Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende risankizumab til behandling af psoriasisartrit

Vers. 1.0

Bilagsoversigt

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

Date: 01.07.2022

AbbVie response to The Danish Medicines Council evaluation report of risankizumab (Skyrizi) for the treatment of psoriatic arthritis

First of all, AbbVie would like to thank The Danish Medicines Council for the evaluation draft report and for the opportunity to comment on the contents of the report.

AbbVie would like to use this opportunity to provide a few comments to the report that can be included in the final assessment of risankizumab.

Risankizumab have demonstrated to have at least similar efficacy to relevant comparators in both bio-naïve and bio-experienced population with PsA

The indirect treatment comparison, using a widely known methodology, and assessing the clinical efficacy compared to adalimumab and ixekizumab, demonstrated no statistical difference for relative risk on relevant joint, skin and PRO outcomes – as is also the conclusion in the Medicines Council report. Furthermore, risankizumab demonstrated a clear benefit on PASI90 compared to adalimumab with a confidence interval considerably weighted above 1, meaning close to statistical significance (1.71 [0.98, 2.98]). The Medicines council only reported relative risk (RR) values from the indirect comparison, and AbbVie would like to note that the Odds Ratio (OR) results for PASI90 from the indirect comparison was statistically significant in favor of risankizumab vs. adalimumab (2.19 [1.21, 3.94], P-value: 0.009). This further suggests an added benefit on skin symptoms with risankizumab.

For many patients with PsA, symptoms related to skin is still most burdensome and there is a need for treatments with great efficacy on skin as well as maintaining good efficacy on joint symptoms

The Medicines Council comments that for most PsA patients, the burden of disease is mostly connected to joint symptoms. AbbVie acknowledges that for many PsA patients' symptoms related to joints can be most burdensome and risankizumab have demonstrated that there is no statistically significant difference between risankizumab and other treatment options on joint symptoms and that Skyrizi by this maintain the effect on joint symptoms.

However, AbbVie would like to point out that there still are a significant proportion of PsA patients where skin symptoms constitutes the main proportion of their disease burden. Skin symptoms associated with PsA manifest often as moderate-to-severe forms of the disease (1,2) and approximately one third of patients with psoriasis develop psoriatic arthritis. Additionally, the presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA (3,4). Skin symptoms is therefore an important symptom that many of PsA patients need better treatment for. Risankizumab, with its better efficacy on skin symptoms as well as maintained effect on joint symptoms, represent a very valuable treatment alternative for patients with PsA, especially for patients who predominantly suffer from skin symptoms.

Risankizumab represent a new MoA, currently not included in treatment recommendations for PsA

In the current treatment recommendations for PsA in Denmark, there exist no selective IL-23 inhibitor. Ustekinumab exist in the treatment recommendations, however it is selective to both IL-12 and IL-23. It is also not considered clinically equal to other approved treatment for PsA in Denmark.

There is therefore a need for new mode-of-actions (MoA) in the treatment recommendations that is considered clinically equal. Risankizumab have in this report demonstrated to provide good efficacy on skin with maintained efficacy on joint symptoms and represents a new MoA that is not covered by current treatment options in the recommendations. Risankizumab also provide another benefit with a 12-week maintenance dosing interval, which is considerably lower than the other treatment options included in the recommendations, reducing the burden of injections for patients.

Introduction of new treatment options always lead to more competition

The use of risankizumab for the treatment of PsA in clinical practice will be dictated by the ranking in the treatment recommendations, resulting in that risankizumab will only be used for eligible patients ahead of more expensive treatments when no cheaper alternatives are available anymore. If risankizumab is used as expected according to ranking in the treatment recommendations, introducing risankizumab will in reality be cost saving.

References:

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Annals of the Rheumatic Diseases. 2005;64(suppl 2):ii14.

2. de Vlam K, Merola JF, Birt JA, Sandoval DM, Lobosco S, Moon R, et al. Skin involvement in psoriatic arthritis worsens overall disease activity, patient-reported outcomes, and increases healthcare resource utilization: an observational, cross-sectional study. Rheumatology and therapy. 2018;5(2):423–36.

3. Scotti L, Franchi M, Marchesoni A, Corrao G. Prevalence and incidence of psoriatic arthritis: a systematic review and meta-analysis. In Elsevier; 2018. p. 28–34.

4. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. Journal of the American Academy of Dermatology. 2008;58(5):826–50.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

09.08.2022

SNI, DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	31.08.2022
Leverandør	AbbVie
Lægemiddel	Skyrizi (risankizumab)
Ansøgt indikation	Psoriasisartrit

Forhandlingsresultat

Amgros har følgende pris på Skyrizi (risankizumab).

Tabel 1: Pris på Skyrizi (risankizumab)

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP	Nuværende SAIP	Rabatprocent ift. AIP
Skyrizi (risankizumab)	150 mg, SC Pen/sprøjte	1 stk.	25.298,93	[redacted]	[redacted]
Skyrizi (risankizumab)	75 mg, SC sprøjte	2 stk.	25.298,93	[redacted]	[redacted]

Skyrizi er en del af det dynamiske udbud, som blev gennemført på baggrund af behandlingsvejledninger for biologiske lægemidler, indenfor reumatologi, dermatologi og gastroenterologi.

I det dynamisk udbud for de biologiske lægemidler, er der mulighed for prisregulering hver 6. måned (næste gang den 01.10.2022).

Konkurrencesituationen

Nedenstående tabel viser et udvalg af lægemidlerne godkendt til samme indikation. Prisen på Hyrimoz er gældende indtil 31.3.2024. Priserne på de øvrige lægemidler er gældende frem til den 01.10.2022, hvor der er mulighed for prisjustering.

Tabel 2: Sammenligning af udvalgte lægemidler fra lægemiddelrekommandationen og deres priser

Lægemiddel	Opstart sammenligningsdosis	Vedligeholdelse sammenligningsdosis	Antal mg/18 måneder	Lægemiddelpris SAIP pr. 18 md. (DKK)
Skyrizi (risankizumab)	150 mg (SC) i uge 0 og 4	150 mg hver 12. uge	1.075 mg	[redacted]
Hyrimoz (adalimumab)	40 mg hver 2. uge		1.560 mg	[redacted]
Taltz (ixekizumab)	160 mg (SC) i uge 0	80 mg hver 4. uge	1.640 mg	[redacted]

Status fra andre lande

Under vurdering i Norge[1].

Konklusion

Leverandøren har mulighed for at justere prisen i den kommende prisregulering for den næste periode 01.10.22 - 31.03.23.

Indenfor psoriasisartrit er der ingen gældende behandlingsvejledning så det vil være regionerne som vil se på lægemidlerne i relation til hinanden.

[1] https://nyemetoder.no/metoder/risankizumab-skyrizi-indikasjon-ii

Application for the assessment of Skyrizi (risankizumab) for the treatment of active psoriatic arthritis

Date: December 6th, 2021

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1. Basic information

Contact information	
Name	**Lars Eskildsen**
Title	Head of Market Access Denmark
Phone number	+45 42 14 28 55
E-mail	lars.eskildsen@abbvie.com
Name	**Christoffer Tærud**
Title	HEOR and HTA Manager, Scandinavia
Phone number	+46 73 035 91 23
E-mail	christoffer.taerud@abbvie.com
Name	**Louise Greve Dal**
Title	HEOR and HTA Manager, Scandinavia
Phone number	+45 30 29 57 00
E-mail	louise.dal@abbvie.com
Name	**Alexandra Nystrand**
Title	Medical advisor, Rheumatology
Phone number	+46 70 352 34 55
E-mail	alexandra.nystrand@abbvie.com

Overview of the pharmaceutical	
Proprietary name	Skyrizi
Generic name	Risankizumab
Marketing authorization holder in Denmark	AbbVie
ATC code	L04AC18
Pharmacotherapeutic group	Immunosuppressants, interleukin inhibitors

Overview of the pharmaceutical	
Active substance(s)	Risankizumab
Pharmaceutical form(s)	Solution for injection in pre-filled pen and pre-filled syringe
Mechanism of action	Humanized monoclonal antibody of the IgG1 subclass that is directed towards IL-23p19
Dosage regimen	150 mg administered as a subcutaneous injection (1x150mg or 2x75mg) at week 0, week 4, and every 12 weeks thereafter.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Alone or in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).
Other approved therapeutic indications	Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Alone or in combination with methotrexate
Packaging – types, sizes/number of units, and concentrations	1x Skyrizi 150 mg solution for injection in pre-filled pen 2x Skyrizi 75 mg solution for injection in pre-filled syringes
Orphan drug designation	N/A

2. Abbreviations

ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse Event
AIP	Apotekets indkøbspris
ALT	Alanine aminotransferase
AO	As Observed
AS	Ankylosing Spondylitis
AST	Aspartate aminotransferase
bDMARD	Biologic DMARD
bDMARD-IR	bDMARD-inadequate responder
BSA	Body surface area
CASPAR	ClaSsification of Psoriatic Arthritis
CFB	Change From Baseline
CRP	C-reactive protein
csDMARD	conventional synthetic DMARD
CSR	Clinical Study Report
CPK	Creatine Phosphokinase
CPDAI	Composite Psoriatic Disease Activity Index

CT	Computerized Tomography
CVD	Cardiovascular Disease
DANBIO	Dansk Reumatologisk Database
DAPSA	Disease Activity for Psoriatic Arthritis
DAS28	Disease Activity Score 28
DIP	Distal interphalangeal
DMARD	Disease-Modifying Anti-Rheumatic Drug
DMARD-IR	DMARD--inadequate responder
EAM	Extra-Articular Manifestation
EBC	Estimated Bases of Comparison (Udvidet Sammenligningsgrundlag)
EMA	European Medicines Agency
eow	Every Other Week
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GP	General Practitioner
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire Disability Index
HLA	Human leukocyte antigen
HRQoL	Health-Related Quality of Life
IBD	Inflammatory Bowel Disease
Ig	Immunoglobulin
IL	Interleukin
IR	Inadequate responder
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITC	Indirect Treatment Comparison
IV	Infusion
JAK	Janus kinase
JAKi	JAK-inhibitor
LDA	Low Disease Activity
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
mAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MAPP	Multinational Assessment of Psoriasis and Psoriatic Arthritis
MCS	Mental Component Summary
MD	Mean Difference
MDA	Minimal Disease Activity
MHC	Major Histocompatibility Complex
MoA	Mode of Action
MRI	Magnetic Resonance Imaging
MSK	Muscoloskeletal
mTSS	modified Total Sharp Score
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NHP	Nottingham Health Profile
NICE	National Institute for Health and Care Excellence
NMA	Network-Meta Analysis

NMSC	Non-Melanoma Skin Cancer
NRI	Non-responder imputation
NSAID	Non-steroid Anti-inflammatory Drugs
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OR	Odds Ratio
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area Severity Index
PBO	Placebo
PCS	Physical Component Summary
PGA	Physician Global Assessment
PICO	Patient, Intervention, Comparator, Outcome
PPP	Pharmacy Purchase Price
PROs	Patient Reported Outcomes
PsO	Psoriasis
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PtGA	Patient Global Assessment
QoL	Quality of life
Q2W	Once every second week
Q4W	Once every four weeks
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
RR	Relative Risk
SAE	Serious adverse event
SAPS	Self-Assessment of Psoriasis Symptom
sPGA	static Physician Global Assessment of psoriasis
SJC	Swollen Joint Count
SF-36	Short Form (36) Health Survey
sIGA	Static Investigator Global Assessmen
SHS	Sharp/van der Heijde score
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Events
Th	T helper
TJC	Tender Joint Count
TNF	Tumor necrosis factor
TNFi	TNF-inhibitor
VAS	Visual analog scale
VLDA	Very Low Disease Activity
VTE	Venous Thromboembolism
Wk	Week

3. Tables and Figures

3.1. List of figures

3.2. List of tables

4. Summary of the application

- Psoriatic arthritis (PsA) is a chronic, heterogeneous, systemic inflammatory disease with co-existing skin and joint manifestations, with the presentation of skin symptoms preceding joint manifestations in 75-80% of the patients.
- PsA is also associated with many comorbidities such as cardiovascular disease, inflammatory bowel disease, uveitis, depression, anxiety etc. and the heterogeneous nature of the disease can have a major impact on patients' quality of life.
- PsA incurs a high economic burden due to patients needing significantly more health care resources than the general population and through high indirect costs related to reduced ability to work and increased productivity loss.
- Long symptom duration before diagnosis is a common phenomenon and challenge in the treatment of PsA. Attention to emerging skin manifestations and earlier treatment initiation is essential for efficient treatment with potential to limit joint damage, improving treatment outcomes and improve patients HRQoL

- There is still a high unmet need in the treatment of PsA. Treatments today are still burdensome due to side effects, and many patients experience lack of efficacy. There is a need for treatments that provides rapid, durable efficacy for the treatment of skin manifestations alongside joint symptoms, whilst maintaining a simple dosing regimen.

- Risankizumab (Skyrizi) represents a new MoA, an IL-23 inhibitor, currently not present in the Danish treatment recommendations. Risankizumab can be used as monotherapy or in combination with methotrexate and is dosed every 12 weeks after initial doses at week 0 and 4.

- Compared to TNF-inhibitors and IL-17 inhibitors risankizumab offers a substantially less frequent dosing schedule, resulting in less patient burden related to injections. The reduced frequency of administration can also result in less need for additional health care resources, which can be very valuable especially given the still present COVID-19 pandemic.

- Risankizumab have in two phase III clinical trials shown to offer superior skin efficacy and a high and maintained effect on joints, as well as on HRQoL outcomes. The safety profile showed no new safety signals and is consistent with previous risankuzmab trials in PsO. Long term week 52 follow-up data confirms that the efficacy and safety profile is maintained in the long term.

- Adalimumab and ixekizumab are considered the relevant comparators. Adalimumab for the bio-naïve patients as adalimumab is ranked as first choice in current pharmaceutical recommendations for the bio-naïve patients who have shown an inadequate response or are intolerant to csDMARDs. Ixekizumab is the next option in the recommendations which is not a TNF-inhibitor and considered the option for patients who have shown an inadequate response or are intolerant to bDMARDs and therefore considered the relevant comparator for bio-experienced patients.

- An indirect comparison, including both skin, joint, PRO and safety outcomes, demonstrates that risankizumab is an important and valuable treatment option, providing improved efficacy on skin with maintained effect on joint symptoms as well as favorable safety related to SAE, compared to the relevant comparators adalimumab and ixekizumab.

- Due to risankizumab's strong efficacy profile related to skin, it is expected that risankizumab will primarily be an alternative for patients with concomitant moderate to severe plaque psoriasis in clinical practice.

- Ranking in treatment recommendations dictate treatment use and risankizumab will only be used ahead of more expensive treatments. The budget impact of introducing risankizumab is minimal and predictable and a positive recommendation for risankizumab will therefore provide a new alternative to optimize treatment for the highly heterogenous disease PsA, provide benefit for eligible patients and lead to increased competition, in total leading to cost savings for society

This application concerns the new IL-23 inhibitor, risankizumab (brand name: Skyrizi) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

PsA is a chronic, heterogeneous, systemic inflammatory disease with co-existing skin and joint manifestations. PsA is defined by the presence of psoriasis (PsO) which can be a precursor for the onset of PsA, with approximately one third of PsO patients subsequently developing PsA. Additionally, the presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA and may occur approximately 10 years before the onset of PsA signs and symptoms. PsA is associated with many comorbidities and extra-articular manifestations, and the clinical characteristics of PsA, including both skin and joint manifestations are very burdensome and HRQoL impairment is greater in patients with both skin and joint involvement when compared to those with joint involvement alone. The disease heterogeneity also has a major negative impact on patient's ability to work and mental health, and the severe physical and mental

impact is associated with a high frequency of healthcare visits, hospitalizations and work impairment, also resulting in a high economic burden.

Long diagnosis delays relative to when disease symptoms begin manifesting is unfortunately common in PsA. Considering that PsO precedes PsA in more than 80% of patients, the diagnosis or suspicion of PsA should be high among dermatologists and regular screening should be carried out to diagnose the disease prior to the initiation of joint symptoms.(1) Timely diagnosis and attention to emerging skin manifestations early in the disease pathway is essential for efficient treatment with potential to limit joint damage.(2) Early diagnosis and prompt initiation of effective treatment can improve the symptoms and treatment outcomes for patients with PsA, helping to improve their HRQoL(2, 3).

Despite the introduction of novel therapies such as IL-17 inhibitors, JAK-inhibitors and additional TNFi there remains unmet needs for therapies with reduced adverse events and with better treatment response. Even though TNFi treatment remain the standard of treatment many patients experience a lack of efficacy and adverse events related to TNFi treatment, and quickly faces the need of new treatment. In order to provide patients the best possible disease control, new treatment with different MoA's are needed to appropriately combat the burden of PsA. Furthermore, due to the heterogeneity of the disease, treatment choices in PsA are far more individual than in many other joint diseases (4), which underlines the need of several treatments with different MoA's to help tailor treatment to patient profiles and needs.

It is difficult to estimate the incidence and prevalence of PsA in Denmark due to unclear diagnostic criteria, but in the Danish National treatment guidelines, it is estimated that the PsA prevalence is between 0,04 % to 0,1% (4). PsA normally develops in early 40s and 50s, with no difference between genders.

Risankizumab (Skyrizi) is an IL-23 inhibitor that is administered subcutaneously every 12 weeks after initial start-up doses at week 0 and week 4 and can be used us a monotherapy or in combination with methotrexate. Risankizumab was granted a CHMP positive opinion for PsA on 14 October 2021. Risankizumab is also approved for the treatment of psoriasis and is included in the pharmaceutical recommendations for psoriasis in Denmark.

Current pharmaceutical recommendations in Denmark differentiate between patients with or without moderate to severe plaque psoriasis, former or existing IBD or former or existing uveitis. Skyrizi does not have an approved indication for IBD yet, and not for uveitis either. Therefore, risankizumab is expected to be an alternative included in the recommendations for patients with or without moderate to severe plaque psoriasis. Due to Risankizumab strong efficacy profile related to skin, it is expected that risankizumab primarily will be an alternative for patients with concomitant moderate to severe plaque psoriasis in clinical practice.

For patients with or without concomitant plaque psoriasis, the TNF-inhibitor adalimumab is ranked as first choice and used by the majority of patients who have shown an inadequate response or are intolerant to csDMARDs (ie. bio-naïve). Next option in the recommendations which is not a TNF-inhibitor is the IL-17 inhibitor ixekizumab, which is considered the option for patients who have shown an inadequate response or are intolerant to bDMARDs (ie. bio-experienced). Therefore, AbbVie considers adalimumab and ixekizumab as the relevant comparators for the bio-naïve and bio-experienced population, respectively.

The clinical efficacy and safety of risankizumab in PsA have been established in two phase III multicenter placebo-controlled trials that assessed risankizumab in patients who have shown inadequate response or intolerance to at least one disease modifying anti-rheumatic agent (bio-naive) or biologic (bio-experienced), KEEPsAKE 1 and KEEPsAKE 2. Both studies met their primary and most secondary endpoints, demonstrating that risankizumab offers strong efficacy on the most important elements of PsA, with superior skin efficacy and a high and maintained effect on joints, as well as on Health-Related Quality of Life (HRQoL). The observed safety profile demonstrated no new safety signals and was consistent with safety in previous PsO trials. Long term 52-week follow-up data from KEEPsAKE 1 and KEEPsAKE 2 confirms that the efficacy and safety of risankizumab is maintained in the long term.

Since no head-to-head trial exist between risankizumab and the relevant comparators adalimumab and ixekizumab, a pairwise indirect comparison (ITC) was undertaken to assess the relative efficacy and safety on key skin, joint, patient reported outcomes (PRO) and safety (ACR20/50, PASI75/90, SF-36 PCS/MCS and severe

adverse events (SAE)). The results of the ITC demonstrated that risankizumab is a valuable treatment option, providing improved efficacy on skin with maintained effect on joint symptoms as well as favorable safety related to SAE's, compared to adalimumab in the bio-naïve population and ixekizumab in the bio-experienced population.

A conservative cost comparison with a limited societal perspective including drug costs and patient time costs over 18 months was undertaken. The result of this comparison shows an incremental 18-month cost per patient cost of 110 321 DKK vs adalimumab and 46 296 DKK vs. ixekizumab. A budget impact analysis was also undertaken and shows as small budget impact of introducing risankizumab, [redacted] DKK (AIP) for the bio-naïve population and [redacted] DKK (AIP) for the bio-experienced population.

The cost comparison and budget impact analysis were done on list price (AIP). Risankizumab is approved for the treatment of psoriasis in Denmark and included in the tender and treatment recommendations for psoriasis. The use of risankizumab for the treatment of PsA in clinical practice will be dictated by the ranking in the treatment recommendations, resulting in that risankizumab will only be used for eligible patients ahead of more expensive treatments when no cheaper alternatives are available anymore. If risankizumab is used as expected according to ranking in the treatment recommendations, introducing risankizumab will in reality be cost saving.

Risankizumab represents an entirely new alternative in the treatment of PsA, with a strong value on skin as well as improvement on peripheral disease, including maintained effect on joints and a well-established and favorable safety profile, demonstrated via two clinical trials and and ITC vs. the relevant comparators adalimumab and ixekizumab. Compared to the other treatments in the recommendations, risankizumab has a substantially lower dosing frequency, with a maintenance dose every 12 weeks, reducing the burden of injections for patients. The budget impact of introducing risankizumab is minimal and predictable. A recommendation of risankizumab will therefore provide a new alternative to optimize treatment for the highly heterogenous disease PsA, provide benefit for eligible patients and lead to increased competition, in total leading to cost savings for society.

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

- PsA is a chronic, heterogeneous, systemic inflammatory disease with co-existing skin and joint manifestations where skin, nail, bone, enthesis in peripheral joints and axial joints can be affected. Presentation of skin symptoms generally precedes joint manifestations.
- PsA is associated with many comorbidities and extra-articular manifestation and besides psoriasis is also cardiovascular disease, inflammatory bowel disease, uveitis, diabetes, osteoporosis, depression, and anxiety common.
- The genetic susceptibility of PsA is mainly associated with the genes of the class I major histocompatibility complex (MHC) alleles. The(5) alleles are often associated with specific sub phenotypes of PsA, where PsA peripheral arthritis is associated with the human leukocyte antigen (HLA)-B38 and HLA-B39 and PsA spondylitis is associated with HLA-B27.(5)
- Research has highlighted that environmental factors, such as infections, trauma, stress, obesity and smoking, appear to impact individuals with genetic susceptibility PsA.
- The disease heterogeneity has a major negative impact on patient's ability to work and mental health, and the severe physical and mental impact is associated with a high frequency of healthcare visits and hospitalizations.
- Treatment guidelines for patients with a high risk of disease progression or inadequate response to csDMARDs specify that the following treatment algorithm should be used (4); 1. TNF inhibitor or IL-17 inhibitors, 2. IL-12/IL-23 inhibitors, 3. Apremilast or abatacept.

- Treatment choice in treatment of PsA is influenced by rankings in the Danish treatment recommendations. Adalimumab is considered relevant comparator for bio-naïve patients as that is ranked first in the recommendations. Ixekizumab is considered relevant comparator for bio-experienced patients as ixekizumab is the next non-TNF option in the recommendations.

- Risankizumab (Skyrizi) represents a new MoA, an IL-23 inhibitor, currently not present in the Danish treatment recommendations. Risankizumab can be used as monotherapy or in combination with methotrexate and is dosed every 12 weeks after initial doses at week 0 and 4.

5.1. The medical condition and patient population

PsA is a chronic, heterogeneous, systemic inflammatory disease with co-existing skin and joint manifestations.(6). PsA can be distinguished from other spondyloarthropathies by the presence of psoriasis, peripheral arthritis, asymmetrical distribution of axial involvement, with lower levels of pain and movement limitation.(7) PsA is defined by the presence of psoriasis, among other musculoskeletal manifestations; often the skin symptoms associated with PsA manifest as moderate-to-severe forms of the disease. (7),(8). PsO can be a precursor for the onset of PsA, with approximately one third of PsO patients subsequently developing PsA. Additionally, the presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA. (9),(10). PsO may occur approximately 10 years before the onset of PsA signs and symptoms, with a typical delay ranging from 7-12 years before joint disease onset (9-12). PsA is associated with many comorbidities and extra-articular manifestation and besides psoriasis is also cardiovascular disease, inflammatory bowel disease, uveitis, diabetes, osteoporosis, depression, and anxiety common. The clinical characteristics of PsA, including both skin and joint manifestations are burdensome and HRQoL impairment is greater in patients with both skin and joint involvement when compared to those with joint involvement alone. (13) The disease heterogeneity also has a major negative impact on patient's ability to work and mental health, and the severe physical and mental impact is associated with a high frequency of healthcare visits and hospitalizations (14),(15).

5.1.1. Pathogenesis

The precise pathophysiology of PsA, as well as the relationship of PsA to PsO and rheumatoid arthritis (RA), is not yet fully understood.(16) As with other chronic inflammatory autoimmune conditions, it is known that PsA is the result of complex interactions between genetic and environmental factors, with variation in the pathophysiology of PsA across the different sites involved.(5, 17)

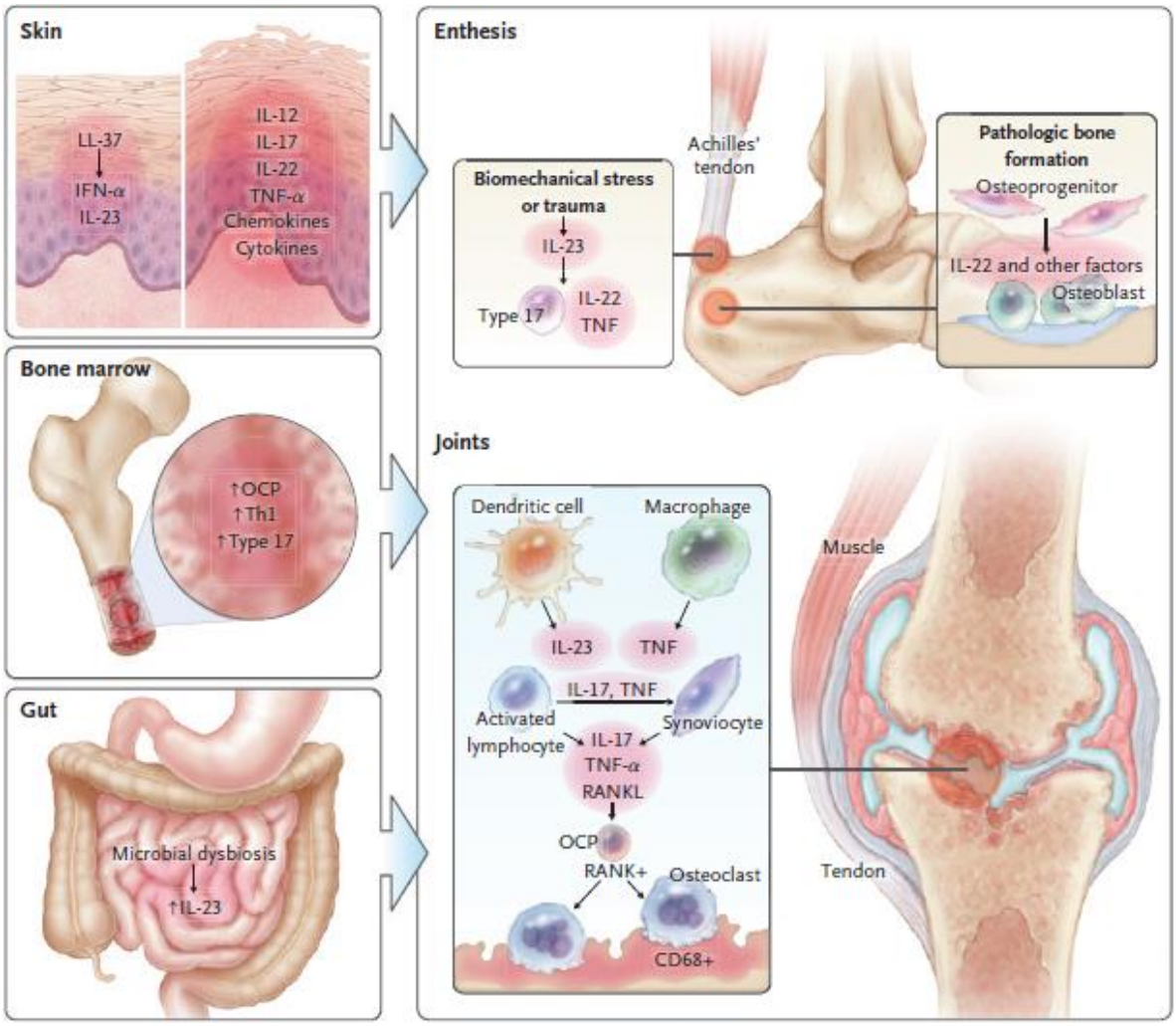
PsA is immune-mediated and possibly shares pathogenic mechanisms with PsO. (18) It affects the skin, nail, bone and enthesis in peripheral joints and may also affect axial joints.(5) The genetic susceptibility of PsA is mainly associated with the genes of the class I major histocompatibility complex (MHC) alleles.(5) Alleles are often associated with specific sub phenotypes of PsA, where PsA peripheral arthritis is associated with the human leukocyte antigen (HLA)-B38 and HLA-B39 and PsA spondylitis is associated with HLA-B27.(5) Research has highlighted that environmental factors appear to impact individuals with genetic susceptibility PsA.(6) These include infections, trauma, stress, obesity and smoking.(6) Studies suggest that recent trauma may act as a catalyst for the onset of the inflammatory response leading to consequential PsA in 8-9% of patients.(6)

After the initial tissue damage has occurred, a cascade of events takes place, giving rise to PsA and other clinical developments (2, 5). Damage caused by environmental factors is detected by dendritic cells which, in turn, activate immune T-cell subpopulations (T helper (Th) 1, Th2, Th9, Th22 and T regulatory cells) which then infiltrate synovial tissues.(6) This is possible due to dysfunctional angiogenesis and the activation of endothelial cells in PsA.(6) Dendritic cells, mast cells, macrophages and other cells that produce proinflammatory cytokines triggering the interleukin (IL) and JAK signaling cascades, with IL-23, IL-7, IL-17, IL-21, IL-22, IL-23 and TNF-α are the key mediators in the pathogenesis of PsA.(6) They activate the secretion of matrix degrading enzymes, resulting in cartilage degradation. IL-23 is a dermal cytokine which is produced by keratinocytes and activates antigen-presenting cells leading to keratinocyte proliferation and chronic inflammation.(2, 5) IL-17 and

receptor activator of nuclear factor kappa-B ligand (RANKL) facilitate osteoclast activation, mediating bone erosion and resorption, known as osteolysis.(18) Combined osteolysis and cartilage degradation result in joint destruction. At the same time, IL-22 upregulates expression of pro-osteogenic factors, contributing to osteoproliferation.(6) Finally, resident cells such as osteoblasts secrete more proinflammatory mediators that can further recruit immune cells into joints, creating a continuous cycle feeding into the immune response.(6)

However, the pathogenesis of PsA varies between the affected anatomical sites, thus resulting in variable clinical presentation at different sites affected (Figure 1).

Figure 1 - Pathogenic pathway in PsA in various body parts



Source: (5); OCP, osteoclast precursor

5.1.2. Comorbidities and extra-articular manifestations

PsA is associated with a number of extra-articular manifestations (EAMs)(19). The most common EAMs associated with PsA include psoriasis (69-98%), uveitis (1%-25%), and Inflammatory Bowel Disease (IBD) (2%-4%).(20-22) Patients with PsA present several types of comorbidities, frequently including CVD, metabolic comorbidities (obesity, diabetes, and metabolic syndrome), osteoporosis, depression, and anxiety.(23) The high number and severity of these comorbidities contribute to the high patient burden in PsA, especially in the psychological comorbidities such as anxiety and depression. The need to be treated for these multiple

comorbidities also increases the treatment burden faced by patients with PsA and the use of healthcare resources.

PsA is significantly associated with gastrointestinal comorbidities, including Crohn's disease (Odds Ratio [OR] 2.4, 95% Confidence Interval [CI], p<0.0001), ulcerative colitis (OR 2.1, 95% CI, p=0.001), reflux esophagitis (OR 1.6, 95% CI, p<0.0001), and Inflammatory Bowel Syndrome (IBS) (OR 1.4, 95% CI, p=0.045).(24) Many patients with PsA have multiple comorbidities which are associated with substantial impact on physical functioning.

Patients with psoriasis have an increased mortality rate compared with the general population, especially for patients with severe psoriasis.(25, 26) Considering that a significant proportion of patients with PsA also have psoriasis, the increased mortality in psoriasis could also possibly suggest an increased mortality rate among patients with PsA. Several risk factors associated with mortality have been identified include disease severity and the leading cause of death being cardiovascular disease (CVD).(27-29)

5.1.3. Diagnosis

There is no specific diagnostic pathway developed for PsA, but classification criteria to assist in diagnosing PsA, such as the Classification Criteria for Psoriatic Arthritis (CASPAR) and Moll and Wright criteria are used to guide diagnosis (30). Due to the heterogeneity of the disease, a diagnosis of PsA needs to include multidisciplinary assessments, physical examinations, imaging and laboratory tests.

Skin disease precedes joint disease in approx. 80% of patients with PsA, and earlier diagnosis with prompt initiation of correct treatment can limit joint damage, improve symptoms and treatment outcomes, and improve patient QoL (2, 3) (1).

Recent European League Against Rheumatism (EULAR) guidelines recommend a method of diagnosis that includes multispecialty assessment, patient reported measures, clinical history, physical examination and imaging tests.(16) Diagnostic markers for PsA identified by laboratory tests are not common and if used are for differential diagnosis of PsA from other conditions, rather than diagnosis of PsA specifically. Five domains are included in the diagnosis of PsA including: PsO, peripheral joint disease, axial disease, enthesitis and dactylitis.(2) As previously mentioned, skin disease generally precedes joint disease in the majority of patients with PsA (~75%-80%), with a typical delay of approximately 7–12 years before joint disease onset.(2, 12) Enthesitis may be one of the earliest musculoskeletal symptoms of PsA, whilst dactylitis is indicative of disease progression.(2) A combination of the above factors should raise suspicion around the potential development of PsA, which can be confirmed by carrying out further physical and imaging examinations.(2)

The Danish Society of Rheumatology endorses the EULAR guidelines. The PsA diagnosis is clinically evaluated based on the patient's clinical history and an objective examination of the skin and musculoskeletal function. A referral to a dermatologist is relevant if PsO is suspected. Additional diagnostic tools are laboratory tests and imaging tests. Long symptom duration before diagnosis is a common phenomenon in PsA and is associated with worse patient outcomes, including poor function, erosive disease, arthritis mutilans and poor HRQoL.(2, 12) A long-term (5-year) observational study (n=197) from the Swedish Early Psoriatic Arthritis registry showed that shorter symptom duration at diagnosis was predictive of low disease severity.(1) Despite this evidence, many patients with PsA still go undiagnosed for many years after initial disease onset. In a national clinical audit of inflammatory arthritis conducted by the British Society of Rheumatology, data from 1,016 patients with a final diagnosis of PsA were analyzed and compared to RA patients. The study reported that PsA patients had significantly longer delays in initial presentation to the general practitioner (8.9 vs 6.6 weeks), time referral to a rheumatology clinic (5.4 vs 4.0 weeks) and time to final diagnosis (28.6 vs 21.6 weeks) compared with RA patients .(3)

Considering that PsO precedes PsA in more than 80% of patients, the diagnosis or suspicion of PsA should be high among dermatologists and regular screening should be carried out to diagnose the disease prior to the initiation of joint symptoms.(1) Timely diagnosis and attention to emerging skin manifestations early in the disease pathway is essential for efficient treatment with potential to limit joint damage.(2) Early diagnosis and

prompt initiation of effective treatment can improve the symptoms and treatment outcomes for patients with PsA, helping to improve their HRQoL.(2, 3)

5.1.3.1. CASPAR criteria

In lack of validated clinical diagnosis criteria of PsA, classifications criteria have been developed in clinical research as a valid diagnosis tool, this tool is known as ClaSsification of Psoriatic Arthritis (CASPAR)-criteria (CASPAR). The recommendation in Denmark is to validate and support the PsA diagnosis using the CASPAR-criteria (4), (31) which have both high sensitivity (99.7%) and high specificity (99.1%) for diagnosing PsA. (30). The CASPAR criteria base classification on clinical presentation, history, radiographic, and laboratory evidence (Table 1).

Table 1 - CASPAR Criteria

Criteria	Points
Psoriasis Present or Previously present or Family history	 2 1 1
Nail lesions	1
Dactylitis	1
Negative rheumatoid factor	1
Juxta-articular new bone formation	1

PsA diagnosis if ≥3 points in CASPAR score

5.1.3.2. Moll and Wright

Researchers Moll and Wright established the original criteria for psoriatic arthritis in 1973, which is the oldest and most widely known guide to diagnosing psoriatic arthritis (32),(33). To meet the Moll and Wright classification for psoriatic arthritis, a person with psoriasis who presented with inflammatory arthritis, and had a negative blood test for rheumatoid arthritis, must also meet one of these five subtypes:

- Polyarticular, symmetric arthritis – affecting many joints on mirror sides of the body
- Oligoarticular and asymmetric – fewer than five joints affected, occurring only on one side of the body
- Distal interphalangeal joint predominant – affecting mainly the joints furthest from the center of the body in the fingers and toes
- Spondylitis predominant – affecting mainly the joints between the vertebrae in the spine
- Arthritis mutilans – the most severe form of psoriatic arthritis which causes digital shortening of the fingers or toes associated with severe bone destruction (34)

The Moll and Wright criteria, although simple to use, lack specificity and has not been validated. The new CASPAR criteria are derived from patient data and are robust with higher specificity and sensitivity (35).

5.1.3.3. Physical examination

Upon examination early in the disease pathway most patients present PsO-style lesions. Later in the disease pathway the peripheral joints of PsA patients may be tender or swollen and the effusions may be tight and difficult to appreciate.(36) Patients may present with a purplish discoloration over their affected joints. The most common joints affected are the joints of the feet and hands, followed by knees, wrists, ankles and shoulders and so they need to be considered during physical examination.(37)

5.1.3.4. Imaging examination

Imaging techniques such as X-ray, magnetic resonance imaging (MRI), and ultrasound have been increasingly used in PsA to aid diagnosis. X-ray is helpful in late advanced stages of the disease, whereas early changes may be diagnosed using ultrasound and MRI.(38)

MRI allows the visualization of the diverse pathological tissues in PsA, including both peripheral and axial disease manifestations. MRI findings including synovitis, tenosynovitis, and bone marrow edema, which all

indicate the presence of an inflammatory process, although not specific to PsA. Hence, this would require differential diagnosis from other conditions that are commonly misdiagnosed instead of PsA, such as RA. MRI in PsA is also sensitive for detection of sacroiliitis and spondylitis, although in PsA it appears to be more asymmetric than ankylosing spondylitis (AS). Whole body MRI is a novel imaging method which allows for scanning of the entire body in one session, allowing for the imaging of multiple joints involved in both axial and peripheral joints of PsA.(39)

Computerized tomography (CT) scan is a useful tool for imaging axial involvement in PsA, however has limited capabilities in assessing peripheral joint involvement. The sensitivity of CT in the detection of erosions of the sacroiliac joints is comparable with that of MRI, however MRI is more effective in monitoring synovial inflammation.(38)

Ultrasound is usually utilized for investigating enthesitis in the Achilles tendon and confirming diagnosis in symptomatic patients. Additionally, ultrasound can assess musculoskeletal and cutaneous manifestations simultaneously. Ultrasound is commonly used to assess disease progression and effect of treatment in patients with PsA.(38)

5.1.4. Measurements of disease activity

The ultimate goal of treatment in inflammatory disease is remission, which if achieved would allow the patient to continue living without being hampered by the disease. However, PsA has a great degree of heterogeneity, and the medical profession is not in agreement of what would be considered remission. Several measurements are used such as:

- ACR Response Criteria
- Minimal Disease Activity (MDA),
- Very Low Disease Activity (VLDA)
- PsA Response Criteria (PsARC)
- Disease Activity for Psoriatic Arthritis (DAPSA)
- Composite Psoriatic Disease Activity Index (CPDAI)
- Psoriatic Arthritis Disease Activity Score (PASDAS)
- Disease Activity Score 28 (DAS28)

Over the last years, significant progress has been made in the development of tools that measure disease activity. These tools, validated by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the Outcome Measures in Rheumatology Clinical Trials (OMERACT), assess different aspects of disease activity ranging from activity of lesioned skin, onycholysis (loss of fingernails), peripheral joints, dactylitis, and enthesitis. Composite indices have been developed to assess all relevant clinical outcomes in a single instrument that will combine all domains into a single score.(40) The most commonly used indices used to identify disease activity, as well as other outcomes commonly used in PsA are:(41)

- Minimal Disease Activity (**MDA**), Very Low Disease Activity (**VLDA**)
- PsA Response Criteria (**PsARC**)
- **ACR** Response Criteria
- Disease Activity for Psoriatic Arthritis (**DAPSA**)

- Composite Psoriatic Disease Activity Index (**CPDAI**)
- Psoriatic Arthritis Disease Activity Score (**PASDAS**)
- Disease Activity Score 28 (**DAS28**)

The different indices evaluate overlapping parameters relevant for describing the PsA disease severity, where many parameters are included in all indices whereas others are only included in a few (Table 2).

Table 2 - The individual assessment of composite measures in PsA

	TJC	SJC	Pain	HAQ	ESR/CRP	PGA	PtGA	PASI/BSA	Enthesitis	Dactylitis	Axial
MDA/VLDA	X	X	X	X			X	X	X		
PsARC	X	X				X	X				
ACR	X	X	X	X	X	X	X				
DAPSA	X	X	X		X		X				
CPDAI	X	X		X				X	X	X	X
PASDAS	X	X		SF-36	X	X	X		X	X	
DAS28	28 only	28 only			X	X	X				

Source: (40, 42-44)

TJC, Tender Joint Count; SJC, Swollen Joint Count; HAQ, Health Assessment Questionnaire; DAS, Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; PASI, Psoriasis Area Severity Index; BSA, Body Surface Area

As in other inflammatory diseases, like RA, disease remission is the ultimate goal of treatment in PsA. However, there is no consensus on the definition of remission in PsA. Partly this is due to PsA being such a variable disease, where remission is both very difficult to achieve and to maintain.

5.1.4.1. Other measurements

Dermatological

- Psoriasis Area Severity Index (**PASI**) – 5-point tool measuring the severity and size of psoriatic skin lesions reported as percent improvement (75/90/100)
- Static Investigator Global Assessment (**sIGA**) – 5-point score based on the investigator's assessment of the average elevation, erythema, and scaling of all psoriatic lesions
- Self-Assessment of Psoriasis Symptoms (**SAPS**) – 11-item self-assessment of psoriasis symptoms that includes questions on: pain, itching, redness, scaling, flaking, bleeding, burning, stinging, tenderness, pain due to skin cracking, and joint paine

Enthesitis

- Leeds Enthesitis Index (**LEI**) – Clinical examination of 6 sites indicating the number of sites of enthesitis
- Spondyloarthritis Research Consortium of Canada (**SPARCC**) – Clinical examination of 18 sites indicating the number of sites of enthesitis

Radiographic

- Sharp/van der Heijde score (**SHS**) – Quantitative assessment for radiographic changes of hands and wrists

Patient-reported outcomes

- Health Assessment Questionnaire Disability Index (**HAQ-DI**) – Self-assessment of the individual's ability to: Dressing/groom, rise, eat, walk, hygiene, reach, grip, and daily activities
- Short Form (36) Health Survey (**SF-36**) – 36-item patient survey that measures health status
- Functional Assessment of Chronic Illness Therapy – Fatigue (**FACIT-F**) – 13-item tool that measures the individual's level of fatigue during usual daily activities over the past week

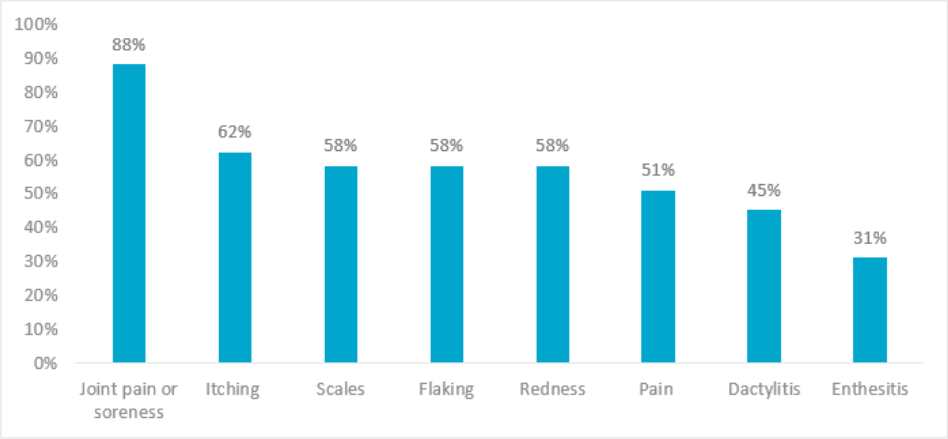
5.1.5. Clinical burden of PsA

- Symptoms of PsA consist of a wide range of articular and EAMs such as psoriasis, nail psoriasis, joint involvement, axial involvement, dactylitis and enthesitis where skin and joint involvement are the largest factors for contributing to the severity and burden of the disease.
- Skin psoriasis and pain and tenderness in joints are also associated with fatigue which can be explained sleep disturbances from the pain and itching from the skin disease. In addition to this, the emotional burden of skin psoriasis largely contributes to fatigue. Similarly, pain, tenderness, and limitation of movement may cause fatigue in daily activities as well as sleep disturbances.(45)
- Skin lesion symptoms include redness, itching, scaling, burning, stinging, crackling, flaking, and psoriasis-induced pain. Nail involvement is a common feature and can be divided into two major groups: involvement of the nail matrix and involvement of the nail bed.
- Signs of inflammation, including tenderness, warmness, and swelling of peripheral and axial joints, cause both pain and limitation of motion.
- Other involvements include axial involvement, dactylitis, a uniform swelling of an entire digit with inflammation and enthesitis, tenderness and swelling is the entheses.
- Psoriasis skin lesions and inflammatory joint pain are the most frequently experienced symptom of PsA as well as the most burdensome symptom experienced by patients.

Symptoms of PsA consist of a wide range of articular and EAMs that are often dependent on disease activity and severity, such as psoriasis, nail psoriasis, joint involvement, axial involvement, dactylitis and enthesitis. The heterogeneity of the disease and EAM's contributes to the severity and burden of the disease with skin and joint involvement being the largest factors.

The US population-based MAPP (Multinational Assessment of Psoriasis and Psoriatic Arthritis) survey that examined the impact of PsA on patient's daily activities, reported several symptoms in patients with PsA. Despite differences in the perspectives of rheumatologists, dermatologists and patients, both joint and skin manifestations represent key causes of symptom burden. Almost 90% of patients reported current joint pain or soreness, 31% reported symptoms resembling enthesitis, 45% reported symptoms resembling dactylitis, and 21% reported nail symptoms. Additionally, more than half of patients reported on symptoms associated with psoriasis skin lesions (Figure 2) (14).

Figure 2 - Symptoms reported by patients with PsA in the MAPP study



Source: (14)

Additionally, symptoms of PsA often occur simultaneously in multidomain disease presentations. A US study from 2016 that analyzed data from the Corrona PsA/SpA register evaluated the prevalence of multidomain disease presentation among patients with PsA (n=2,617).(22) The study reported that 1,814 (69.3%) patients presented with skin disease, 1,523 (68.2%) with peripheral arthritis, 1,042 (39.8%) with nail involvement, 539 (20.6%) with enthesitis, 319 (12.2%) with axial disease, and 235 (9.0%) with dactylitis. Out of the entire study population, 1,698 patients (64.9%) had a multidomain disease presentation, 617 (23.6%) had a single-domain presentation, and 302 (11.5%) did not present with any disease domains at the time of assessment. Overall, the most common single-domain presentation was skin disease (12.7%). The most common multidomain patterns were nail involvement, skin disease, peripheral arthritis (11.6%) and skin disease (11.3%). Table 3 shows the common multidomain presentations.(22)

Table 3 - Patterns of multidomain presentation in patients with PsA (%)

Peripheral Arthritis	Nail Involvement	Skin Disease	Axial Disease	Enthesitis	Dactylitis	% of PsA patients
X	X	X				11.6%
X		X				11.3%
X	X	X		X		8.8%
X		X		X		5.9%
X		X			X	4.2%
	X	X				4.0%
X	X	X			X	3.4%
X	X	X	X	X	X	3.1%
Other multidomain presentations						29.4%

Source: (22)

5.1.5.1. Skin and nail involvement

Since psoriasis predominantly precedes PsA, the patients with PsA usually form skin lesions prior to developing arthritis. Hence, patients with PsA experience the same skin lesion symptoms as in psoriasis, including redness, itching, scaling, burning, stinging, crackling, flaking, and psoriasis-induced pain.(46) A Japanese retrospective questionnaire survey investigated the clinical characteristics of patients with PsA (n=1,000). The most common type of psoriasis among the patients with PsA was psoriasis vulgaris (88%), followed by erythrodermic (4.5%), pustular type (6.4%), and 'unknown' (1.1%).(47)

Nail involvement is a common feature in both psoriasis and PsA.(40) Nail involvement can be divided into two major groups: involvement of the nail matrix and involvement of the nail bed. The first results in changes to the nail plate including pitting and depression of the nail plate surface. The latter presents with abnormalities deeper in the nail, causes oil-drop discoloration, and onycholysis. The association between nail involvement and PsA pathophysiology is still unclear.(40) A retrospective analysis investigating this in PsA (n=118), reported that the incidence of nail involvement in patients with PsA was 67.6%.(48) The study reported that the

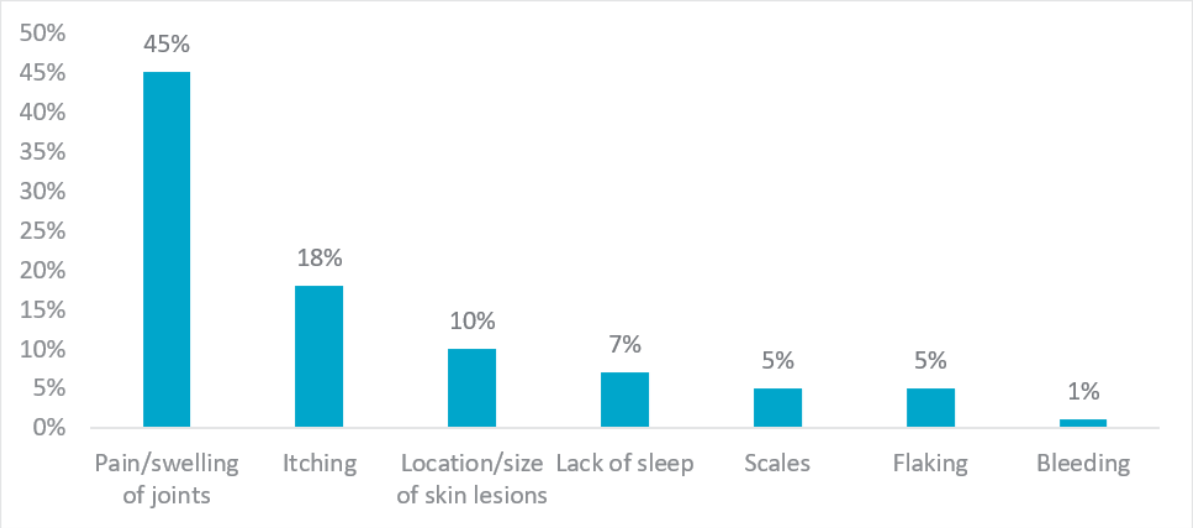
presence of transverse grooves, onycholysis, and splinter hemorrhages were significantly associated to PsA, with transverse grooves having the strongest association (OR 5.01; 95% CI, P<0.01).(48)

5.1.5.2. *Inflammatory joint pain*

Signs of inflammation, including tenderness, warmness, and swelling of peripheral and axial joints, are prominent features of PsA, causing both pain and limitation of motion.(49) Inflammatory joint pain is, together with psoriasis skin lesions, the most frequently experienced symptom of PsA as well as the most burdensome symptom experienced by patients, as reported in a 2018 online global survey.(50) This study evaluated the patient's perspective of the impact of PsA in 1,286 PsA patients across 8 countries and reported that 97% of patients reported experiencing musculoskeletal symptoms within the past year. The most frequently reported symptom was joint pain and joint tenderness/swelling in 79% and 60% of patients, respectively. Additionally, joint pain and inflammatory back pain were reported to be the most burdensome symptoms by the largest percentage of patients (32% and 12%, respectively).(42) In addition, inflammatory joint pain is burdensome for patients with PsA as it causes physical dysfunction and immobility, and consequently it is one of the main reasons why PsA impacts several multiple areas of a patient's life.(49)

Additionally, inflammatory joint pain is a large contributing factor to disease severity. This was demonstrated in the previously mentioned MAPP study, that evaluated the impact of psoriasis and PsA on the QoL of patients (n=712 patients with PsA) in North America and Europe (51). The study reported that the largest contributors to disease severity included pain (45%), itching (18%), and the location/size of skin lesions (10%). The most important factors contributing to disease severity, as reported in this study, are shown in Figure 3 (51).

Figure 3 - The most important contributing factors to PsA disease severity



Source: (51)

5.1.5.3. *Other involvements associated with PsA*

Axial involvement in patients with PsA has not been extensively studied, which limits the current understanding of prevalence and impact of axial involvement in patients with PsA.(52) Partly, this is for PsA due to the late radiographic visibility of axial structural damage, prolonging time to diagnosis of axial involvement. Additionally, radiographic evidence of axial involvement is less common in patients with PsA than for example in patients with AS, which further hinders diagnosis.(53) Nevertheless, the presence of axial involvement is associated with higher disease severity and effect on QoL.(54)

Dactylitis is described as a uniform swelling of an entire digit with inflammation and can be either acute (swelling, redness of the skin, and pain) or chronic (swelling without inflammation).(5) A longitudinal study (n=537) carried out in Canada identified dactylitis in 48% of patients with PsA. Dactylitis that only affected the feet was seen in 65% of the cases with dactylitis, only affecting the hands in 24% of the cases, and affecting

both hands and feet in 12% of the cases. Recurrent dactylitis occurred in 44% of patients.(55) The morbidity of dactylitis increases with the duration of disease.(38)

In PsA, the most common site of tenderness and swelling is the entheses, thus making enthesitis a hallmark of the clinical spectrum of PsA.(49) Pain and loss of function at the entheses are dependent on location and severity of disease as well as the intensity of pain.(49) In a prospective longitudinal study, 803 patients with PsA were followed between 2008 and 2014 to assess the incidence, prevalence, and characteristics of clinical enthesitis for patients with PsA.(56) By 2014, 281 of 803 patients had enthesitis, leading to a 35% prevalence. During the observation period, 192 patients developed enthesitis resulting in an annual incidence of 0.9%. Most of the patients had one (48.4%) or two (32.3%) tender entheseal sites. The three most common entheseal sites were the Achilles tendon, plantar fascia on the calcaneus, and the lateral epicondyles (24.2%, 20.8%, and 17.2% respectively). Additionally, enthesitis was associated with higher disease activity and higher levels of pain.(56)

5.1.6. Impact of PsA on QoL

- PsA will negatively impact many aspects of the patients' life. Majority of patients with PsA report skin and joint symptoms to have the most debilitating impact on patients' physical, psychological, and social lives. Inflamed or broken skin have by some patients been reported to be more bothersome than joint pain (13). Maybe even more worrisome is the impact on emotional and social wellbeing, as well as the problem for romantic intimacy, which can lead to depression. Of note, this is significantly worse for patients with PsA compared with patients with psoriasis alone and in patients with RA.
- Many patients stop participating in social activities or in certain sports/recreational activities as a consequence of their PsA Figure 6and over half of the PsA population feels that their disease has affected their social life in one or more ways
- Patients with PsA have a high rate of both depression and anxiety. Depression has been reported in up to 22% of patients with PsA, with anxiety reported in up to 30%. Increased depression was also associated with the reduced ability to work.
- Psoriasis skin lesions cause impaired confidence and psychological well-being due to the appearance of lesions especially in visible anatomical locations such as the scalp.

QoL burden in patients with PsA was found to be significantly worse than in patient with RA, according to a Norwegian study that compared SF-36 scores for 1,515 patients with PsA and 3,898 patients with RA.(57) The analyses, when adjusted for age, gender, and DAS28, found significantly worse values in patients with PsA compared with patients RA for all measured scores (Physical Component Score [PCS], Mental Component Score [MCS], SF-6D, Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, and Role Emotional) at baseline. In addition, the study also showed significantly worse scores for most components for patients with PsA compared with patients with RA after at 3 and 6 months of DMARD treatment.(57)

5.1.6.1. Physical impact of PsA

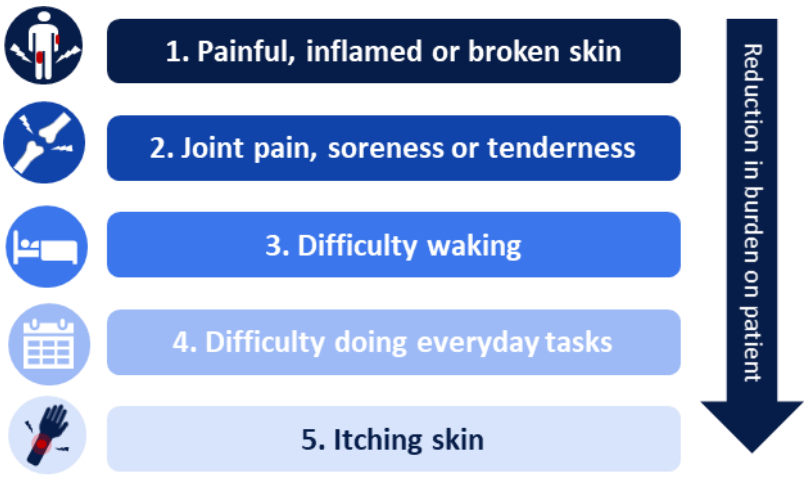
A study from Turkey showed that patients with PsA (n=40) reported considerably more pain (32.4 vs. 6.7 points, $p<0.05$), worse physical function (21.8 vs. 7.1 points, $p<0.05$), and more social isolation (32.1 vs. 8.4, $p<0.05$) on the Nottingham Health Profile (NHP) compared with healthy controls (n=40). The study also showed that among patients with PsA there was a statistical correlation between increased pain and both decreased physical mobility ($p<0.01$) and energy ($p<0.05$) determined using NHP. Furthermore, increased pain also correlated with lower life satisfaction measured by the Life Satisfaction Index ($p<0.05$) (58).

The majority of PsA patients report PsO skin lesions and symptoms impacting their daily life (59). The most impact factor affecting self-perceived severity in patients with PsA was pain or swelling of the joints (45%), itching of skin lesions (18%), location and size of skin lesions (10%) and lack of sleep (7%) (59).

In the DISCONNECT online survey completed by PsA patients (n=200), dermatologists (n=150) and rheumatologists (n=150), patients reported that painful, inflamed or broken skin is more bothersome than joint pain (13). The most bothersome PsA symptoms are presented in

Figure 4.

Figure 4. Most bothersome PsA symptoms from the DISCONNECT online survey (13)

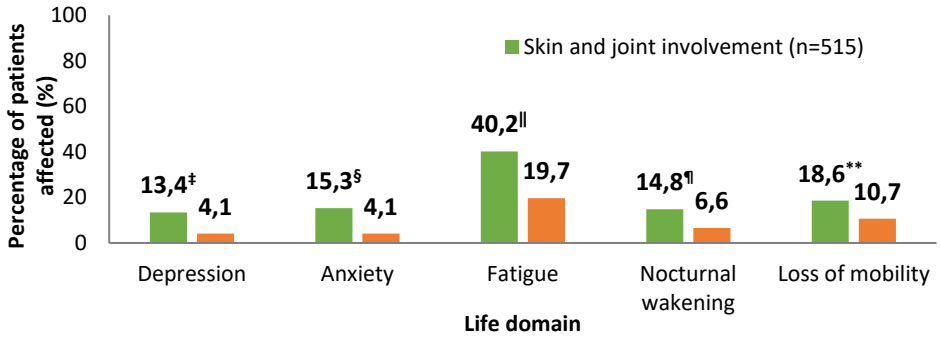


Source: Husni et al, 2018.
PsA: psoriatic arthritis.

Additionally, a retrospective analysis of patients with skin and joint involvement (n=515) versus patients with only joint involvement (n=515), impaired HRQoL was greater in patients with both skin and joint involvement when compared to those with just joint involvement alone (

Figure 5). There was a disconnect between the perceptions of patients and their rheumatologists regarding their overall disease, which may be due to the additional psychological burden of skin involvement in the disease that healthcare professionals do not consider when treating the present symptoms of PsA.(8)

Figure 5. The impact of PsA on HRQoL.(8)



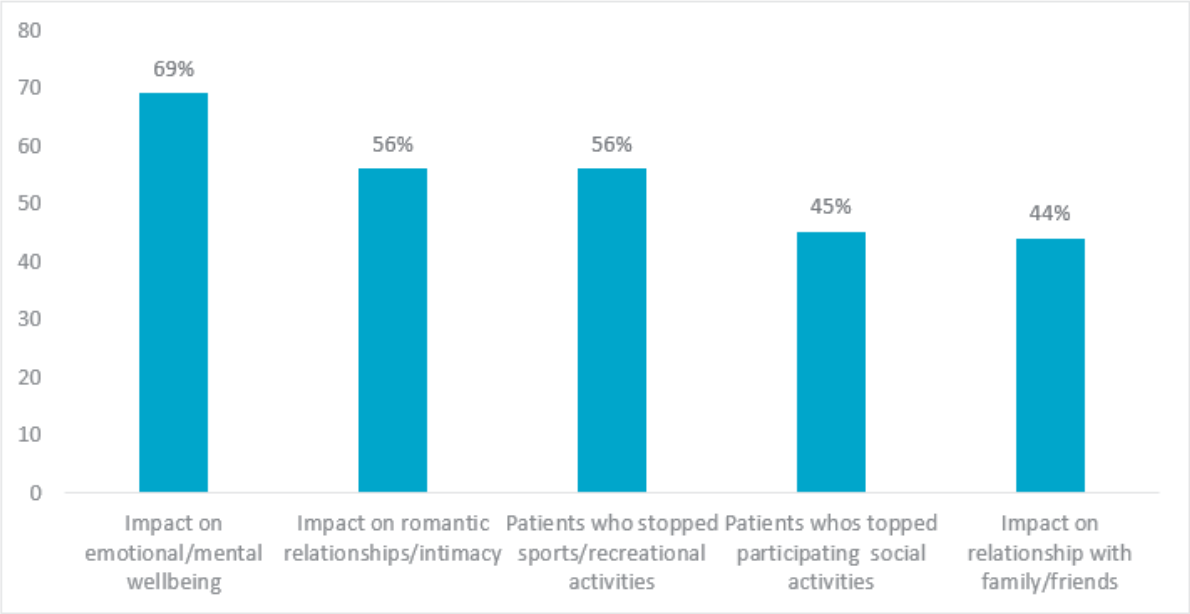
Source: de Vlam et al, 2018.
‡p=0.0026; §p=0.0005; ‖p<0.0001; ¶p=0.00166; **p=0.0440 versus those with joint involvement alone for all comparisons.
n: number; PsA: psoriatic arthritis; HRQoL: health-related quality of life.

Skin psoriasis and pain and tenderness in joints and are also associated with fatigue, a common symptom of PsA.(45). A Canadian cross-sectional study (n=499), identified that 50% of patients with PsA reported moderate fatigue and 28% of patients reported severe fatigue.(60) The association between fatigue and skin psoriasis can be explained by the pain and itching from the skin disease resulting in sleep disturbances, which may further lead to fatigue. In addition to this, the emotional burden of skin psoriasis largely contributes to fatigue. Similarly, pain, tenderness, and limitation of movement may cause fatigue in daily activities as well as sleep disturbances.(45)

5.1.6.2. Social impact of PsA

PsA has a large social impact on patients, in terms of activities (leisure) and social participation (social, relationships, intimacy, community participation), which in turn severely affects a patient's QoL.(61) In an online global survey that aimed to understand patient's perspective of PsA and the impact of the disease on QoL (n=1,286), more than half of patients reported an effect on their social life.(42) In specific, patients reported an impact on emotional/mental wellbeing (69%), romantic relationships/intimacy (56%), and relationships with family and friends (44%). Additionally, patients reported that they had stopped participating in social activities (45%) or in certain sports/recreational activities (56%) as a consequence of their PsA (Figure 6). The study suggests that over half of the PsA population feels that their disease has affected their social life in one or more ways (42).

Figure 6 - The social impact of PsA on patients (%)



Source: (42)

5.1.6.3. Psychological impact of PsA

Patients with PsA have a high rate of both depression and anxiety. Depression has been reported in up to 22% of patients with PsA, with anxiety reported in up to 30%. Increased depression was associated with the reduced ability to work. Additionally, an increased likelihood of depression and anxiety were in patients with PsA associated with a higher actively inflamed joint count and a worse score on the Physician Global Assessment (PGA).(62) Depression and anxiety in patients with PsA are associated with embarrassment and shame due to appearance, feeling rejected, concentration difficulties, frustration, preoccupation with the illness, and grieving over the loss of previous lifestyle.(61) Psoriasis skin lesions cause impaired confidence and psychological well-being due to the appearance of lesions especially in visible anatomical locations such as the scalp. The impact of lesions on the psychological well-being of patients is largely affected by the extent of skin lesions.(46) This may prevent patients from social participation and building relationships as well as avoiding social activities and roles such as work.

The impact of PsA on patients' ability to work has also been evaluated in the previously mentioned MAPP study. Of 3,426 included patients with PsA reported 20–30% that PsA affected their ability to work full time, choose a career, and either get or keep a job.(59) Additionally, PsA has a substantial impact on patients' mental health, equivalent to that seen in patients with AS.(5) Additionally, a cross-sectional study in patients with PsA (n=83) showed 22% identified as suffering from moderate-to-severe depression.(15)

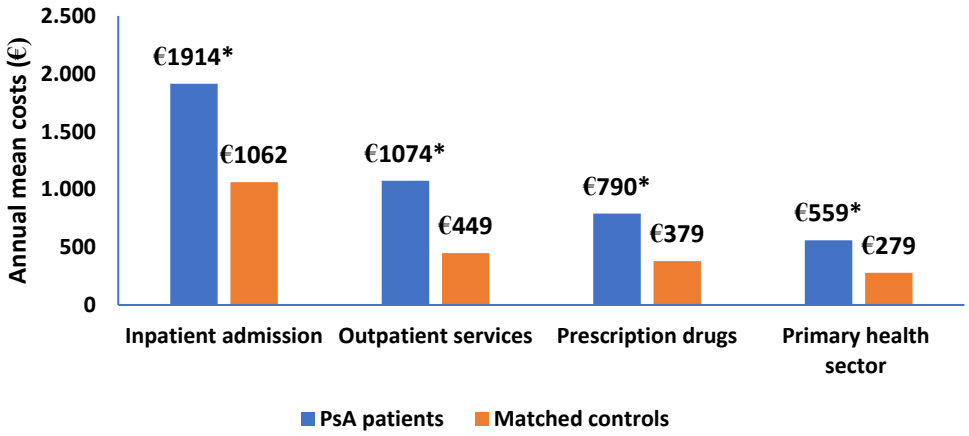
5.1.7. Economic burden of PsA

PsA incurs a high socioeconomic burden and is associated with high direct healthcare resource and medical costs as well as high indirect costs, driven by presenteeism, absenteeism and overall impaired ability to work. (63). Of note, studies show that patients with PsA and active PsO incur higher annual total costs than patients with PsO or PsA without active PsO (64).

5.1.7.1. Direct costs

In order to manage the variable clinical burden and symptoms of PsA, patients require substantial use of multiple healthcare resources, leading to high healthcare costs.(63) This was evaluated in a Danish cohort study comparing healthcare costs of patients with PsA (n=10,525) with a general population control group (n=20,777) between 1998 and 2014.(65) The study also assessed healthcare costs for patients with PsA before and after diagnosis. Healthcare costs increased from <€2,000 per year 5 years prior to diagnosis to >€5,000 per year around the time of PsA diagnosis, reflecting the increased utilization of healthcare resources associated with reaching a diagnosis. At all timepoints, the total healthcare costs were higher for PsA patients compared to the control population, although the difference in costs was more significant following diagnosis (p<0.001) (Figure 7). During the 10-year period following diagnosis, the average annual total cost of healthcare resource utilization was €4,336 and €2,170, with the highest contributor being inpatient admissions €1,914 and €1,062, in patients with PsA compared to controls, respectively.(65)

Figure 7. Average annual healthcare costs of PsA patients compared to controls during a 10-year period following diagnosis.(65)



Source: Kristensen et al, 2017
*p<0.001 versus controls PsA.
PsA: psoriatic arthritis.

Additionally, research has highlighted that healthcare resource utilization and costs are higher in PsA patients even before diagnosis of the disease. This was investigated in a 2020 Canadian matched cohort study that aimed to measure the healthcare utilization for musculoskeletal (MSK)-related issues in PsA patients (n=462) and matched comparators (n=2,310) during the 5-year period prior to the date of diagnosis or first claim of an inflammatory arthritis diagnosis by a rheumatologist (the index date) (66). The study reported that overall, healthcare resource use for MSK-related issues was relatively higher in the years preceding the index date in PsA patients compared to their matched controls. Total and MSK-related health care costs were higher in patients who developed PsA than their comparators at any point during the 5-year period prior to the index date. Total healthcare cost increased gradually in patients with PsA from a mean ± SD of $4,873±8,480 Canadian Dollars (CAD) 5 years prior to the index date to $6,995±11,270 CAD 1 year prior to the index date, compared to a relatively stable total mean healthcare cost of around $2,500 CAD observed in the comparator group (66).

This study suggests that the cost associated with healthcare resource utilization in PsA is potentially much larger than estimated, contributing to an even larger economic burden of the disease(66). Additionally, this study concluded that a prodromal PsA phase, characterized by non-specific MSK symptoms may exist. The early identification and appropriate management of non-MSK symptoms, such as skin manifestations, may present an opportunity to help minimize the economic burden associated with PsA management (66).

5.1.7.1.1. *Drivers of direct costs*

Direct costs in PsA are influenced by a number of factors including functional impairment, disease severity, disease duration and also skin involvement.

In a study evaluating the socioeconomic burden of rheumatic diseases (RA, AS, PsA and systemic lupus erythematosus) in Germany, the effect of functional disability on the PsA direct cost of illness was assessed in 908 PsA patients (67). The study reported that patients with a poor functional status of <50% had direct costs more than twice the cost of patients with good functional status of >70%. This was evident for costs of inpatient treatment, visits to the doctor, non-drug treatment and out-of-pocket expenses where the costs were directly correlated to functional status.(67) Therefore, direct costs in PsA are positively correlated to disease severity, where a high functional disability results in higher direct costs.

The skin manifestations of PsA represent an additional economic burden to the more established and commonly recognized expenditure associated with joint manifestations. In a cross-sectional non-interventional survey, the presence and worsening of skin symptoms were found to contribute to higher total direct medical costs (68). Patients with active skin involvement (n=2,139) reported greater hospitalization, dermatologist and GP costs per patient than those with joint involvement alone (n=531). Furthermore, those patients who displayed moderate-to-severe skin symptoms also displayed greater hospitalization, dermatologist and GP costs per 1,000 patients than those with none-to-mild skin symptoms (Table 4) (68).

Table 4. The presence and worsening skin symptoms contribute to higher total direct medical costs (N=2,670) (68)*

Costs (€)*	Skin involvement		Severity of skin symptoms	
	Active (2,139)	Inactive (n=531)	Moderate-severe (n=919)	None-mild (n=1,747)
Hospitalization	€2,098,000	€1,407,000	€2,361,000	€1,405,000
Dermatologist	€126,000	€95,000	€158,000	€101,000
GP	€95,000	€84,000	€99,000	€96,000

Source: Tillet et al, 2018.
*Costs have been scaled up to costs for 1,000 patients and rounded to nearest whole number.
GP: general practitioner.

Furthermore, since PsA is a very heterogeneous disease patients will require a very individual treatment approval involving several treatments and therapies which will further add to the economic burden of PsA. Skin involvement is a manifestation that can have significant impact on the cost burden if the patients are not adequately helped by their drug treatment and need additional expensive therapies to treat the skin, such as phototherapy.

These findings demonstrate how both the presence and severity of skin manifestations can contribute to and exacerbate the economic burden of PsA. Furthermore, as up to a third of PsO patients go on to develop PsA, which is associated with a substantial direct cost increase ($2,126 versus $3,638 per patient per year), the early identification and subsequent treatment of the skin manifestations may help further reduce the healthcare expenditure and resource utilization associated with PsA diagnoses.(63, 69)

5.1.7.2. *Indirect costs*

PsA is associated with substantial indirect costs due to high levels of disability and loss of work productivity, with high PsA disease activity directly driving indirect costs (5, 70, 71). Annual indirect costs can be substantial due to the extent of functional impairment and mental burden of PsA on patients' ability to remain in employment and their ability to work in terms of absenteeism and presenteeism (67, 70, 72).

5.1.7.3. *Impact of PsA on ability to work*

Impaired physical function leads to a loss of productivity in everyday life but also in the work setting. Patients with PsA often reduce their working hours or days in order to cope with their illness. Some PsA patients are obliged to quit their job or change their occupation as they cannot cope with the requirements of their job (70).

Reported employment rates for PsA range from 54% to 63%. Compared with the general population, PsA patients have significantly lower employment rates, similar to the employment rates of AS. Almost one-third of PsA patients claim either short-term or permanent disability (63).

The ability to work in patients with PsA was evaluated in a Spanish cross-sectional, observational multi-center study assessing 287 patients across 18 centers (n=287) (70). Of the entire study population, 55% patient were employed at the time of study, whilst 16% of patients had retired early due to their disease. Approximately 6% of patients had changed their job due to their disease and 16% reported that they were disabled.

Absenteeism is common among PsA patients who have an impaired ability to work. In a large UK multicenter study, 236 PsA patients of working age were assessed to report on work disability and the factors affecting it (73). The study reported that out of the entire study population, 14% of participants reported presenteeism whilst 39% of patients reported absenteeism.

Approximately 16% to 49% of PsA patients have reported health-related limitations at work (74). This was assessed in a retrospective cross-sectional study of productivity loss in working PsA patients (n=107) (74). The study reported that work productivity was reduced by 6.7% (SD 5.3%) in PsA patients compared to employees without limitations. Additionally, the study identified that fatigue was associated with work productivity loss. The average decrease in health-related work productivity was 4.5% in patients who did not experience fatigue but was almost double (8.6%) in patients with fatigue, compared to employees without limitations (74).

The effect of PsA on patients' productivity was also investigated in a 2019 Canadian study (n=292). The study reported that 17.8% of patients were unemployed due to their disease, while employed PsA patients reported a productivity loss score of 8.3% (SD 6.0), as measured by the Work Limitations Questionnaire (75).

5.1.7.3.1. Indirect cost burden of reduced work

The indirect costs of PsA include absenteeism, presenteeism, early retirement and unemployment in patients with impaired ability to work as a result of their disease.

A systematic review and meta-analysis collected data on the indirect costs associated with PsA (76). The average annual cost per patient was calculated and expressed using consumer price index for 2013 and converted in US dollars using data from eight studies in total. The study reported that the average annual indirect cost per patient using the friction costs method was between $1,694 and $12,318, while using the human capital approach the cost ranged between $1,751 to $50,271. Despite the method used to calculate, PsA is associated with significant indirect costs largely contributing to the economic burden of the disease to society (76).

A retrospective, cross-sectional observational study (n=318) conducted at 22 centers in Spain reported high direct non-healthcare costs and indirect costs in patients with PsA (n=43), PsO, (n=193) and PsA and PsO (n=79) (64). Direct non-healthcare costs included social services, home care, physical adaptations, private health and non-health professionals, non-reimbursed and non-pharmaceutical therapies whilst indirect cost was loss of productivity associated with the disease. The average annual direct non-healthcare and indirect cost per patient were numerically higher for patients with PsA and active PsO than patients with PsA and patients with PsO, see Table 5 (64). This study highlights that patients with PsA and active PsO incur higher annual total costs than patients with PsO or PsA without active PsO. (64).

Table 5. Annual direct non-healthcare and indirect costs per patient per year (64)

Average annual costs per patient (SD)	PsO (n=193)	PsA (n=43)	PsA and active PsO (n=79)
Direct non-healthcare cost	€749.57 (€2,393.77)	€750.50 (€1,641.82	€1,247.56 (€4,467.19)
Average annual indirect cost	€293.14 (€2,855.27)	€387.35 (€2,409.63)	€582.71 (€3,842.12)

Source: Castañeda et al, 2020.
PsA: psoriatic arthritis; PsO: psoriasis; SD: standard deviation.

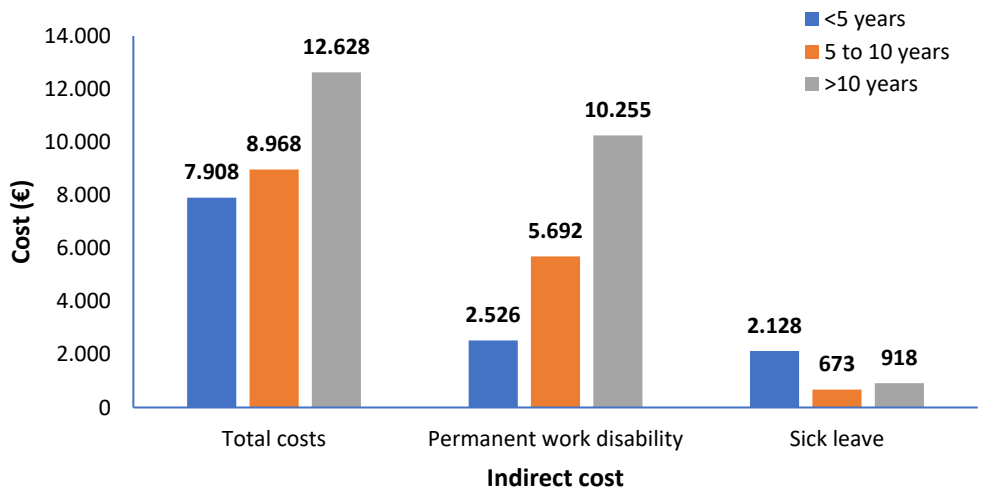
5.1.7.3.2. Drivers of indirect costs

The indirect costs associated with PsA are variable and are dependent on HRQoL, functional disability, disease severity and duration;(67) research has highlighted that there is a directly proportional relationship between disease severity and indirect costs (77). As reported in a systematic review evaluating the cost of PsA in 5 European countries (4 articles, n=3,828), disease severity is positively correlated with an increase in indirect costs (77). Overall, the annual indirect costs per PsA patient were between $2,053 and $3,716 (using the friction costs method) and $12,192 (using the human capital method). This value increased in studies that focused on patients with severe disease to $48,834 per patient annually (77).

In the German study, also mentioned above (see chapter *Drivers of direct costs*), evaluating the socioeconomic burden of rheumatic diseases (RA, AS, PsA and systemic lupus erythematosus), the effect of disease duration and functional disability on indirect costs associated with PsA were assessed in 908 patients (67). When assessing functional disability, the study reported that patients with a poor functional status of <50% had 4 to 10-fold greater indirect costs due to only a small number of patients being able to work. Patients who still worked had frequent and long sick leave. Hence patients with lower disease activity had lower indirect costs such as patients with functional ability of >70% who had the lowest costs within the entire study population (67). The study reported that patients with longer disease duration had the highest indirect costs. When assessing permanent work disability, the study also reported a 5-fold increase in costs between patients with <5 years of disease and patients with >10 years of PsA (

Figure 8). This suggests a large increase in indirect costs that follows disease duration, which is associated with more severe and progressed disease as well as higher functional impairment (67).

Figure 8. Direct costs by increasing PsA disease duration (67).



Source: Huscher et al, 2006.
PsA: psoriatic arthritis.

As reported through these studies, indirect costs are the major contributor of the total cost of PsA. Drivers of indirect costs include disease severity and duration, functional impairment and HRQoL. Hence, an intervention that could allow PsA patients to maintain an overall stable disease state would significantly decrease indirect costs in terms of ability to work and hence have a large impact of the socioeconomic impact of PsA.

5.1.8. Epidemiology in Denmark

The prevalence is difficult to estimate due to unclear diagnostic criteria, however in the Danish National treatment guidelines, it is estimated that the PsA prevalence is between 0,04 % to 0,1% (4). PsA normally develops in early 40s and 50s, with no difference between genders.

According to DANBIO (Danish Rheumatology Database) 2560 patients were registered with being treated with a biologic treatment in 2019. 330 patients were registered as being treated with a biologic for the first time (ie.

biologic-naïve). Since prevalence and incidence numbers are difficult to estimate, these numbers are used as the basis for estimated incidence and prevalence for PsA on biologic treatment in Denmark.

Table 6: Estimated incidence and prevalence of PsA patients on biologic treatment in the last 5 years

Year	[Year, e.g. 2017]	[Year, i.e. 2018]	[Year, i.e. 2019]	[Year, i.e. 2020]	[Year, i.e. 2021]
Incidence for biologic treatment in Denmark	330	330	330	330	330
Prevalence for biologic treatment in Denmark	1.900	2.230	2.560	2.890	3.220
Global prevalence *					

Numbers for estimated number of patients who is expected to use the pharmaceutical is based on the numbers estimated in the budget impact calculations.

Table 7: Estimated number of PsA patients eligible for treatment with risankizumab

Year	[Year, i.e. 2022]	[Year, i.e. 2023]	[Year, i.e. 2024]	[Year, i.e. 2025]	[Year, i.e. 2026]
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	■	■	■	■	■

5.1.9. Patient population relevant for this application

The patient population relevant for this assessment are patients who have active psoriatic arthritis with or without concomitant plaque psoriasis and who have shown inadequate response or intolerance to csDMARDs (defined as bio-naive), and patients previously treated with bDMARDs (defined as bio-experienced

Therefore, this application is concerning reimbursement of the use of risankizumab for the treatment of active psoriatic arthritis in bio-naïve and bio-experienced patients with or without concomitant plaque psoriasis.

The relative efficacy and safety assessment as well as the cost comparison and budget impact analysis are done for both the bio-naive and bio-experienced population compared to relevant comparators in these populations.

5.2. Current treatment options, choice of comparators and unmet need in the treatment of PsA

5.2.1. Current treatment options

The Danish Society of Rheumatology advice that the treatment of PsA should be a shared decision between the physician and the patient (4). When selecting the treatment, the physician should take disease manifestations and its severity into account, as well as comorbidities. The treatment chosen should also be based on

considerations of PsO severity, other medical treatments, and the occurrence of extra articular manifestations (4).

The current treatment guidelines for PsA in Denmark differentiates between patients with a low risk of progression and patients with a high risk of progression or inadequate response to csDMARDs(4). The treatment recommendations for patients with low disease activity and at low risk for progression are treatment with csDMARD ≥ 3 months. The efficacy of the treatment should be examined after 3-6 months and optimized if needed. MTX, leflunomide and salazopyrin have no or minimal documented efficacy on PsA(4).

Treatment guidelines for patients with a high risk of disease progression or inadequate response to csDMARDs specify that the following treatment algorithm should be used (4).

1. TNF inhibitor or IL-17 inhibitors
2. IL-12/IL-23 inhibitors
3. Apremilast or abatacept

Due to the heterogeneity of the PsA disease it might be hard to tell which treatment that will work out best for a specific patient. The following parameters should be taken into consideration when selecting treatment: malignancies, tuberculosis, metabolic syndrome and other comorbidities, previous treatment of skin condition, phototherapy and extraarticular manifestations. The treatment choices in PsA are far more individual than in many other joint diseases (4).Therefore, there is a need for a broad range of different treatment options in order to tailor treatment to which manifestations are most burdensome for patients.

Treatment choice in Denmark as mainly dictated by the pharmaceutical treatment recommendations from the Danish Medicines Council. The treatment guidelines assumes that all treatments with the exception of ustekinumab are clinically equal in efficacy and safety and the ranking in the recommendation is based on price only (31). The current recommendations from The Danish Medicines Council for PsA in Denmark was updated 15 January 2021 and differentiate between patients with or without concomitant moderate to severe plaque psoriasis and former or existing uveitis or former or existing inflammatory bowel disease (IBD) (31). For all these groups, the TNF inhibitor adalimumab is ranked highest and recommended as 1st choice. After that, for patients with or without concomitant plaque psoriasis the treatment choice is another TNF inhibitor, IL-17 inhibitors or IL12/23 inhibitor. For patients with former or existing comorbidities, uveitis or IBD (Ulcerative colitis, Crohn's disease), options are limited. The only choice for patients with uveitis is another TNF inhibitor and for patients with IBD another TNF-inhibitor or IL12/23 inhibitor (Crohn's disease only) (31).

Risankizumab is expected to be an alternative included in the pharmaceutical recommendations for patients with or without moderate to severe plaque psoriasis who have failed a TNFi-treatment, due to also having an approved indication for moderate to severe plaque psoriasis. As described previously PsA is a heterogeneous disease where patients with skin involvement have a large need for new treatment options that at the same time have good effect on joints and where AbbVie see's that Skyrizi will meet a large unmet need.

5.2.2. Choice of comparator(s)

Relevant comparators are based on the treatment recommendations from the Danish Medicines Council.

Risankizumab is expected to be a treatment alternative that can be included in the treatment recommendations for the treatment of patients with PsA with or without moderate to severe plaque psoriasis. The use of risankizumab will be according to ranking in the treatment guidelines and the two relevant populations for this assessment are patients who have not received any prior biologic treatment (ie. bio-naïve) and patients who have showed insufficient efficacy on TNFi (ie. bio-experienced).

According to The Medicines Councils treatment recommendations for PsA, adalimumab is first choice treatment and should be used for at least 90% of the population. Therefore, AbbVie consider the TNF-inhibitor adalimumab as the most relevant comparator for the bio-naïve population.

Next option for patients who have previously been treated with TNFi inhibitors in the treatment recommendations is the IL-17 inhibitor ixekizumab. Based on current treatment recommendations and clinical practice it is expected that risankizumab will primarily be used for a similar population as what is relevant for

ixekizumab today. Therefore, AbbVie considers ixekizumab as the relevant comparator for the bio-experienced population in the cost comparison.

Since the treatment recommendations considers all treatments to be scientifically equal, AbbVie considers it sufficient to demonstrate relative efficacy and safety vs. adalimumab and ixekizumab to be included in the recommendations.

Note that AbbVie do not expect risankizumab to increase the total population eligible for treatment, but to become an additional alternative in the recommendations, increasing competition and taking existing market shares from the current recommendations.

5.2.3. Description of the comparator(s)

	Adalimumab	Ixekizumab
Generic name (ATC)	Hyrimoz, Amgevita, Humira, Imraldi (L04AB04)	Taltz (L04AC13)
Mode of action	TNF-inhibitor	IL-17 inhibitor
Pharmaceutical form	Solution in pre-filled syringe/pen	Solution in pre-filled syringe/pen
Posology	40 mg every other week	160mg week 0, then 80mg every four weeks
Method of administration	Subcutaneous injection	Subcutaneous injection
Co-medication	Monotherapy	Monotherapy or in combination with methotrexate
Necessary monitoring	N/A	N/A
Diagnostics or other tests	N/A	N/A
Packaging1 pc.	2pc 40mg solution on pre-filled syringe/pen	1pc 80mg solution in pre-filled syringe/pen

5.2.4. Unmet needs in the treatment of PsA

The clinical variability of PsA makes both diagnosis and treatment challenging, resulting in disability and reduced QoL among PsA patients. Despite the introduction of novel therapies such as IL-17 inhibitors, JAK-inhibitors and additional TNFi there remains unmet needs for therapies with reduced adverse events and with better treatment response.(78, 79) A Danish study, using data from the DANBIO register demonstrated that a high percentage of PsA patients treated with a TNFi switch treatment due to lack of efficacy or adverse events, showing there is a need for novel therapies with new mode of actions in PsA.

Patients have highlighted that existing therapies are often burdensome due to side effect profiles and the need for frequent blood monitoring. Additionally, for the majority of patients, dermatologists and rheumatologists, there is a need for better therapies for the management of PsA.(59, 80)

The introduction of a new therapy that provides rapid, durable efficacy for the treatment of skin manifestations alongside joint symptoms, whilst maintaining a simple dosing regimen, is required to help combat the burden of PsA.

Overall, current treatments are associated with burdensome adverse events that often impact patient QoL or have reduced efficacy over time resulting in patients needing to switch treatments frequently. In the 21st annual international Advances in Targeted Therapies meeting from 2019, more than 100 scientists and clinical researchers were brought together to discuss the unmet need in a range of rheumatologic diseases, including PsA (79). The discussion group identified a range of unmet needs in PsA. There is a need for a greater

understanding in the effect of pain on disease severity, and there is also an unmet need for a therapy that adequately controls PsA symptoms in patients who have tried all currently available treatment and have no response or tolerance. Novel treatments will meet the needs of such patients (79).

Patients with PsA have an unmet need for additional therapies that provide:

- Improved efficacy
- Achievement of minimal disease activity (MDA) and remission
- A favorable safety profile that is sustained over the long-term
- Have formulations that offer can greater patient convenience

5.2.4.1. Improved efficacy

TNFi treatment remains the first treatment option for patients who does not have a sufficient effect on more conventional treatment, such as MTX. However, a high percentage of patients treated with TNFi also experience a gradual loss of efficacy that results in reappearance of both signs and symptoms of PsA.

In the Danish nationwide DANBIO observational study, the aim was to describe the frequency and outcomes of switching TNFi in PsA patients (81). Out of 1,422 patients starting TNFi, 548 (39%) switched to a second biologic. Of these, 42% continued treatment, 34% switched to a third TNFi, and the rest of the subjects stopped treatment altogether. The main reasons for switching were lack of effect (57%) or adverse events (28%). The response rates to treatment were significantly lower in patients receiving the second or third treatment compared with those who stayed with the first TNFi treatment (81). Clearly, in a large number of patients with PsA, TNFi treatment has reduced efficacy over time resulting in a need to switch treatments. However, TNFi are associated with even lower efficacy upon switching, resulting in inadequate available treatments for patients with PsA, which demonstrates the need for new treatments with different modes of action.

The lack of efficacy of TNFi inhibitors is also supported by another prospective cohort study which assessed the efficacy of TNFi in patients with PsA (n=765) where treatment response rates were recorded at 6 months. Patients receiving a TNFi as their first bDMARD showed a higher response than patients receiving a second or third bDMARD. However, even for patients receiving TNFi as their first bDMARD, response rates were still low, where less than 50% of patients achieved a EULAR good response and only 51% achieved the low disease target of ACR20 (82).

In this same study described above, 4.5%, 9.4% and 17% of patients discontinued treatment after 3, 6 and 12 months respectively, mostly due to lack of efficacy (82). High discontinuation rates have been reported in a number of studies including a retrospective, observational study using the US administrative claims data between 2013 and 2015 where 1,235 patients with PsA who were receiving bDMARD therapy for the first time, the majority discontinued their first-line bDMARD before 12 months (83).

5.2.4.2. Achieving remisson

With current treatments, a large proportion of patients do not achieve remission. For example, in a retrospective analysis of longitudinal cohort, patients with PsA, treated with csDMARDs or TNFi, were followed up prospectively every 3–6 months and assessed for sustained remission (defined as DAPSA score ≤ 4 and/or VLDA for at least 12 months). Of these patients, only 17.5% achieved a sustained VLDA while 30% achieved sustained remission according to the DAPSA criteria. The mean duration of remission in patients achieving VLDA and DAPSA ≤ 4 was 17 months for both criteria (84).

5.2.4.3. A favorable safety profile

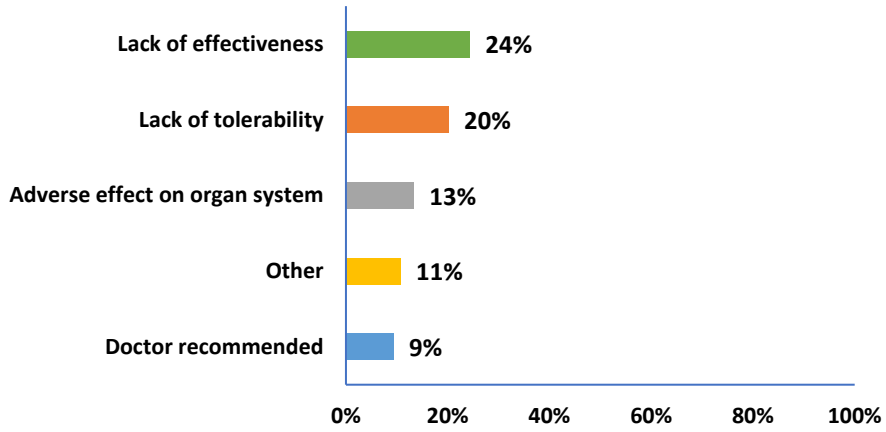
Currently available treatments in PsA are associated with a high number of adverse events. Long-term NSAID treatment is associated with hypertension, abdominal pain, cardiovascular and renal related side effects, csDMARDs are primarily associated with nausea (85),(86) Among biologics, common safety concerns include hepatitis B virus reactivation and interstitial pneumonia. TNF inhibitors have also resulted in safety issues, with usage associated with increased risk of serious infection, tuberculosis, paradoxical reaction, lupus and infusion reactions. IL-17 inhibitors are associated with candidiasis, neutropenia, and inflammatory bowel disease (87). Such adverse events result in patients frequently discontinuing treatment, highlighting the unmet need in PsA

treatment for novel therapies that have a long-term safety profile and result in reduced adverse events in PsA patients.

5.2.4.4. *Treatment burden*

In a population-based survey of 3,426 patients with PsA (a MAPP study), PsA patients also reported that they found existing bDMARDs and DMARDs for PsA burdensome therapies. Overall, 54% of patients receiving bDMARDs reported their treatment as burdensome with almost one third finding them 'very' or 'moderately' burdensome. Lack of effectiveness and tolerability as well as adverse events were the most common reasons that patients considered their treatment to be burdensome (Figure 9) (14).

Figure 9. Reasons that PsA patients discontinue bDMARDs. (14)



Source: Kavanaugh et al 2016; bDMARDs: biologic disease-modifying anti-rheumatic drugs; PsA: psoriatic arthritis.

Approximately one third of patients reported that their therapies were 'very' or 'moderately' burdensome (14). Most commonly, patients considered DMARDs burdensome, due to the side effects following treatment as well as the need for frequent blood monitoring. Overall, 90% of PsA patients reported that there was a need for better therapies for PsA (14).

Another MAPP survey, a population-based survey of patients with PsA (n=270), rheumatologists (n=100) and dermatologists (n=101) in the US, investigated perceptions to current treatments in PsA (80). Overall, 40.7% of patients with PsA reported that their primary goals of therapy, including reducing symptoms, itching and flaking, were not met by current treatments (80). Additionally, 87.8% of patients and 98.0% of dermatologists and rheumatologists reported that they felt a strong or moderate need for better therapies. Among patients, 51.5% reported that current therapies were worse than the condition itself. Additionally, 48.5% of dermatologists and 31.0% of rheumatologists reported that an important issue is patients leaving their practice because of frustration or dissatisfaction with currently available treatments (80).

There is a strong desire among patients, dermatologists and rheumatologists for new treatment options in PsA as there are unmet needs in the current treatment landscape. Current treatment options offer limited efficacy and are associated with side effect concerns, as well as being burdensome with high levels of discontinuation and lack of efficacy, especially in cases where patients are treated with a similar mode of action (MoA). After TNFi treatment, the next treatment options for PsA patients in Denmark is another TNFi or an IL-17 inhibitor. Although there are several alternatives within same MoA, there are still limited options that can meet the needs of PsA patients. IL-17 inhibitors have also shown to cause the exacerbation of co-existing EAMs such as IBD, and patients with this clinical profile are ineligible for IL17A-inhibitor treatment and are also in need of alternative and effective treatment options.

There is therefore still a huge need for new therapies that can provide improved efficacy outcomes with a favorable safety profile. Risankizumab is a new IL-23 inhibitor that has the potential to meet these needs and provide improved skin and joint outcomes, together with a favorable safety profile and with a simple dosing regime with maintenance dosing only every 12th week.

5.3. The intervention - risankizumab

Risankizumab is a humanized immunoglobulin (Ig) G1 antagonistic monoclonal antibody (mAb) directed against the p19 subunit of the human cytokine IL-23. IL-23 plays a critical role in the differentiation and function of T helper (Th) 17 cells, which have emerged as an important T-cell subpopulation involved in the pathogenesis of immune mediated disorders. Activation of pathogenic Th17 cells produces the effector cytokine IL-17 and stimulates inflammation in psoriatic and rheumatic diseases. By inhibiting IL-23 in PsA, the effect of targeting the immunomodulatory and disease modifying IL-23 pathway has been studied with risankizumab. Risankizumab treatment is associated with steadily increasing efficacy up to 52 weeks with a well-tolerated safety profile. Risankizumab is approved by the FDA and EMA for the treatment of psoriasis. Besides psoriatic arthrithis, risankizumab is also being investigated for other immunology indications, such as Crohn´s disease and ulcerative colitis.

5.3.1. Product profile

Compound name	Rizankizumab (Trade name Skyrizi)
Mode of action	Humanized monoclonal antibody of the IgG1 subclass that is directed towards IL-23p19
Pharmacotherapeutic class	Immunosuppressants, interleukin inhibitors, ATC code: L04AC18
Form of administration	Solution for injection in pre-filled pen and pre-filled syringe
Dosage	Risankizumab 150 mg solution for injection in pre-filled pen and pre-filled syringe The recommended dose is 150 mg administered as a subcutaneous injection at week 0, week 4, and every 12 weeks thereafter. Risankizumab 75 mg solution for injection in pre-filled syringe The recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.
Treatment plan (combination therapy or premedication)	Skyrizi (risankizumab), alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).
Packaging type, size, durability, strengths	1 pc Skyrizi 150 mg solution for injection in pre-filled pen Pre-filled glass syringe assembled in a pre-filled pen with an automatic needle sleeve. 1 pc Skyrizi 150 mg solution for injection in pre-filled syringe Pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard. 2x Skyrizi 75 mg solution for injection in pre-filled syringes Pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard.

Handling requirements that may affect usability	Cold storage
Monitoring (blood tests, scans, biomarker etc)	N/A
Expected position in Danish practice	Expected to be used according to positioning in treatment guidelines

6. Literature search and identification of efficacy and safety studies

6.1. Documentation of clinical effect and safety for the intervention and comparator(s)

A targeted systematic literature search via MEDLINE and CENTRAL was conducted on October 13th to identify relevant studies and data for assessing the clinical efficacy and safety of risankizumab vs. adalimumab for the bio-naïve population and vs. ixekizumab for the bio-experienced population.

The search was carried out according to pre-defined PICO criteria, shown in Table 8 below.

Table 8: Pre-defined PICO criteria for literature search

PICO criteria	
Population	• bDMARD therapy naïve patients with PsA • bDMARD experienced patients with PsA
Intervention	Risankizumab s.c, 150mg week 0, 4 and thereafter every 12 weeks
Comparator	• Adalimumab s.c, 40mg every other week • Ixekizumab s.c, 160mg week 0, 80mg every four weeks. • Placebo
Outcome	At least 24-week follow-up with placebo-controlled arm and these outcomes: • ACR20 • ACR50 • PASI75 • PASI90 • SF-36 physical component summary (PCS) • SF-36 mental component summary (MCS) • Serious adverse events (SAE)

A total of 210 potentially relevant references were identified through searching MEDLINE and CENTRAL. A total of 24 reference duplicates were identified and 186 references were subsequently screened, 164 records were excluded based on titles and abstracts and 22 published full-text papers were subsequently assessed for eligibility. Of these, 19 references were excluded in full text review. In total, 3 references reporting results from 3 studies were included. The PRISMA flow diagram and lists of studies included and excluded is shown in appendix A.

The 3 references identified and included in this submission reported primary and secondary endpoints from the SELECT PsA-1, SPIRIT P1 and SPIRIT P2 clinical trials.

SELECT PsA-1 and SPIRIT P1, reported primary and secondary efficacy and safety results for the bio-naïve population including adalimumab as an active treatment arm. SELECT PsA-1 and SPIRIT P1 included both adalimumab and a placebo-controlled arm and reported primary and secondary results at week 24 timepoint for the bio-naïve population.

SPIRIT P2 reported primary and secondary results at the week 24 timepoint for ixekizumab compared to placebo for the bio-experienced population.

KEEPsAKE 1 and KEEPsAKE 2 were not identified in the literature review since the results from these studies have not been published in a manuscript yet at the date of the literatue search. Data from these trials have been extracted from internal Clinical Study Reports (CSR).See table

Table 9 below for studies included in the assessment and their primary publications.

6.2. List of relevant studies

Table 9: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, Adams DH, Kerr L, Lee C, Shuler CL, Genovese M; SPIRIT-P2 Study Group. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017 Jun 10;389(10086):2317-2327.	SPIRIT P2	NCT02349295	Start: December 31, 2024 Completion: June 26, 2019	Ixekizumab vs. placebo for bio-experienced population. Data used in indirect comparison vs. risankizumab for bio-experienced population.
McInnes IB, Anderson JK, Magrey M, Merola JF, Liu Y, Kishimoto M, Jeka S, Pacheco-Tena C, Wang X, Chen L, Zueger P, Liu J, Pangan AL, Behrens F. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. N Engl J Med. 2021 Apr 1;384(13):1227-1239.	SELECT PsA-1	NCT03104400	Start: April 27, 2017 Estimated completion: August 4, 2024	Upadacitinib vs. adalimumab and placebo for bio-naïve population. Data on adalimumab used in comparison vs. risankizumab for bio.naive population.
Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, Lin CY, Braun DK, Lee CH, Gladman DD; SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific	SPIRIT P1	NCT01695239	Start: December 2012 Completion: September 2017	Ixekizumab vs adalimumab and placebo for bio-naïve population. Data on adalimumab used in comparison vs. risankizumab for bio-naïve population

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017 Jan;76(1):79-87.				
Kristensen LE, Keiserman M, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis 2022;81:225–231.	KEEPsAKE 1	NCT03675308	Start: March 25, 2019 Estimated completion: September 1, 2024	Risankizumab vs. placebo for bio-naïve population Data used in comparison vs. adalimumab for bio-naïve population.
Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for activ psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial Ann Rheum Dis 2022;81:351–358.	KEEPsAKE 2	NCT03671148	Start: March 7, 2019 Estimated completion: May 17, 2024	Risankizumab vs. placebo in bio-naïve and bio-experienced population. Data for bio-naïve population used in comparison with adalimumab. Data for bio-experienced population used in comparison with ixekizumab.

See Appendix B Main characteristics of included studies for more information regarding these studies.

6.3. Ongoing studies for intervention and comparator

Patients who had completed the 24-week randomized period in KEEPsAKE 1 and 2 will continue in a long-term open label extension period so data on efficacy and safety for this study population will continuously be collected up until week 208 (estimated study completion September 1st 2024 for KEEPsAKE 1 and May 17, 2024 for KEEPsAKE 2).

SELECT PsA-1 is currently in a long-term extension phase and will follow-up patients for a total of approximately 5 years (estimated study completion August 4, 2024), head to head vs. adalimumab.

SPIRIT P1 and 2 and their long-term follow-up periods were completed in September 2017 and June 2019, respectively.

Other than what is mentioned above there is, to best of AbbVies knowledge, no other studies (randomized or long-term extensions) currently assessing the efficacy and safety of the intervention (risankizumab) or comparators (adalimumab and ixekizumab) for the treatment of psoriatic arthritis.

7. Efficacy and safety of Risankizumab in PsA

- The efficacy and safety of risankizumab in patients with moderate to severe PsA with an inadequate response or intolerance to ≥1 DMARD or ≥1 biologic have been investigated in two phase III, global, mulitcenter placebo-controlled studies, KEEPsAKE 1 and KEEPsAKE 2.
- Results demonstrate that risankizumab offers the familiar high-level and durable skin clearance observed in PsO patients to patients with PsA, with a significantly higher proportion of patients with PsA achieving ACR20, ACR50 and ACR70 in KEEPsAKE-1 and KEEPsAKE-2.
- Treatment with risankizumab maintained high ACR20, ACR50 and ACR70 response rates in both trials from week 24 to week 52 and demonstrate initial and durable, skin clearance and symptom relief for patients with active PsA.
- Majority of patients achieved PASI90 at week 24 and maintained skin clearance on PASI 90 and symptom relief at week 52 in both KEEPsAKE 1 and KEEPsAKE 2. The rate of radiographic progression remained low in patients who received continuous risankizumab at week 52 in both trials.
- Treatment with risankizumab displayed clear quality of life benefits, with significant improvements in HAD-DI, SF-36 and FACTIT-FATIGUE in both trials which were maintained at week 52.
- In KEEPsAKE 1 and KEEPsAKE 2, patients switched from placebo-to-risankizumab at week 16 displayed comparable efficacy results at week 52 with patients who received continuous risankizumab, highlighting how risankizumab can display clinical improvements post treatment switch.
- Risankizumab has a comparable safety profile to placebo with an improved benefit/risk profile. No new or unexpected safety signals have been observed at week 52 in the trials, highlighting the value of risankizumab in the treatment of PsA.
- Risankizumab is a convenient treatment option that does not require the frequent blood monitoring necessary with some existing DMARDs therapies.

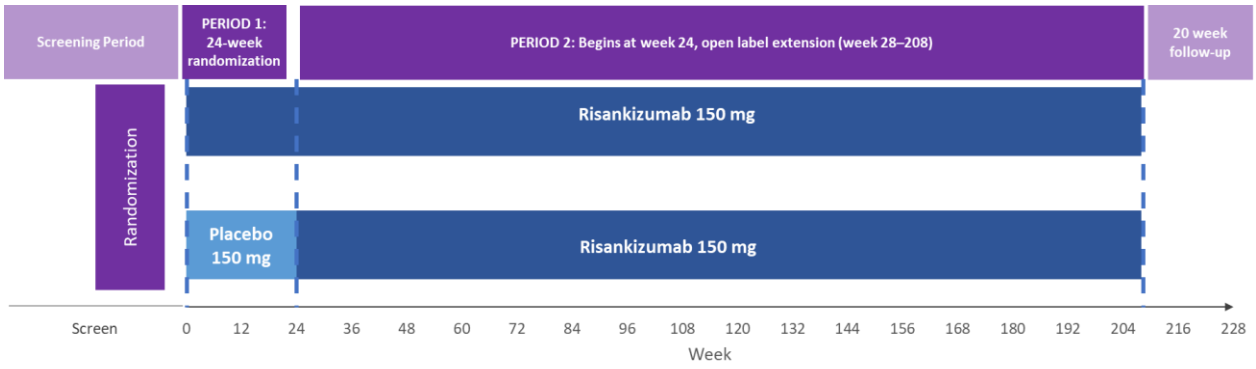
7.1. Efficacy and safety of risankizumab compared to placebo for bio-naïve and bio-experienced population (KEEPsAKE 1 and KEEPsAKE 2)

The efficacy and safety of risankizumab in patients with moderate-to-severe PsA with an inadequate response or intolerance to at least one disease modifying anti-rheumatic agent (DMARD-IR) or biologic (BIO-IR) has been assessed in the Phase III trials KEEPsAKE-1 (NCT03675308) and KEEPsAKE-2 (NCT03671148).(88-90)

KEEPsAKE-1 and KEEPsAKE-2 are Phase III, global, multicenter placebo-controlled studies examining the efficacy and safety of risankizumab in patients with moderate-to-severe PsA.(88, 89) Patients were randomized to receive either risankizumab 150 mg or placebo for 24 weeks, see Figure 10.

At week 24, patients receiving placebo were switched to risankizumab 150 mg. Non-responders at week 12 and week 16 were allowed to adjust rescue concomitant therapies. Non-responders at week 36 were discontinued from the study.(88, 89). Efficacy and safety data at week 52 are presented in section 7.1.4.

Figure 10. KEEPsAKE-1 and KEEPsAKE-2 study design(88)



Source: AbbVie data on file.

At week 16, non-responders (defined as not achieving at least a 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both week 12 and week 16 compared to baseline) had the option to add or modify rescue concomitant medications/therapy. At week 36, non-responders were discontinued from study drug.

97.9% and 96% of patients on risankizumab completed the 24-week randomized placebo-controlled period vs. 97.1% and 90.9% of patients on placebo in KEEPsAKE 1 and KEEPsAKE 2, respectively. See Figure 11 and Figure 12 for patient disposition and more information regarding reasons for discontinuation in KEEPsAKE 1 and KEEPsAKE 2.
A summary of the KEEPsAKE-1 and KEEPsAKE-2 study design can be found in Table 10, and a description of the patient disposition and reasons for study discontinuation in these studies can be found in Figure 11 and Figure 12 below .

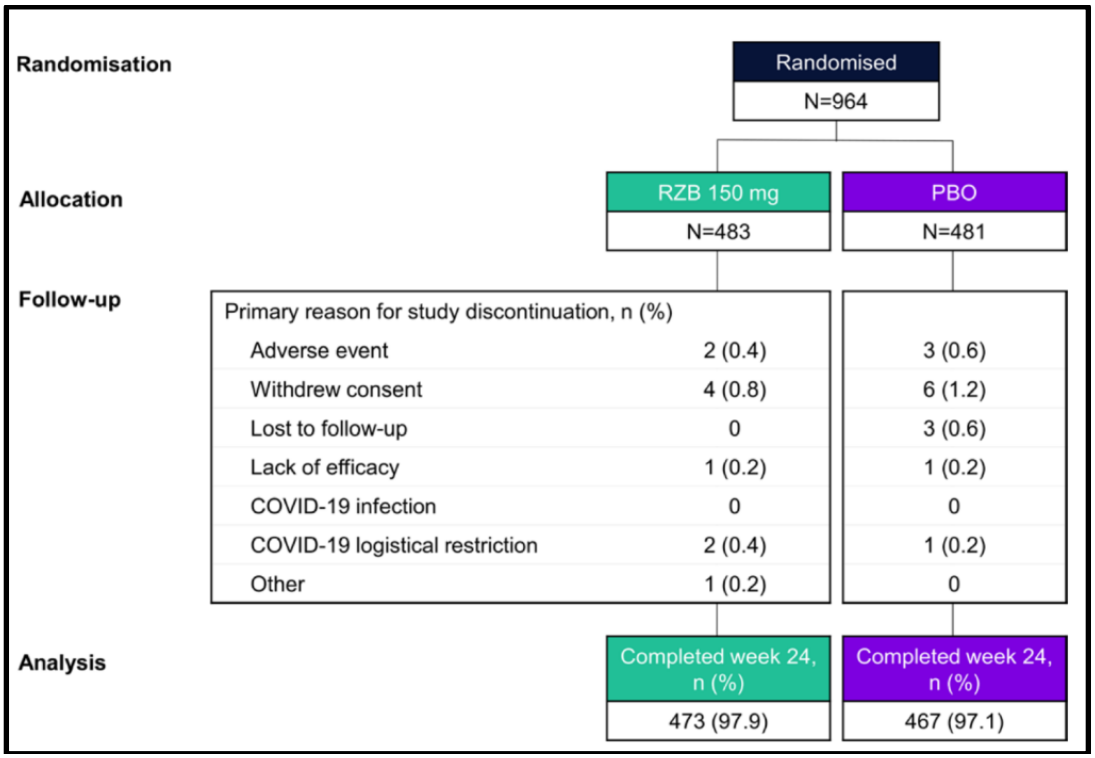
Table 10. Summary of KEEPsAKE-1 and KEEPsAKE-2 clinical trials(88, 91)

Characteristic	KEEPsAKE-1	KEEPsAKE-2
Patient population	DMARD-IR	DMARD-IR and BIO-IR
Comparator	Placebo	Placebo
Arm	Risankizumab 150 mg Placebo	Risankizumab 150 mg Placebo
Study duration	24 weeks (blinded) OLE 208 weeks, 20 week follow-up	24 weeks (blinded) OLE 208 weeks, 20 week follow-up
Primary endpoint	ACR20 response at week 24	ACR20 response at week 24
Ranked secondary endpoints	**At week 16:** ACR20 response **At week 24:** CFB HAQ-DI	**At week 16:** ACR20 response **At week 24:** CFB HAQ-DI

	PASI90 MDA CFB mNAPSI CFB PGA-F Resolution of enthesitis (pooled) Resolution of dactylitis (pooled) CFB mTSS CFB SF-36 CFB FACiT-Fatigue	PASI90 MDA CFB SF-36 CFB FACiT-Fatigue
Other secondary endpoints	**At week 24:** ACR50 response ACR70 response	**At week 24:** ACR50 response ACR70 response
Additional efficacy endpoints	**At week 24:** Resolution of enthesitis Resolution of dactylitis PASI 75 SF-36 MCS	**At week 24:** Resolution of enthesitis Resolution of dactylitis PASI 75 SF-36 MCS
Sample size	964	443

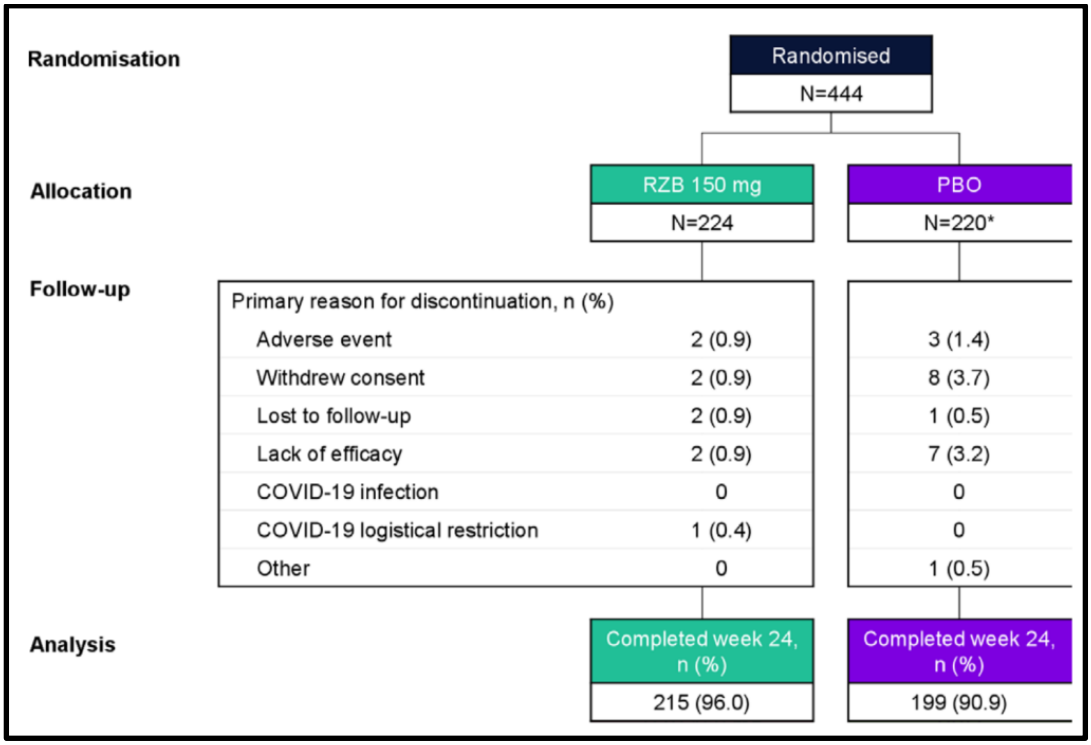
Source: AbbVie data on file, AbbVie Press release, 2021.
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; OLE: open label extension; PASI: psoriasis area severity index; PGA F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

Figure 11: Patient disposition and primary reasons for study discontinuation in the 24-week period, KEEPsAKE 1, PBO:placebo, RZB:risankizumab



Source: Kristensen et al, 2022 (92)

Figure 12: Patient disposition and primary reasons for study discontinuation in the 24-week period, KEEPsAKE 2, PBO:placebo, RZB:risankizumab



Source: Ostor et al, 2022 (93)- * *One patient was randomised but never received study drug and was therefore excluded from the efficacy analyses, resulting in 219 patients included in the PBO group in the full analysis set.

For more detailed information regarding study characteristics and baseline characteristics, see Appendix table 12 and Appendix table 14 for KEEPsAKE 1 and Appendix table 13 and Appendix table 17 for KEEPsAKE 2.

7.1.1. Overview of efficacy results

The primary endpoint of the study was the proportion of patients who achieved ACR20 at week 24.(88)

KEEPsAKE-1 and KEEPsAKE-2 met the primary endpoint of significantly greater rates of ACR20 at week 24 versus placebo (p<0.001), see Table 11 and Table 12. (88) In KEEPsAKE-1, the majority of ranked secondary endpoints, including PASI90, HAQ-DI, and MDA, were met. The ranked secondary endpoint PsA-mTSS showed a numerical improvement compared to placebo in the risankizumab/placebo groups at week 24[1]. In KEEPsAKE-2, all skin and joint secondary endpoints were met. See Table 11 and Table 12 for an overview of results on primary and secondary endpoints (88).

Table 11: Overview of primary and secondary endpoint results in KEEPsAKE-1

Efficacy endpoint[a]	**KEEPsAKE-1** (100% DMARD-IR)			
	Risankizumab 150 mg (N=483)	Placebo (N=481)	Difference (95% CI)	P-value
Primary endpoint at week 24				
ACR20, n (%)	277 (57.3%)	161 (33.5%)	24.0 (18.0, 30.0)	<0.001*
Secondary endpoint at week 16				
ACR20 at week 16, n (%)	272 (56.3%)	161 (33.4%)	23.1 (16.8, 29.4)	<0.001*
Secondary endpoint at week 24				
CFB HAQ-DI, mean (95% CI)	-0.31 (-0.36, -0.27)	-0.11 (-0.16, -0.06)	-0.20 (-0.26, 0.14)	<0.001*
PASI90[a], n (%)	143/273 (52.3%)	27/272 (9.9%)	42.5 (35.6, 49.3)	<0.001*
MDA, n (%)	121 (25.0%)	49 (10.2%)	14.8 (10.2, 19.4)	<0.001*
CFB mNAPSI[b], mean (95% CI)	N=309, -9.8 (-11.0, -8.6)	N= 338, -5.6 (-6.7, -4.4)	-4.2 (-5.7, -2.7)	<0.001*
CFB PGA-F[b], mean (95% CI)	N=309 -0.8 (-1.0, -0.7)	N=338 -0.4 (-0.5, -0.3)	-0.4 (-0.6, -0.3)	<0.001*
Enthesitis resolution[c], n (%) (Pooled)	215/444 (48.4%)	156/448 (34.8%)	13.9 (7.6, 20.2)	<0.001*
Dactylitis resolution[d], n (%) (Pooled)	128/188 (68.1%)	104/204 (51.0%)	16.9 (7.5, 26.4)	<0.001*
CFB mTSS, mean (95% CI)	0.23 (0.02, 0.44)	0.32 (0.11, 0.53)	-0.09 (-0.4, 0.2)	0.50
CFB SF-36 PCS, mean (95% CI)	6.5 (5.8, 7.2)	3.2 (2.5, 3.9)	3.3 (2.4, 4.2)	<0.001*
CFB FACIT-FATIGUE, mean (95% CI)	6.5 (5.6, 7.3)	3.9 (3.1, 4.7)	2.6 (1.5, 3.7)	<0.001*
Other Secondary endpoints at week 24				
ACR50 response wk 24, n (%)	162 (33.4%)	54 (11.3%)	22.2 (17.3, 27.2)	<0.001
ACR70 response wk 24, n (%)	74 (15.3%)	23 (4.7%)	10.5 (6.9, 14.2)	<0.001
Additional endpoints at week 24				
PASI 75[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CFB SF-36 MCS, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Source: AbbVie data on file, AbbVie Press release, 2021.
*Statistically significant under overall type 1 error control.
[a]Summarized for subjects with baseline body surface area affected by psoriasis ≥ 3% (placebo N=272; risankizumab N=273).
[b]Summarized for subjects with baseline nail psoriasis (placebo N=338; risankizumab N=309).
[c]Summarized from pooled data from studies M15-998 and M16-011 for subjects with baseline Leeds Enthesitis Index >0 (placebo N=448; risankizumab N=444).
[d]Summarized from pooled data from KEEPsAKE-1 and KEEPsAKE-2 for subjects with baseline Leeds Dactylitis Index >0 (placebo N=204; risankizumab N=188).
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

[1] P=0.016

Table 12: Overview of primary and secondary endpoint results in KEEPsAKE-2

Efficacy endpoint[a]	KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)			
	Risankizumab 150 mg (N=224)	Placebo (N=219)	Difference (95% CI)	P-value
Primary endpoint at week 24				
ACR20, n (%)	115 (51.3%)	58 (26.5%)	24.5 (15.9, 33.0)	<0.001*
Secondary endpoint at week 16				
ACR20 at week 16, n (%)	108 (48.3%)	55 (25.3%)	22.6 (13.9 to 31.2)	<0.001*
Secondary endpoint at week 24				
CFB HAQ-DI, mean (95% CI)	-0.22 (-0.28, -0.15)	-0.05 (-0.12, 0.02)	-0.16 (-0.26, 0.07)	<0.001*
PASI90[a], n (%)	68/123 (55.0%)	12/119 (10.2%)	44.3 (33.9 to 54.6)	<0.001*
MDA, n (%)	57 (25.6%)	25 (11.4%)	14.0 (7.0 to 21.0)	<0.001*
CFB mNAPSI (LS-Mean)	-	-		
CFB PGA-F (LS-Mean)	-	-		
Enthesitis resolution (%) (Pooled)	-	-		
Dactylitis resolution (%) (Pooled)	-	-		
CFB mTSS (LS-Mean)	-	-		
CFB SF-36 PCS, mean (95% CI)	5.9 (4.9, 6.9)	2.0 (0.9, 3.1)	3.9 (2.4 to 5.3)	<0.001*
CFB FACIT-FATIGUE, mean (95% CI)	4.9 (3.7, 6.0)	2.6 (1.4, 3.9)	2.2 (0.6 to 3.9)	<0.01*
Other Secondary endpoints at week 24				
ACR50 response, n (%)	59 (26.3%)	20 (9.3%)	16.6 (9.7 to 23.6)	<0.001
ACR70 response, n (%)	27 (12.0%)	13 (5.9%)	6.0 (0.8 to 11.3)	<0.05
Additional endpoints at week 24				
Enthesitis resolution[b], n (%)	63/147 (42.9%)	48/158 (30.4%)	13.8 (3.5 to 24.2)	<0.01
Dactylitis resolution[c], n (%)	29/40 (72.5%)	24/57 (42.1%)	38.8 (22.9 to 54.8)	<0.001
PASI 75[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CFB SF-36 MCS, mean (95% CI)	[redacted]	[redacted]		[redacted]

Source: AbbVie data on file, AbbVie Press release, 2021.
*Statistically significant under overall type 1 error control.
[a]Summarized for subjects with baseline body surface area affected by psoriasis ≥ 3% (PBO N=119; RZB N=123).
[b]Defined as LEI=0 among patients with LEI >0 at baseline (RZB, n=147; PBO, n=158).
[c]Defined as LDI=0 among patients with LDI>0 at baseline (RZB, n=40; PBO, n=57)
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

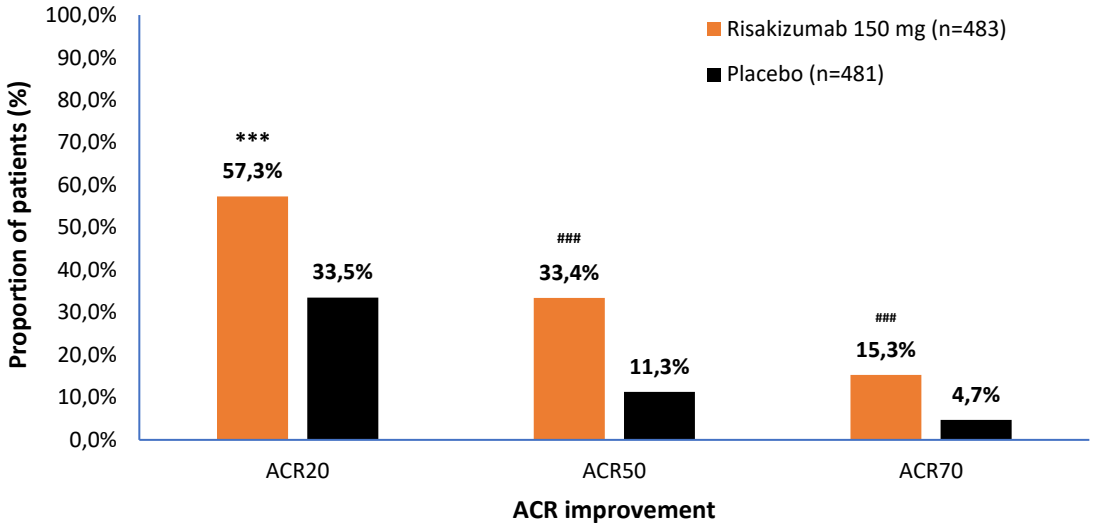
7.1.2. Results on key efficacy endpoints from KEEPsAKE 1 and KEEPsAKE 2

Below, a summary of key efficacy endpoints from the KEEPsAKE-1 and -2 studies will be presented, as well as KEEPsAKE 2 results by bio-naïve and bio-experienced subgroup.

7.1.2.1. ACR response rates

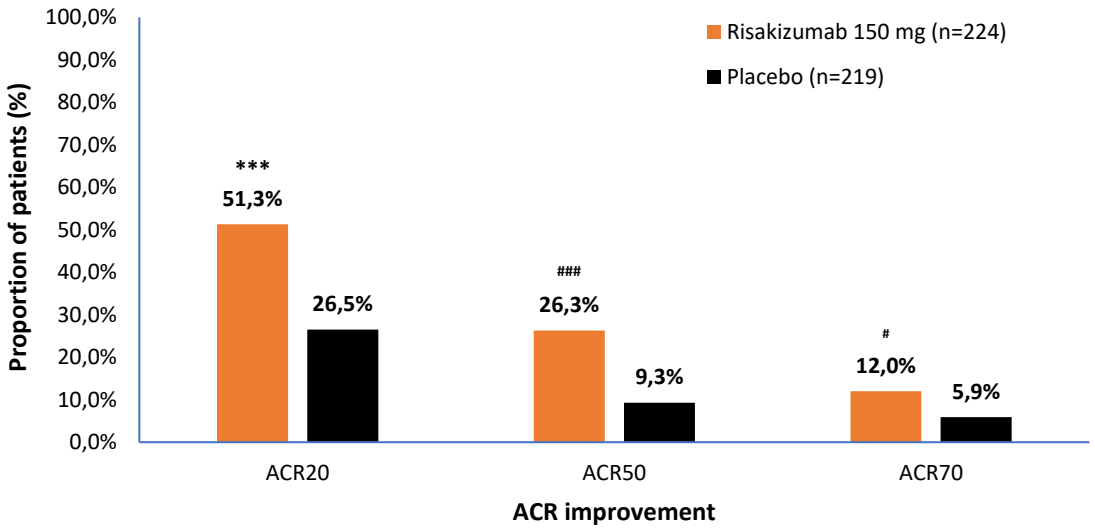
In KEEPsAKE-1, patients receiving risankizumab achieved significantly greater rates of ACR20, ACR50 and ACR70 at week 24, see Figure 13.(88) These results were mirrored in KEEPsAKE-2, demonstrating that risankizumab is efficacious in both DMARD-IR and BIO-IR patients, see Figure 14.

Figure 13. KEEPsAKE-1 ACR response rates at week 24 (88)



Source: AbbVie data on file, AbbVie Press release, 2021.
***p<0.001; ###nominal p<0.001.
ACR: American College of Rheumatology.

Figure 14. KEEPsAKE-2 ACR response rates at week 24 (88)

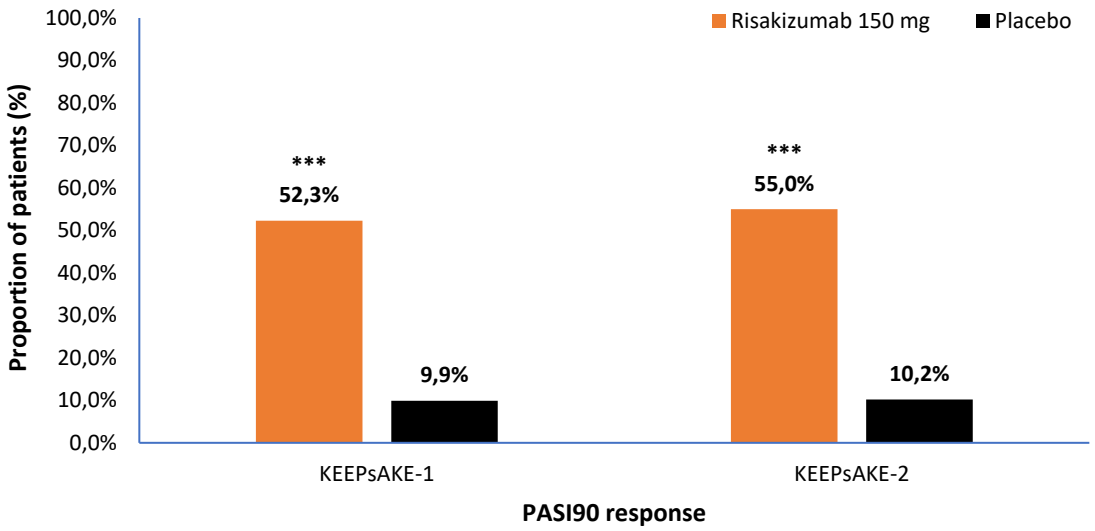


Source: AbbVie data on file, AbbVie Press release, 2021.
***p<0.001; ###nominal p<0.001; #nominal p<0.05.
ACR: American College of Rheumatology.

7.1.2.2. PASI response rates

PASI75 and 90 response rates were significantly higher (p<0.001) for patients receiving risankizumab 150 mg than for those receiving placebo in both KEEPsAKE-1 and KEEPsAKE-2. See Table 11 and Table 12 for PASI 75 results and Figure 15 below for PASI90 results. (88)

Figure 15. KEEPsAKE-1 and KEEPsAKE-2 PASI90 response at week 24(88)



Source: AbbVie data on file, AbbVie Press release, 2021.
***p<0.001.
PASI: Psoriasis area and severity index.

7.1.2.3. KEEPsAKE 2 key results by bio-naïve and bio-experienced subgroup

The efficacy of risankizumab for the treatment of PsA in patients that were bio-naïve (csDMARD-IR) or who had experience with one or two biologic therapies (Bio-IR) was evaluated in the KEEPsAKE-2 trial(94). Below follows a summary of results on ACR20/50/70, PASI 75/90, SF-36 PCS/MCS and other additional endpoints stratified by these subgroups at week 24, see

Table 13.

Patients treated with risankizumab showed improvement in multiple disease severity measures compared to placebo, including ACR20/50/70, PASI75/90, MDA achievement, and resolution of enthesitis and dactylitis(94). Additionally, patient reported outcomes demonstrated larger changes in SF-36 PCS, SF-36-MCS and FACIT-Fatigue scores from baseline for patients treated with risankizumab compared to placebo(94). In summary,

these data demonstrate that PsA patients treated with risankizumab demonstrate improvement regardless of prior biologic experience or not(94).

Table 13. KEEPsAKE 2 efficacy results by bio-naïve and bio-experienced subgroup at week 24(94)

Parameter	Bio-naive (csDMARD-IR)			Bio-experienced (Bio-IR)		
	RZB (n=119)	PBO (n=118)	Diff (95% CI)	RZB (n=105)	PBO (n=101)	Diff (95% CI)
ACR20, n (%)	67 (56.3)	43 (36.6)	[redacted]	48 (45.7)	15 (14.9)	[redacted]
ACR50, n (%)	39 (33.1)	15 (13.1)	[redacted]	19 (18.5)	5 (5.0)	[redacted]
ACR70, n (%)	21 (17.6)	10 (8.3)	[redacted]	6 (5.7)	3 (3.0)	[redacted]
PASI75,[a], n (%)	46/65 (70.8)	11/62 (18.2)	[redacted]	42/58 (72.4)	8/57 (14.0)	[redacted]
PASI90,[a] , n (%)	37/65 (56.5)	7/62 (11.5)	[redacted]	31/58 (53.4)	5/57 (8.8)	[redacted]
MDA, n (%)	37 (31.4)	19 (16.1)	[redacted]	20 (19.0)	6 (5.9)	[redacted]
Resolution of enthesitis,[b] , n (%)	29/72 (40.3)	29/86 (33.7)	[redacted]	34/75 (45.3)	19/72 (26.4)	[redacted]
Resolution of dactylitis,[c] , n (%)	13/17 (76.5)	13/28 (46.4)	[redacted]	16/23 (69.6)	11/29 (37.9)	[redacted]
HAQ-DI, change from baseline, mean (95% Ci)	-0.24 (-0.33, -0.15)	-0.12 (-0.21, -0.03)	[redacted]	-0.19 (-0.29, -0.09)	0.04 (-0.07, 0.14)	[redacted]
FACIT-Fatigue score, change from baseline, mean (95% CI)	5.8 (4.2, 7.4)	4.1 (2.4, 5.8)	[redacted]	4.1 (2.4, 5.8)	1.0 (-0.8, 2.9)	[redacted]
SF-36 PCS score, change from baseline, mean (95% CI)	6.09 (4.66, 7.52)	3.04 (1.58, 4.50)	[redacted]	5.58 (4.14, 7.03)	0.51 (-1.08, 2.10)	[redacted]
SF-36 MCS score, change from baseline, mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For all continuous variables, all changes are mean changes from baseline.

[a]For patients with involved body surface area ≥3% at baseline (RZB no prior biologic N = 65; PBO no prior biologic N = 62; RZB prior biologic N = 58; PBO prior biologic N = 57).

[b]For patients with enthesitis at baseline (RZB no prior biologic N = 72; PBO no prior biologic N = 86; RZB prior biologic N = 75; PBO prior biologic N = 72).

[c]For patients with dactylitis at baseline (RZB no prior biologic N = 17; PBO no prior biologic N = 28; RZB prior biologic N = 23; PBO prior biologic N = 29).

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; MDA: minimal disease activity; PASI75: ≥ 75% reduction in Psoriasis Area Severity Index; PASI90: ≥ 90% reduction in Psoriasis Area Severity Index PBO: placebo; PBO: placebo RZB: risankizumab; SF-36 PCS: 36-Item Short Form Health Survey Physical Component Summary; SF-36 MCS: 36-Item Short Form Health Survey Mental Component Summary.

7.1.3. Overview of safety data

The safety profile of risankizumab in KEEPsAKE-1 and KEEPsAKE-2 was consistent with safety findings previously reported in other psoriasis studies, see Table 14 and Table 15. (88)

Serious treatment emergent adverse events (TEAEs) were reported in 2.5% of patients receiving risankizumab and 3.7% of patients receiving placebo in KEEPsAKE-1. In KEEPsAKE-2 5.0% of patients receiving risankizumab and 5.1% of patients receiving placebo in the bio-naïve (DMARD-IR) experienced a TEAE, while 2.9% of patients receiving risankizumab and 5.9% of patients receiving placebo experienced a TEAE, see Table 14.(88) TEAEs leading to discontinuation were reported in 0.8% of both patients treated with risankizumab and placebo in KEEPsAKE-1. In KEEPsAKE-2 no patients on risankizumab and 1.7% of patients on placebo in the bio-naïve population experienced a TEAE, while the rates were 1.9% for risankizumab and 3.0% for placebo in the bio-experienced population. One death was reported in the risankizumab group of KEEPsAKE-1 however this was not deemed to be related to the study drug. No deaths were reported in KEEPsAKE-2.(88)

Table 14. TEAEs in KEEPsAKE-1 and KEEPsAKE-2 up to week 24 (88)

TEAEs, n (%)	KEEPsAKE-1 (100% DMARD-IR)		KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)					
			Whole study population		DMARD-IR		Bio-IR	
	Risankizumab 150 mg (N=483)	Placebo (N=481)	Risankizumab 150 mg (N=224)	Placebo (N=219)	Risankizumab 150 mg (N=119)	Placebo (N=118)	Risankizumab 150 mg (N=105)	Placebo (N=101)
Any TEAEs	195 (40.4)	186 (38.7)	124 (55.4)	120 (54.8)	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19 related TEAEs	1 (0.2)	2 (0.4)	1 (0.4)	0	[redacted]	[redacted]	[redacted]	[redacted]
TEAE related to Study Drug[a]	53 (11.0)	50 (10.4)	39 (17.4)	39 (17.8)	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	12 (2.5)	18 (3.7)	9 (4.0)	12 (5.5)	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAE	10 (2.1)	9 (1.9)	6 (2.7)	7 (3.2)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to discontinuation of study drug	4 (0.8)	4 (0.8)	2 (0.9)	5 (2.3)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE leading to death	1[b] (0.2)	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
All deaths	1[b] (0.2)	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]

Source: Kristensen et al 2022 (92), AbbVie data on file.
[a]As assessed by investigator.
[b]Death in 81 year old male with dementia, pneumonia followed by urosepsis.
TEAEs: treatment emergent adverse events.

Table 15. KEEPsAKE-1 and KEEPsAKE-2 adverse events up to week 24 (88)

AEs, n (%)	KEEPsAKE-1 (100% DMARD-IR)		KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)					
			Whole study population		DMARD-IR		Bio-IR	
	Risankizumab 150 mg (N=483)	Placebo (N=481)	Risankizumab 150 mg (N=224)	Placebo (N=219)	Risankizumab 150 mg (N=119)	Placebo (N=118)	Risankizumab 150 mg (N=105)	Placebo (N=101)
Serious infections	5[a] (1.0)	6 (1.2)	2[b] (0.9)	5 (2.3)	[redacted]	[redacted]	[redacted]	[redacted]
Active Tuberculosis	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infections excluding Tuberculosis and Herpes Zoster	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]

Herpes Zoster[d]	2 (0.4)	1 (0.2)	0	1 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Malignant tumors	0	2 (0.4)	1 (0.4)	1 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Non-melanoma skin cancer (NMSC)	0	0	1 (0.4)	1 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Malignant tumors excluding NMSC	0	2 (0.4)	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity[c]	10 (2.1)	3 (0.6)	6 (2.7)	7 (3.2)	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated anaphylactic reactions	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic events[c]	32 (6.6)	21 (4.4)	5 (2.2)	6 (2.7)	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reactions (ISR)	3 (0.6)	0	3 (1.3)	1 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated MACE	0	0	1 (0.4)	0	[redacted]	[redacted]	[redacted]	[redacted]
Adjudicated extended MACE	0	1 (0.2)	1 (0.4)	0	[redacted]	[redacted]	[redacted]	[redacted]

Source: Kristensen et al 2022 (92), AbbVie data on file,
[a]Five subjects had six events of cellulitis, gastroenteritis, pneumonia viral (associated with COVID), pneumonia, urosepsis, viral upper respiratory tract infection.
[b]One subject with events of abscess and cellulitis and one subject with viral gastroenteritis.
[c]All events were non-serious.
ISR: injection site reaction; MACE: major adverse cardiac events; NMSC: non-melanoma skin cancer.

Incidence of serious infection was consistent or lower for patients treated with risankizumab compared to placebo across all patient populations. Adverse events were consistent between KEEPsAKE-1 and 2 through week 24, see Table 15.(88)

7.1.4. Week 52 efficacy and safety results

At week 24, patients receiving placebo were switched to risankizumab 150 mg. Non-responders at week 12 and week 16 were allowed to adjust rescue concomitant therapies. Non-responders at week 36 were discontinued from the study.(88, 89)

The results of the KEEPsAKE-1 and KEEPsAKE-2 at week 52 are displayed in Table 16.(95) In both KEEPsAKE 1 and KEEPsAKE 2, the improvements in primary and non-radiographic secondary efficacy endpoints at week 24 either continued to increase or were maintained through to week 52 in the continuous risankizumab cohort.(95)

In the placebo-to-risankizumab cohort, the improvements in efficacy endpoints after switching from placebo-to-risankizumab at week 24 were similar to those observed in the continuous risankizumab cohort in both KEEPsAKE-1 and KEEPsAKE-2.(95) Additionally, the improvements in mTSS at week 52 were consistent with that reported at week 24 in KEEPsAKE-1. Furthermore, the rate of radiographic progression remained low in the continuous risankizumab cohort at week 52 in KEEPsAKE-1.(95)

Since risankizumab inhibits the important regulatory cytokine IL-23, which in turn affects several immunomodulatory pathways downstream, the efficacy of risankizumab increases over time. Therefore, the week 52 data shown below is highly relevant to show that risankizumab has sustained efficacy over time (96).

Table 16. KEEPsAKE-1 and KEEPsAKE-2 efficacy results at week 52, observed cases(95)

Efficacy endpoint[a]	KEEPsAKE-1 (100% DMARD-IR)		KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)	
	Treatment		Treatment	
	PBO to RZB	RZB to RZB	PBO to RZB	RZB to RZB
ACR20 response, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
ACR50 response, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
ACR70 response, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI, change from baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
Resolution of enthesitis, n/N (%)[b]	[redacted]	[redacted]	-	-
Resolution of dactylitis, n/N (%)[c]	[redacted]	[redacted]	-	-
mTSS, change from baseline, mean[d]	[redacted]	[redacted]	[redacted]	[redacted]
MDA response, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
PASI75 response, n/N (%)e	[redacted]	[redacted]	[redacted]	[redacted]
PASI90 response, n/N (%)e	[redacted]	[redacted]	[redacted]	[redacted]
mNAPSI, change from baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
PGA-F, change from baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-Fatigue, mean	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 PCS, change from baseline, (%)	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 MCS, change from baseline, (%)	[redacted]	[redacted]	[redacted]	[redacted]
No radiographic progression, change from baseline mTSS<0	[redacted]	[redacted]	[redacted]	[redacted]
No radiographic progression, change from baseline mTSS<0.5	[redacted]	[redacted]	[redacted]	[redacted]

Source: AbbVie data on file.

[a]Analyses based on as observed data unless otherwise noted.

[b]For subjects with enthesitis (LEI>0) at baseline in pooled data from studies KEEPsAKE1 and KEEPsAKE 2.

[c]For subjects with enthesitis (LDI>0) at baseline in pooled data from studies KEEPsAKE1 and KEEPsAKE 2.

[d]Based on linear extrapolation. For the PBO to RZB cohort, all data at week 52 were imputed by linear extrapolation.

[e]For subject with BSA ≥ 3% at baseline.

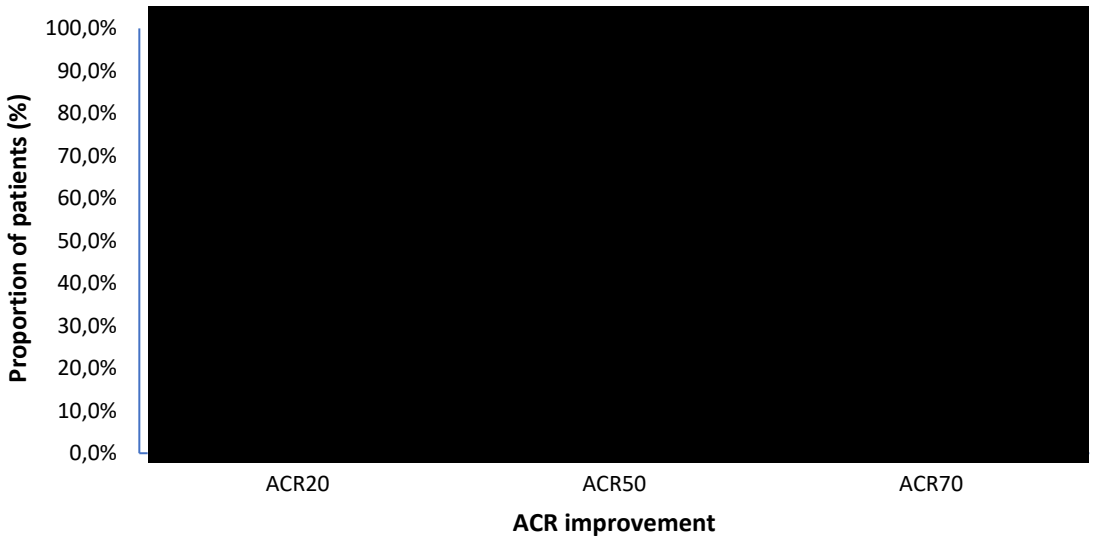
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

7.1.4.1. ACR response rates

Patients who received risankizumab through week 52 maintained their ACR response rates demonstrating the long term-efficacy of risankizumab, see Figure 16, Figure 17,

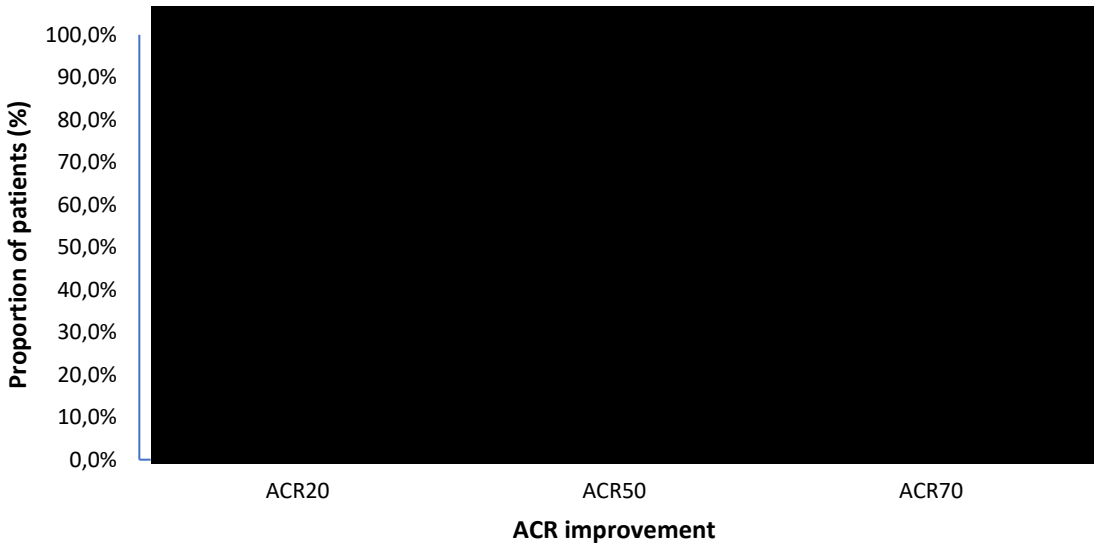
Figure 18 and Figure 19.(95, 97-99) Furthermore, patients who switched from placebo-to-risankizumab at week 24 demonstrated comparable ACR response rates to those observed in the continuous risankizumab cohort at week 52.(95) This finding reiterates the benefit of risankizumab therapy, highlighting that patients can display improvements post-treatment switch.

Figure 16. KEEPsAKE-1 ACR response rates at week 52, observed cases(95)



Source: AbbVie data on file.
Placebo-to-risankizumab: ACR20 n=429; ACR50 n=432; ACR70 n=433.
Continuous risankizumab: ACR20 n=433; ACR50 n=435; ACR70 n=437.
ACR: American College of Rheumatology.

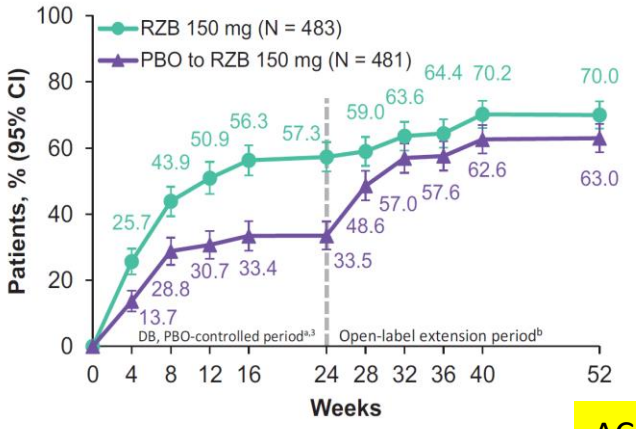
Figure 17. KEEPsAKE-2 ACR response rates at week 52, observed cases(95)



Source: AbbVie data on file.
Placebo-to-risankizumab: ACR20 n=180; ACR50 n=181; ACR70 n=181.
Continuous risankizumab: ACR20 n=191; ACR50 n=192; ACR70 n=192.
ACR: American College of Rheumatology.

Figure 18. ACR response rates over time KEEPsAKE-1(98, 99)

A



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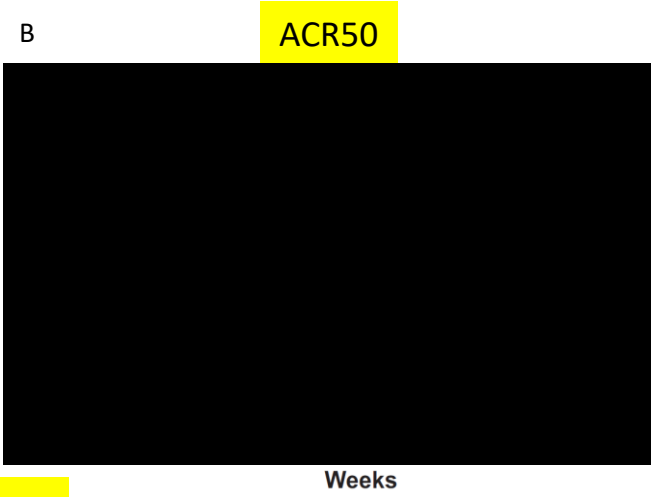
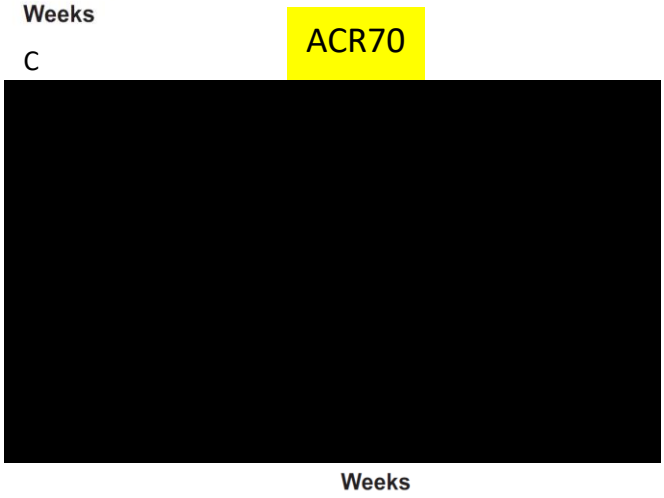


C



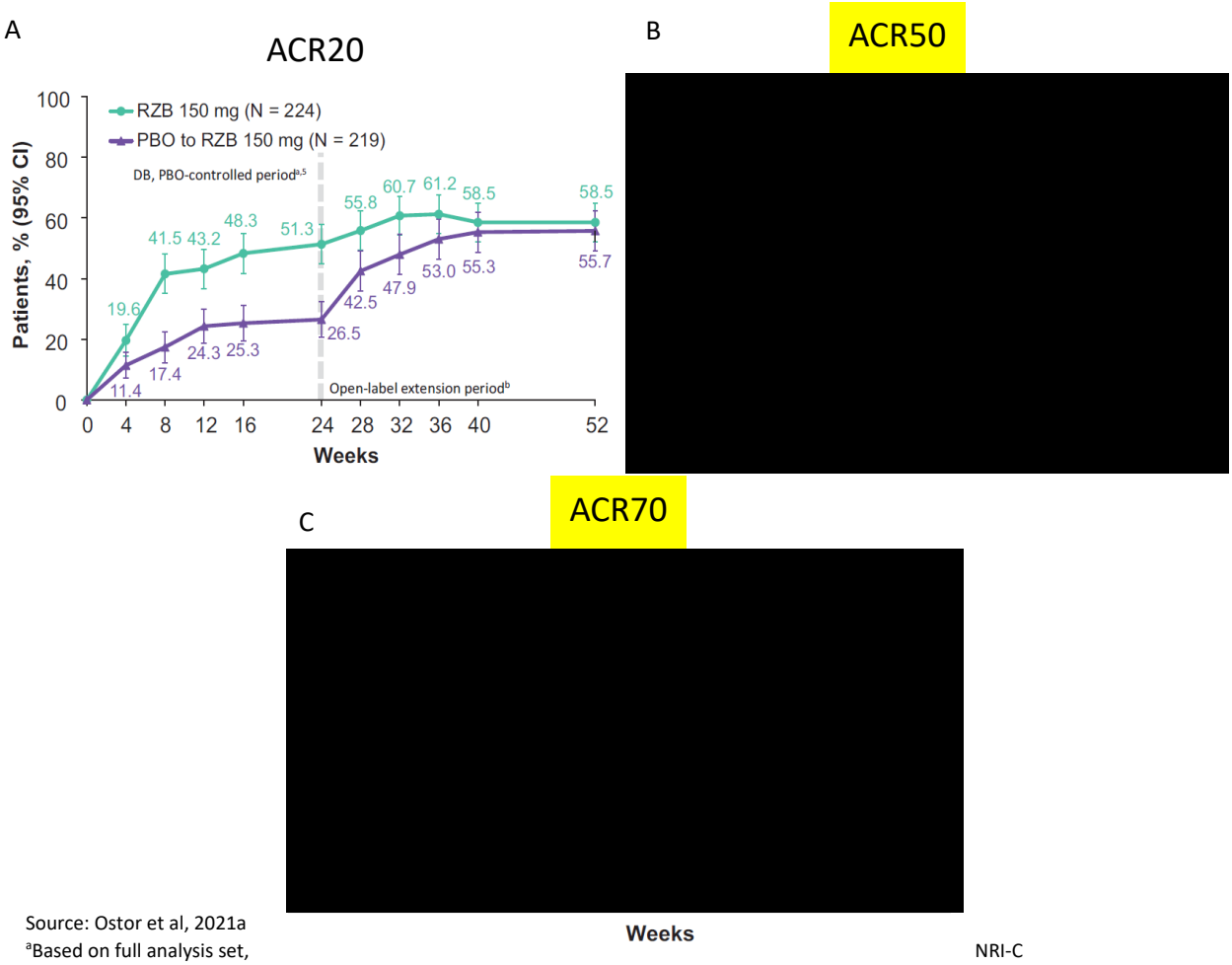
Source: Kristensen et al, 2021

[a]Based on full analysis set, NRI-C

[b]Based on full analysis set, NRI (as observed with imputation) was used for missing data.

ACR20/50/70: ≥20/50/70% improvement in American College of Rheumatology score; DB: double-blind; NRI: Non-responder imputation; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO: placebo; RZB: risankizumab.

Figure 19. ACR response over time for KEEPsAKE-2(97)



Source: Ostor et al, 2021a

[a]Based on full analysis set, NRI-C

[b]Based on full analysis set, NRI (as observed with imputation) was used for missing data.

ACR20/50/70: ≥20/50/70% improvement in American College of Rheumatology score; DB: double-blind; NRI: Non-responder imputation; NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO: placebo; RZB: risankizumab.

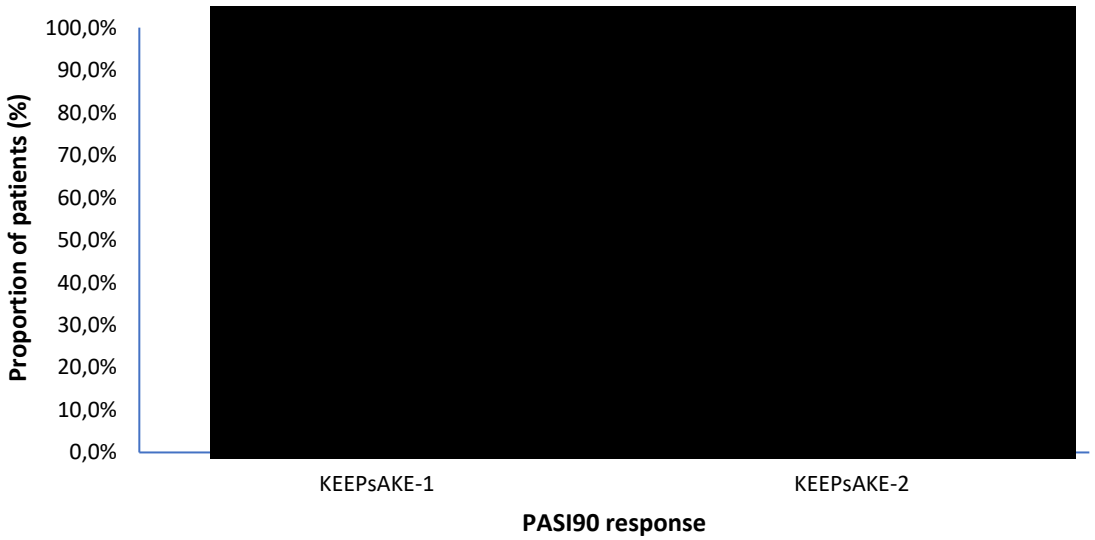
7.1.4.2. PASI response rates

At week 52, PASI75 and PASI90 response rates were maintained in the continuous risankizumab cohort, with a numerically greater proportion of patients treated with risankizumab achieving PASI75 and PASI90 at week 52 when compared to week 24, see Table 16,

Figure 20 and

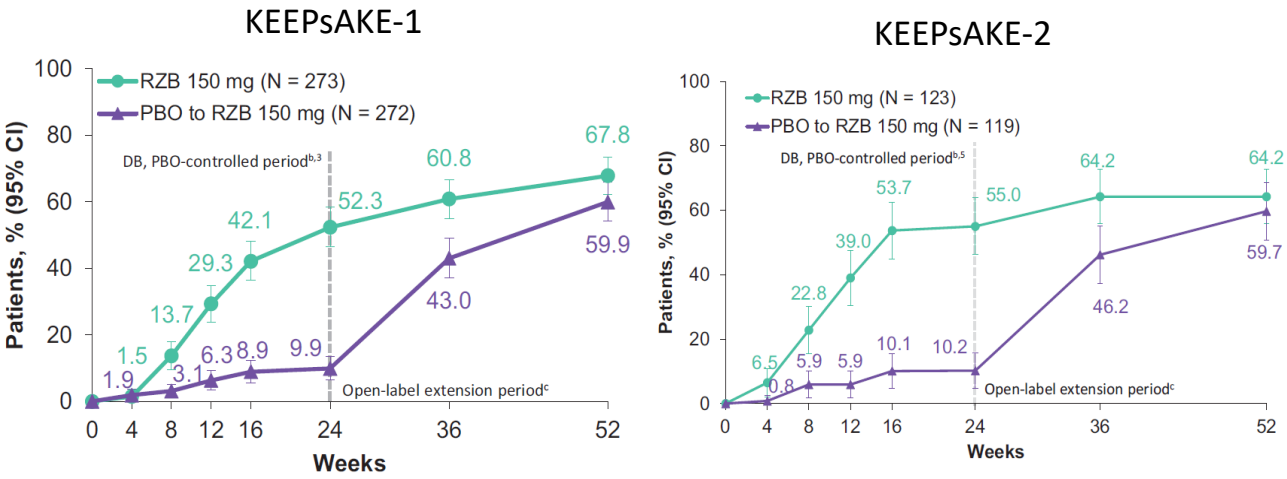
Figure 21. Additionally, patients that switched from placebo-to-risankizumab at week 24 displayed similar results to the continuous risankizumab cohort in both KEEPsAKE-1 and KEEPsAKE-2.(95)

Figure 20. KEEPsAKE-1 and KEEPsAKE-2 PASI90 response at week 52, observed cases(95)



Source: AbbVie data on file.
KEEPsAKE-1: Placebo-to-risankizumab n=247; continuous risankizumab n=261.
KEEPsAKE-2: Placebo-to-risankizumab n=101; continuous risankizumab n=109.
PASI: Psoriasis area and severity index.

Figure 21. PASI90 Response over time[a] (98, 99)



Source: Kristensen et al, 2021a, Kristensen et al, 2021b

[a]Among patients with ≥3% body surface area affected by psoriasis at baseline.

[b]Based on full analysis set, NRI-C.

[c]Based on full analysis set, NRI (as observed with imputation) was used for missing data.

DB, double-blind; PASI90, ≥90% reduction in Psoriasis Area and Severity Index; NRI, non-responder imputation; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; PBO, placebo; RZB, risankizumab.

7.1.4.3. Safety

The overall rates of AEs, serious AEs and AEs leading to discontinuation of study drug at week 52 were comparable relative to week 24, see Table 17 and Table 18.(95) Additionally, the overall safety profile for risankizumab at week 52 in both KEEPsAKE 1 and KEEPsAKE 2 was generally consistent with that observed in the PsO studies, with no new safety concerns identified.(95)

Table 17. TEAEs in KEEPsAKE-1 and KEEPsAKE-2 up to week 52, observed cases (95)

TEAEs, n (%)	KEEPsAKE-1	KEEPsAKE-2
Any TEAEs	[redacted]	[redacted]
COVID-19 related TEAEs	[redacted]	[redacted]
TEAE related to Study Drug[a]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Severe TEAE	[redacted]	[redacted]
TEAE leading to discontinuation of study drug	[redacted]	[redacted]
TEAE leading to death	[redacted]	[redacted]
All deaths	[redacted]	[redacted]

Source: AbbVie data on file.

[a]As assessed by investigator.

[b][redacted]

TEAEs: treatment emergent adverse events.

Table 18. KEEPsAKE-1 and KEEPsAKE-2 adverse events up to week 52, observed cases (95)

AEs, n (%)	KEEPsAKE-1	KEEPsAKE-2
Serious infections[a]	[redacted]	[redacted]
Active Tuberculosis	[redacted]	[redacted]
Opportunistic infections excluding Tuberculosis and Herpes Zoster	[redacted]	[redacted]
Herpes Zoster[b]	[redacted]	[redacted]

Malignant tumors	[redacted]	[redacted]
Non-melanoma skin cancer (NMSC)	[redacted]	[redacted]
Malignant tumors excluding NMSC	[redacted]	[redacted]
Hypersensitivity[c]	[redacted]	[redacted]
Adjudicated anaphylactic reactions	[redacted]	[redacted]
Hepatic events	[redacted]	[redacted]
Injection site reactions (ISR)[c]	[redacted]	[redacted]
Adjudicated MACE	[redacted]	[redacted]
Adjudicated extended MACE	[redacted]	[redacted]

Source: AbbVie data on file.

[a] [redacted]

[b]All were non-serious and mild or moderate in severity.

[c]None resulted in discontinuation.

ISR: injection site reaction; MACE: major adverse cardiac events; NMSC: non-melanoma skin cancer.

7.2. Efficacy and safety of adalimumab compared to placebo for bio-naïve population (SELECT PsA-1 and SPIRIT P1)

7.2.1. Select PsA-1: Overview of efficacy and safety results

SELECT PsA-1 is a phase III, randomized, double-blind, study investigating the safety and efficacy of upadacitinib vs. adalimumab and placebo in patients with PsA that previously failed ≥1 non-biologic DMARD(100). The primary endpoint was ACR20 response at week 12, while measurement of secondary endpoints ranged from week 12 to week 24. In this section, patient disposition, results on primary and ranked secondary endpoints as defined in the study protocol as well as safety for adalimumab and placebo is described- See

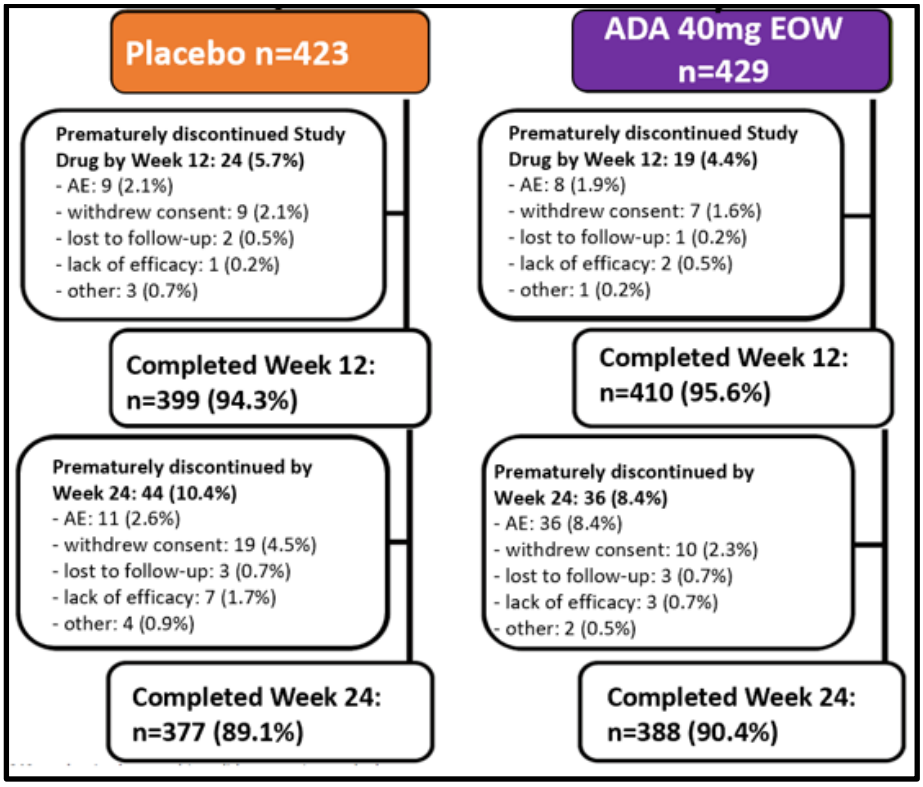
Figure 22 for patient disposition and reasons for study discontinuations,

Table 19 for results on primary and ranked secondary endpoints and Table 20 for an overview of adverse events up to week 24. For the purpose of this submission only data on placebo and adalimumab is presented.

For more information regarding study characteristics and baseline characteristics for SELECT PsA-1, see Appendix table 9 and Appendix table 15.

In order to have an as relevant indirect comparison as possible with the latest available data, data on relevant outcomes at week 24 have been extracted from the SELECT PsA-1 clinical study report for the indirect comparison. For information regarding the 24-week data extracted for relevant outcomes in the ITC, see chapter 7.4.4.

Figure 22: Patient disposition and primary reasons for study discontinuation in the 24-week period, SELECT PsA-1, placebo and adalimumab.



Source: McInnes et al, 2021 (100)

Table 19. Primary and key ranked secondary results, adalimumab and placebo, SELECT PsA-1

Ranked endpoints		Endpoint	Placebo (N=423)	Response rate (95% CI)	Adalimumab 40 mg EOW (N=429)	Response rate (95% CI)
Primary		ACR20 (Week 12), n (%)	153 (36.2%)	36.2 (31.6, 40.7)	279 (65.0%)	65 (60.5, 69.5)
Ranked Key Secondary	1	HAQ-DI (Week 12), mean (95% CI)	-0.14 (-0.18, -0.09)		-0.34 (-0.38, -0.29)	
	2	sIGA (Week 16)[b], n (%)	34/313 (10.9%)	10.9 (7.4, 14.3)	127/330 (38.5%)	38.5 (33.2, 43.7)
	3	PASI 75 (Week 16)[c], n (%)	45/211 (21.3%)	21.3 (15.8, 26.9)	112/211 (53.1%)	53.1 (46.3, 59.8)
	4	mTSS (Week 24), mean (95% CI)	0.25 (0.13, 0.36)		0.01 (-0.11, 0.13)	
	5	MDA (Week 24), n (%)	52 (12.3%)	12.3 (9.2, 15.4)	143 (33.3%)	33.3 (28.9, 37.8)
	6	Enthesitis Resolution LEI = 0 (Week 24)[d], n (%)	78/241 (32.4%)	32.4 (26.5, 38.3)	125/265 (47.2%)	47.2 (41.2, 53.2)
	7	ACR20 NI versus ADA (Week 12) [e], n (%)	153 (36.2%)	36.2 (31.6, 40.7)	279 (65.0%)	65 (60.5, 69.5)
	8	SF-36 PCS (Week 12), mean (95% CI)	3.2 (2.4, 4.0)		6.8 (6.1, 7.6)	
	9	FACIT-F (Week 12), mean (95% CI)	2.8 (1.9, 3.7)		5.7 (4.8, 6.6)	
	10	ACR20 Sup. versus ADA (Week 12) [f]	153 (36.2%)	65 (60.5, 69.5)	279 (65.0%)	65 (60.5, 69.5)
	11	Dactylitis resolution (Week 24)[g], n (%)	50/126 (39.7%)	39.7 (31.1, 48.2)	94/127 (74.0%)	74.0 (66.4, 81.6)

	12	Pain Sup. versus ADA (Week 12) [f] , mean (95% CI)	-0.9 (-1.2, -0.7)		-2.3 (-2.5, -2.1)	
	13	HAQ-DI Sup. versus ADA (Week 12) [f]	-0.14 (-0.18, -0.09)		-0.34 (-0.38, -0.29)	
	14	SAPS (Week 16), mean (95% CI)	-8.2 (-10.2, -6.3)		-22.7 (-24.7, -20.8)	
Other Key Secondary		ACR50 (Week 12)	56 (13.2%)	13.2 (10.0, 16.5)	161 (37.5%)	37.5 (32.9, 42.1)
		ACR70 (Week 12)	10 (2.4%)	2.4 (0.9, 3.8)	59 (13.8%)	13.8 (10.5, 17.0)
		ACR20 (Week 2)	51 (12.1%)	12.1 (9.0, 15.2)	130 (30.3%)	30.3 (26.0, 34.7)

Source: McInnes et al 2021 (100)

[a], Results for binary endpoints are based on NRI analysis. Results for MDA and enthesitis resolution at week 24 are based on non-responder imputation with additional rescue handling, where subjects rescued at week 16 are imputed as non-responders. Results for dactylitis resolution at Week 24 is based on NRI with additional rescue handling, where subjects rescued at week 16 are imputed as non-responders. Results for continuous endpoints are based on MMRM model with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no) and baseline measurement. [b], Summarized for subjects with baseline sIGA ≥ 2; N(PBO) = 313, N(ADA) = 330, N(UPA_{15}) = 322, N(UPA_{30}) = 324. [c], Summarized for subjects with baseline BSA affected by psoriasis ≥ 3%; N(PBO) = 211, N(ADA) = 211, N(UPA_{15}) = 214, N(UPA_{30}) = 210. [d], Summarized for subjects with baseline LEI >0; N(PBO) = 241, N(ADA) = 265, N(UPA_{15}) = 270, N(UPA_{30}) = 267. [e]Non-inferiority test of upadacitinib versus adalimumab, preserving 50% of adalimumab effect. [f], Superiority test of upadacitinib versus adalimumab. [g], Summarized for subjects with baseline LDI >0; N(pbo) = 126, N(ADA) = 127, N(UPA_{15}) = 136, N(UPA_{30}) = 127.

Table 20. Overview of AEs in SELECT PsA-1 through to Week 24 (placebo-controlled analysis set)

	Placebo (N=423)		Adalimumab 40mg EOW (N=429)	
Subjects with:	**n**	**(%)**	**n**	**(%)**
Any Adverse Event (AE)	252	(59.6)	278	(64.8)
Any Serious AE	13	(3.1)	16	(3.7)
Any AE Leading to Discontinuation of Study Drug	13	(3.1)	22	(5.1)
Any Severe AE	16	(3.8)	27	(6.3)
Any AE With Reasonable Possibility of Being Related to Study Drug	120	(28.4)	167	(38.9)
Deaths	1	(0.2)	0	
Occurring ≤30 days (for ADA 70 days) after last dose)	1	(0.2)	0	
Occurring >30 days (for ADA 70 days) after last dose)	0		0	
Any Infection	140	(31.1)	146	(34.0)
Any Serious Infection	4	(0.9)	3	(0.7)
Any Opportunistic Infection excluding TB and herpes zoster	0		0	
Any possible malignancy	1	(0.2)	4	(0.9)
Any Malignancy	1	(0.2)	3	(0.7)
Any Non-Melanoma Skin Cancer (NMSC)	1	(0.2)	0	
Any malignancy other than NMSC	0		3	(0.7)
Any Lymphoma	0		0	
Any Hepatic Disorder	16	(3.8)	67	(15.6)
Any Gastrointestinal Perforation	0		0	
Any Anemia	4	(0.9)	1	(0.2)
Any Neutropenia	1	(0.2)	10	(2.3)
Any Lymphopenia	5	(1.2)	1	(0.2)
Any herpes zoster	3	(0.7)	0	
Any Creatine Phosphokinase (CPK) Elevation	6	(1.4)	24	(5.6)
Any Renal Dysfunction	1	(0.2)	0	

Subjects with:	Placebo (N=423)		Adalimumab 40mg EOW (N=429)	
	n	(%)	n	(%)
Any active tuberculosis	0		0	
Any Adjudicated MACE*	1	(0.2)	2	(0.5)
Any Adjudicated VTE **	1	(0.2)	2	(0.5)

Source: McInnes et al 2021 (100)

*MACE, Major adverse cardiovascular events, defined as cardiovascular death (includes fatal acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal myocardial infarction and non-fatal stroke.

**Venous Thromboembolic Events (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE).

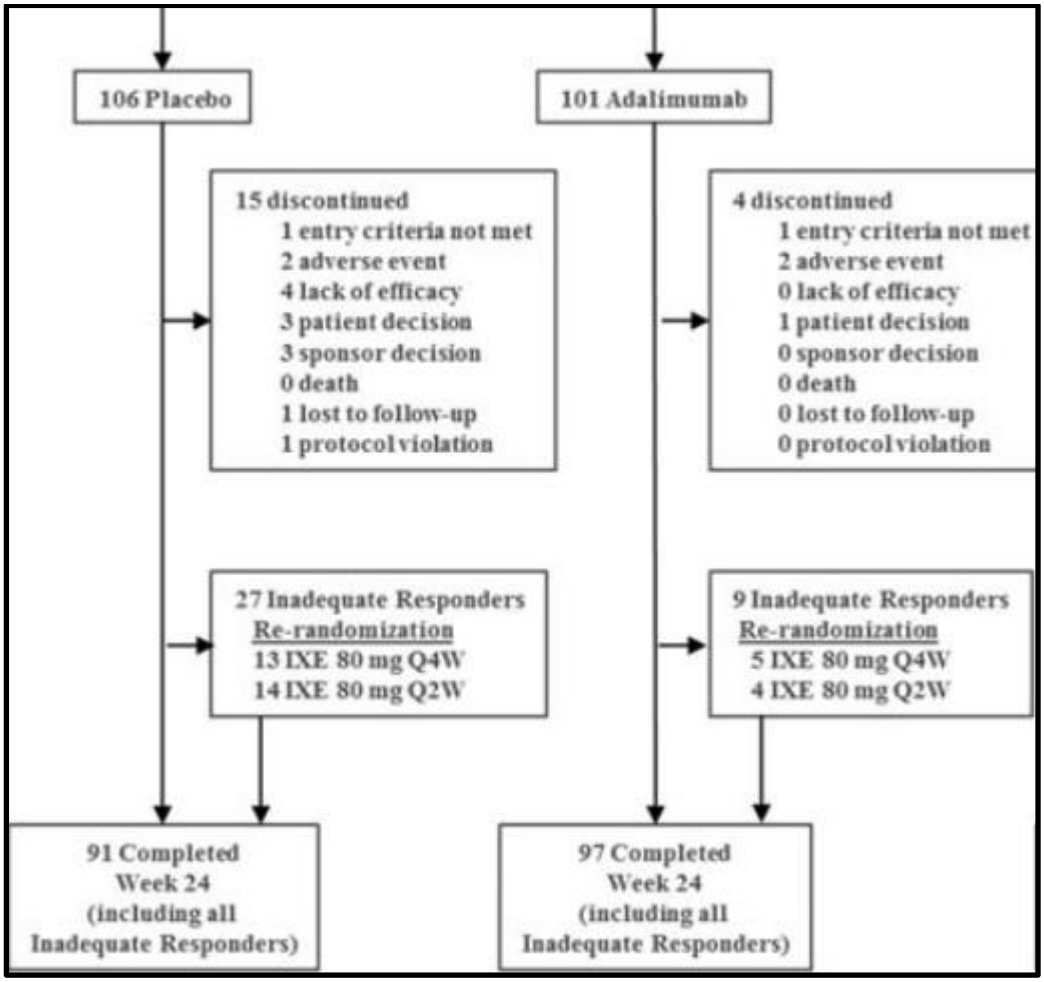
7.2.2. SPIRIT P1: Overview of efficacy and safety results

SPIRIT-P1 is a phase III, double blind, randomized placebo-controlled and active controlled trial that investigated the efficacy and safety of ixekizumab vs. placebo and adalimumab in patients not previously treated with biologic agents for plaque psoriasis or PsA (101). The double-blind period of the study occurred in the first 24 weeks. The primary objective was to compare the proportion of patients treated with ixekizumab who attained an at least 20% improvement in the American College of Rheumatology response criteria (ACR-20) response at week 24 versus placebo and adalimumab. In this section, patient disposition and reasons for study discontinuation (Figure 23), key efficacy results (Table 21)as well as safety for adalimumab and placebo (Table 22) is described. For the purpose of this submission only data on placebo and adalimumab is presented.

For more information regarding the study characteristics and baseline characteristics from SPIRIT P1, see Appendix table 10 and Appendix table 16.

For information regarding the 24-week data extracted for relevant outcomes in the ITC, see chapter 7.4.4.

Figure 23: Patient disposition and primary reasons for study discontinuation in the 24-week period, SPIRIT P1, placebo and adalimumab



Source: Mease et al, 2017 (101)

Table 21: Efficacy overview SPIRIT P1, week 24

Endpoint	Placebo	Adalimumab	P-value vs. PBO
Responder rate			
	N=106	N=101	
ACR20, %	30.2	57.4*	≤0.001
ACR50, %	15.1	38.6*	≤0.001
ACR70, %	5.7	25.7*	≤0.001
	N=92	N=89	
HAQ-DI MCID, %, §	26.1	49.4*	≤0.001
	N=28	N=18	
LDI-B (Dactylitis) %, #	25.0	77.8*	≤0.001
	N=57	N=54	
LEI (Enthesitis) %, ¤	19.3	33.3	
	N=67	N=68	
PASI 75, %, ¥	10.4	54.4*	≤0.001
PASI 90, %, ¥	6.0	36.8*	≤0.001
PASI100, %, ¥	3.0	23.5**	≤0.01
	N=41	N=37	
sPGA (0,1), %, ***	17.1	62.2*	≤0.001
sPGA (0), %, ***	2.4	18.9**	≤0.01
	N=74	N=71	
NAPSI, %, ¶	18.9	39.4*	≤0.001
Mean change from baseline (SE)			
	N=106	N=101	
DAS28-CRP	-0.84 (0.13)	-1.74 (0.12)*	≤0.001

HAQ-DI	-0.18 (0.05)	-0.37 (0.05)**	≤0.01
SF-36 PCS	2.9 (1.0)	6.8 (0.9)*	≤0.001
	N=28	N=18	
LDI-B, #	-33.7 (9.7)	-76.0 (10.9)*	≤0.001
	N=57	N=56	
LEI, ¤¤	-0.8 (0.26)	-0.9 (0.23)	
	N=102	N=97	
% BSA, ¥ ¥	-2.7 (1.4)	-9.5 (1.4)*	≤0.001
	N=74	N=71	
NAPSI, ¶	-2.4 (1.7)	-10.7 (1.5)*	≤0.001

Source: (101)

*p≤0.001 vs placebo, ** p≤0.01 vs placebo

§Data reported for patients with a baseline HAQ-DI score ≥0.35. The MCID for HAQ-DI is an improvement from baseline ≥0.35.

#Data are reported for patients with dactylitis, as qualitatively assessed by the investigator, at baseline and baseline LDI-B score >0.

¤Data are reported for patients with enthesitis, as qualitatively assessed by the investigator, at baseline and baseline LEI score >0.

¥Data are reported for patients with baseline psoriatic lesion(s) involving ≥3% BSA.

***Data are reported for patients with sPGA ≥3 at baseline.

¶Data are reported for patients with fingernail psoriasis, as qualitatively assessed by the investigator, at baseline

¤¤Data are reported for patients with enthesitis, as qualitatively assessed by the investigator, at baseline.

¥ ¥Data are reported for patients with psoriasis, as qualitatively assessed by the investigator, at baseline.

ACR20/50/70, 20/50/70% American College of Rheumatology response; BSA, body surface area; DAS28-CRP, 28-joint Disease Activity Score using C reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; 4 weeks; LDI-B, Leeds Dactylitis Index-Basic; LEI, LeedsEnthesitis Index; LS, least squares; MCID, minimal clinically important difference; NAPSI, Nail Psoriasis Severity Index; PASI 75/90/100, Psoriasis Area and Severity Index Improvement Response for 75/90/100%; Q2W, every 2 weeks; SF-36 PCS, Short Form (36 Items) Health Survey Physical Component Score; sPGA, static Physician Global Assessment of psoriasis.

Table 22: Safety overview SPIRIT P1, week 24

Adverse event	**Placebo (N=106)**	**Adalimumab (N=101)***
Most frequent treatment-emergent adverse events, n (%)		
Injection site reaction	0	2 (2.0)
Injection site erythema	0	2 (2.0)
Nasopharyngitis	5 (4.7)	7 (6.9)
Headache	1 (0.9)	3 (3.0)
Upper respiratory tract infection	7 (6.6)	5 (5.0)
ALT increased	0	3 (3.0)
Diarrhoea	3 (2.8)	3 (3.0)
Muscle spasms	1 (0.9)	1 (1.0)
Bronchitis	3 (2.8)0	4 (4.0)
AST increased	0	2 (2.0)
Nausea	2 (1.9)	4 (4.0)
Psoriatic arthropathy	1 (0.9)	3 (3.0)
Back pain	0	3 (3.0)
Adverse events, n (%)		
Serious adverse events	2 (1.9)	5 (5.0)
Serious infection	0	2 (2.0)
Discontinued due to adverse event	2 (1.9)	2 (2.0)
Adverse events of special interest, n (%)		
Infection	27 (25.5)	26 (25.7)
Any candida infection	0	0
Active or reactivated tuberculosis	0	0
Injection-site reactions	5 (4.7)	6 (5.9)
Hepatic events	7 (6.6)	13 (12.9)
Allergic reactions or hypersensitivities	3 (2.8)	5 (5.0)
Cytopenia (all types)	6 (5.7)	4 (4.0)
Neutropenia	0	0

Depression	0	1 (1.0)
Cerebrocardiovascular event	0	3 (3.0)
Malignancies	1 (0.9)	1 (1.0)

Source: (101)
ALT, alanine aminotransferase; AST, aspartate aminotransferase

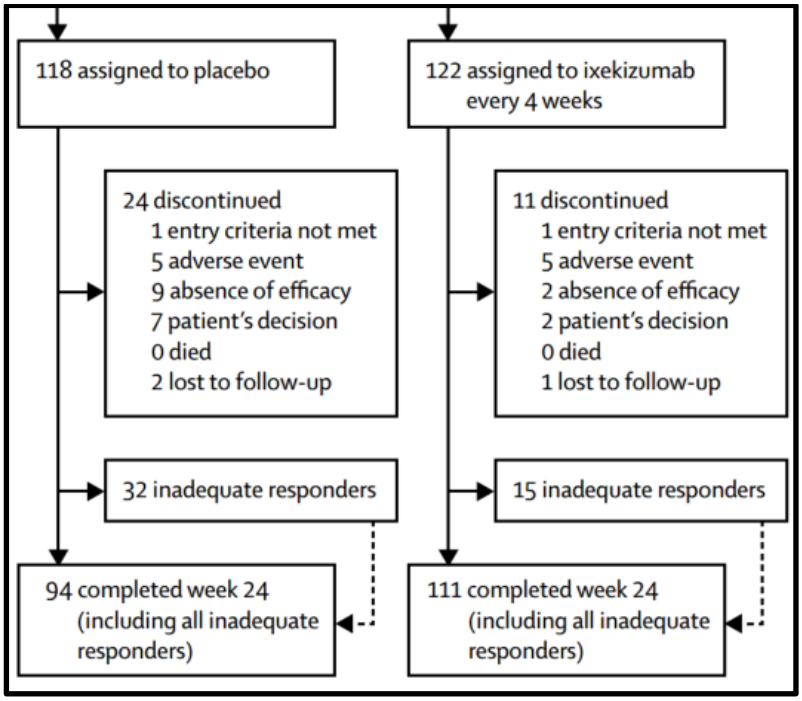
7.3. Efficacy and safety of ixekizumab compared to placebo for bio-experienced population (SPIRIT P2)

7.3.1. Overview of efficacy and safety results

SPIRIT-P2 is a double blind, randomized placebo-controlled trial that investigated the efficacy and safety of ixekizumab in patients who have had an inadequate response to tumor necrosis factor inhibitors, distinguished by being refractory to therapy or had loss of efficacy, or were intolerant to tumor necrosis factor (102). The primary objective was to compare the proportion of patients treated with ixekizumab who attained an at least 20% improvement in the American College of Rheumatology response criteria (ACR-20) response at week 24 versus placebo. In this section, patient disposition and reasons for study discontinuation (Figure 24), key efficacy results (Table 23) as well as safety for ixekizumab and placebo (Table 24) is described. The relevant dosing which is included in the Danish treatment recommendations for PsA is the 160mg week and 80mg every 4 weeks thereafter (named Q4W below) and for the purpose of this submission only data for this dosing is presented.

For more information regarding study characteristics and baseline characteristics from SPIRIT P2, see Appendix table 11 and Appendix table 18.

Figure 24: Patient disposition and primary reasons for study discontinuation in the 24-week period, SPIRIT P2, placebo and ixekizumab Q4W



Source: Nash et al 2017 (102)

Table 23: SPIRIT-P2 key efficacy results at week 24

Endpoint	Placebo (N=118)	IXE Q4w (N=122)	Diff vs. PBO (95% CI)	P-value	
ACR20 week 24, n (%)	23 (19%)	65 (53%)	33·8% (22·4 to 45·2)	<0·0001	
ACR50 week 24, n (%)	6 (5%)	43 (35%)	30·2% (20·8 to 39·5)	<0·0001	
ACR70 week 24, n (%)	0 (0%)	27 (22%)	22·1% (14·8 to 29·5)	<0·0001*	
HAQ-DI MCID week 24, n (%)	18/107 (17%)	45/104 (43%)	26·4% (14·6 to 38·3)	<0·0001	
MDA week 24, n (%)	4 (3%)	34 (28%)	24·5% (15·9 to 33·1)	<0·0001	
LDI-B=0 week 24, n (%)	3/14 (21%)	21/28 (75%)	53·6% (26·8 to 80·4)	0·002*	
LEI=0 week 24, n (%)	15/69 (22%)	24/68 (35%)	13·6% (–1·4 to 28·5)	0·08	
PASI-75 week 24, n (%)	10/67 (15%)	38/68 (56%)	41·0% (26·4 to 55·5)	<0·0001	
PASI-90 week 24, n(%)	8/67 (12%)	30/68 (44%)	32·2% (18·1 to 46·3)	<0·0001	
PASI-100 week 24, n (%)	3/67 (4%)	24/68 (35%)	30·8% (18·4 to 43·2)	<0·0001	
sPGA (0) week 24, n (%)	1/55 (2%)	22/60 (37%)	34·8% (22·2 to 47·5)	<0·0001*	
NAPSI week 24, n (%)	5/73 (7%)	18/89 (20%)	13·4% (3·2 to 23·5)	0·02*	
	Least squares mean change from baseline (SE)				
DAS28-CRP	–0·8 (0·2)	-2·1 (0·2)	–1·3 (–1·6 to –0·9)	<0·0001	
HAQ-DI	–0·2 (0·1)	–0·6 (0·1)	–0·4 (–0·5 to –0·3)	<0·0001	
SF-36 PCS	3·3 (1·4)	8·9 (1·3)	5·6 (3·2 to 8·0)	<0·0001	
SF-36 MCS	0·9 (1·3)	3·6 (1·2)	2·7 (0·4 to 5·0)	0·02	
LDI-B	-36·2 (8·4)	-34·7 (6·7)	1·5 (–15·0 to 18·0)	0·85	
LEI	–1·0 (0·4)	–1·1 (0·3	–0·1 (–0·8 to 0·5)	0·73	
NAPSI	1·0 (2·4)	–10·5 (2·1)	–11·5 (–16·0 to –7·0)	<0·0001	

Source: (102)

*p value derived with the Fisher's exact test

ACR20/50/70, 20/50/70% American College of Rheumatology response; BSA, body surface area; DAS28-CRP, 28-joint Disease Activity Score using C reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; 4 weeks; LDI-B, Leeds Dactylitis Index-Basic; LEI,

LeedsEnthesitis Index; LS, least squares; MCID, minimal clinically important difference; NAPSI, Nail Psoriasis Severity Index; PASI 75/90/100, Psoriasis Area and Severity Index Improvement Response for 75/90/100%; Q2W, every 2 weeks; SF-36 PCS, Short Form (36 Items) Health Survey Physical Component Score; sPGA, static Physician Global Assessment of psoriasis.

Table 24: Overview of safety from SPIRIT P2

Adverse event	Placebo (N=118)	IXE Q4W (N=122)	
Most frequent treatment-emergent adverse events			
Injection site reaction	1 (1%)	8 (7%)	
Upper respiratory tract infection	9 (8%)	11 (9%)	
Nasopharyngitis	4 (3%)	8 (7%)	
Sinusitis	2 (2%)	7 (6%)	
Diarrhoea	3 (3%)	5 (4%)	
Urinary tract infection	3 (3%)	6 (5%)	
Cough	3 (3%)	4 (3%)	
Oropharyngeal pain	0	7 (6%)	
Headache	3 (3%)	5 (4%)	
Hypertension	3 (3%)	2 (2%)	
Injection-site erythema	0	2 (2%)	
Injection-site hypersensitivity	0	1 (1%)	
Back pain	2 (2%)	5 (4%)	
Bronchitis	4 (3%)	1 (1%)	
Psoriatic arthropathy	8 (7%)	2 (2%)	
Adverse events			
Serious adverse events	4 (3%)	3 (2%)	
Serious infection	0	0	
Discontinued due to adverse event	6 (5%)	5 (4%)	
Adverse events of special interest			
Infection	5 (30%)	47 (39%)	
Any candida infection	0	2 (2%)	
Active or reactivated tuberculosis	0	0	
Hepatic events	2 (2%)	2 (2%)	
Allergic reactions or hypersensitivities	1 (1%)	8 (7%)	
Injection-site reactions	5 (4%)	14 (11%)	
Cerebrocardiovascular event	2 (2%)	0	
Malignancies	0	2 (2%)	
Depression	3 (3%)	2 (2%)	

Source: (102)

7.4. Comparative analysis of risankizumab vs. adalimumab and ixekizumab for bio-naïve and bio-experienced population

Due to the lack of direct comparative data of risankizumab vs. the relevant comparators adalimumab and ixekizumab, an indirect treatment comparison (ITC) was conducted. Objective of the ITC was to compare the relative efficacy and safety of risankizumab to adalimumab at week 24 for the treatment of active PsA in adult biologic-naïve patients and to ixekizumab at week 24 for the treatment of active PsA in adult patients who have already been exposed to a biologic (ie. bio-experienced). The indirect comparison included both skin, joint, PRO and safety outcomes with the following measurements; ACR20/50, PASI75/90, SF-36 PCS/MCS and severe adverse events (SAE).

The results of the analysis showed that for the bio-naïve population, results in general favored risankizumab vs. adalimumab with risankizumab being either statistically or numerically better on the majority of the outcomes, with adalimumab not being statistically better for any of the outcomes. Risankizumab demonstrated significantly better results on PASI 90 and a high numerical favorability on PASI 75 and SAE.

For the bio-experienced population vs. ixekizumab there were no statistically significant differences on any of the outcomes. Risankizumab was numerically better on ACR 20 and demonstrated a large numerical improvement on PASI 75 and 90 compared to ixekizumab.

7.4.1. Objective

The primary objective of the ITC was to compare the relative efficacy and safety of risankizumab to adalimumab at week 24 for the treatment of active PsA in adult biologic-naïve patients and to ixekizumab at week 24 for the treatment of active PsA in adult patients who already have been exposed to a biologic (ie. bio-experienced). See chapter 5.2.2 for a description of why adalimumab and ixekizumab are deemed as the most relevant comparators to risankizumab in the bio-naïve and bio-experienced population, respectively.

The efficacy and safety were measured by the following endpoints evaluating effect on the most common symptoms of PsA, joints and skin as well as quality of life and safety:

- Proportion of patients achieving 20% and 50% improvement in the American College of Rheumatology (ACR) criteria (ACR 20, ACR 50)
- Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 and PASI 90 response
- Change from baseline in 36-Item Short Form Health Survey (SF-36) Mental Component Summary (MCS) [SF-36 MCS] and Physical Component Summary (PCS) [SF-36 PCS]
- Proportion of patients with serious adverse events (SAE)

7.4.2. Definition, validity and clinical relevance of included outcome measures

Table 25: Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
ACR20	ACR20 is defined as at least 20% improvement in swollen joint count, tender joint count, and at least 3 out of the following 5 variables: 1) Patient's Assessment of psoriatic arthritis (PsA) Pain Intensity visual analog scale (VAS), 2) Patient's Global Assessment of Disease VAS, 3) Physician's Global Assessment of Disease Activity VAS, 4) Patient's Assessment of Disability on Health Assessment Questionnaire Disability Index (HAQ-DI), and 5) Serum high-sensitivity C-reactive protein (serum hs-CRP).	ACR20 is the primary endpoint used in all clinical trials in this analysis. Widely known and used endpoint in PsA.	ACR is a key component in assessing swollen and tender joints, which is one of the key symptoms related to PsA that affects the severity of the disease.
ACR50	ACR50 response is defined as at least 50% reduction (improvement) compared with baseline in tender joint count (TJC), swollen joint count (SJC), and at least 3 of the 5 remaining ACR core set measures: patient's assessment of pain, patient's global assessment of disease activity (PtGA); physician's global assessment of disease activity (PhGA), Health Assessment Questionnaire - Disability Index (HAQ-DI), and high-sensitivity C-reactive protein (hsCRP).	A more stringent version of ACR20. Widely known and used endpoint in PsA trial.	ACR is a key component in assessing swollen and tender joints, which is one of the key symptoms related to PsA that affects the severity of the disease.
PASI75	PASI 75 denotes greater than or equal to 75% improvement in PASI score.	PASI provides a quantitative assessment of psoriasis disease state based on the amount of body surface area that is affected and the degree of severity. Most widely known and used endpoint for skin in psoriasis and PsA trials.	The presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA. (9),(10), and is also one of the key symptoms related to PsA that impacts the severity of the disease. PASI is a key tool to assess the severity and extent of the skin involvement.
PASI90	PASI 90 denotes greater than or equal to 90% improvement in PASI score.	PASI provides a quantitative assessment of psoriasis disease state based on the amount of body surface area that is affected and the degree of severity. Most widely known and used endpoint for skin in psoriasis and PsA trials.	The presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA. (9),(10), and is also one of the key symptoms related to PsA. PASI is a key tool to assess the severity and extent of the skin involvement.
SF-36 PCS	Change from Baseline to Week 24 in the 36-Item Short Form Health Questionnaire (SF-36) Physical Component Summary (PCS) Score	The SF-36 is a 36-item, general health, self-administered questionnaire, widely used to assess Quality of Life in clinical trials.	Quality of Life measurements is a key outcome which indicate how well patients fare with the treatment, both physically and mentally. Therefore it is highly relevant to assess the impact of

Outcome measure	Definition	Validity	Clinical relevance
			new treatments on patients physical and mental health.
SF-36 MCS	Change from Baseline to Week 24 in the 36-Item Short Form Health Questionnaire (SF-36) Mental Component Summary (MCS) Score	The SF-36 is a 36-item, general health, self-administered questionnaire, widely used to assess Quality of Life in clinical trials.	Quality of Life measurements is a key outcome which indicate how well patients fare with the treatment, both physically and mentally. Therefore it is highly relevant to assess the impact of new treatments on patients physical and mental health.
SAE	Serious Adverse Events		Serious adverse event (SAE) is a relevant outcome since these effects can be particularly bothersome for patients and can cause treatment discontinuation, worse outcomes and increased resource use.

7.4.3. Methods

Indirect treatment effect estimates were produced by using the frequentist method described in Rücker (2012), and Rücker and Schwarzer (2014) (103, 104). This approach is widely used and aligned with guidance from NICE, ISPOR and the Cochrane institute (105-109). The methodology describes how to indirectly compare the odds ratios (OR) and risk ratios (RR) from randomized trials that share a common reference arm. The advantage of this approach lies in a combination of the Bucher's method and the adjustment for multi arm studies (110).

The DerSimonian and Laird method was used for conducting a random-effects meta-analyses of each treatment versus the common comparator, placebo (111). Associated 95% confidence intervals and P-values from pairwise comparisons were calculated.

All analyses were conducted in R (112). For more information regarding the methodology of the analysis, see Appendix F Comparative analysis of efficacy and safety.

7.4.4. Data source

Relevant studies to include in the ITC were identified in a systematic literature review in addition to data from the KEEPsAKE 1 and 2 trials for risankizumab in PsA. See chapter 6 for a description of the literature search.

Three-placebo controlled trials were identified meeting the PICO criteria for this analysis, including placebo-controlled data on adalimumab and ixekizumab: SELECT PsA 1, SPIRIT P1 and SPIRIT P2. SELECT PsA-1 and SPIRIT P1 are recent studies also including both an adalimumab and placebo arm up until the week 24 timepoint, and the data from these trials were the ones included in the comparison for the bio-naïve population. Note that the primary endpoint in SELECT PsA-1 was ACR20 at week 12, however since the study was placebo-controlled up until week 24 it made it possible to use week 24 data for this indirect comparison, which is the latest available placebo-controlled timepoint in all studies used in this analysis. Therefore, all data used from SELECT PsA-1 in this analysis is from week 24.

For the bio-experienced population only one placebo-controlled study (SPIRIT P2) including the relevant comparator ixekizumab was identified and used in the analysis.

While it is reasonable to assume that efficacy and PRO outcomes may differ between bio-naïve and bio-experienced populations, making an indirect comparison only on the bio-naïve and bio-experienced population appropriate, AbbVie strongly believe that there is no medical reason why safety should differ between the bio-naïve and bio-experienced population, and there exists no evidence that risk of SAE is driven by prior biologic use or not. Therefore, AbbVie have in the indirect comparison of SAE not split up data from KEEPsAKE 2 into bio-naive and bio-experienced data, but included the data for the whole study population both in the bio-naive and bio-experienced comparison.

AbbVie believes also that this mixed population approach on SAE allows for a larger and more robust and meaningful analysis by increasing the ability to detect a difference if a difference truly exists between treatments. This is an approach to the indirect comparison of safety that The Medicines Council have accepted in previous submissions.

In summary, week 24 data from the following studies were used in the indirect treatment comparison, stratified by bio-naïve and bio-experienced populations:

Efficacy and PRO outcomes:

- Bio-naïve: KEEPsAKE 1, KEEPsAKE 2 (bio-naïve subgroup), SELECT PsA 1, SPIRIT P1
- Bio-experienced: KEEPsAKE 2 (bio-experienced subgroup), SPIRIT P2

SAE:

- Bio-naïve: KEEPsAKE 1, KEEPsAKE 2 (whole study population), SELECT PsA-1, SPIRIT P1
- Bio-experienced: KEEPsAKE 2 (whole study population), SPIRIT P2

Endpoints of interest were extracted from primary publications for SPIRIT P1 and SPIRIT P2. For risankizumab studies (KEEPsAKE 1 and 2) and SELECT PsA-1, data were extracted from Clinical Study Reports (CSR) and post-hoc analysis results. Table 26 and Table 27 show the extracted data for each study arm and outcome for the biologic-experienced and biologic-naive networks, respectively.

Table 26: Extracted data per study [n/N or mean/(SD)], arm, and outcome (biologic-naive network)

Study	Arm	ACR20	ACR50	PASI 75	PASI 90	SAE	SF-36 MCS	SF-36 PCS
KEEPsAKE 1	PBO	161/481	54/481	[redacted]	27/272	18/481	[redacted]	3.20 (7.74)
KEEPsAKE 1	RISA	277/483	162/483	[redacted]	143/273	12/483	[redacted]	6.52 (7.67)
KEEPsAKE 2	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
KEEPsAKE 2	RISA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPIRIT P1	PBO	32/106	16/106	7/67	4/67	2/106	NR	2.90 (10.30)
SPIRIT P1	ADA	58/101	39/101	37/68	25/68	5/101	NR	6.80 (9.04)
SELECT PsA1	PBO	191/423	80/423	56/211	35/211	13/423	2.44 (8.93)	4.26 (8.19)
SELECT PsA1	ADA	288/429	190/429	124/211	95/211	16/429	4.06 (8.88)	7.80 (8.17)

Abbreviations: ACR, American College of Rheumatology; NR, not reported; PASI, Psoriasis Area and Severity Index; SAE, serious adverse events; SD, standard deviation; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, SF-36 Physical Component Summary.

Table 27: Extracted data per study [n/N or mean/(SD)], arm, and outcome (biologic-experienced network)

Study	Arm	ACR20	ACR50	PASI 75	PASI 90	SAE	SF-36 MCS	SF-36 PCS
KEEPsAKE 2	PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KEEPsAKE 2	RISA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPIRIT P2	PBO	23/118	6/118	10/67	8/67	4/118	0.9 (14.12)	3.3 (15.21)
SPIRIT P2	IXE	65/122	43/122	38/68	30/68	3/122	3.6 (13.25)	8.9 (14.36)

Abbreviations: ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; SAE, serious adverse events; SD, standard deviation; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, SF-36 Physical Component Summary.

See Appendix F Comparative analysis of efficacy and safety and separate ITC report for more information about included studies, baseline characteristics and data included in the analysis.

7.4.5. Results

Table 28 and

Table 29 represent the results for the indirect comparison for the bio-naïve and bio-experienced population, respectively.

Table 28: Indirect treatment comparison result risankizumab vs. adalimumab (biologic-naive), week 24 – Random effects

End-point	OR (95% CI)	P-value	RR (95% CI)	P-value
ACR 20	[redacted]	[redacted]	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
	MD (95% CI)			
SF-36 MCS	[redacted]	[redacted]		
SF-36 PCS	[redacted]	[redacted]		

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; MD, mean difference; PASI, Psoriasis Area and Severity Index; OR, odds ratio; RR, risk ratio; SAE, serious adverse events; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, SF-36 Physical Component Summary.
Values in bold indicate statistically significant results.

Table 29: Indirect treatment comparison results risankizumab vs. ixekizumab (biologic-experienced network), week 24.

End-point	OR (95% CI)	P-value	RR (95% CI)	P-value
ACR 20	[redacted]	[redacted]	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]
	MD (95% CI)			
SF-36 MCS	[redacted]	[redacted]		
SF-36 PCS	[redacted]	[redacted]		

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; MD, mean difference; PASI, Psoriasis Area and Severity Index; OR, odds ratio; RR, risk ratio; SAE, serious adverse events; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, SF-36 Physical Component Summary.
Values in bold indicate statistically significant results.

For the bio-naive population statistically significant differences were observed for PASI 90 where [redacted] demonstrated clearly better effect for risankizumab compared to adalimumab. There were

no statistically significant differences on the other outcomes, although risankizumab showed a large numerical improvement on PASI 75 and serious adverse events (SAE)vs adalimumab as well.

For the bio-experienced population, there were no statistically significant differences between risankizumab and ixekizumab on any of the outcomes. Risankizumab demonstrated a large numerical improvement over ixekizumab on PASI 75 and 90.

7.4.6. Discussion

In total, 14 indirect comparisons were conducted examining 7 endpoints (ACR 20, ACR 50, PASI 75, PASI 90, SF-36 MCS, SF-36 PCS, SAE) at 24 weeks in two different populations (biologic-experienced and biologic-naïve). Estimates of relative efficacy and safety were obtained using a widely known and accepted methodology. All the trials included in the analysis were derived from an SLR and were randomized controlled trials with similar design and baseline characteristics. Two studies were excluded due to not reporting endpoints at the relevant timepoint and one study was subtracted from the analysis due to being much older than the other studies and having significantly different baseline characteristics, which were considered to negatively impact the validity of the results.

The results of the analysis showed that for the bio-naïve population, results in general favored risankizumab vs. adalimumab with risankizumab being either statistically or numerically better on the majority of the outcomes, with adalimumab not being statistically better for any of the outcomes. Risankizumab demonstrated significantly better results on PASI 90 and a high numerical favorability on PASI 75 and SAE.

For the bio-experienced population vs. ixekizumab there were no statistically significant differences on any of the outcomes. Risankizumab was numerically better on ACR 20 and demonstrated a large numerical improvement on PASI 75 and 90 compared to ixekizumab.

This indirect comparison, including both skin, joint, PRO and safety outcomes, demonstrates that Risankizumab is a valuable treatment option, providing better efficacy on skin with maintained effect on joint symptoms and patients QoL as well as favorable safety related to SAE, compared to adalimumab in the bio-naïve population and ixekizumab in the bio-experienced population.

8. Health economic analysis

Results of the indirect comparison demonstrate that risankizumab is at least as safe and effective as adalimumab and ixekizumab in the treatment of PsA (see chapter 7.4 for details on the indirect comparison). Furthermore, adalimumab and ixekizumab are both assessed to be clinically equal to the rest of the drugs mentioned in the Medicines Council recommendation for the treatment of PsA. Therefore, AbbVie has performed a cost comparison analysis, comparing the costs of risankizumab vs adalimumab and ixekizumab in the relevant populations.

The results of the analysis is presented in chapter 8.6.

8.1. Model

The analysis is a simple cost analysis comparing costs of risankizumab with the costs of adalimumab and ixekizumab for the treatment of PsA in a Danish setting. Costs included in the analysis are drug costs and costs related to patient time for treatment administration. Drug costs are based on the PPP (AIP) from medicinpriser.dk, while patient time costs are based on the Medicines Council “cost analysis regarding treatment for moderate to severe plaque psoriasis” and “unit costs catalogue” from 2022.

Costs related to adverse events are not included in the cost analysis since it is challenging to find all relevant codes and costs related to each adverse event category. However, an initial analysis based on adverse events and costs that could be found is included in chapter 8.5.4. This analysis is not, however, included in the final cost analysis.

The cost analysis has a limited societal perspective with a time horizon of 18 months. This time horizon is used as the basis for calculating treatment length for RA in the Medicines Council’s treatment guidelines as well as

by RADS in developing pharmaceutical recommendations for PsA (115). Furthermore, treatments for RA and PsA are primarily the same type of treatments with the same dosing schedule regardless of indication. Therefore, AbbVie has also based the cost calculations on an 18-month time horizon. This timeline will also capture all relevant differences in the treatments.

Costs after 1 year will be discounted with 3,5% in line with suggested methodology.

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

Chapter 8.2 together with related subheadings are N/A due to a simple cost comparison analysis being performed, not a cost per QALY.

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

N/A

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

N/A

8.3. Extrapolation of relative efficacy

Chapter 8.3 together with related subheadings are N/A due to a simple cost comparison analysis being performed, not a cost per QALY.

8.3.1. Time to event data – summarized:

N/A

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

Chapter 8.4 together with related subheadings are N/A due to a simple cost comparison analysis being performed, not a cost per QALY.

8.4.1. Overview of health state utility values (HSUV)

N/A

8.4.2. Health state utility values used in the health economic model

N/A

8.5. Resource use and costs

8.5.1. Costs of pharmaceuticals

All drug costs in the cost analysis and budget impact analysis are based on the PPP (AIP) from medicinpriser.dk.

Doses are estimated based on the approved dosing regimen in SmPC. See Table 30 for strength, pack size, units and price per pack. The price is based on the lowest possible pharmacy purchase price (PPP) for the comparators. Treatment with methotrexate is excluded in the analysis as it is expected to be the same between treatments. For the cost comparison only costs for risankizumab and the relevant comparators adalimumab and ixekizumab will be considered. Costs for the other treatments included in the treatment recommendation will however be included in the budget impact analysis (chapter 9).

Drug wastage is not included in this analysis. Drug wastage is not expected for these treatments as they consist of prefilled syringes/pens that contains the exact amount a patient needs for their dose, reducing the risk for any drug wastage.

Table 30: Strength, pack size, cost per pack and dosing schedule for relevant comparators (risa, ada and ixe) and other relevant treatments for budget impact analysis

Drug	Strength	Pack size	AIP (DKK)	Dosing schedule PsA
Risankizumab	75 mg	2 pc.	25.298,93	150mg week 0, 4 and every 12 weeks
	150mg	1 pc.		
Adalimumab	40 mg	2 pc.	4.594,44	40mg every other week
Ixekizumab	80 mg	1 pc.	7 .376,35	160mg week 0 followed by 80mg every 4 weeks
Secukinumab	150 mg	2 pc.	7.908,00	**Bio-experienced:** 300mg week 0,1,2,3,4 and thereafter every 4 weeks **Bio-naïve:** 150mg week 0,1,2,3,4 and thereafter every 4 weeks
	300 mg	1 pc.		
Certolizumab	200 mg	2 pc.	7.296,74	400mg week 0,2,4 followed by 200mg every other week

8.5.2. Hospital costs

According to the Medicine council's cost analysis of treatment for moderate to severe plaque psoriasis hospital and transportation costs are the same between adalimumab, ixekizumab and risankizumab. Hospital and administration costs between adalimumab, ixekizumab and risankizumab are assumed to be similar since these treatments have a similar administration method which require similar amount of resources regarding starting up treatment and training patients to handle subcutaneous injections. Furthermore patients stable on these treatments are expected to be followed up at a similar rate, meaning that total hospital- and administration costs will not differ significantly between the treatments.. Therefore, for the purpose of this cost comparison, hospital and administration costs are assumed to be the same between the treatments and not included as they will not impact the final result.

8.5.3. Transport costs and time spent by patients and relatives

. Risankizumab differs quite substantially from adalimumab and ixekizumab with a lower dosing frequency, which provides a benefit for patients spending less time on their injections which is also reflected in the patient time costs. Transportation costs are assumed to be the same between all treatments for the same reasons as mentioned above for hospital and monitoring costs. Patient time cost is estimated based on the Medicines Council's "Cost analysis of treatments in moderate to severe plaque psoriasis" from 2022. The unit time for the patient to take one subcutaneous injection is estimated to be 10 minutes, and two administrations following each other is estimated to take 15 minutes for the patient. The unit cost per minute is estimated based on the Medicines council's "Catalogue of unit cost" from 2022.

See Table 31 for costs related to patient time and costs included in the analysis.

Table 31: Patient time cost over 18 months, undiscounted

(DKK)	Adalimumab	Risankizumab	Ixekizumab
Number of units (minutes)	390 (min)	80 (min)	205 (min)
DKK pr. minute	3,01 DKK	3,01 DKK	3,01 DKK
Total patient time costs	1 173,90 DKK	240,8 DKK	617,05 DKK

Reference: (116) (117)

8.5.4. Adverse events costs

The cost difference between AE's were estimated for the argumentation of exclusion. Only AE's experienced by ≥5% of the patients in SELECT PsA-1 and SPIRIT-P1 for adalimumab, SPIRIT-P2 for ixekizumab and KEEPsAKE 1 and KEEPsAKE 2 for risankizumab are included (see Table 32 and Table 33).

Table 32: Adverse events reported by ≥5% of patients in SELECT PsA-1, SPIRIT-P1 and KEEPsAKE 1

	Select PsA-1 Adalimumab N=429		SPIRIT-P1 Adalimumab N=101		KEEPsAKE 1 Risankizumab N=483	
Subjects with:	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any Hepatic Disorder	67	(15.6)	N/A	N/A	32	(6.6)
Any Creatine Phosphokinase (CPK) Elevation	24	(5.6)	N/A	N/A	N/A	N/A
Nasopharyngitis	N/A	N/A	7	(6.9)	N/A	N/A
Upper respiratory tract infection	N/A	N/A	5	(5.0)	N/A	N/A
Injection site reactions	N/A	N/A	6	(5.9)	N/A	N/A
Hepatic events	N/A	N/A	13	(12.9)	N/A	N/A
Allergic reactions or hypersensitivities	N/A	N/A	5	(5.0)	N/A	N/A

Table 33: Adverse events reported by ≥5% of patients in SPIRIT-P2 and KEEPsAKE 2

	SPIRIT P2 Ixekizumab		KEEPsAKE 2 Risankizumab	
Subjects with:	**n**	**(%)**	**n**	**(%)**
Injection site reaction	8	(7)	N/A	N/A
Upper respiratory tract infections	11	(9)	17	(7.6)
Nasopharyngitis	8	(7)	N/A	N/A
Sinusitis	7	(6)	N/A	N/A
Urinary tract infection	6	(5)	N/A	N/A
Oropharyngeal pain	7	(6)	N/A	N/A
Allergic reaction or hypersensitivities	8	(7)	N/A	N/A

See

Table 34 for the cost resources used per AE.

Table 34: AE'S UNIT COST AND DRG TARIFF

AE	Unit cost (DKK)	SOURCE
Hepatic Disorder	2 610	DRG 2021: 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år
Creatine Phosphokinase (CPK) Elevation	1 617	DRG 2021: 08MA98: MDC08 1-dagsgruppe, pat. mindst 7 år
Injection site reaction	481	DRG 2021: 70AK02 - Småskader

Upper respiratory tract infection	1 862	DRG 2021: 03MA98: MDC03 - 1-dagsgruppe, pat. Mindst 7 år
Urinary tract infection	1 906	DRG 2021: 11MA98: MDC11 1-dagsgruppe, pat. mindst 7 år
Nasopharyngitis	147,09	GP visit (2021 value): https://www.laeger.dk/sites/default/files/honorartabel_01.10.20.pdf
Sinusitis	147,09	GP visit (2021 value): https://www.laeger.dk/sites/default/files/honorartabel_01.10.20.pdf
Oropharyngeal pain	147,09	GP visit (2021 value): https://www.laeger.dk/sites/default/files/honorartabel_01.10.20.pdf
Allergic reactions or hypersensitivities	4 488	DRG2021: 21MA01: Allergiske og allergi lignende reaktioner

See Table **35** for cost difference in AE's between risankizumab and adalimumab

Table 35: AE COST DIFFERENCE UPA VS. ADA

AE	ADA (SELECT PsA-1)	ADA (SPIRIT-P1)	RISA (KEEPsAKE 1)
Hepatic Disorder	407,16	-	172,26
Creatine Phosphokinase (CPK) Elevation	90,55	-	-
Nasopharyngitis	-	10,15	-
Upper respiratory tract infection	-	93,1	-
Injection site reactions	-	28,38	-
Hepatic events	-	336,69	-
Allergic reactions or hypersensitivities	-	224,4	-
Total cost	497,71	692,718	172,26
Cost difference (RISA vs. ADA SELECT PsA-1)	-	-	**-325,45**
Cost difference (RISA vs. ADA SPIRIT-P1)	-	**-520,458**	-

See

Table 36 for the cost difference in AE's between risankizumab and ixekizumab.

Table 36: AE COST DIFFERENCE UPA VS. IXE

AE	IXE (SPIRIT P2)	RISA (KEEPsAKE 2)
Injection site reaction	33,67	-
Upper respiratory tract infection	167,58	141,51
Nasopharyngitis	10,30	-
Sinusitis	8,83	-
Urinary tract infection	95,30	-
Oropharyngeal pain	8,83	-
Allergic reactions or hypersensitivities	314,16	-
Total cost	638,66	141,51
Cost difference (RISA vs. IXE)		**-497,15**

The results comparing costs related to adverse events reported in more than 5% of the patients indicate that there are higher costs related to adverse events for adalimumab and ixekizumab compared to risankizumab. This is due to the rate of adverse events reported in the publications being lower for risankizumab than for adalimumab and ixekizumab. Not including AE's in the cost analysis can therefore be considered to be a conservative approach. However, it is difficult to fully compare the cost of adverse events between the treatments since the reported adverse events differs between the studies. For instance, more information about unit cost exists for AE's in SPIRIT-P2 than for the other studies. Therefore, Abbvie find it reasonable to assume similar costs regarding safety although it can be conservative not to include.

8.6. Results of cost comparison

8.6.1. Base case results

Table 37 shows the result for the cost difference between risankizumab compared to adalimumab and ixekizumab on list price (AIP).

Table 37: Per patient cost over 18 months, discounted, DKK, AIP

	Risankizumab	Adalimumab	Ixekizumab
Drug cost	199 825	88 582	153 157
Monitoring cost	-	-	-
Patient cost	238	1 161	610
Total cost	200 063	89 742	153 767
Incremental cost	-	**110,321**	**46 296**

Results of the analysis show that the incremental cost per patient at list price (AIP) over 18 months is 110 321DKK per patient for risankizumab vs adalimumab.

For risankizumab compared to Ixekizumab the incremental cost per patient at list price (AIP) over 18 months is 46 296 DKK per patient.

8.7. Sensitivity analyses

Chapter 8.7 and related subheadings is N/A due to this being a cost comparison with drug costs being the primary cost driver.

8.7.1. Deterministic sensitivity analyses

N/A

8.7.2. Probabilistic sensitivity analyses

N/A

9. Budget impact analysis

For the recommendation of risankizmab the cost consequences for the regions needs to be assessed. Therefore, budget impact is estimated in two scenarios.

- Risankizumab is recommended by the Medicine Council as a standard treatment for patients with PsA.
- Risankizumab is not recommended by the Medicine Council as a standard treatment for patients with PsA.

The budget impact is the difference between the two scenarios.

9.1. Estimating patient population

In 2019, 2560 patients were registered with being treated with csDMARDs for PsA in the DANBIO registry, of which 330 patients started the treatment that year (bio naïve) and approximately 860 patients switched treatment (bio experienced).

Bio-naïve:

In the current treatment recommendations, TNF-inhibitors (adalimumab, infliximab and etanercept) are ranked highest and we assume that it will be used by at least [redacted] of bio-naïve patients. We assume that the other [redacted] will need a different treatment due to contraindications, patient preference etc., most likely secukinumab 150mg or ixekizumab as they are the next alternatives in the recommendations for bio-naïve patients.

Since risankizumab potentially will be the only IL-23 inhibitor in the recommendation we assume a minor proportion of patients eligible for secukinumab and ixekizumab will instead be treated with risankizumab. See Table 38 and

Table 39 for assumed market shares based on whether or not risankizumab will be recommended.

Table 38: MARKET UPTAKE BIO NAIVE, NOT RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 39: MARKET UPTAKE BIO NAIVE, RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bio-experienced:

For the bio experienced population, we assume that [redacted] will be treated with a TNF-inhibitor (most likely adalimumab) and that most patients ([redacted]) will get ixekizumab since that is the cheapest alternative for biologic treatments after TNF's today. We assume that risankizumab will take market shares from secukinumab 300mg and certolizumab pegol since they are preferred after ixekizumab in the recommendation for PsA. See Table 40 and Table 41 for market shares.

Table 40: MARKET UPTAKE BIO EXPERIENCED, NOT RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab Pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 41: MARKET UPTAKE BIO EXPERIENCED, RECOMMENDED

	Year 1	Year 2	Year 3	Year 4	Year 5
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab Pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2. Result budget impact analysis

The budget impact analysis does not include patient costs and discounting. Time on treatment for bio-naïve patients is estimated to be1,5 years, in accordance with the Medicine Council's "Cost analysis of treatments in moderate to severe plaque psoriasis"(116) After this period patients in the bio-naïve budget impact calculation are assumed to discontinue and not followed further as they are not bio-naïve anymore.

For the bio-experienced population we assume that the starting population is [redacted] patients each year and that time on treatment is on average the same as for the bio-naïve population, ie. 1,5 years. This is a simplification since in clinical practice bio-experienced patients will start on another treatment (3th and 4th treatment lines) when they stop responding or become intolerant to treatment. However, this scenario would complicate the model without contributing with a more realistic outcome as it is uncertain how the treatment pattern and market share is between all the drugs included in the recommendation, and how it will look in the future due to the treatment recommendations and rankings can change on a yearly basis.

The results of the budget impact analysis for the bio-naïve and bio-experienced population are presented below in Table 42 and Table 43.

Table 42: BUDGET IMPACT RESULTS, BIO NAÏVE, DKK, AIP

	Year 1	Year 2	Year 3	Year 4	Year 5
If recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
if not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 43: BUDGET IMPACT RESULTS, BIO EXPERIENCED, DKK, AIP

	Year 1	Year 2	Year 3	Year 4	Year 5

If recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
if not recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]			

Results shows that if risankizumab is recommended for the bio-naïve population the budget impact (when using AIP) is [redacted] DKK in year 5. If risankizumab is recommended for the bio-experienced population, the budget impact on AIP [redacted] DKK in year 5.

Overall, the budget impact analysis has demonstrated that recommending risankizumab and give patients with PsA another very valuable treatment alternative, will only bring a small additional budget impact.

9.3. Discussion and conclusion of the cost and budget impact analysis:

The cost comparison including drug costs and patient time costs showed an incremental cost of risankizumab vs. adalimumab and ixekizumab per patient over 18 months to be 110 321DKK (AIP) and 46 296 DKK (AIP), respectively. The budget impact analysis shows a small incremental budget impact of introducing risankizumab to be [redacted] DKK (AIP) and [redacted] DKK (AIP) at year 5 for the bio-naïve and bio-experienced population respectively.

. In the "Cost analysis for treatment in moderate to severe plaque psoriasis" only costs related to patient time were calculated to be different between ixekizumab, adalimumab and risankizumab with all other costs being the same.. Risankizumab is dosed only 8 times over a period of 18 months compared to 39 times for adalimumab and 21 times for ixekizumab. This can have a bigger impact on reducing the need for additional health care contacts, doctor and nurse working time, less adverse events related to injection site reactions etc. than what is reflected in this cost analysis, possibly making the calculations in the cost analysis conservative.

All costs used in the cost and budget impact analysis are based on list prices (AIP). Risankizumab is approved for the treatment of psoriasis and included in the tender and treatment recommendations for psoriasis. Furthermore, the use of these treatments will be dictated by the ranking they receive in the recommendations which is based on price. It is also not expected that the introduction of risankizumab will results in an increased patient population eligible for treatment but take market share from the existing population. In reality, this means that risankizumab will only be used ahead of more expensive alternatives when cheaper options are not available anymore, resulting in increased competition and lower total costs. Therefore, a recommendation of risankizumab for the treatment of PsA will be of benefit for patients, health care sector and society.

10. Discussion and conclusion

This application has documented the efficacy and safety of risankizumab in the treatment of PsA, as well as the relative efficacy of risankizumab compared to the relevant comparators adalimumab and ixekizmab.

As demonstrated through this application, PsA is a highly heterogeneous disease, primarily consisting of skin and joint manifestations, but also associated with several other extra articular manifestations and comorbidities. This nature of the disease leads to a high patient burden, reduced QoL and increased economic burden. 75-80% of patients diagnosed with PsA have existing psoriasis which can occur approximately 10 years before the onset of PsA signs and symptoms. Attention to emerging skin manifestations and earlier treatment initiation is essential for efficient treatment with potential to limit joint damage, improving treatment outcomes and improve patients HRQoL.

Despite the introduction of novel therapies such as IL-17 inhibitors, JAK-inhibitors and additional TNFi there remains unmet needs for therapies with reduced adverse events and with better treatment response. Even though TNFi treatment remain the standard of treatment many patients experience a lack of efficacy and adverse events related to TNFi treatment, and quickly faces the need of new treatments. Furthermore, the highly heterogeneous nature and different severities of the manifestations patients with PsA can experience

leads to the need of additional treatment alternatives with different MoA's to appropriately tailor the treatment and combat the burden of PsA.

The clinical efficacy and safety of risankizumab in PsA have been established in two phase III multicenter placebo-controlled trials that assessed risankizumab in patients who have shown inadequate response or intolerance to at least one disease modifying anti-rheumatic agent (bio-naive) or biologic (bio-experienced), KEEPsAKE 1 and KEEPsAKE 2. It is a strength that risankizumab have been assessed in the bio-naïve and bio-experienced population. The primary endpoint of both studies was ACR20 at week 24, a very common primary endpoint in PsA clinical trials. Secondary endpoint included PASI 90, HAQ-DI, MDA, SF-6 PCS etc. Both studies met their primary and most secondary endpoints, demonstrating that risankizumab offers strong efficacy on the most important elements of PsA, with superior skin efficacy and a high and maintained effect on joints, as well as on Health Related Quality of Life (HRQoL). The observed safety profile demonstrated no new safety signals and was consistent with previous PsO trials. Long term 52-week follow-up data from KEEPsAKE 1 and KEEPsAKE 2 confirms that the efficacy and safety of risankizumab is maintained in the long term. AbbVie acknowledges that it is a weakness that the clinical trials only included a placebo-controlled arm and not an active comparator, but to establish the relative efficacy of risankizumab vs. the relevant comparators adalimumab and ixekizumab, an indirect treatment comparison was undertaken.

The indirect comparison used a widely known frequentist methodology aligned with guidance from NICE, ISPOR and the Cochrane institute, and compared risankizumab vs. adalimumab for the bio-naïve population and vs. ixekizumab for the bio-experienced population on the following key outcomes:

- ACR 20 and 50
- PASI 75 and 90
- SF-36 PCS and MCS
- Severe adverse events (SAE)

The results of the ITC demonstrated that risankizumab is a valuable treatment option, providing better efficacy on skin with maintained effect on joint symptoms as well as favorable safety related to SAE's, compared to adalimumab in the bio-naïve population and ixekizumab in the bio-experienced population.

The strength of the indirect comparison is that all the comparators are linked via a common comparator arm (placebo), with a proven methodology that provides robust and trustable results. A general limitation to the ITC are the assumptions underlying it and similarity and homogeneity must be carefully considered, otherwise the results of the ITC might be jeopardized. AbbVie have performed comparisons of the different baseline characteristics to assess the feasibility and fit of the data and decided to remove one study (ADEPT) with significantly different baseline characteristics in the bio-naïve population. Therefore, the analysis and results are based on the latest and most relevant data.

The cost comparison used in this analysis is based on a limited societal perspective including drug costs and patient time costs. Drug costs are based on lowest AIP for comparators and unit costs and assumptions regarding patient costs are based The Medicines Council cost analysis regarding moderate to severe plaque psoriasis. Except for drug costs and patient time costs all other hospital related costs, transportation costs and costs related to adverse events are assumed to be the same between all of the treatments. This might be a conservative assumption due to the substantially longer dosing interval for risankizumab compared to adalimumab and ixekizumab, and also due to the results in section 8.5.4 indicating that there are higher costs for adverse events for adalimumab and ixekizumab compared to risankizumab.

The results of the cost analysis show an incremental 18-month cost per patient of 110 321 DKK vs adalimumab and 46 296 DKK vs. ixekizumab. Budget impact on AIP of introducing is relatively small, [redacted] DKK (AIP) for the bio-naïve population and [redacted] DKK (AIP) for the bio-experienced population.

The cost comparison and budget impact analysis were done on list price (AIP). Risankizumab is approved for the treatment of psoriasis in Denmark and included in the tender and treatment recommendations for psoriasis. The use of risankizumab for the treatment of PsA in clinical practice will be dictated by the ranking in

the treatment recommendations, resulting in that risankizumab will only be used for eligible patients ahead of more expensive treatments when no cheaper alternatives are available anymore. If risankizumab is used as expected according to ranking in the treatment recommendations, introducing risankizumab will in reality be cost saving.

To conclude, risankizumab represents an entirely new alternative in the treatment of PsA, with a strong value on skin as well as improvement on peripheral disease, including maintained effect on joints and a well-established and favorable safety profile, demonstrated via two large clinical trials and an ITC vs. the relevant comparators adalimumab and ixekizumab. Compared to the other treatments in the recommendations, risankizumab has a substantially lower dosing frequency, with a maintenance dose every 12 weeks, reducing the burden of injections for patients. The budget impact of introducing risankizumab is minimal and predictable. A recommendation of risankizumab will therefore provide a new alternative to optimize treatment for the highly heterogenous disease PsA, provide benefit for eligible patients and lead to increased competition, in total leading to cost savings for society.

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

The systematic literature review was conducted on October 13th 2021 via the MEDLINE and CENTRAL database with the objective to identify relevant studies and data for assessing the clinical efficacy and safety of risankizumab vs. adalimumab for the bio-naïve population and vs. ixekizumab for the bio-experienced population.

The search was carried out according to pre-defined PICO criteria, see Appendix table 1: Pre-defined PICO criteria for literature search below.

Appendix table 1: Pre-defined PICO criteria for literature search

PICO criteria	
Population	• bDMARD therapy naïve patients with PsA • bDMARD experienced patients with PsA
Intervention	Risankizumab s.c, 150mg week 0, 4 and thereafter every 12 weeks
Comparator	• Adalimumab s.c, 40mg every other week • Ixekizumab s.c, 160mg week 0, 80mg every four weeks.
Outcome	At least 24-week follow-up with placebo-controlled arm and these outcomes: • ACR20 • ACR50 • PASI75 • PASI90 • SF-36 physical component summary (PCS) • SF-36 mental component summary (MCS) • Serious adverse events (SAE)

Appendix table 2: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Central	Cochrane	No defined time period	13.10.2021
Medline	Pubmed	No defined time period	13.10.2021

Appendix table 3: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov		13.10.2021

Search strategy

The search is developed by first defining the wanted population, in this instance patients with psoriasis arthritis had to be included in either title or abstract. The following strings determine which interventions we wish to have included in the studies, for this search the interventions was risankizumab, adalimumab and ixekizumab which also had to be included in either title or abstract. To exclude studies of irrelevant design search strings were made and finally set to be not included in the final search.

Appendix table 4: Search string MEDLINE(via PubMed)

No.	Query	Results
#1	"Arthritis, Psoriatic"[mh]	6965
#2	PsA[tiab] OR (psoria*[tiab] AND (arthriti*[tiab] OR arthropath*[tiab] OR polyarthriti*[tiab] OR poly-arthriti*[tiab] OR oligoarthr*[tiab] OR oligo-arthr*[tiab] OR rheumato*[tiab]))	48532
#3	#1 OR #2	49482
#4	risankizumab [nm]	89
#5	risankizumab [tiab] OR ABBV-066 [tiab] OR Skyrizi*[tiab]	200
#6	adalimumab[mh]	6024
#7	adalimumab[tiab] OR humira*[tiab] OR D2E7[tiab] OR amjevita*[tiab] OR cyltezo*[tiab]	8003
#8	ixekizumab[nm]	357
#9	ixekizumab[tiab] OR taltz*[tiab] OR LY-2439821[tiab] OR LY2439821[tiab]	691
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	10328
#11	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])	1340061
#12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Guideline[pt] OR Review[pt] OR case report[ti]	6780120
#13	animal*[ti] OR murine[ti] OR mouse[ti] OR mice[ti] OR rat[ti] OR rats[ti] OR rodent[ti]	1584497
#14	#12 OR #13	8310592
#15	#3 AND #10 AND #11 NOT #14	149

Feltkoder: mh = MeSH Term nm = Supplementary Concept/Substance tiab = title/abstract, inkl. forfatterkeywords pt = publication type

Appendix table 5: Search string CENTRAL (via Cochrane Library)

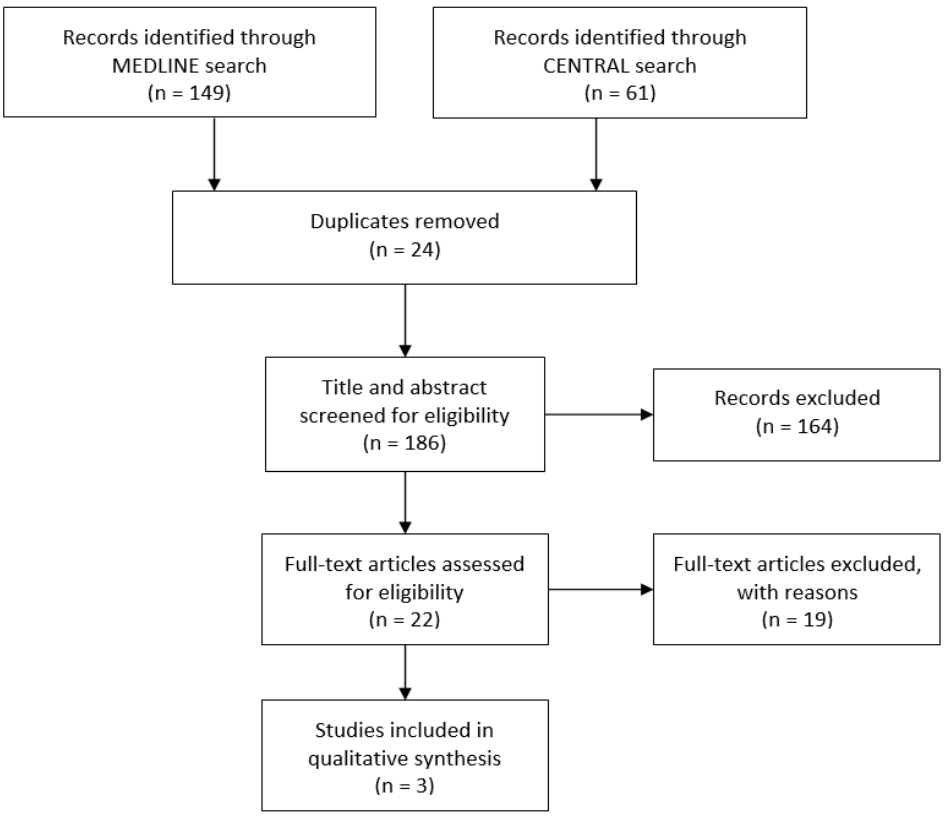
No.	Query	Results
#1	[mh "Arthritis, Psoriatic"]	494

No.	Query	Results
#2	(psoria* near (arthriti* or arthropath* or polyarthriti* or poly-arthriti* or oligoarthr* or oligo-arthr* or rheumato*)):ti,ab,kw	2569
#3	(PsA):ti,ab	7425
#4	#1 or #2 or #3	8344
#5	(risankizumab or ABBV-066 or Skyrizi*):ti,ab,kw	142
#6	(adalimumab or humira* or D2E7 OR amjevita* OR cyltezo*):ti,ab,kw	3479
#7	(ixekizumab or taltz* or LY-2439821 or LY2439821):ti,ab,kw	554
#8	#5 or #6 or #7	4015
#9	#4 and #8	567
#10	("conference abstract" or review):pt	201016
#11	(clinicaltrials.gov or trialsearch):so	376877
#12	NCT*:au	214753
#13	#10 or #11 or #12	578063
#14	#9 not #13	138
#15	#14 not pubmed:an	61

Feltkoder: ti: title ab: abstract kw: keywords, her kontrollerede/indekserede termer fra databaserne Medline og/eller Embase. pt = publication type

Systematic selection of studies

Appendix figure 1: Prisma flow diagram



A total of 210 potentially relevant references were identified through searching MEDLINE and CENTRAL. A total of 24 reference duplicates were identified and 186 references were subsequently screened, 164 records were excluded based on titles and abstracts and 22 published full-text papers were subsequently assessed for eligibility. Of these, 19 references were excluded in full text review. In total, 3 references were included.

The 3 references reported primary and secondary endpoints from 3 different placebo-controlled trials including relevant populations (bio-naïve, bio-experienced) and relevant comparators adalimumab and/or ixekizumab: SELECT PsA-1, SPIRIT P1 and SPIRIT P2..

Data for risankizumab from KEEPsAKE 1 and 2 were extracted from internal clinical study reports as results from these trials was not published at the moment of the search.

Therefore, the studies included in the assessment for the different population and comparators were:

Bio-naïve:

- Adalimumab data: SELECT PsA-1 and SPIRIT P1
- Risankizumab data: KEEPsAKE 1

Bio-experienced:

- Ixekizumab data: SPIRIT P2
- Risankizumab: KEEPsAKE 2

See Appendix table 6: List of excluded references/full text papers with a short reason for excluded references, Appendix table 7: References identified and included in literature search for included references and Appendix table 8: Overview of study design for studies included in the technology assessment/analysis: for an overview of studies relevant for this assessment.

Appendix table 6: List of excluded references/full text papers with a short reason

Title	Publication	Reason for exclusion

Rapid and sustained improvements in patient-reported signs and symptoms with ixekizumab in biologic-naive and TNF-inadequate responder patients with psoriatic arthritis.	Orbai AM, Gladman DD, Goto H, Birt JA, Gellett AM, Lin CY, Kvien TK. Clin Exp Rheumatol. 2021 Mar-Apr;39(2):329-336.	Wrong population. Not bio-IR. Improvements in patient reported outcomes for ixekizumab in bio-naïve patients and patients with inadequate response to 1 or 2 TNF-inhibitors.
Ixekizumab, with or without concomitant methotrexate, improves signs and symptoms of PsA: week 52 results from Spirit-P1 and Spirit-P2 studies	Combe B, Tsai TF, Huffstutter JE, Sprabery AT, Lin CY, Park SY, Kronbergs A, Hufford MM, Nash P. Arthritis Res Ther. 2021 Jan 27;23(1):41.	Wrong population and intervention. Not bio-IR and treatment with and without concomitant MTX.
Ixekizumab efficacy and safety with and without concomitant conventional disease-modifying antirheumatic drugs (cDMARDs) in biologic DMARD (bDMARD)-naïve patients with active psoriatic arthritis (PsA): results from SPIRIT-P1.	Coates LC, Kishimoto M, Gottlieb A, Shuler CL, Lin CY, Lee CH, Mease PJ. RMD Open. 2017 Dec 22;3(2):e000567.	Wrong population and intervention. Not bio-IR and treatment with and without concomitant cDMARD.
Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy	Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, Medich J, Sasso EH; M02-570 Study Group. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol. 2007 May;34(5):1040-50. Epub 2007 Apr 15. Erratum in: J Rheumatol. 2007 Jun;34(6):1439. PMID: 17444593.	Placebo controlled period only up to 12 weeks, so timepoint is not relevant for ITC.
Efficacy and Safety of Ixekizumab with or Without Methotrexate in Biologic-Naïve Patients with Psoriatic Arthritis: 52-Week Results from SPIRIT-H2H Study	Smolen JS, Sebba A, Ruderman EM, Schulze-Koops H, Sapin C, Gellett AM, Sprabery AT, Li L, de la Torre I, Gallo G, Liu-Leage S, Pillai S, Reis P, Nash P. Rheumatol Ther. 2020 Dec;7(4):1021-1035.	Wrong population and intervention. Not bio-IR and treatment with and without concomitant MTX.
Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. (OPAL Broaden)	Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, Cieślak D, Graham D, Wang C, Menon S, Hendrikx T, Kanik KS. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med. 2017 Oct 19;377(16):1537-1550. doi: 10.1056/NEJMoa1615975. PMID: 29045212.	Patients on placebo switched to active treatment after 3 months, so adalimumab and placebo data not relevant for ITC.
Prediction and benefits of minimal disease activity in patients with psoriatic arthritis and active skin disease in the ADEPT trial	Mease PJ, Kavanaugh A, Coates LC, McInnes IB, Hojnik M, Zhang Y, Anderson JK, Dorr AP, Gladman DD. RMD Open. 2017 Jul 18;3(1):e000415.	Wrong endpoint. Only looking at MDA prediction and benefits.
SPIRIT H2H study group. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial	Mease PJ, Smolen JS, Behrens F, Nash P, Liu Leage S, Li L, Tahir H, Gooderham M, Krishnan E, Liu-Seifert H, Emery P, Pillai SG, Helliwell PS;. Ann Rheum Dis. 2020 Jan;79(1):123-131.	Wrong intervention. Head-to-head comparison of ADA and IXE in bio-naïve patients.
Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-	Strand V, de Vlam K, Covarrubias-Cobos JA, Mease PJ, Gladman DD, Graham D, Wang C, Cappelleri JC, Hendrikx T, Hsu MA. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL	Wrong endpoints and patients on placebo switched to active treatment after 3 months, so adalimumab and placebo data not relevant for ITC.

modifying antirheumatic drugs. (OPAL Broaden)	Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. RMD Open. 2019 Jan 11;5(1):e000806. doi: 10.1136/rmdopen-2018-000806. PMID: 30713721; PMCID: PMC6340575.	
Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, Birbara C, Thomson GT, Perdok RJ, Medich J, Wong RL, Gladman DD. Ann Rheum Dis. 2009 May;68(5):702-9.	Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).	Study excluded due to having significantly different baseline characteristics related to age, PsA disease duration, tender joint count, swollen joint count, BSA ≥3%, HAQ-Di etc. See chapter 8.1 in ITC report for more information. Wrong timepoint as well. Not relevant for ITC.
Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Ann Rheum Dis. 2007 Feb;66(2):163-8.	Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial.	Study excluded due to having significantly different baseline characteristics related to age, PsA disease duration, tender joint count, swollen joint count, BSA ≥3%, HAQ-Di etc. See chapter 8.1 in ITC report for more information.
Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, Sharp JT, Ory PA, Perdok RJ, Weinberg MA; Arthritis Rheum. 2005 Oct;52(10):3279-89.	Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial.	Study excluded due to having significantly different baseline characteristics related to age, PsA disease duration, tender joint count, swollen joint count, BSA ≥3%, HAQ-Di etc. See chapter 8.1 in ITC report for more information.
Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, Perdok RJ, Sasso EH. Arthritis Rheum. 2007 Feb;56(2):476-88.	Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial.	Study excluded due to having significantly different baseline characteristics related to age, PsA disease duration, tender joint count, swollen joint count, BSA ≥3%, HAQ-Di etc. See chapter 8.1 in ITC report for more information. Wrong timepoint as well. Not relevant for ITC.
Genovese MC, Combe B, Kremer JM, Tsai TF, Behrens F, Adams DH, Lee C, Kerr L, Nash P. Rheumatology (Oxford). 2018 Nov 1;57(11):2001-2011.	Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2.	Long term follow-up, no pbo controlled arm and wrong timepoint for assessment of outcomes. Not relevant for ITC.
Orbai AM, Gratacós J, Turkiewicz A, Hall S, Dokoupilova E, Combe B, Nash P, Gallo G, Bertram CC, Gellett AM, Sprabery AT, Birt J, Macpherson L, Geneus VJ, Constantin A. Rheumatol Ther. 2021 Mar;8(1):199-217.	Efficacy and Safety of Ixekizumab in Patients with Psoriatic Arthritis and Inadequate Response to TNF Inhibitors: 3-Year Follow-Up (SPIRIT-P2).	Long term follow-up, no pbo controlled arm and wrong timepoint for assessment of outcomes. Not relevant for ITC.
Kavanaugh A, Marzo-Ortega H, Vender R, Wei CC, Birt J, Adams DH, Benichou O, Lin CY, Nash P. Clin Exp Rheumatol. 2019 Jul-Aug;37(4):566-574. Epub 2018 Nov 19.	Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks.	Long term follow-up, no pbo controlled arm and wrong timepoint for assessment of outcomes. Not relevant for ITC.
Chandran V, van der Heijde D, Fleischmann RM, Lespessailles E,	Ixekizumab treatment of biologic-naïve patients with active psoriatic	Long term follow-up, no pbo controlled arm and wrong timepoint

Helliwell PS, Kameda H, Burgos-Vargas R, Erickson JS, Rathmann SS, Sprabery AT, Birt JA, Shuler CL, Gallo G. Rheumatology (Oxford). 2020 Oct 1;59(10):2774-2784.	arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1).	for assessment of outcomes. Not relevant for ITC.
van der Heijde D, Gladman DD, Kishimoto M, Okada M, Rathmann SS, Moriarty SR, Shuler CL, Carlier H, Benichou O, Mease PJ. J Rheumatol. 2018 Mar;45(3):367-377.	Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52-week Results from a Phase III Study (SPIRIT-P1).	Long term follow-up, no pbo controlled arm and wrong timepoint for assessment of outcomes. Not relevant for ITC.
Gottlieb AB, Strand V, Kishimoto M, Mease P, Thaçi D, Birt J, Lee CH, Shuler CL, Lin CY, Gladman DD. Rheumatology (Oxford). 2018 Oct 1;57(10):1777-1788.	Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naïve patients with active psoriatic arthritis (SPIRIT-P1).	Long term follow-up, no pbo controlled arm and wrong timepoint for assessment of outcomes. Not relevant for ITC.

Appendix table 7: References identified and included in literature search

Author and publication	Title
Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, Adams DH, Kerr L, Lee C, Shuler CL, Genovese M; SPIRIT-P2 Study Group **Lancet. 2017 Jun 10;389(10086):2317-2327.**	**Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial.**
McInnes IB, Anderson JK, Magrey M, Merola JF, Liu Y, Kishimoto M, Jeka S, Pacheco-Tena C, Wang X, Chen L, Zueger P, Liu J, Pangan AL, Behrens F. **N Engl J Med. 2021 Apr 1;384(13):1227-1239.**	**Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis**
Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, Lin CY, Braun DK, Lee CH, Gladman DD; SPIRIT-P1 Study Group **Ann Rheum Dis. 2017 Jan;76(1):79-87.**	**Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1.**

Appendix table 8: Overview of study design for studies included in the technology assessment/analysis:

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
SPIRIT-P1	To assess the safety and efficacy of Ixekizumab.	A 3-year, phase III, randomised, double-blind, placebo-controlled and activecontrolled clinical trial	Patients naive to biologic therapy with active PsA	Placebo (106) ADA (101) IXEQ2W (103) IXEQ4W (107)	ACR20 (24 weeks)	See Appendix table 10

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
SPIRIT-P2	To assess efficacy and safety of ixekizumab in patients with active psoriatic arthritis and previous inadequate response to tumour necrosis factor inhibitors	Double-blind, multicentre, randomised, placebo-controlled, phase 3 study	Patients were aged 18 years or older, had a confirmed diagnosis of psoriatic arthritis for at least 6 months, and had a previous inadequate response, distinguished by being refractory to therapy or had loss of efficacy, or were intolerant to tumour necrosis factor inhibitors.	Placebo (118) IXEQW2 (123) IXEQW4 (122)	ACR20 (24 weeks)	See Appendix table 11
SELECT-PsA1	To assess the efficacy and safety of upadacitinib as compared with adalimumab	A double-blind, phase 3 trial were patients was randomly assigned in a 1:1:1:1 ratio	Patients were 18 years of age or older, had received a diagnosis of psoriatic arthritis, and had historical or current plaque psoriasis. And had an inadequate response or unacceptable side effects with at least one nonbiologic DMARD.	Placebo (423) ADA (429) UPA 15mg (429) UPA 30mg (423)	ACR20 (24 weeks)	See Appendix table 9
KEEPsAKE 1	See Appendix table 12 for information					
KEEPsAKE 2	See Appendix table 13 for information					

Quality assessment

Literature search performed very recently (October 2021) in well-known databases with a targeted approach, identifying the most recent and relevant studies and data for relevant comparators and populations for the relative efficacy assessment.

Unpublished data

Appendix B Main characteristics of included studies

Appendix table 9: SELECT PsA-1 characteristics

Trial name: SELECT-PsA1	**NCT number: NCT03104400**
Objective	*To assess the efficacy and safety of upadacitinib as compared with adalimumab, a tumor necrosis factor α inhibitor, in patients who have an inadequate response to nonbiologic disease-modifying antirheumatic drugs*
Publications – title, author, journal, year	*Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. McInnes IB et al, N Engl J Med., 2021*
Study type and design	*SELECT-PsA 1 is a double-blind, phase 3 trial were patients was randomly assigned in a 1:1:1:1 ratio to receive oral upadacitinib at a dose of 15 mg or 30 mg once daily, placebo, or subcutaneous adalimumab (40 mg every other week).*
Sample size (n)	*1704*

Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) criteria.* • *Participant has active disease at Baseline defined as >= 3 tender joints (based on 68 joint counts) and >= 3 swollen joints (based on 66 joint counts) at Screening and Baseline Visits.* • *Presence of either at Screening:* 1. *>= 1 erosion on x-ray as determined by central imaging review or;* 2. *hs-CRP > laboratory defined upper limit of normal (ULN).* • *Diagnosis of active plaque psoriasis or documented history of plaque psoriasis.* • *Participant has had an inadequate response (lack of efficacy after a minimum 12 week duration of therapy) to previous or current treatment with at least 1 non-biologic DMARD at maximally tolerated dose (MTX, Sulfasalazine (SSZ), Leflunomide (LEF), cyclosporine, apremilast, bucillamin or iguratimod), or participant has an intolerance to or contraindication for DMARDs as defined by the investigator.* • *Participant who is on current treatment with concomitant non-biologic DMARDs at study entry must be on <= 2 non-biologic DMARDs (except the combination of MTX and leflunomide). The following non-biologic DMARDs are allowed: MTX, sulfasalazine, leflunomide, apremilast, Hydroxychloroquine (HCQ) , bucillamine or iguratimod, and have been ongoing for >= 12 weeks and at stable dose for >= 4 weeks prior to the Baseline Visit. No other DMARDs are permitted during the study.* • *Participants who need to discontinue DMARDs prior to the Baseline Visit to comply with this inclusion criterion must follow the procedure specified below or at least five times the mean terminal elimination half-life of a drug:* 1. *>= 8 weeks for LEF if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine, or 30 days washout with activated charcoal or as per local label);* 2. *>= 4 weeks for all others.* *Exclusion Criteria:* • *Prior exposure to any Janus Kinase (JAK) inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, and filgotinib).* • *Current treatment with > 2 non-biologic DMARDs; or use of DMARDs other than methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychloroquine, bucillamine, or iguratimod; or use of methotrexate in combination with leflunomide.* • *History of fibromyalgia, any arthritis with onset prior to age 17 years, or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus). Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and nonradiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made. Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly.*

Trial name: SELECT-PsA1	NCT number: NCT03104400
Intervention	*upadacitinib p.o. at a dose of 15 mg once daily* *or* *upadacitinib p.o. at a dose of 30 mg once daily*
Comparator(s)	*placebo p.o. at a dose of 15 mg once daily* *or* *placebo p.o. at a dose of 30 mg once daily* *or* *adalimumab s.c. at a dose of 40 mg every other week*
Follow-up time	*24 weeks, with a 5 year extended follow-up period*
Is the study used in the health economic model?	*N/A*
Primary, secondary and exploratory endpoints	*Primary endpoint:* • *Percentage of Participants Achieving American College of Rheumatology (ACR) 20 Response* *Secondary endpoint:* • *Change in HAQ-DI* • *Percentage of Participants Achieving a Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point Improvement From Baseline* • *Psoriasis Area Severity Index (PASI) 75 Response (For Participants With >= 3% Body Surface Area (BSA) Psoriasis at Baseline)* • *Change in Modified PsA Sharp/van der Heijde Score (SHS)* • *Percentage of Participants Achieving Minimal Disease Activity (MDA)* • *Percentage of Participants With Resolution of Enthesitis (Leeds Enthesitis Index (LEI)=0)* • *Change in Physical Component Summary (PCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)* • *Change in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Questionnaire* • *Percentage of Participants With Resolution of Dactylitis* • *Change in Patient's Assessment of Pain Numerical Rating Scale (NRS)* • *Change in HAQ-DI* • *Change in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire* • *ACR 50 Response* • *ACR 70 Response*

Trial name: SELECT-PsA1	NCT number: NCT03104400
Method of analysis	*Efficacy analyses were conducted in the modified intention-to-treat population, which included all the patients who had undergone randomization and had received at least one dose of upadacitinib, placebo, or adalimumab. All power and sample size calculations were performed at a two-sided significance level of 0.025, with a dropout rate of 10% taken into account.*
Subgroup analyses	*N/A*
Other relevant information	

Appendix table 10: SPIRIT P1 characteristics

Trial name: SPIRIT-P1	NCT number: NCT01695239
Objective	*To assess the safety and efficacy of ixekizumab, a monoclonal antibody that inhibits interleukin-17A, in a double-blind phase III trial enrolling patients with active psoriatic arthritis (PsA).*
Publications – title, author, journal, year	*Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1., Mease PJ et al, Ann Rheum Dis., 2017.*
Study type and design	*SPIRIRT-P1 is a randomized, double-blind, placebo controlled and active (adalimumab)-controlled, phase III trial.* *Patients were randomized at a 1:1:1:1 ratio to one of four treatment groups: ixekizumab 80 mg every 2 weeks (IXEQ2W), ixekizumab 80 mg every 4 weeks (IXEQ4W), adalimumab 40 mg Q2W, or placebo, all administered via subcutaneous injection.*
Sample size (n)	*417*

Trial name: SPIRIT-P1	NCT number: NCT01695239
Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Presents with established diagnosis of active psoriatic arthritis for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria* • *Active psoriatic arthritis (PsA) defined as the presence of at least 3 tender and at least 3 swollen joints* • *Presence of active psoriatic skin lesion or a personal history of plaque psoriasis (Ps)* • *Men must agree to use a reliable method of birth control or remain abstinent during the study* • *Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment* *Exclusion Criteria:* • *Current or prior use of biologic agents for treatment of Ps or PsA* • *Inadequate response to greater than or equal to 4 conventional disease-modifying antirheumatic drugs (DMARDs)* • *Current use of more than one conventional DMARD* • *Evidence of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA* • *Have participated in any study with interleukin 17 (IL-17) antagonists, including ixekizumab* • *Serious disorder or illness other than psoriatic arthritis* • *Serious infection within the last 3 months* • *Breastfeeding or nursing (lactating) women*
Intervention	*ixekizumab 80 mg every 2 weeks (IXEQ2W) s.c. with a 160 mg starting dose at week 0* *or* *ixekizumab 80 mg every 4 weeks (IXEQ4W) s.c. with a 160 mg starting dose at week 0*
Comparator(s)	*adalimumab 40 mg every 2 weeks Q2W s.c.* *or* *placebo s.c.*
Follow-up time	*24 weeks, with a 3 year extended follow-up period*
Is the study used in the health economic model?	*N/A*

Primary, secondary and exploratory endpoints	*Primary endpoint:* • *Percentage of Participants Achieving American College of Rheumatology 20 (ACR20) Response at Week 24* *Secondary endpoint:* • *Percentage of Participants Achieving ACR20 Response* • *Percentage of Participants Achieving American College of Rheumatology 50 (ACR50) Response* • *Percentage of Participants Achieving American College of Rheumatology 70 (ACR70) Score Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Scores* • *Change From Baseline in Modified Total Sharp Score (mTSS)* • *Percentage of Participants Achieving Psoriasis Area and Severity Index 75%, 90%, 100% (PASI 75, 90, 100)* • *Change From Baseline in Leeds Enthesitis Index (LEI)* • *Change From Baseline in Itching Severity Using the Itch Numeric Rating Scale (NRS)* • *Change From Baseline in Fatigue Severity NRS Score* • *Change From Baseline in Joint Space Narrowing Score (JSN) And Bone Erosion Score (BES)* • *Change From Baseline in Medical Outcomes Study 36-item Short Form Health Survey (SF-36): Physical Component Summary (PCS) and Mental Component Summary (MCS)* • *Change From Baseline in Quick Inventory of Depressive Symptomatology-Self Reported 16 Items (QIDS-SR16)* • *Change From Baseline in Disease Activity Score (28 Diarthrodial Joint Count)* • *Percentage of Participants Meeting the Psoriatic Arthritis Response Criteria (PsARC Modified)* • *Percentage of Participants Achieving Static Physician Global Assessment (sPGA) of 0 or 1 and With at Least a 2-point Improvement From Baseline* • *Percent Change From Baseline in Body Surface Area (BSA)* • *Change From Baseline in the Nail Psoriasis Severity Index (NAPSI) Score Fingernail Involvement at Baseline* • *Change From Baseline in Leeds Dactylitis Index-Basic (LDI-B)* • *Change From Baseline in in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)* • *Number of Participants With Treatment Emergent Anti-Ixekizumab Antibodies (TE-ADA) and Neutralizing Antibodies (NAb)* • *Number of Participants With Treatment Emergent Anti-Ixekizumab Antibodies (TE-ADA) and Neutralizing Antibodies (NAb)* • *Percent Change in American College of Rheumatology-N (ACR-N) Score* • *Change From Baseline in Tender Joint Counts (TJC)* • *Change From Baseline in Swollen Joint Counts (SJC)* • *Change From Baseline in Patient's Assessment of Pain VAS*

Trial name: SPIRIT-P1	NCT number: NCT01695239
	• *Change From Baseline in Patient's Global Assessment of Disease Severity (PatGA) VAS* • *Change From Baseline in Physician's Global Assessment of Disease Activity VAS* • *Change From Baseline in C-Reactive Protein (CRP)* • *Change From Baseline in Leeds Enthesitis Index (LEI)* • *Percentage of Participants Achieving Psoriasis Area and Severity Index 75%, 90%, 100% (PASI 75, 90, 100)* • *Change From Baseline in Itching Severity Using the Itch NRS*
Method of analysis	*Efficacy analyses were conducted on the intent-to-treat population (all randomised patients). Primary analyses of categorical variables were based on a logistic regression analysis with treatment, geographical region and baseline cDMARD experience in the model. Missing data were imputed using a non-responder imputation method, in which patients who were Inadequate Responders, or who discontinued treatment before week 24, were defined as non-responders.*
Subgroup analyses	*N/A*
Other relevant information	

Appendix table 11: SPIRIT P2 characteristics

Trial name: SPIRIT-P2	NCT number: NCT02349295
Objective	*To compare the proportion of patients treated with ixekizumab who attained an at least 20% improvement in the American College of Rheumatology response criteria (ACR-20) response at week 24 versus placebo.*
Publications – title, author, journal, year	*Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial, P. Nash et al.,* The Lancet*, 2017*
Study type and design	*Double-blind, multicentre, randomised, placebo-controlled, phase 3 study. Patients were randomly assigned (1:1:1) by a computer-generated random sequence to receive a subcutaneous injection of 80 mg ixekizumab every 4 weeks or every 2 weeks after a 160 mg starting dose or placebo.*
Sample size (n)	*417*

Trial name: SPIRIT-P2	NCT number: NCT02349295
Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Presents with established diagnosis of active psoriatic arthritis (PsA) for at least 6 months, and currently meets Classification for Psoriatic Arthritis (CASPAR) criteria* • *Active PsA defined as the presence of at least 3 tender and at least 3 swollen joints* • *Presence of active psoriatic skin lesion or a history of plaque psoriasis (Ps)* • *Men must agree to use a reliable method of birth control or remain abstinent during the study* • *Women must agree to use reliable birth control or remain abstinent during the study and for at least 12 weeks after stopping treatment* • *Have been treated with 1 or more conventional disease-modifying antirheumatic drugs (cDMARDs)* • *Have had prior treatment with at least 1 and not more than 2 tumor necrosis factor (TNF) inhibitors. The participant must have discontinued at least 1 TNF inhibitor due to either an inadequate response (based on a minimum of 12 weeks on therapy) or documented intolerance.* *Exclusion Criteria:* • *Current use of biologic agents for treatment of Ps or PsA* • *Inadequate response to greater than 2 biologic DMARDs* • *Current use of more than one cDMARDs* • *Diagnosis of active inflammatory arthritic syndromes or spondyloarthropathies other than PsA* • *Have received treatment with interleukin (IL) -17 or IL12/23 targeted monoclonal antibody (MAb) therapy* • *Serious disorder or illness other than psoriatic arthritis* • *Serious infection within the last 3 months* • *Breastfeeding or nursing (lactating) women*
Intervention	*Ixekizumab 80 mg s.c. every 4 weeks (IXE Q4W) following a 160 mg starting dose* *OR* *Ixekizumab 80 mg s.c. every 2 weeks (IXE Q2W) following a 160 mg starting dose*
Comparator(s)	*Placebo s.c.*
Follow-up time	*24-weeks, with a 3 year extended follow-up period*
Is the study used in the health economic model?	*N/A*

Trial name: SPIRIT-P2	NCT number: NCT02349295

Primary, secondary and exploratory endpoints

Primary endpoint:

- *Percentage of Participants Achieving American College of Rheumatology 20 Index (ACR20)*

Secondary endpoint:

- *Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score*
- *Percentage of Participants Achieving ACR20 (at 12 weeks)*
- *Percentage of Participants Achieving American College of Rheumatology 50 Index (ACR50)*
- *Percentage of Participants Achieving American College of Rheumatology 70 Index (ACR70)*
- *Percentage of Participants With Psoriasis Area and Severity Index (PASI) 75*
- *Percentage of Patients Achieving Minimal Disease Activity (MDA)*
- *Percentage of Patients Achieving Complete Resolution in Enthesitis as Assessed by the Leeds Enthesitis Index (LEI)*
- *Change From Baseline in Itch Numeric Rating Scale (NRS)*
- *Change From Baseline in Tender Joint Count (TJC)*
- *Change From Baseline in Swollen Joint Count (SJC)*
- *Change From Baseline in Participants Assessment of Pain Visual Analog Scale (VAS)*
- *Change From Baseline in Patients Global Assessment of Disease Activity VAS*
- *Change From Baseline in Physicians Global Assessment of Disease Activity VAS*
- *Change From Baseline in C-Reactive Protein (CRP)*
- *Change From Baseline in Disease Activity Score-CRP (DAS28-CRP)*
- *Change From Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) Score*
- *Change From Baseline in Fatigue Severity Numeric Rating Scale (NRS) Score*
- *Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Scores: Physical Component Summary (PCS)*
- *Change From Baseline in 36-Item Short-Form Health Survey (SF-36) Scores: Mental Component Summary (MCS)*
- *Number of Participants With Treatment Emergent Anti-Drug Antibodies (TE-ADA)*
- *Pharmacokinetics (PK):Minimum Observed Serum Concentration at Steady State (Ctrough,ss) of Ixekizumab*
- *Pharmacokinetics: Area Under the Concentration-Time Curve for Dosing Interval (Tau) at Steady State of Ixekizumab*

Trial name: SPIRIT-P2	NCT number: NCT02349295
Method of analysis	*Efficacy and health outcomes were analysed with the intention-to-treat population defined as all patients who were randomly assigned. For categorical data, a logistic* *regression model was used for comparisons unless otherwise noted. Patients who had missing data, who were deemed inadequate responders at week 16, or who discontinued treatment early were imputed as non-responders. For continuous data, a mixed-effect model repeated measurement was used for comparisons. This model used treatment, visit, geographical region, previous TNF inhibitor use, treatment-by-visit interaction, geographical region-by-visit interaction, and TNF inhibitor use by visit as factors and with baseline and baseline value by visit interactions as continuous, fixed covariates. For patients classified as inadequate responders at week 16, data after week 16 are not included. Additional statistical analyses were done per the study protocol.*
Subgroup analyses	*N/A*
Other relevant information	

Appendix table 12: KEEPsAKE 1 characteristics

Trial name: KEEPsAKE 1	NCT number: NCT03675308
Objective	*To compare the efficacy and safety of RZB vs placebo (PBO) for the treatment of active PsA in patients who have had inadequate response or intolerance to ≥ 1 conventional synthetic disease modifying antirheumatic drug (csDMARD-IR).*
Publications – title, author, journal, year	*EFFICACY AND SAFETY OF RISANKIZUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AFTER INADEQUATE RESPONSE OR INTOLERANCE TO DMARDs: 24-WEEK RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND KEEPsAKE 1 TRIAL, L. E. Kristensen et al, 2022*
Study type and design	*KEEPsAKE 1 is a randomized, double-blind fase 3 study. Eligible adults* *were randomized (1:1) to receive blinded subcutaneous RZB 150 mg or PBO at weeks 0, 4, and 16. Results reported here are from the 24-week double-blind period; the open-label period with all patients receiving RZB is ongoing.*
Sample size (n)	*964*

Trial name: KEEPsAKE 1	NCT number: NCT03675308

Main inclusion and exclusion criteria	*Inclusion Criteria:*
	• *Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) at the Screening Visit.*
	• *Participant has active disease at Baseline*
	• *Diagnosis of active plaque psoriasis.*
	• *Participant has demonstrated an inadequate response or intolerance to or contraindication for conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) therapy(ies).*
	• *Presence of either at Screening:*
	  ○ *≥ 1 erosion on radiograph as determined by central imaging review or;*
	  ○ *High sensitivity C-Reactive Protein (hsCRP) ≥ 3.0 mg/L.*
	Exclusion Criteria:
	• *Participant is considered by investigator, for any reason, to be an unsuitable candidate for the study.*
	• *Participant has a known hypersensitivity to risankizumab.*
	• *Participant has previous treatment with biologic agent.*

Intervention	*Risankizumab s.c. 150 mg at week 0, 4 and 16*
Comparator(s)	*Placebo s.c. at week 0, 4 and 16*
Follow-up time	*24 weeks, with a 4 year extended follow-up period*
Is the study used in the health economic model?	*N/A*

Trial name: KEEPsAKE 1	NCT number: NCT03675308
Primary, secondary and exploratory endpoints	*Primary endpoint:* • *Percentage of Participants Achieving at least 20% Improvement in American College of Rheumatology (ACR20* *Secondary endpoint:* • *Change In Health Assessment Questionnaire-Disability Index (HAQ-DI)* • *Percentage Of Participants Achieving Psoriasis Area Severity Index (PASI) 90 Response* • *Percentage of Participants Achieving ACR20* • *Percentage of Participants Achieving Minimal Disease Activity (MDA)* • *Change in Modified Nail Psoriasis Severity Index (mNAPSI) in the Subset of Participants with Nail Psoriasis at Baseline* • *Change in Fingernail-Physician Global Assessment (PGA-F) in the Subset of Participants with Nail Psoriasis at Baseline* • *Percentage Of Participants With Resolution Of Enthesitis (Leeds Enthesitis Index [LEI] = 0) In Participants with Enthesitis at Baseline* • *Percentage Of Participants With Resolution Of Dactylitis (Leeds Dactylitis Index [LDI] = 0) In Participants With Dactylitis at Baseline* • *Change in modified Total Sharp Score (PsA-mTSS)* • *Change In 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS)* • *Change In Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Questionnaire* • *Percentage Of Participants Achieving at least 50% Improvement in American College of Rheumatology (ACR50) Response* • *Percentage Of Participants Achieving at least 70% Improvement in American College of Rheumatology (ACR70) Response*
Method of analysis	*All efficacy analyses were analyzed as defined in study protocol. Primary endpoint and other categorical variables were analyzed using Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factors. Continuous variables were analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method.* *The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).*
Subgroup analyses	*N/A*
Other relevant information	

Appendix table 13: KEEPsAKE 2 characteristics

Trial name: KEEPsAKE 2	**NCT number: NCT03671148**
Objective	*To compare the efficacy and safety of RZB vs placebo (PBO) for the treatment of active PsA in patients who have had inadequate response or intolerance to 1 or 2 biologic therapies (Bio-IR) or to ≥ 1 conventional synthetic disease modifying antirheumatic drug (csDMARD-IR).*
Publications – title, author, journal, year	*EFFICACY AND SAFETY OF RISANKIZUMAB FOR ACTIVE PSORIATIC ARTHRITIS, INCLUDING PATIENTS WITH INADEQUATE RESPONSE OR INTOLERANCE TO BIOLOGIC THERAPIES: 24-WEEK RESULTS FROM THE PHASE 3, RANDOMIZED, DOUBLE-BLIND, KEEPSAKE 2 TRIAL, A. Ostor et al, 2022*
Study type and design	*KEEPsAKE 2 is a randomized, double-blinded, phase 3 study. Patients were randomized to receive blinded subcutaneous RZB 150 mg or PBO at weeks 0, 4, and 16. Results reported here are from the 24-week double-blind period; the open-label period with all patients receiving RZB is ongoing.*
Sample size (n)	*443*
Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) at Screening Visit.* • *Participant has active disease at both Screening Visit and Baseline.* • *Diagnosis of active plaque psoriasis.* • *Participant has demonstrated an inadequate response or intolerance to biologic therapy(ies) or conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) therapy(ies).* *Exclusion Criteria:* • *Participant is considered by investigator, for any reason, to be an unsuitable candidate for the study.* • *Participant has a known hypersensitivity to risankizumab.*
Intervention	*Risankizumab s.c. 150 mg at week 0, 4 and 16*
Comparator(s)	*Placebo s.c. at week 0, 4 and 16*
Follow-up time	*24 weeks, with a 4 year follow-up extension*
Is the study used in the health economic model?	*N/A*

Trial name: KEEPsAKE 2	NCT number: NCT03671148
Primary, secondary and exploratory endpoints	*Primary endpoint:* • *Percentage of Participants Achieving at least 20% Improvement in American College of Rheumatology (ACR20)* *Secondary endpoint:* • *Change In Health Assessment Questionnaire-Disability Index (HAQ-DI)* • *Percentage Of Participants Achieving Psoriasis Area Severity Index (PASI) 90 Response* • *Percentage of Participants Achieving ACR20* • *Percentage of Participants Achieving Minimal Disease Activity (MDA)* • *Change In 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS)* • *Change In Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Questionnaire* • *Percentage Of Participants Achieving at least 50% Improvement in American College of Rheumatology (ACR50) Response* • *Percentage Of Participants Achieving at least 70% Improvement in American College of Rheumatology (ACR70) Response* • *Percentage Of Participants With Resolution Of Enthesitis (Leeds Enthesitis Index [LEI] = 0) In Participants With Enthesitis At Baseline* • *Percentage Of Participants With Resolution Of Dactylitis (Leeds Dactylitis Index [LDI] = 0) In Participants With Dactylitis At Baseline*
Method of analysis	*All efficacy analyses were analyzed as defined in study protocol. Primary endpoint and other categorical variables were analyzed using Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factors. Continuous variables were analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method.* *The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).*
Subgroup analyses	*KEEpSAKE 2 included both patients who were bio-naïve and bio-experienced, but primary results was reported for the whole population.* *A post-hoc analysis was performed to include the relevant data for the relevant populations in the indirect comparison. See appendix F for information regarding data used in the indirect comparison.*
Other relevant information	

European public assessment reports (EPAR)

Risankizumab: https://www.ema.europa.eu/en/documents/assessment-report/skyrizi-epar-public-assessment-report_en.pdf

Ixekizumab: https://www.ema.europa.eu/en/documents/variation-report/taltz-h-c-3943-ii-0009-epar-assessment-report-variation_en.pdf

Adalimumab: https://www.ema.europa.eu/en/documents/scientific-discussion-variation/humira-h-c-481-ii-22-epar-scientific-discussion-variation_en.pdf

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

Baseline characteristics per intervention group in included studies

Appendix table 14: Baseline characteristics for PBO and Skyrizi, KEEPsAKE-1, study population

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	PLACEBO (N=481)	RZB 150 MG (N=483)
Female, n (%)	247 (51.4%)	231 (47.8%)
Age (years) (median range)	52 (22-79)	52 (22-85)
Duration of PsA diagnosis, years, mean (SD)	7.1 (7.7)	7.1 (7.0)
TJC68, mean (SD)	20.5 (12.8)	20.8 (14.1)
SJC66, mean (SD)	12.2 (8.0)	12.1 (7.8)
HAQ-DI, mean (SD)	1.17 (0.65)	1.15 (0.66)
≥3% BSA-Ps, n (%)	272 (56.5%)	273 (56.5%)
LEI > 0, n (%)	290 (60.3%)	297 (61.5%)
LEI[a], mean (SD)	2.6 (1.5)	2.7 (1.5)
LDI>0 , n (%)	147 (30.6%)	148 (30.6%)
LDI[b], mean (SD)	92.5 (125.5)	98.6 (120.4)
Number of prior DMARDs used, n (%)		
0	2 (0.4)	2 (0.4)
1	311 (64.7%)	338 (70.0%)
2	136 (28.3%)	105 (21.7%)
≥3	32 (6.7%)	38 (7.9%)

Appendix table 15: Baseline characteristics for PBO and adalimumab SELECT-PSA 1, study population

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	PLACEBO (N=423)	ADALIMUMAB 40 MG EOW (N=429)
Female, n (%)	211 (49.9%)	222 (51.7%)
Age (years), , mean (SD)	50.4 (12.2)	51.4 (12.0)
Duration of PsA diagnosis, years, mean (SD)	6.2 (7.0)	5.9 (7.1)
TJC68, mean (SD)	20.0 (14.3)	20.1 (13.8)
SJC66, mean (SD)	11.0 (8.6)	11.6 (8.8)
HAQ-DI, mean (SD)	1.12 (0.6)	1.12 (0.6)
≥3% BSA-Ps, n (%)	211 (49.9%)	211 (49.2%)
LEI > 0, n (%)	241 (57.0%)	265 (61.8%)
LEI[a], mean (SD)	2.7 (1.5)	2.5 (1.4)

LDI>0, n (%)	126 (29.8%)	127 (29.6%)
LDI[b], mean (SD)	87.7 (114.8)	99.0 (163.1)
Number of prior DMARDs used, n (%)		
0	0	2 (0.5)
1	274 (64.8%)	286 (66.7%)
2	105 (24.8%)	112 (26.1%)
≥3	44 (10.4%)	29 (6.8%)

Appendix table 16: Baseline characteristics for PBO and adalimumab SPIRIT-P1, study population

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	**Placebo n=106**	**adalimumab n=101 (Q2W)**
Age (years), mean (SD)	50.6 (12.3)	48.6 (12.4)
Sex		
Male, n (%)	48 (45.3%)	51 (50.5%)
Female, n (%)	58 (54.7%)	50 (49.5%)
Weight (kg), mean (SD)	83.8 (19.6)	91.6 (21.9)
BMI (kg/m2), mean (SD)	29.2 (6.3)	32.1 (11.4)
Race, n (%)		
White, n (%)	99 (93.4%)	95 (94.1%)
Asian, n (%)	5 (4.7%)	3 (3%)
Other, n (%)	2 (1.9%)	3 (3%)
Time since psoriatic arthritis diagnosis (years), mean (SD)	6.3 (6.9)	6.9 (7.5)
Time since psoriasis diagnosis (years), mean (SD)	16.0 (13.8)	15.7 (12.7)
Background cDMARD therapy, n (%)		
Naive, n (%)	13 (12.3%)	14 (13.9%)
Past use, n (%)	24 (22.6%)	20 (19..8%)
Present use of cDMARD, n (%)	69 (65.1%)	67 (66.3%)
Present use of methotrexate, n (%)	59 (55.7%)	57 (56.4%)
Patients with specific disease characteristics, n (%)		
Present psoriasis†, n (%)	102 (96.2%)	97 (96%)
Psoriasis ≥3% of body surface area† , n (%)	67 (67.7%)	68 (72.3%)
Fingernail psoriasis†, n (%)	74 (69.8%)	71 (70.3%)
Dactylitis‡, n (%)	39 (36.8%)	23 (22.8%)
Enthesitis§, n (%)	57 (53.8%)	56 (55.4%)
Baseline disease and quality of life scores, mean (SD)		
Tender joint count (68 joints), mean (SD)	19.2 (13.0)	19.3 (13.0)
Swollen joint count (66 joints), mean (SD)	10.6 (7.3)	9.9 (6.5)
HAQ-DI, mean (SD)	1.2 (0.6)	1.1 (0.59)
Patient-reported pain¶, mean (SD)	58.5 (23.0)	58.7 (19.7)
Patient-assessed global disease¶, mean (SD)	61.1 (22.7)	59.1 (19.1)
Physician-assessed global disease¶, mean (SD)	55.9 (19.3)	55.4 (18.7)
C-reactive protein (mg/L), mean (SD)	15.1 (23.6)	13.2 (19.1)
mTSS, mean (SD)	17.6 (28.6)	15.9 (27.4)

28-joint Disease Activity Score with C-reactive protein, mean (SD)	4.9 (1.0)	4.9 (1.0)
LEI§, mean (SD)	2.9 (1.7)	3.0 (1.6)
LDI Basic‡, mean (SD)	46.2 (65.5)	93.9 (111.9)
Psoriasis body surface area involved (%)|,mean (SD)	14.4 (20.2)	14.8 (19.2)
PASI total score||, mean (SD)	6.2 (7.5)	5.5 (6.5)
NAPSI**, mean (SD)	19.8 (17.2)	20.9 (17.5)
SF-36 physical component summary score, mean (SD)	34.0 (8.3)	33.9 (8.8)

Data are mean (SD) or n (%). BMI=body-mass index. cDMARD=conventional disease-modifying antirheumatic drug. TNFi=tumour necrosis factor inhibitor. HAQ-DI=Health Assessment Questionnaire-Disability Index. LDI=Leeds Dactylitis Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index Improvement. NAPSI=Nail Psoriasis Severity Index. SF-36=Short Form (36 Items) Health Survey. *Patients had previously received a TNFi and had discontinued. †Qualitatively assessed by the investigator at baseline. ‡Defined as LDI>0. §Defined as LEI>0. ¶Visual analogue scale 0–100. ||Assessed only in patients with psoriasis. **Assessed only in patients with fingernail psoriasis.

Appendix table 17: Baseline characteristics PBO and Skyrizi, KEEPsAKE-2, bio-naïve and bio-experienced study population

	DMARD-IR		BIO-IR	
Key Demographic and Baseline Characteristics Mean (SD) or n (%)	**PLACEBO**	**RZB 150 MG**	**PLACEBO**	**RZB 150 MG**
Female, n (%)				
Age (years) (median range)				
Duration of PsA diagnosis, years, mean (SD)				
TJC68, mean (SD)				
SJC66, mean (SD)				
HAQ-DI, mean (SD)				
≥3% BSA-Ps, n (%)				
LEI > 0, n (%)				
LEI[a], mean (SD)				
LDI>0 , n (%)				
LDI[b], mean (SD)				
Number of prior DMARDs used, n (%)				
0				
1				
2				
≥3				

Appendix table 18: Baseline characteristics PBO and ixekizumab, SPIRIT-P2, study population

Key Demographic and Baseline Characteristics Mean (SD) or n (%)	**Placebo n=118**	**Ixekizumab n=122 (every 4 weeks)**	**Ixekizumab n=123 (every 2 weeks)**
Age, (SD)	51.5 (10.4)	52.6 (13.6)	51.7 (11.9)
Sex			
Male, n (%)	56 (47%)	63 (52%)	50 (41%)
Female, n (%)	62 (53%)	59 (48%)	73 (59%)

Weight (kg), mean (SD)	91.0 (22.1)	89.9 (22.0)	85.2 (20.7)
BMI (kg/m2), mean (SD)	31.6 (7.6)	30.9 (7.1)	30.1 (6.8)
Race			
White, n (%)	108 (92%)	111 (91%)	113 (93%)
Asian, n (%)	7 (6%)	7 (6%)	7 (6%)
Other, n (%)	3 (3%)	4 (3%)	2 (2%)
Time since psoriatic arthritis diagnosis (years) (SD)	9.2 (7.3)	11.0 (9.6)	9.9 (7.4)
Time since psoriasis diagnosis (years) (SD)	15.3 (12.6)	15.7 (12.3)	16.5 (13.0)
Present use of cDMARD, n (%)	52 (44%)	60 (49%)	73 (59%)
Present use of methotrexate, n (%)	40 (34%)	48 (39%)	61 (50%)
Previous TNFi treatment			
Inadequate response to one TNFi, n (%)	68 (58%)	71 (58%)	65 (53%)
Inadequate response to two TNFi, n (%)	41 (35%)	41 (34%)	46 (37%)
Intolerance to a TNFi*, n (%)	9 (8%)	10 (8%)	12 (10%)
Patients with specific disease characteristics			
Present psoriasis†, n (%)	108 (92%)	118 (97%)	113 (92%)
Psoriasis ≥3% of body surface area†, n (%)	67 (57%)	68 (56%)	68 (55%)
Fingernail psoriasis†, n (%)	73 (62%)	89 (73%)	74 (60%)
Dactylitis‡, n (%)	14 (12%)	28 (23%)	20 (16%)
Enthesitis§, n (%)	69 (58%)	68 (56%)	84 (68%)
Baseline disease and quality of life scores			
Tender joint count (68 joints), (SD)	23.0 (16.2)	22.0 (14.1)	25.0 (17.3)
Swollen joint count (66 joints), (SD)	10.3 (7.4)	13.1 (11.2)	13.5 (11.5)
HAQ-DI, (SD)	1.2 (0.7)	1.2 (0.6)	1.2 (0.6)
Patient-reported pain¶, (SD)	63.9 (20.1)	63.9 (21.4)	62.7 (20.9)
Patient-assessed global disease¶, (SD)	64.1 (21.5)	66.4 (20.5)	66.0 (20.5)
Physician-assessed global disease¶, (SD)	58.9 (20.7)	60.3 (20.9)	64.6 (16.8)
C-reactive protein (mg/L), (SD)	12.1 (19.6)	17.0 (27.5)	13.5 (26.1)
28-joint Disease Activity Score with C-reactive protein, (SD)	5.0 (1.1)	5.1 (1.1)	5.1 (1.1)
LEI§, (SD)	2.9 (1.7)	2.9 (1.4)	3.0 (1.7)
LDI Basic‡, (SD)	37.3 (25.2)	31.5 (33.8)	53.9 (37.6)
Psoriasis body surface area involved (%),n (%)	9.0 (13%)	12.5 (17%)	11.6 (19%)
PASI total score||, (SD)	5.2 (6.3)	6.4 (7.9)	6.2 (8.7)
NAPSI**, (SD)	18.7 (18.8)	20.5 (20.0)	21.0 (22.0)
SF-36 physical component summary score, (SD)	33.9 (9.0)	34.8 (8.8)	34.3 (9.1)
SF-36 mental component summary score, (SD)	48.0 (13.1)	49.6 (11.3)	49.1 (11.5)

Data are mean (SD) or n (%). BMI=body-mass index. cDMARD=conventional disease-modifying antirheumatic drug. TNFi=tumour necrosis factor inhibitor. HAQ-DI=Health Assessment Questionnaire-Disability Index. LDI=Leeds Dactylitis Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index Improvement. NAPSI=Nail Psoriasis Severity Index. SF-36=Short Form (36 Items) Health Survey. *Patients had previously received a TNFi and had discontinued. †Qualitatively assessed by the investigator at baseline. ‡Defined as LDI>0. §Defined as LEI>0. ¶Visual analogue scale 0–100. ||Assessed only in patients with psoriasis. **Assessed only in patients with fingernail psoriasis.

Baseline characteristics per patient population (bio-naïve and bio-experienced) included in the comparative analysis

Appendix table 19: Baseline characteristics for biologic-naive network in comparative analysis

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety contributing to the biologic-naive network of evidence			
Mean (SD) or n (%)	**KEEPsAKE 1 and KEEPsAKE 2 bio-naïve subgroup**	**SPIRIT P1**	**SELECT PsA 1**
	[redacted]	**N=207**	**N=852**
Age (years) (SD)	[redacted]	49.6 (12.4)	50.9 (12.1)
Sex			
Male, n (%)	[redacted]	99 (47.8%)	419 (49.2%)
Female, n (%)	[redacted]	108 (52.2%)	433 (50.8%)
BMI (kg/m^2) (SD)	[redacted]	30.6 (9.2)	NA
PsA disease duration (years) (SD)	[redacted]	6.6 (7.2)	6.0 (7.0)
Tender joint count (68 joints) (SD)	[redacted]	19.2 (13.0)	20.1 (14.0)
Swollen joint count (66 joints) (SD)	[redacted]	10.3 (6.9)	11.3 (8.5)
BSA ≥3%, n (%)	[redacted]	135 (65.2%)	422 (49.5%)
HAQ-DI score (SD)	[redacted]	1.15 (0.60)	1.10 (0.60)
C-reactive protein (mg/L) (SD)	[redacted]	14.2 (21.5)	NA
PASI (#) (SD)	[redacted]	5.9 (7.0)	10.3 (10.1)
SF-36 physical component summary score (~),(SD)	[redacted]	NA	35.7 (NA)
SF-36 mental component summary score (~),(SD)	[redacted]	NA	45.4 (NA)
DMARD use at baseline, n (%)	[redacted]	136 (65.7%)	694 (81.5%)
Methotrexate, n (%)	[redacted]	116 (56.0%)	537 (63.0%)
Other, n (%)	[redacted]	20 (9.7%)	157 (18.4%)
mTSS (*) (SD)	[redacted]	16.8 (28.0)	14.2 (NA)

Appendix table 20: Baseline characteristics for biologic-experienced network in comparative analysis

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety contributing to the biologic-experienced network of evidence		
Mean (SD) or n (%)	KEEPsAKE 2 bio-experienced subgroup	SPIRIT P2
	[redacted]	N=240
Age (years) (SD)	[redacted]	52.1 (12.1)
Sex		
Male, n (%)	[redacted]	119 (49.6%)
Female, n (%)	[redacted]	121 (50.4%)
BMI (kg/m²) (SD)	[redacted]	31.2 (7.3)
Time since psoriatic arthritis diagnosis (years) (SD)	[redacted]	10.1 (8.6)
Tender joint count (68 joints) (SD)	[redacted]	22.5 (15.1)
Swollen joint count (66 joints) (SD)	[redacted]	11.7 (9.6)
BSA ≥3%, n (%) (SD)	[redacted]	135 (56.3%)
HAQ-DI (SD)	[redacted]	1.2 (0.6)
C-reactive protein (mg/L) (SD)	[redacted]	14.6 (24.0)
PASI total score ||(SD)	[redacted]	5.8 (7.2)
SF-36 physical component summary score (~) (SD)	[redacted]	34.4 (8.9)
SF-36 mental component summary score (~), (SD)	[redacted]	48.8 (12.2)
Present use of cDMARD, n (%)	[redacted]	112 (46.7%)
Present use of methotrexate, n (%)	[redacted]	88 (36.7%)
Previous TNFi treatment		
Inadequate response to 1 TNFi, n (%)	[redacted]	139 (57.9%)
Inadequate response to 2 TNFi, n (%)	[redacted]	82 (34.2%)
Inadequate response to 3 or more TNFi, n (%)	[redacted]	0 (0.0%)
Intolerance to a TNFi, n (%)	[redacted]	19 (7.9%)

Comparability of patients across studies

Baseline characteristics were generally similar across KEEPsAKE and SPIRIT trials [redacted]. KEEPsAKE 1, KEEPsAKE 2 (subgroup) and SELECT PsA 1 trials were similar with respect to all baseline characteristics [redacted].

Overall, there appeared to be minimal cross-study heterogeneity with respect to baseline patient characteristics in the studies included and it was not considered necessary to adjust for these characteristics in the analysis.

Comparability of the study populations with Danish patients eligible for treatment

The study population in the study is relevant for the Danish population in clinical practice.

Appendix D - Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Appendix table 21: Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
ACR20	ACR20 is defined as at least 20% improvement in swollen joint count, tender joint count, and at least 3 out of the following 5 variables: 1) Patient's Assessment of psoriatic arthritis (PsA) Pain Intensity visual analog scale (VAS), 2) Patient's Global Assessment of Disease VAS, 3) Physician's Global Assessment of Disease Activity VAS, 4) Patient's Assessment of Disability on Health Assessment Questionnaire Disability Index (HAQ-DI), and 5) Serum high-sensitivity C-reactive protein (serum hs-CRP).	ACR20 is the primary endpoint used in all clinical trials in this analysis. Widely known and used endpoint in PsA.	ACR is a key component in assessing swollen and tender joints, which is one of the key symptoms related to PsA that affects the severity of the disease.
ACR50	ACR50 response is defined as at least 50% reduction (improvement) compared with baseline in tender joint count (TJC), swollen joint count (SJC), and at least 3 of the 5 remaining ACR core set measures: patient's assessment of pain, patient's global assessment of disease activity (PtGA); physician's global assessment of disease activity (PhGA), Health Assessment Questionnaire - Disability Index (HAQ-DI), and high-sensitivity C-reactive protein (hsCRP).	A more stringent version of ACR20. Widely known and used endpoint in PsA trial.	ACR is a key component in assessing swollen and tender joints, which is one of the key symptoms related to PsA that affects the severity of the disease.
PASI75	PASI 75 denotes greater than or equal to 75% improvement in PASI score.	PASI provides a quantitative assessment of psoriasis disease state based on the amount of body surface area that is affected and the	The presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA. (9),(10), and is also one of the key symptoms

Outcome measure	Definition	Validity	Clinical relevance
		degree of severity. Most widely known and used endpoint for skin in psoriasis and PsA trials.	related to PsA that impacts the severity of the disease. PASI is a key tool to assess the severity and extent of the skin involvement.
PASI90	PASI 90 denotes greater than or equal to 90% improvement in PASI score.	PASI provides a quantitative assessment of psoriasis disease state based on the amount of body surface area that is affected and the degree of severity. Most widely known and used endpoint for skin in psoriasis and PsA trials.	The presentation of skin symptoms generally precedes joint manifestations (~75%-80%) in patients with PsA. (9),(10), and is also one of the key symptoms related to PsA. PASI is a key tool to assess the severity and extent of the skin involvement.
SF-36 PCS	Change from Baseline to Week 24 in the 36-Item Short Form Health Questionnaire (SF-36) Physical Component Summary (PCS) Score	The SF-36 is a 36-item, general health, self-administered questionnaire, widely used to assess Quality of Life in clinical trials.	Quality of Life measurements is a key outcome which indicate how well patients fare with the treatment, both physically and mentally. Therefore it is highly relevant to assess the impact of new treatments on patients physical and mental health.
SF-36 MCS	Change from Baseline to Week 24 in the 36-Item Short Form Health Questionnaire (SF-36) Mental Component Summary (MCS) Score	The SF-36 is a 36-item, general health, self-administered questionnaire, widely used to assess Quality of Life in clinical trials.	Quality of Life measurements is a key outcome which indicate how well patients fare with the treatment, both physically and mentally. Therefore it is highly relevant to assess the impact of new treatments on patients physical and mental health.
SAE	Serious Adverse Events		Serious adverse event (SAE) is a relevant outcome since these effects can be particularly bothersome for patients and can cause treatment discontinuation, worse outcomes and increased resource use.

Results per study

Appendix table 22: Results SELECT PsA-1, week 24

SELECT-PsA1 (NCT03104400)											
				Estimated Odds ratio			Estimated relative risk difference			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**OR, ADA vs. PBO**	**95% CI**	***P* value**	**RR, ADA vs. PBO**	**95% CI**	***P* value**		
ACR20 wk. 24	ADA	429	67.1%	2.48	1.88-3.28	<0.0001	1.49	1.31-1.68	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	Mcinnes et al 2021 (100), AbbVie data-on-file 2020 (118)
	PBO	423	45.2%								
ACR50 wk. 24	ADA	429	44.3%	3.41	2.50-4.64	<0.0001	2.34	1.87-2.93	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	423	18.9%								
PASI75 wk. 24	ADA	211	58.8%	3.94	2.62-5.95	<0.0001	2.21	1.72-2.85	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	211	26.5%								
SAE wk. 24	ADA	429	3.7%	1.22	0.58-2.57	0.5979	1.21	0.59-2.49	0.5980	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	423	3.1%								
PASI90 wk. 24	ADA	211	45.0%	4.12	2.62-6.48	<0.0001	2.71	1.94-3.80	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	211	16.6%								
SF-36 PCS wk. 24	ADA	429	7.80 (8.17)	NA	NA	NA	3.54	2.44-4.64	<0.0001	Mean difference was estimated using a mixed-effect model repeat-measurement method	
	PBO	423	4.26 (8.19)								
SF-36 MCS wk. 24	ADA	429	4.06 (8.88)	NA	NA	NA	1.62	0.42-2.82	0.0081	Mean difference was estimated using a mixed-	

SELECT-PsA1 (NCT03104400)											
	PBO	423	2.44 (8.93)							effect model repeat-measurement method	

Appendix table 23: Results SPIRIT P1, week 24

SPIRIT-P1 (NCT01695239)											
				Estimated Odds ratio			Estimated relative risk difference			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**OR, ADA vs. PBO**	**95% CI**	***P* value**	**RR, ADA vs. PBO**	**95% CI**	***P* value**		
ACR20 wk. 24	ADA	101	57.4%	3.12	1.76-5.53	0.0001	1.90	1.36-2.66	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	106	30.2%								
ACR50 wk 24	ADA	101	38.6%	3.54	1.82-6.89	0.0002	2.56	1.53-4.28	0.0003	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	106	15.1%								
PASI75 wk. 24	ADA	68	54.4%	10.23	4.09-25.59	<0.0001	5.21	2.50-10.85	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	Mease et al 2017 (101)
	PBO	67	10.4%								
SAE wk. 24	ADA	101	5.0%	2.71	0.51-14.29	0.2403	2.62	0.52-13.22	0.2423	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	106	1.9%								
PASI90 wk. 24	ADA	68	36.8%	9.16	2.97-28.19	0.0001	6.16	2.27-16.74	0.0004	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	67	6.0%								
SF-36 PCS wk. 24	ADA	101	6.80 (0.9)	NA	NA	NA	3.90	1.26-6.54	0.0043	Mean difference was estimated using a mixed-	

SPIRIT-P1 (NCT01695239)										
	PBO	106	2.90 (1.0)							effect model repeat-measurement method
SF-36 MCS wk. 24	ADA	101	NR	NA	NA	NA	NA	NA	NA	Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO	106	NR							

Appendix table 24: Results SPIRIT P2, week 24

SPIRIT-P2 (NCT02349295)											
				Estimated Odds ratio			Estimated relative risk difference			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**OR, IXE vs. PBO**	**95% CI**	***P* value**	**RR, IXE vs. PBO**	**95% CI**	***P* value**		
ACR20 wk. 24	IXE	122	53%	4.71	2.64-8.39	<0.0001	2.73	1.83-4.09	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	Nash et al, 2017 (102)
	PBO	118	19%								
ACR50 wk. 24	IXE	122	35%	10.16	4.13-25.03	<0.0001	6.93	3.07-15.67	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	118	5%								
PASI75 wk. 24	IXE	68	56%	7.22	3.16-16.48	<0.0001	3.74	2.04-6.89	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	67	15%								
SAE wk. 24	IXE	122	2%	0.72	0.16-3.28	0.6696	0.73	0.17-3.17	0.6698	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	118	3%								
PASI90 wk. 24	IXE	68	44%	5.82	2.42-14-04	0.0001	3.69	1.83-7.46	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel	
	PBO	67	12%								

SPIRIT-P2 (NCT02349295)										
										analysis with a 95% confidence interval
SF-36 PCS wk. 24	IXE	122	8.9 (1:3)	NA	NA	NA	5.6	3.2-8.0	<0.0001	Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO	118	3.3 (1.4)							
SF-36 MCS wk. 24	IXE	122	3.6 (1.2)	NA	NA	NA	2.7	0.4-5.0	0.02	Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO	118	0.9 (1.3)							

Appendix table 25: Results KEEPsAKE 1, week 24

KEEPsAKE 1 (NCT03675308)											
				Estimated Odds ratio			Estimated relative risk difference			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**OR, RISA vs. PBO**	**95% CI**	***P* value**	**RR, RISA vs. PBO**	**95% CI**	***P* value**		
ACR20 wk. 24	RISA	483	57.3%	2.67	2.06-3.47	<0.0001	1.71	1.48-1.99	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	Kristensen et al, 2022 (92)
	PBO	481	33.5%								
ACR50 wk. 24	RISA	483	33.4%	3.99	2.84-5.61	<0.0001	2.99	2.26-3.96	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	481	11.3%								
PASI75 wk. 24	RISA	273	67.8%	10.60	7.05-15.95	<0.0001	4.10	3.10-5.42	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	272	16.6%								
SAE wk. 24	RISA	483	2.5%	0.66	0.31-1.38	0.2641	0.66	0.32-1.36	0.2645	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel	
	PBO	481	3.7%								

KEEPsAKE 1 (NCT03675308)										
										analysis with a 95% confidence interval
PASI90 wk. 24	RISA	273	52.3%	9.98	6.28-15.86	<0.0001	5.28	3.63-7.68	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval
	PBO	272	9.9%							
SF-36 PCS wk. 24	RISA	483	6.5 (5.8, 7.2)	NA	NA	NA	3.3	2.4-4.2	<0.0001	Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO	481	3.2 (2.5, 3.9)							
SF-36 MCS wk. 24	RISA	[redacted]		[redacted]						Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO									

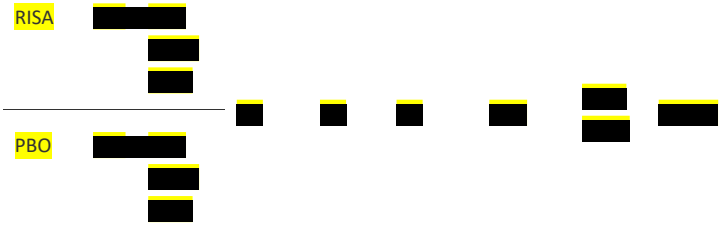
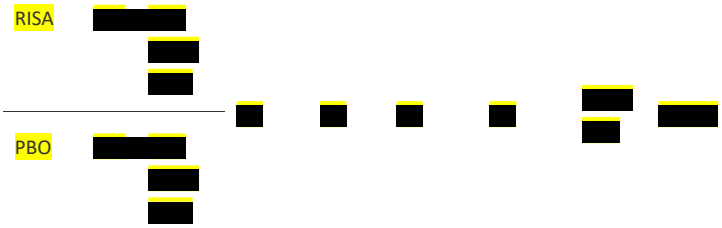
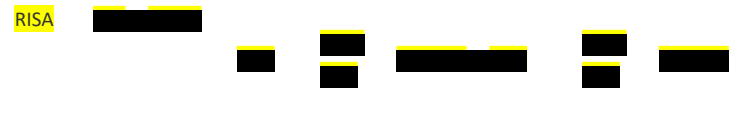
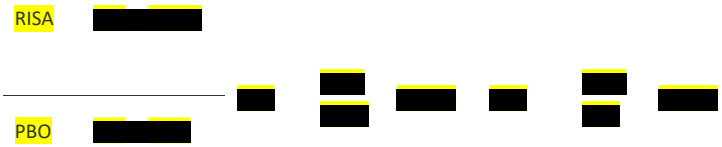
Appendix table 26: Results KEEPsAKE 2, whole study population, week 24

KEEPsAKE 2 (NCT03675308), whole study population											
				Estimated Odds ratio			Estimated relative risk difference			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**OR, RISA vs. PBO**	**95% CI**	***P* value**	**RR, RISA vs. PBO**	**95% CI**	***P* value**		
ACR20 wk. 24	RISA	224	51.3%	2.93	1.97-4.36	<0.0001	1.95	1.51-2.50	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	Östör et al, 2022 (93)
	PBO	219	26.5%								
ACR50 wk. 24	RISA	224	26.3%	3.56	2.06-6.15	<0.0001	2.88	1.80-4.62	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
	PBO	219	9.3%								
PASI75 wk. 24	RISA	123	70.7%	12.72	6.80-23.78	<0.0001	4.43	2.89-6.79	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel	
	PBO	119	16.2%								

										analysis with a 95% confidence interval
SAE wk. 24	RISA PBO	224 219	4.0% 5.5%	0.72	0.30-1.75	0.4709	0.73	0.32-1.71	0.4712	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval
PASI90 wk. 24	RISA PBO	123 119	55.0% 10.2%	11.02	5.50-22.08	<0.0001	5.48	3.13-9.58	<0.0001	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval
SF-36 PCS wk. 24	RISA PBO	224 219	5.9 (4.9-6.9) 2.0 (0.9-3.1)	NA	NA	NA	3.9	2.4-5.3	<0.0001	Mean difference was estimated using a mixed-effect model repeat-measurement method
SF-36 MCS wk. 24	RISA PBO	[redacted]								Mean difference was estimated using a mixed-effect model repeat-measurement method

Appendix table 27: Results KEEPsAKE 2, split by bio-naive and bio-experienced subgroup, week 24

KEEPsAKE 2 (NCT03671148) by bio-naïve and bio-experienced subgroup											
				Estimated Odds ratio			Estimated relative risk difference			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**OR, RISA vs. PBO**	**95% CI**	***P* value**	**RR, RISA vs. PBO**	**95% CI**	***P* value**		
Biologic-naïve subgroup, week 24											
ACR20 wk. 24	RISA PBO	[redacted]								Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
ACR50 wk. 24	RISA PBO	[redacted]								Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	AbbVie data on file (88) (119)
PASI75 wk. 24	RISA PBO	[redacted]								Relative Risk difference and Odds Ratio was estimated using Mantel-	

KEEPsAKE 2 (NCT03671148) by bio-naïve and bio-experienced subgroup				
			Haenszel analysis with a 95% confidence interval	
SAE wk. 24	RISA PBO		Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
PASI90 wk. 24	RISA PBO		Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
SF-36 PCS wk. 24	RISA PBO		Mean difference was estimated using a mixed-effect model repeat-measurement method	
SF-36 MCS wk. 24	RISA PBO		Mean difference was estimated using a mixed-effect model repeat-measurement method	
Biologic-experienced subgroup, week 24				
ACR20 wk. 24	RISA PBO		Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	
ACR50 wk. 24	RISA PBO		Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	AbbVie data on file (119)
PASI75 wk. 24	RISA PBO		Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval	

KEEPsAKE 2 (NCT03671148) by bio-naïve and bio-experienced subgroup

SAE wk. 24	RISA	[redacted]	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval
	PBO	[redacted]	
PASI90 wk. 24	RISA	[redacted]	Relative Risk difference and Odds Ratio was estimated using Mantel-Haenszel analysis with a 95% confidence interval
	PBO	[redacted]	
SF-36 PCS wk. 24	RISA	[redacted]	Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO	[redacted]	
SF-36 MCS wk. 24	RISA	[redacted]	Mean difference was estimated using a mixed-effect model repeat-measurement method
	PBO	[redacted]	

Appendix E - Safety data for intervention and comparator(s)

Appendix table 28: Overview of safety in SELECT PsA-1 through week 24 (placebo vs. adalimumab)

	Placebo (N=423)		Adalimumab 40mg EOW (N=429)	
Subjects with:	**n**	**(%)**	**n**	**(%)**
Any Adverse Event (AE)	252	(59.6)	278	(64.8)
Any Serious AE	13	(3.1)	16	(3.7)
Any AE Leading to Discontinuation of Study Drug	13	(3.1)	22	(5.1)
Any Severe AE	16	(3.8)	27	(6.3)
Any AE With Reasonable Possibility of Being Related to Study Drug	120	(28.4)	167	(38.9)
Deaths	1	(0.2)	0	
Occurring ≤30 days (for ADA 70 days) after last dose)	1	(0.2)	0	
Occurring >30 days (for ADA 70 days) after last dose)	0		0	
Any Infection	140	(31.1)	146	(34.0)
Any Serious Infection	4	(0.9)	3	(0.7)
Any Opportunistic Infection excluding TB and herpes zoster	0		0	

Subjects with:	Placebo (N=423)		Adalimumab 40mg EOW (N=429)	
	n	(%)	n	(%)
Any possible malignancy	1	(0.2)	4	(0.9)
Any Malignancy	1	(0.2)	3	(0.7)
Any Non-Melanoma Skin Cancer (NMSC)	1	(0.2)	0	
Any malignancy other than NMSC	0		3	(0.7)
Any Lymphoma	0		0	
Any Hepatic Disorder	16	(3.8)	67	(15.6)
Any Gastrointestinal Perforation	0		0	
Any Anemia	4	(0.9)	1	(0.2)
Any Neutropenia	1	(0.2)	10	(2.3)
Any Lymphopenia	5	(1.2)	1	(0.2)
Any herpes zoster	3	(0.7)	0	
Any Creatine Phosphokinase (CPK) Elevation	6	(1.4)	24	(5.6)
Any Renal Dysfunction	1	(0.2)	0	
Any active tuberculosis	0		0	
Any Adjudicated MACE*	1	(0.2)	2	(0.5)
Any Adjudicated VTE **	1	(0.2)	2	(0.5)

Source: McInnes et al 2021

*MACE, Major adverse cardiovascular events, defined as cardiovascular death (includes fatal acute myocardial infarction, sudden cardiac death, heart failure, cardiovascular procedure-related death, death due to cardiovascular hemorrhage, fatal stroke, pulmonary embolism and other cardiovascular causes), non-fatal mdyocardial infarction and non-fatal stroke.

**Venous Thromboembolic Events (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE).

Appendix table 29: Overview of safety SPIRIT-P1, through week 24 (placebo vs. adalimumab)

Adverse event	Placebo (N=106)	Adalimumab (N=101)*
Most frequent treatment-emergent adverse events, n (%)		
Injection site reaction	0	2 (2.0)
Injection site erythema	0	2 (2.0)
Nasopharyngitis	5 (4.7)	7 (6.9)
Headache	1 (0.9)	3 (3.0)
Upper respiratory tract infection	7 (6.6)	5 (5.0)
ALT increased	0	3 (3.0)
Diarrhoea	3 (2.8)	3 (3.0)
Muscle spasms	1 (0.9)	1 (1.0)
Bronchitis	3 (2.8)0	4 (4.0)
AST increased	0	2 (2.0)
Nausea	2 (1.9)	4 (4.0)
Psoriatic arthropathy	1 (0.9)	3 (3.0)
Back pain	0	3 (3.0)
Adverse events, n (%)		
Serious adverse events	2 (1.9)	5 (5.0)
Serious infection	0	2 (2.0)
Discontinued due to adverse event	2 (1.9)	2 (2.0)
Adverse events of special interest, n (%)		
Infection	27 (25.5)	26 (25.7)
Any candida infection	0	0
Active or reactivated tuberculosis	0	0

Injection-site reactions	5 (4.7)	6 (5.9)
Hepatic events	7 (6.6)	13 (12.9)
Allergic reactions or hypersensitivities	3 (2.8)	5 (5.0)
Cytopenia (all types)	6 (5.7)	4 (4.0)
Neutropenia	0	0
Depression	0	1 (1.0)
Cerebrocardiovascular event	0	3 (3.0)
Malignancies	1 (0.9)	1 (1.0)

Source:

Appendix table 30: Overview of safety from SPIRIT-P2 through week 24 (Placebo vs. ixekizumab)

Adverse event	Placebo (N=118)	IXE Q4W (N=122)	IXE Q2W (N=123)
Most frequent treatment-emergent adverse events			
Injection site reaction	1 (1%)	8 (7%)	15 (12%)
Upper respiratory tract infection	9 (8%)	11 (9%)	12 (10%)
Nasopharyngitis	4 (3%)	8 (7%)	4 (3%)
Sinusitis	2 (2%)	7 (6%)	5 (4%)
Diarrhoea	3 (3%)	5 (4%)	5 (4%)
Urinary tract infection	3 (3%)	6 (5%)	4 (3%)
Cough	3 (3%)	4 (3%)	4 (3%)
Oropharyngeal pain	0	7 (6%)	1 (1%)
Headache	3 (3%)	5 (4%)	2 (2%)
Hypertension	3 (3%)	2 (2%)	5 (4%)
Injection-site erythema	0	2 (2%)	4 (3%)
Injection-site hypersensitivity	0	1 (1%)	5 (4%)
Back pain	2 (2%)	5 (4%)	1 (1%)
Bronchitis	4 (3%)	1 (1%)	4 (3%)
Psoriatic arthropathy	8 (7%)	2 (2%)	3 (2%)
Adverse events			
Serious adverse events	4 (3%)	3 (2%)	8 (7%)
Serious infection	0	0	3 (2%)
Discontinued due to adverse event	6 (5%)	5 (4%)	8 (7%)
Adverse events of special interest			
Infection	5 (30%)	47 (39%)	47 (38%)
Any candida infection	0	2 (2%)	6 (5%)
Active or reactivated tuberculosis	0	0	0
Hepatic events	2 (2%)	2 (2%)	5 (4%)
Allergic reactions or hypersensitivities	1 (1%)	8 (7%)	9 (7%)
Injection-site reactions	5 (4%)	14 (11%)	29 (24%)
Cerebrocardiovascular event	2 (2%)	0	0
Malignancies	0	2 (2%)	0
Depression	3 (3%)	2 (2%)	2 (2%)

Source:

Appendix table 31: Treatment emergent adverse events (TEAEs) in KEEPsAKE-1 and KEEPsAKE-2 up to week 24

TEAEs, n(%)	KEEPsAKE-1 (100% DMARD-IR)		KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)	
	Treatment		Treatment	
	Risankizumab 150 mg (N=483)	Placebo (N=481)	Risankizumab 150 mg (N=224)	Placebo (N=219)
Any TEAEs	195 (40.4)	186 (38.7)	124 (55.4)	120 (54.8)
COVID-19 related TEAEs	1 (0.2)	2 (0.4)	1 (0.4)	0
TEAE related to Study Drug[a]	53 (11.0)	50 (10.4)	39 (17.4)	39 (17.8)
Serious TEAE	12 (2.5)	18 (3.7)	9 (4.0)	12 (5.5)
Severe TEAE	10 (2.1)	9 (1.9)	6 (2.7)	7 (3.2)
TEAE leading to discontinuation of study drug	4 (0.8)	4 (0.8)	2 (0.9)	5 (2.3)
TEAE leading to death	1[b] (0.2)	0	0	0
All deaths	1[b] (0.2)	0	0	0

Source: AbbVie data on file, AbbVie Press release, 2021. [a]As assessed by investigator. [b]Death in 81 year old male with dementia, pneumonia followed by urosepsis. TEAEs: treatment emergent adverse events.

Appendix table 32: KEEPsAKE-1 and KEEPsAKE-2 adverse events up to week 24

AEs, n (%)	KEEPsAKE-1 (100% DMARD-IR)		KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)	
	Treatment		Treatment	
	Risankizumab 150 mg (N=483)	Placebo (N=481)	Risankizumab 150 mg (N=224)	Placebo (N=219)
Serious infections	5[a] (1.0)	6 (1.2)	2[b] (0.9)	5 (2.3)
Active Tuberculosis	0	0	0	0
Opportunistic infections excluding Tuberculosis and Herpes Zoster	0	0	0	0
Herpes Zoster[c]	2 (0.4)	1 (0.2)	0	1 (0.5)
Malignant tumors	0	2 (0.4)	1 (0.4)	1 (0.5)
Non-melanoma skin cancer (NMSC)	0	0	1 (0.4)	1 (0.5)
Malignant tumors excluding NMSC	0	2 (0.4)	0	0
Hypersensitivity[c]	10 (2.1)	3 (0.6)	6 (2.7)	7 (3.2)
Adjudicated anaphylactic reactions	0	0	0	0
Hepatic events[c]	32 (6.6)	21 (4.4)	5 (2.2)	6 (2.7)
Injection site reactions (ISR)	3 (0.6)	0	3 (1.3)	1 (0.5)
Adjudicated MACE	0	0	1 (0.4)	0
Adjudicated extended MACE	0	1 (0.2)	1 (0.4)	0

Source: AbbVie data on file, AbbVie Press release, 2021. [a]Five subjects had six events of cellulitis, gastroenteritis, pneumonia viral (associated with COVID), pneumonia, urosepsis, viral upper respiratory tract infection. [b]One subject with events of abscess and cellulitis and one subject with viral gastroenteritis. [c]All events were non-serious. ISR: injection site reaction; MACE: major adverse cardiac events; NMSC: non-melanoma skin cancer.

Appendix F Comparative analysis of efficacy and safety

Methodology

The relative efficacy and safety of risankizumab vs. adalimumab for the biologic-naïve population and vs ixekizumab for the bio-experienced population was established in an indirect treatment comparison (ITC).

The ITC compared the efficacy and safety on the following end-points:

- Proportion of patients achieving 20% and 50% improvement in the American College of Rheumatology (ACR) criteria (ACR 20, ACR 50)
- Proportion of patients achieving Psoriasis Area and Severity Index (PASI) 75 and PASI 90 response
- Change from baseline in 36-Item Short Form Health Survey (SF-36) Mental Component Summary (MCS) [SF-36 MCS] and Physical Component Summary (PCS) [SF-36 PCS]
- Proportion of patients with serious adverse events (SAE)

Relevant comparator studies were identified in a systematic literature review (SLR) to capture the evidence available for a wide range of treatments for PsA (see

Appendix A - Literature search for efficacy and safety of intervention and comparator(s) Relevant studies identified in the SLR and used in the ITC were classified by whether patients have already been exposed to a biologic (biologic-experienced) or not (biologic-naïve):

- Biologic-naive studies: KEEPsAKE 1, KEEPsAKE 2 (subgroup), SELECT PsA 1, SPIRIT P1
- Biologic-experienced studies: KEEPsAKE 2 (subgroup), SPIRIT P2

Data on end-points of interest were extracted from primary publications for IXE and ADA studies. For RISA studies, data were extracted from Clinical Study Reports and post-hoc analysis results.

Indirect treatment effect estimates were produced by using the method described in Rücker (2012), and Rücker and Schwarzer (2014). This approach, widely used and aligned with guidance from NICE, ISPOR and the Cochrane institute, is derived from graph theoretical techniques, which were originally developed for electrical network. The advantage of this model lies in a combination of the Bucher's method and the adjustment for multi-arm studies.

The DerSimonian and Laird method was used for conducting a random-effects meta-analyses of each treatment versus the common comparator, placebo. Associated 95% confidence intervals and P-values from pairwise comparisons were calculated.

For the biologic-naïve population (where more than 2 trials were included), indirect estimates and their 95% confidence intervals obtained from random-effects models were presented. Results from fixed-effects models were also generated (see ITC report).

Results

Appendix table 33: Indirect treatment effect estimates (biologic-naive, risankizumab vs. adalimumab) – Random effects

End-point	OR (95% CI)	RR (95% CI)
ACR 20	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]
SAE	[redacted]	[redacted]
	MD (95% CI)	
SF-36 MCS	[redacted]	
SF-36 PCS	[redacted]	

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; MD, mean difference; PASI, Psoriasis Area and Severity Index; OR, odds ratio; RR, risk ratio; SAE, serious adverse events; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, SF-36 Physical Component Summary. **Values in bold indicate statistically significant results.**

Appendix table 34: Indirect treatment effect estimates (biologic-experienced network, risankizumab vs. ixekizumab)

End-point	OR (95% CI)	RR (95% CI)
ACR 20	[redacted]	[redacted]
ACR 50	[redacted]	[redacted]
PASI 75	[redacted]	[redacted]
PASI 90	[redacted]	[redacted]
SAE	[redacted]	[redacted]
	MD (95% CI)	
SF-36 MCS	[redacted]	
SF-36 PCS	[redacted]	

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; MD, mean difference; PASI, Psoriasis Area and Severity Index; OR, odds ratio; RR, risk ratio; SAE, serious adverse events; SF-36 MCS, 36-Item Short Form Health Survey Mental Component Summary; SF-36 PCS, SF-36 Physical Component Summary.

For more information regarding the methodology, data sources, data extraction and baseline characteristics, see ITC report that is submitted together with this submission.

Appendix G – Extrapolation

N/A as no extrapolation was done for this analysis

Appendix H – Literature search for HRQoL data

N/A as a cost utility was not performed.

Appendix I Mapping of HRQoL data

N/A as a cost utility was not performed.

Appendix J Probabilistic sensitivity analyses

N/A as a cost utility was not performed.

Appendices K Report on comparison and efficacy of risankizumab, ixekizumab and adalimumab in patients with active psoriatic arthritis

See report that is attached separately to this submission.

Baseline characteristics for bio-naïve and bio-experienced population from KEEPsAKE 2 and hs-CRP at baseline from SELECT PsA-1:

Table 1: Baseline characteristics PBO and Skyrizi, KEEPsAKE-2, bio-naïve and bio-experienced study population

	DMARD-IR		Bio-IR	
Key Demographic and Baseline Characteristics Mean (SD) or n (%)	**Placebo**	**RZB 150 mg**	**Placebo**	**RZB 150 mg**
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Age (years) (median range)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n(%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black or African-American	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic/Latino, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Duration of PsA diagnosis, years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Swollen joint count 66, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Tender joint count 68, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Patient's assessment of pain,‡mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
PtGA of disease activity,‡mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
PGA of disease activity,‡ mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
HAQ-DI, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP (mg/L),§ mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Presence of psoriasis affecting ≥3% BSA, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
BSA (%),¶ mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
PASI,¶ mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
MDA, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Presence of enthesitis (LEI >0), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
LEI,†† mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Presence of dactylitis (LDI >0), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
LDI,§§ mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
SF-36 PCS score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-Fatigue score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior csDMARDs used, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]
Prior failed biologics, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
≥2	[redacted]	[redacted]	[redacted]	[redacted]
Prior TNF antagonist, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication at baseline, n (%)				
MTX¶¶	[redacted]	[redacted]	[redacted]	[redacted]
csDMARD other than MTX§§§	[redacted]	[redacted]	[redacted]	[redacted]
MTX and another csDMARD	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]

Source: AbbVie data on file, 2022

‡ Scored as millimeters on a 100 mm horizontal visual analogue scale

§ Reference range: 0–10 mg/dL

¶ Among patients with ≥3% BSA affected by psoriasis

†† Among patients with LEI >0

§§ Among patients with LDI >0

¶¶ As monotherapy or in combination with another csDMARD

§§§ Sulfasalazine, leflunomide or apremilast without MTX

BMI, body mass index; BSA, body surface area; csDMARD, conventional synthetic disease- modifying antirheumatic drug; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI, Health Assessment Questionnaire–Disability Index; hsCRP, high- sensitivity C reactive protein; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; MDA, minimal disease activity; MTX, methotrexate; NSAID, non-steroidal anti- inflammatory drug PASI,

Psoriasis Area and Severity Index; PBO, placebo; SF-36 PCS , 36- Item Short Form Health Survey Physical Component Summary; PGA, physician's global assessment; PsA, psoriatic arthritis; PtGA, patient's global assessment; RZB, risankizumab; TNF, tumour necrosis factor

Table 2: hs-CRP at baseline for adalimumab and placebo from SELECT PsA-1

Baseline characteristic	Adalimumab 40mg EOW	Placebo
hsCRP (mg/L), mean (SD)	[redacted]	[redacted]

Source: AbbVie data on file, 2021

Indirect treatment comparison on % of patients with change in mTSS ≤0, Skyrizi vs. adalimumab for the bio-naïve population in PsA

The indirect comparison on mTSS follows the same methodology as described in chapter 7.4 in the submitted dossier for Skyrizi.

Data on % of patients with change in mTSS≤0 for the bio-naïve population was extracted from the studies identified in the literature search for the comparator adalimumab (SELECT PsA-1 and SPIRIT P1) and from KEEPsAKE 1 for Skyrizi – see table 1 below for data extracted from the studies.

Unfortunately, mTSS was not measured in the studies including bio-experienced patients (KEEPsAKE 2 or SPIRIT-P2) so it is not possible to perform an analysis on mTSS for the bio-experienced population. Therefore, the analysis and results shown below is only presented for the bio-naïve population.

Table 1: Extracted data per study (n/N) on % of patients with change in mTSS≤0

Study	Arm	n of mTSS non progressors/ N of patients	% of mTSS non-progressors	Source
KEEPsAKE 1	PBO	401/457	87,7%	**Kristensen et al, 2022 (1)** Supplementary material table S4
KEEPsAKE 1	RISA	423/458	92,4%	
SPIRIT P1	PBO	76/106	71,7%	**Mease et al, 2017 (2)** Table 3
SPIRIT P1	ADA	92/101	91,7%	
SELECT PsA1	PBO	332/372	89,2%	**McInnes et al, 2021 (3)** Supplementary material figure S14
SELECT PsA1	ADA	357/384	93,0%	

Looking at the extracted data very similar results were observed in SELECT PsA-1 and KEEPsAKE 1 for in both arms. Similar results were also observed between Skyrizi and adalimumab in SPIRIT P1, however the proportion of patients experiencing no progression in the placebo arm in SPIRIT P1 is very low compared with the proportions in KEEPsAKE 1 and SELECT PsA-1, which can favor adalimumab from SPIRIT P1 compared to the other studies. Furthermore, SPIRIT P1 is also a much smaller trial with smaller patient numbers compared to KEEPsAKE 1 and SELECT PsA-1. These factors should be taken into consideration when interpreting the results seen below in table 2.

Table 2: Indirect treatment comparison results % of patients with change in mTSS ≤0, Skyrizi vs. adalimumab, week 24

End-point	OR (95% CI); p-value	RR (95% CI); p-value
% of patients with change in mTSS ≤0	[redacted]	[redacted]

The results of the indirect comparison demonstrated no statistically significant difference between Skyrizi and adalimumab on % of patients with change in mTSS ≤0.

References:

1. Kristensen LE, Keiserman M, Papp K, McCasland L, White D, Lu W, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis. 2022;81(2):225-31.
2. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76(1):79-87.
3. McInnes IB, Anderson JK, Magrey M, Merola JF, Liu Y, Kishimoto M, et al. Trial of Upadacitinib and Adalimumab for Psoriatic Arthritis. N Engl J Med. 2021;384(13):1227-39.

Table 1. KEEPsAKE-1 and KEEPsAKE-2 efficacy results at week 52, observed cases

Efficacy endpoint[a]	KEEPsAKE-1 (100% DMARD-IR)			
	PBO to RZB	95% CI*	RZB to RZB	95% CI*
ACR20 response, n/N (%)				
ACR50 response, n/N (%)				
ACR70 response, n/N (%)				
HAQ-DI, change from baseline, mean				
Resolution of enthesitis, n/N (%)[b]				
Resolution of dactylitis, n/N (%)[c]				
mTSS, change from baseline, mean				
MDA response, n/N (%)				
PASI75 response, n/N (%)[d]				
PASI90 response, n/N (%)[d]				
mNAPSI, change from baseline, mean				
PGA-F, change from baseline, mean				
FACIT-Fatigue, mean				
SF-36 PCS, change from baseline, mean				
SF-36 MCS, change from baseline, mean				
No radiographic progression, change from baseline mTSS<0, n/N (%)				
No radiographic progression, change from baseline mTSS<0.5, n/N (%)				

Efficacy endpoint[a]	KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)							
	DMARD-IR				Bio-IR			
	PBO to RZB	95% CI*	RZB to RZB	95% CI*	PBO to RZB	95% CI*	RZB to RZB	95% CI*
ACR20 response, n/N (%)								
ACR50 response, n/N (%)								
ACR70 response, n/N (%)								
HAQ-DI, change from baseline, mean								
Resolution of enthesitis, n/N (%)[b]								
Resolution of dactylitis, n/N (%)[c]								
mTSS, change from baseline, mean	Not assessed							
MDA response, n/N (%)								
PASI75 response, n/N (%)[d]								

PASI90 response, n/N (%)[d]	
mNAPSI, change from baseline, mean	Not assessed
PGA-F, change from baseline, mean	Not assessed
FACIT-Fatigue, mean	
SF-36 PCS, change from baseline, mean	
SF-36 MCS, change from baseline, mean	
No radiographic progression, change from baseline mTSS<0	Not assessed
No radiographic progression, change from baseline mTSS<0.5	Not assessed

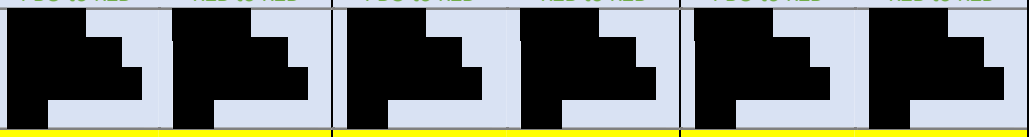
Source: AbbVie data on file.
[a]Analyses based on as observed data unless otherwise noted.
[b]For subjects with baseline LEI>0.
[c]For subjects with baseline LDI>0.
[d]For subject with BSA ≥ 3% at baseline.
*For binary outcomes 95% CI is calculated based on normal approximation to the binomial distribution and for continuous outcomes the 95% CI is calculated using t-statistics.
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

Table 2. Treatment-emergent adverse events (TEAEs) in KEEPsAKE-1 and KEEPsAKE-2 up to week 52, observed cases

TEAEs, n (%)	**KEEPsAKE-1** (100% DMARD-IR)		**KEEPsAKE-2** (50% DMARD-IR, 50% Bio-IR)			
			DMARD-IR		**Bio-IR**	
	PBO to RZB	RZB to RZB	PBO to RZB	RZB to RZB	PBO to RZB	RZB to RZB
Any TEAEs						
COVID-19 related TEAEs						
TEAE related to Study Drug[a]						
Serious TEAE						
Severe TEAE						
TEAE leading to discontinuation of study drug						
TEAE leading to death						
All deaths						

Source: AbbVie data on file.
[a]As assessed by investigator.
[b] .
Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of risankizumab and up to 140 days after the last dose of risankizumab if subject discontinued study drug prematurely.
E/100 PYs = Events per 100 patient-years.

Table 3. KEEPsAKE-1 and KEEPsAKE-2 TEAE's of safety interest up to week 52, observed cases

AEs, n (%)	KEEPsAKE-1 (100% DMARD-IR)		KEEPsAKE-2 (50% DMARD-IR, 50% Bio-IR)			
			DMARD-IR		Bio-IR	
	PBO to RZB	RZB to RZB	PBO to RZB	RZB to RZB	PBO to RZB	RZB to RZB
						
Serious infections[a]						
Active Tuberculosis						
Opportunistic infections excluding Tuberculosis and Herpes Zoster						
Herpes Zoster[b]						
Malignant tumors						
Non-melanoma skin cancer (NMSC)						
Malignant tumors excluding NMSC						
Hypersensitivity[c]						
Adjudicated anaphylactic reactions						
Hepatic events						
Injection site reactions (ISR)[c]						
Adjudicated MACE[d]						
Adjudicated extended MACE[e]						

Source: AbbVie data on file.

[a]At week 52, ■ subjects had serious infections of COVID-19 versus two subjects at week 24.

[b]All where non-serious and mild or moderate in severity.

[c]None resulted in discontinuation.

[d]MACE is defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

[e]Extended MACE is defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, and coronary revascularization procedures.

ISR: injection site reaction; MACE: major adverse cardiac events; NMSC: non-melanoma skin cancer.

Note: Treatment-emergent AE (TEAE) is defined as an AE with an onset date that is on or after the first dose of risankizumab and up to 140 days after the last dose of risankizumab if subject discontinued study drug prematurely.

E/100 PYs = Events per 100 patient-years.

Primary and secondary endpoints of bio-naïve and bio-experienced patients treated with concomitant methotrexate and with risankizumab monotherapy from KEEPsAKE 1 and KEEPsAKE 2

The analysis of patients with concomitant methotrexate use is based on subjects who were reported to have concomitant methotrexate use at baseline.

The analysis of patients with Skyrizi monotherapy is based on subjects who reported no concomitant csDMARDs, nonsteroidal anti-inflammatory drug (NSAID) use and oral corticosteroid use at baseline.

Data on bio-naïve patients are derived from the pooled population of bio-naïve patients from KEEPsAKE 1 and 2, while data on bio-experienced patients are derived from the bio-experienced population from KEEPsAKE 2.

AbbVie would like to highlight that the results should be interpreted with caution. When splitting the population in several ways (concomitant MTX vs. Skyrizi monotherapy, bio-naïve vs. bio-experienced), the patient numbers become very small, increasing the uncertainty of the results and can lack power to be able to make comparative analyses. This is especially evident for the KEEPsAKE-2 data split into the different populations where patient numbers are as low as [redacted] patients. The results should be interpreted with this in mind. In general, results show favorability or statistical significance in favor of risankizumab on most outcomes.

Table 1: Overview of primary and secondary endpoint results for bio-naive patients treated with concomitant methotrexate (MTX) from KEEPsAKE-1 and KEEPsAKE-2

Efficacy endpoint	KEEPsAKE-1/KEEPsAKE-2 pooled bio-naive (Subjects with concomitant methotrexate)		
	Risankizumab 150 mg [redacted]	Placebo [redacted]	Difference (95% CI)
Primary endpoint at week 24			
ACR20, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 16			
ACR20 at week 16, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 24			
CFB HAQ-DI, mean (95% CI)	[redacted]	[redacted]	[redacted]
PASI90[a], n (%)	[redacted]	[redacted]	[redacted]
MDA, n (%)	[redacted]	[redacted]	[redacted]
CFB mNAPSI[b], mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB PGA-F[b], mean (95% CI)	[redacted]	[redacted]	[redacted]
Enthesitis resolution[c], n (%)	[redacted]	[redacted]	[redacted]
Dactylitis resolution[d], n (%)	[redacted]	[redacted]	[redacted]
CFB mTSS[e], mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB SF-36 PCS, mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB FACIT-FATIGUE, mean (95% CI)	[redacted]	[redacted]	[redacted]
Other Secondary endpoints at week 24			
ACR50 response wk 24, n (%)	[redacted]	[redacted]	[redacted]
ACR70 response wk 24, n (%)	[redacted]	[redacted]	[redacted]

Source: AbbVie data on file, 2022.

Note: Analysis population is based on the subjects with concomitant MTX use at baseline.
[a]Summarized for subjects with baseline body surface area affected by psoriasis ≥ 3% (placebo [redacted]; risankizumab [redacted]).
[b]Summarized for subjects with baseline nail psoriasis (placebo [redacted]; risankizumab [redacted]), only measured in KEEPsAKE 1.
[c]Summarized for subjects with concomitant MTX and baseline Leeds Enthesitis Index >0 (placebo [redacted]; risankizumab [redacted]).
[d]Summarized for subjects with concomitant MTX and baseline Leeds Dactylitis Index >0 (placebo [redacted]; risankizumab [redacted].
[e]Only measured in KEEPsAKE 1
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; MTX: methotrexate; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

Table 2: Overview of primary and secondary endpoint results for bio-naïve patients treated with risankizumab monotherapy in KEEPsAKE-1 and KEEPsAKE-2

Efficacy endpoint	KEEPsAKE-1/KEEPsAKE-2 pooled bio-naive (Subjects with risankizumab monotherapy)		
	Risankizumab 150 mg [redacted]	Placebo [redacted]	Difference (95% CI)
Primary endpoint at week 24			
ACR20, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 16			
ACR20 at week 16, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 24			
CFB HAQ-DI, mean (95% CI)	[redacted]	[redacted]	[redacted]
PASI90[a], n (%)	[redacted]	[redacted]	[redacted]
MDA, n (%)	[redacted]	[redacted]	[redacted]
CFB mNAPSI[b], mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB PGA-F[b], mean (95% CI)	[redacted]	[redacted]	[redacted]
Enthesitis resolution[c], n (%)	[redacted]	[redacted]	[redacted]
Dactylitis resolution[d], n (%)	[redacted]	[redacted]	[redacted]
CFB mTSS[e], mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB SF-36 PCS, mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB FACIT-FATIGUE, mean (95% CI)	[redacted]	[redacted]	[redacted]
Other Secondary endpoints at week 24			
ACR50 response wk 24, n (%)	[redacted]	[redacted]	[redacted]
ACR70 response wk 24, n (%)	[redacted]	[redacted]	[redacted]

Source: AbbVie data on file, 2022.
Note: Analysis population is based on the subjects without concomitant csDMARD, Nonsteroidal Anti-Inflammatory Drug (NSAID) use and oral Corticosteroid use at baseline
[a]Summarized for subjects with baseline body surface area affected by psoriasis ≥ 3% (placebo [redacted]; risankizumab [redacted].
[b]Summarized for subjects with baseline nail psoriasis (placebo [redacted] risankizumab [redacted]), only measured in KEEPsAKE 1.
[c]Summarized for subjects with risankizumab monotherapy and baseline Leeds Enthesitis Index >0 (placebo [redacted]; risankizumab [redacted].
[d]Summarized for subjects with risankizumab monotherapy and baseline Leeds Dactylitis Index >0 (placebo [redacted]; risankizumab [redacted]).
[e]Only measured in KEEPsAKE 1
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

Table 3: Overview of primary and secondary endpoint results for bio-experienced patients treated with concomitant methotrexate (MTX) in KEEPsAKE-2

Efficacy endpoint	KEEPsAKE-2 (Bio-experienced subjects with concomitant methotrexate)		
	Risankizumab 150 mg [redacted]	Placebo [redacted]	Difference (95% CI)
Primary endpoint at week 24			
ACR20, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 16			
ACR20 at week 16, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 24			
CFB HAQ-DI, mean (95% CI)	[redacted]	[redacted]	[redacted]
PASI90[a], n (%)	[redacted]	[redacted]	[redacted]
MDA, n (%)	[redacted]	[redacted]	[redacted]
Enthesitis resolution[b], n (%) (Pooled)	[redacted]	[redacted]	[redacted]
Dactylitis resolution[c], n (%) (Pooled)	[redacted]	[redacted]	[redacted]
CFB SF-36 PCS, mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB FACIT-FATIGUE, mean (95% CI)	[redacted]	[redacted]	[redacted]
Other Secondary endpoints at week 24			
ACR50 response wk 24, n (%)	[redacted]	[redacted]	[redacted]
ACR70 response wk 24, n (%)	[redacted]	[redacted]	[redacted]

Source: AbbVie data on file, 2022.
Note: Analysis population is based on the subjects with concomitant MTX use at baseline.
[a]Summarized for subjects with baseline body surface area affected by psoriasis ≥ 3% (placebo [redacted]; risankizumab [redacted]).
[b]Summarized from pooled data from KEEPsAKE-1 and KEEPsAKE-2 for subjects treated with concomitant MTX and baseline Leeds Enthesitis Index >0 (placebo [redacted] risankizumab [redacted]
[c]Summarized from pooled data from KEEPsAKE-1 and KEEPsAKE-2 for subjects treated with concomitant MTX with baseline Leeds Dactylitis Index >0 (placebo [redacted]; risankizumab [redacted]).
ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; MTX: methotrexate; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.

Table 4: Overview of primary and secondary endpoint results for bio-experienced patients treated with risankizumab monotherapy in KEEPsAKE-2

Efficacy endpoint	KEEPsAKE-2 (Bio-experienced subjects with risankizumab monotherapy)		
	Risankizumab 150 mg [redacted]	Placebo [redacted]	Difference (95% CI)
Primary endpoint at week 24			
ACR20, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 16			
ACR20 at week 16, n (%)	[redacted]	[redacted]	[redacted]
Secondary endpoint at week 24			
CFB HAQ-DI, mean (95% CI)	[redacted]	[redacted]	[redacted]
PASI90[a], n (%)	[redacted]	[redacted]	[redacted]
MDA, n (%)	[redacted]	[redacted]	[redacted]
Enthesitis resolution[b], n (%) (Pooled)	[redacted]	[redacted]	[redacted]
Dactylitis resolution[c], n (%) (Pooled)	[redacted]	[redacted]	[redacted]
CFB SF-36 PCS, mean (95% CI)	[redacted]	[redacted]	[redacted]
CFB FACIT-FATIGUE, mean (95% CI)	[redacted]	[redacted]	[redacted]
Other Secondary endpoints at week 24			
ACR50 response wk 24, n (%)	[redacted]	[redacted]	[redacted]

ACR70 response wk 24, n (%)	[redacted]		[redacted]		[redacted]

Source: AbbVie data on file, 2022.

Note: Analysis population is based on the subjects without concomitant csDMARD, Nonsteroidal Anti-Inflammatory Drug (NSAID) use and oral Corticosteroid use at baseline.

[a]Summarized for subjects with baseline body surface area affected by psoriasis ≥ 3% (placebo [redacted]; risankizumab [redacted].

[b]Summarized from pooled data from KEEPsAKE-1 and KEEPsAKE-2 for subjects treated with risankizumab monotherapy and with baseline Leeds Enthesitis Index >0 (placebo [redacted]; risankizumab [redacted]).

[c]Summarized from pooled data from KEEPsAKE-1 and KEEPsAKE-2 for subjects treated with risankizumab monotherapy and with baseline Leeds Dactylitis Index >0 (placebo [redacted]; risankizumab [redacted]). [redacted] bio experienced patients on risankizumab monotherapy had baseline LDI>0.

ACR: American college of Rheumatology; BIO-IR: biologic inadequate responder; CFB: change from baseline; DMARD-IR: disease modifying anti-rheumatic drug inadequate responder; FACIT-Fatigue: functional assessment of chronic illness therapy-fatigue; HAD-DI: health assessment questionnaire-disability index; MDA: minimal disease activity; mNAPSI: median nail psoriasis severity index; mTSS: modified total Sharp score; PASI: psoriasis area severity index; PGA-F: physician's global assessment of fingernails; SF-36 PCS: short form-36 physical component summary.