightly smaller treatment benefit.

Comparability of the study populations with Danish patients eligible for treatment

The patients eligible for treatment with upadacitinib in Denmark are not expected to differ in any significant way from the patients included in the clinical studies used in this application.

Appendix D - Efficacy and safety results per study.

Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
ASAS40	ASAS 40 response was defined as improvement of ≥ 40% relative to Baseline and absolute improvement of ≥ 2 units (on a scale from 0 to 10) in ≥ 3 of the following 4 domains with no deterioration (defined as a net worsening of > 0 units) in the potential remaining domain: • Patient's global assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (no activity) to 10 (severe activity); • Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe pain); • Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible); • Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).	ASAS40 is defined as the preferred primary endpoint in in EMA:s Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis (1)	ASAS40 has previously been used to evaluate products for nr-axSpA in Denmark (2) , and the ASAS 40 response criteria is described as a preferred primary endpoint in EMA:s Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis.(1): The ASAS 40 response criteria would be the preferred primary endpoint. This index has been already used in several trials and may be considered an appropriate primary efficacy end point to assess clinically relevant responses.
BASDAI50	The BASDAI assesses disease activity by asking the participant to answer 6 questions (each on an 11 point numeric rating scale [NRS]) pertaining to symptoms experienced for the past week. For Questions 1 to 5 (level of fatigue/tiredness, level of AS neck, back or hip pain, level of pain/swelling in joints, other than neck, back or hips, level of discomfort	BASDAI 50 is recommended as an endpoint in EMA:s Guideline on the Clinical	BASDAI 50 has previously been used to evaluate products for nr-axSpA in Denmark (2). BASDAI 50 is recommended as an endpoint in EMA:s Guideline on the Clinical

Outcome measure	Definition	Validity	Clinical relevance
	from any areas tender to touch or pressure, and level of morning stiffness), the response is from 0 (none) to 10 (very severe); for Question 6 (duration of morning stiffness), the response is from 0 (0 hours) to 10 (≥ 2 hours). The overall BASDAI score ranges from 0 to 10. Lower scores indicate less disease activity. A BASDAI 50 response is defined as improvement of 50% or more from Baseline in BASDAI score.	Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis(1)	Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis.(1): It (BASDAI) 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
ASDAS>2.1	ASDAS is a composite index to assess disease activity in Ankylosing Spondylitis. ASDAS combines the following 5 disease activity variables using a weighted formula • Patient's assessment of total back pain (BASDAI Question 2; NRS score 0 [none] - 10 [very severe]) • Patient global assessment of disease activity (NRS score 0 [no activity] - 10 [severe activity]) • Peripheral pain/swelling (BASDAI Question 3; NRS score 0 [none] - 10 [very severe]) • Duration of morning stiffness (BASDAI Question 6; NRS score 0 [0 hours] - 10 [2 or more hours]) • High-sensitivity C-reactive protein (hs-CRP) in mg/L. The overall score ranges from 0 with no defined upper score. ASDAS Low Disease Activity is defined as an ASDAS score < 2.1.	ASDAS is recommended as an endpoint in EMA:s Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis(1)	ASDAS<2.1 has previously been used to evaluate products for nr-axSpA in Denmark (2). ASDAS is recommended as an endpoint in EMA:s Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis.(1)
Withdrawal due to adverse events	Proportion of patients withdrawing from treatment due to adverse events.	-	Commonly used to describe of adverse events in clinical trials.

Outcome measure	Definition	Validity	Clinical relevance
Withdrawal from treatment	Proportion of patients withdrawing from treatment	-	Commonly used in reporting of clinical trials.
ASQoL	The ASQoL consists of 18 items related to quality of life, including the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. Each item is answered as yes (scored as 1) or no (scored as 0). Scores are summed to obtain the overall score which ranges from 0 to 18, where higher scores indicate a worse quality of life. A negative change from Baseline in ASQoL indicates improvement in quality of life.	ASQoL is recommended as an endpoint in EMA:s Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis(1)	ASQoL is recommended as an endpoint in EMA:s Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis(1)

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Table A3a Results of ABILITY-1 (NCT00939003) at week 12, full study population												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		(3)
ASAS40 at week 12	Adalimumab	91	36.3 %	21.4 percentage units	8.84; 33.15	0.001	2.43	1.40; 4.24	0.001	See appendix B	
	Placebo	94	14.9 %								
BASDAI50 at week 12	Adalimumab	91	38.5%	22.5 percentage units	10.1; 35.0	0.001	2.41	1.42; 4.10	0.001	See appendix B	
	Placebo	94	16.0%								
Withdrawal due to adverse events	Adalimumab	95	2.10 %	1,13 percentage units	-2.52; 4.80	NC	2.07	0,19; 22.4	0.562	See appendix B	
	Placebo	97	1.03 %								
Withdrawal from treatment	Adalimumab	91	4.39 %	2.26 percentage units	-2.86; 7.39	NC	2,07	0.39; 11,0	0.402	See appendix B	
	Placebo	94	2,13%								
Results for patients in ABILITY-1 (NCT00939003) with OSI+ at baseline at week 12											
ASAS 40	Adalimumab	69	40.6%	26.9 percentage units	12.9; 40.0	NC	2.96	1.56; 5.63	0.001	See appendix B	(4)
	Placebo	73	13.7%								
BASDAI 50	Adalimumab	69	39.1%	25.0 percentage units	11.5; 39.4	NC	2.86	1.50; 5.45	0.002	See appendix B	
	Placebo	73	13.7%								

NC Not Calculated

Table A3b Results of PREVENT (NCT02696031) at week 16

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		(5)
ASAS40 at week 16	Secukinumab, Load	185	40.0	12.0 pertentage units	2.44; 21.6	0.0108	1.43	1.05; 1.94	0.023	See appendix B	
	Placebo	186	28.0								
BASDAI50 at week 16	Secukinumab, Load	185	37.3	16.3 percentage units	7.2; 24.4	0.0001	1.78	1.25; 2.52	0.001	See appendix B	
	Placebo	186	21.0								
ASDAS<2.1	NA										
	NA										
ASQoL, CFB	Secukinumab, Load	185	-3,45	-1.61	-2.54; -0.67	0.008	NC (data is CFB)				
	Placebo	186	-1,84								
Withdrawal from	Secukinumab, Load	185	5.41 %	-0.5 percentage units	-5.21; 4.19	1.00	0.91	0.40; 2.10	1.00	See appendix B	

Table A3b Results of PREVENT (NCT02696031) at week 16										
treatment at week 24	Placebo	186	5.91%							
Withdrawal due an adverse events at week 20	Secukinumab, Load	185	0.0%	-1.61 percentage units	-3.42; 0.197	0.3717	0.2513	0.028-2.228	0.3717	See appendix B
	Placebo	186	1.61%							

Table A3c Results of PREVENT (NCT02696031) at week 52										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		(5)
ASAS40 at week 52	Secukinumab, Load	185	33.5%	14.1 percentage units	5.24; 23.0	0.0015	1.73	1.2; 2.5	0.003	See appendix B	
	Placebo	186	19.4%								
BASDAI50 at week 52	Secukinumab, Load	185	30.8%	10.9 percentage units	2.1; 19.7	0.0001	1.55	1.1; 2.2	0.017	See appendix B	
	Placebo	186	19.9%								
Serious infections	Secukinumab, Load	185	1.8%	0,02 percentage units	-2.4; 2.8	-	1.13	0.24; 5.3	-		

Table A3c Results of PREVENT (NCT02696031) at week 52											
	Placebo	186	1.6%								
Serious Adverse events	Secukinumab, Load	185	10.8%	3.6 percentage units	-2.2; 9.4	-	1.5	0.77; 2.9	-		
	Placebo	186	7.2%								
Withdrawal from treatment	Secukinumab, Load	185	15.7%	1.7 percentage units	--5.5; 8.9	-	1.12	0.69; 1.8	-	See appendix B	
	Placebo	186	14.0%								
Withdrawal due an adverse events	Secukinumab, Load	185	3.8%	-0.6 percentage units	-4.6; 3.4	-	0.86	0.32; 2.3	-	See appendix B	
	Placebo	186	4.4%								

Table A3d Results of SELECT-AXIS 2: (NCT04169373) at week 14											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		(6)
ASAS40 at week 14	Upadacitinib	156	44.9%	22.2 percentage units	12.1; 32.3	< 0.0001	2.01	1.43; 2.83	0.0001	See Appendix B	
	Placebo	157	22.5%								

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Table A3d Results of SELECT-AXIS 2: (NCT04169373) at week 14

BASDAI50 at week 14	Upadacitinib	156	42.3%	20.1 percentage units	10.1; 30.1	<0.0001	1.90	1.34; 2.68	0.0003	See Appendix B	
	Placebo	157	22.1%								
ASDAS<2.1at week 14	Upadacitinib	156	42.3%	23.8 percentage units	14.2; 33.4	<0.0001	2.29	1.57; 3.34	<0.0001	See Appendix B	
	Placebo	157	18.3%								
ASQoL (Mean CFB)	Upadacitinib	156	-5.38	-2.23	-3.26; -1.21	<0.0001	NC (data is CFB)	See Appendix B			
	Placebo	157	-3.15								
Withdrawal from treatment	Upadacitinib	156	7.05%	2.59 percentage units	-2.56; 7.75%	NC	1.58	0.63; 3.97	0.335	See Appendix B	
	Placebo	157	4.46%								
Withdrawal due to adverse events	Intervention	156	2,56%	1.29 percentage units	-1.75; 4.33	NC	2.01	0.37; 10.83	0.423	See Appendix B	
	Comparator	157	1,27%								
SF-36 PCS (Mean CFB)	Upadacitinib	156	8.2	3.9	-	<0.001	NC (data is CFB)			See Appendix B	(7)
	Placebo	157	4.3								

Table A3e Results of SELECT-AXIS 2: (NCT04169373) at week 12

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Source

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Table A3e Results of SELECT-AXIS 2: (NCT04169373) at week 12

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		AbbVie data on file
ASAS40 at week 12	Upadacitinib	156	46.15%	23.2 percentage units	13.0; 33.44	N	2.01	1.44; 2.81	<0.0001	See Appendix B	
	Placebo	157	22.9%								
BASDAI50 at week 12	Upadacitinib	156	21.0%	21.9 percentage units	12.05; 31.79	NC	2.15	1.48, 23.12	0.0001	See Appendix B	
	Placebo	157	19.11%								

NC Not Calculated

Table A3f Results of SELECT-AXIS 2: (NCT04169373) at week 52

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		(8)
ASAS40 at week 52	Upadacitinib	157	62.8 %	20.1 percentage units	9.26; 30.9	<0.001	1.47	1.18; 1.83		See Appendix B	
	Placebo	156	42.7%								
BASDAI50 at week 52	Upadacitinib	157	56 %	16.0 percentage units	5.07, 26.9	<0.01	1.4	1.10; 1,77		See Appendix B	
	Placebo	156	40 %								
	Upadacitinib	157	55.8 %		12.6, 34.0	<0.0001	1.72	1.32; 2.24		See Appendix B	

Table A3f Results of SELECT-AXIS 2: (NCT04169373) at week 52											
ASDAS<2.1at week 52	Placebo	156	32.5 %	23.3 percentage units							
ASQoL (Mean CFB) at week 52	Upadacitinib	157	-7.2	1.4	-	<0.05	NC (Data is CFB)				
	Placebo	156	-5.8								
Withdrawal from treatment	Upadacitinib	156	17%	0 percentage units	-	NC	0	-	-		
	Placebo	157	17%								
Withdrawal from treatment due to adverse events	Upadacitinib	156	3.8%	1.3 percentage units	-2.6; 5.2	NC	1.520	0,43; 5.34			
	Placebo	157	2.5%								
Serious adverse events	Upadacitinib	157	3.8%	0 percentage units	-	-	-	-	See Appendix B	(8)	
	Placebo	156	3.8%								
Serious infections	Upadacitinib	157	1.3%	0.6 percentage units	-1.5; 2.8	-	1.99	0.18; 21.7	See Appendix B	(8)	
	Placebo	156	0.6%								

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Table A3g Results of SELECT-AXIS 2: (NCT04169373) at week 14 b/tsDMARD experienced population

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		**AbbVie data on file**
ASAS40 at week 14	Upadacitinib	49	32.7 (19.5;45.8)	8.7 percentage units	-8.4; 25.7		1.36	0.73; 2.52		See Appendix B	
	Placebo	54	24.1 (12.7;35.5)								
BASDAI50 at week 14	Upadacitinib	49	32.7 (19.5;45.8)	8.3 percentage units	-8.2; 24.8		1.36	0.73; 2.52		See Appendix B	
	Placebo	54	24.1 (12.7; 35.5)								
ASDAS<2.1at week 14	Upadacitinib	49	30.6 (17.7; 43.5)	13.6 percentage units	-2.1; 29.4		1.84	0.89; 3.81		See Appendix B	
	Placebo	54	16.7 (6.7; 26.6)								
ASQoL (Mean CFB)	Upadacitinib	46	-3.97	-0.06	-1.87; 1.75		NC (Data is CFB)				
	Placebo	52	-4.03								

Table A3h Results of SELECT-AXIS 2: (NCT04169373) at week 52 b/tsDMARD experienced population

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		**AbbVie data on file**
ASAS40 at week 52	Upadacitinib	49	57.1 (43.3; 71.0)	10.9 percentage units	-8.2; 29.9		1.23	0.85; 1.80		See Appendix B	
	Placebo	54	46.3 (33.0; 59.6)								
BASDAI50 at week 52	Upadacitinib	49	46.9 (33.0; 60.9)	6.1 percentage units	-12.9; 25.2		1.15	0.74; 1.79		See Appendix B	
	Placebo	54	40.7 (27.6, 53.8)								
ASDAS<2.1at week 52	Upadacitinib	49	42.9 (29.0, 56.7)	13.0 percentage units	-1.5; 31.1		1.45	0.86; 2.44		See Appendix B	
	Placebo	54	29.6 (17.5, 41.8)								
ASQoL (Mean CFB) at week 52	Upadacitinib	38	-5.74 (-7.14, -4.34)	0.11	-1.81, 2.03		NC (Data is CFB)				
	Placebo	41	-5.85 (-7.18, -4.52)								

Appendix E - Safety data for intervention and comparators

Safety outcomes reported in the SELECT AXIS 2 trial.

	Placebo group (n=157)		Upadacitinib group (n=156)	
Any adverse event	72	45,9%	75	48,1%
Serious adverse events	2	1,3%	4	2,6%
Discontinuation of study drug due to adverse event	2	1,3%	4	2,6%
COVID-19-related adverse event	10	6,4%	8	5,1%
Death	0	0,0%	0	0,0%
Infection	36	22,9%	36	23,1%
Serious infection	1	0,6%	2	1,3%
Opportunistic infection	0	0,0%	0	0,0%
Active tuberculosis	0	0,0%	0	0,0%
Herpes zoster	1	0,6%	2	1,3%
Malignancy	1	0,6%	0	0,0%
Malignancy other than NMSC	0	0,0%	0	0,0%
Non-melanoma skin cancer	1	0,6%	0	0,0%
Lymphoma	0	0,0%	0	0,0%
Hepatic disorder	5	3,2%	4	2,6%
Anaemia	0	0,0%	1	0,6%
Neutropenia	0	0,0%	5	3,2%
Lymphopenia	0	0,0%	0	0,0%
Renal dysfunction	0	0,0%	0	0,0%
Gastrointestinal perforation (adjudicated)	0	0,0%	0	0,0%
Major adverse cardiovascular events (adjudicated)	0	0,0%	0	0,0%
Venous thromboembolic events (adjudicated)	0	0,0%	0	0,0%
Uveitis	0	0,0%	1	0,6%
Inflammatory bowel disease	0	0,0%	0	0,0%
Psoriasis	0	0,0%	0	0,0%

Adverse events reported during the in ABILITY-1.

	Placebo (N=97), n (%)	Adalimumab (N=95), n (%)
Any AE	57 (58,8)	55 (57,9)
Serious AE	1 (1,0)	3 (3,2)
AE leading to discontinuation of study drug	1 (1,0)	2 (2,1)
Infectious AE	28 (28,9)	28 (29,5)
Serious infection	0	0
Malignancy	0	0
Hepatic-related AE	4 (4,1)	4 (4,2)

Appendix F - Comparative analysis of efficacy and safety

Indirect treatment effect estimates and their 95% confidence intervals, were produced by using the method described by Rücker (9), and Rücker and Schwarzer (10). This approach, widely used and aligned with guidance from NICE (11), ISPOR (12) and the Cochrane institute (13), is derived from graph theoretical techniques, which were originally developed for electrical networks. The advantage of this model lies in a combination of the Bucher's method and the adjustment for multi-arm studies (14). When only indirect comparisons are envisioned (there is no closed loop in the evidence network), such as in our scenario, the method described by Rücker and Schwarzer corresponds to the method of adjusted indirect comparison as described by Bucher.

The netmeta package allows to perform a network meta-analysis within a frequentist framework. It is based on a frequentist weighted least squares approach, described by Rücker (9), and Rücker and Schwarzer (10). Extensive examples as well as the R code and the statistical methods involved, are presented in the book Meta-Analysis with R (Chapter 8 on network meta-analysis https://link.springer.com/book/10.1007/978-3-319-21416-0). As netmeta package uses contrast-level data as input, we used the function pairwise available in the R package netmeta to convert the arm-level data into contrast-level data in each trial (relative treatment effect for OR and RR using the logarithmic transformation, absolute treatment effect for RD).

Results of indirect treatment comparison between upadacitinib and adalimumab

Endpoint	OR (95% CI)	RR (95% CI)	Method used for indirect treatment comparison
ASAS40	0,67 (0,26, 1,74)	0,68 (0,33, 1,40)	Bucher analysis
BASDAI50	0,73 (0,28, 1,92)	0,75 (0,36, 1,59)	

. Results of the indirect treatment comparison of upadacitinib versus secukinumab

Endpoint	OR (95% CI)	RR (95% CI)	Method used for indirect treatment comparison
ASAS40	1,65 (0,86; 3,18)	1,41 (0,90; 2,20)	Bucher analysis
BASDAI50	1,14 (0,58; 2,24)	1,07 (0,66; 1,73)	

Appendix G - Extrapolation

No extrapolations of relative efficacy are included in the cost minimization analysis as treatments are assumed to be equally efficacious.

Appendix H - Literature search for HRQoL data

No health-related quality of life data is included in the analysis, as treatments are assumed to be equally efficacious with no difference in HRQoL outcomes. A literature search for HRQoL data was not considered necessary.

Appendix I - Mapping of HRQoL data

No health-related quality of life data is included in the model, as treatments are assumed to be equally efficacious with no difference in HRQoL outcomes.

Appendix J Probabilistic sensitivity analyses

No probabilistic sensitivity analyses were performed.

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